Journal of Pharmacreations

PharmaCreations

ISSN: 2348-6295

Pharmacreations | Vol.9 | Issue 2 | Apr- Jun- 2022

Journal Home page: www.pharmacreations.com

Research article *Clinical research*

Formulation and evaluation of anti-hypertensive buccal tablets (labetalol HCL)

***Sayyed Wamique Aquil, *H. Parameshwar, *A.V. Jithan *Mekala Sai Lakshmi,*Chandrakanth**

**Omega College of Pharmacy, Edulabad, Ghatkesar, Affiliated to Osmania University, Hyderabad, Telangana, India*

Corresponding Author: H. Parameshwar

ABSTRACT

The purpose of this research was to develop and characterize Bioadhesive buccal tablets of Labetalol using sodium alginate, xanthan gum and Ethylcellulose. The tablets were evaluated for weight variation, thickness, hardness, friability, surface pH, mucoadhesive strength, swelling index, in vitro drug release. The swelling index, friability and in vitro drug release. F3 formulation was considered optimum based on good Bioadhesive strength and maximum similarity factor. The drug release from optimum batch followed zero order kinetics with non-Fickian diffusion. Drug and excipients compatibility study showed no interaction between drug and excipients. Stability study of optimized formulation showed that tablets were stable at accelerated environment condition. Thus, buccal adhesive tablet of Labetalol could be an alternative route to bypass hepatic first pass metabolism and to improve bioavailability of Labetalol.

Keywords: Bioadhesion, buccal drug delivery, Labetalol, polymers, in vitro drug release studies, Zero order kinetics.

INTRODUCTION

Buccal Drug Delivery System

This system provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of administration problems such as high first pass metabolism, drug degradation in harsh gastro intestinal environment can be circumvented by administering a drug via buccal route1,2&3. More over buccal drug absorption can be terminated promptly in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer the drug to patients who cannot be dosed orally to prevent accidental swallowing. Buccal delivery refers to drug release which can occur when a dosage form is placed in the outer vestibule between the buccal mucosa and gingiva. Various advantages and other aspects of this route are elucidated of the following.

Oral Cavity

Oral cavity is the foremost part of digestive system of human body due to its excellent accessibility and reasonable patient compliance, oral mucosal cavity offers attractive route of drug administration for the local and systemic therapy. Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions,

1. Outer oral vestibule, which is bounded by cheeks, lips, teeth and gingiva (gums).
2. Oral cavity proper, which extends from teeth and gums back to the faces (which lead to pharynx) with the roof comprising the hard and soft palate. The tongue projects from the floor of the cavity.

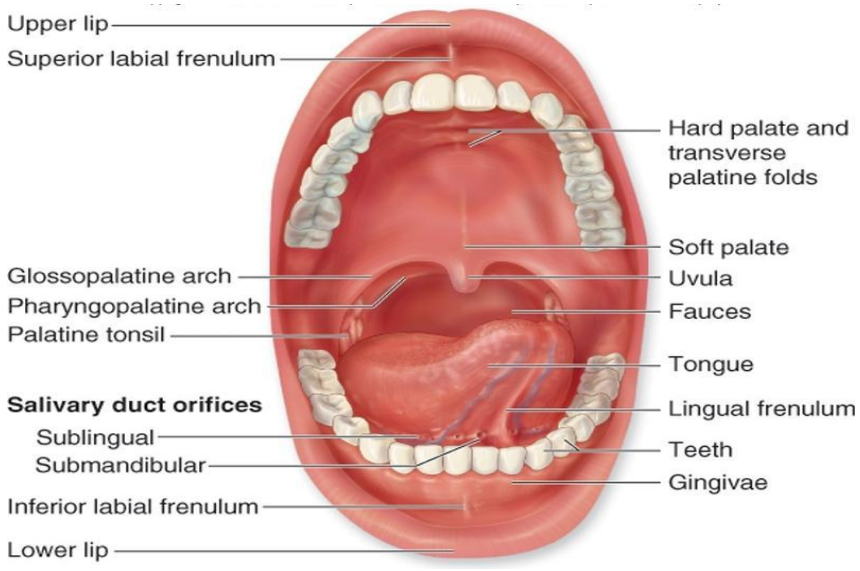


Fig 1: Buccal cavity

The drug administered via the oral mucosa gain access to the systemic circulation through a network of arteries and capillaries. The major artery supplying the blood to the oral cavity is the external carotid artery. The venous back flow goes through branches of capillaries and veins and finally taken up by the jugular vein8. The secretion in the oral cavity includes saliva, crevicular fluid and mucus. From that, Saliva is a complex fluid containing organic and inorganic materials. It is produced by the three pairs of major glands (parotid, submandibular and sublingual) each situated outside the oral cavity and in minor salivary glands situated in the tissues lining most of the oral cavity. The total average volume of saliva produced daily in an adult is around 750 ml. The flow rates of saliva depend upon the type of stimulus used, the time of day, the length of time, glands had been stimulated, the age and sex of the individual and by their state of health. Chemically, saliva is 99.5% water and 0.5% solutes. The solutes include ions (sodium, potassium, magnesium, phosphate, bicarbonate and chloride), dissolved gases, urea, uric acid,\serum albumin, globulin, mucin and enzymes [lysozyme and amylase (ptyalin)]. Second was the crevicular fluid it is a fluid secreted from the gingival glands of oral cavity. The third type was the mucus, it is a thick secretion composed mainly of water, electrolytes and a mixture of several glycoprotein, which themselves are composed of large polysaccharides bound with smaller quantities of protein. It is secreted over many biological membranes of body for example, throughout the gastrointestinal tract walls. Mucus is secreted by special type of epithelia called mucosa. The mucus secreted in buccal cavity admixtures with saliva of salivary glands in oral cavity to produce whole saliva. The two main glycoproteins found in buccal mucus or mucin is MG1 and MG2.

Buccal tablets

Buccal tablets are small, flat, and oval shaped dosage form. Unlike conventional tablets Buccal mucoadhesive tablets allow for drinking and speaking without major discomfort. They so often adhere to the mucosa and are retained in position until dissolution and/or release is complete. These tablets can be applied to different sites in the oral cavity including the palate the mucosa lining the cheek as well as between the lip and the gum.

Advances in Buccal Drug Delivery Dosage Forms

Type I: It is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing. Type II: It is a device in which an impermeable backing layer is superimposed on top of the drug loaded bioadhesive layer creating a double- layered device and preventing drug loss from the top surface into the oral cavity. Type III: It is a unidirectional drug release device, from which drug loss is minimal, since the drug is released only from the side adjacent to the buccal mucosa. This can be achieved by coating every face of the dosage form, except the one that is in contact with the buccal mucosa.

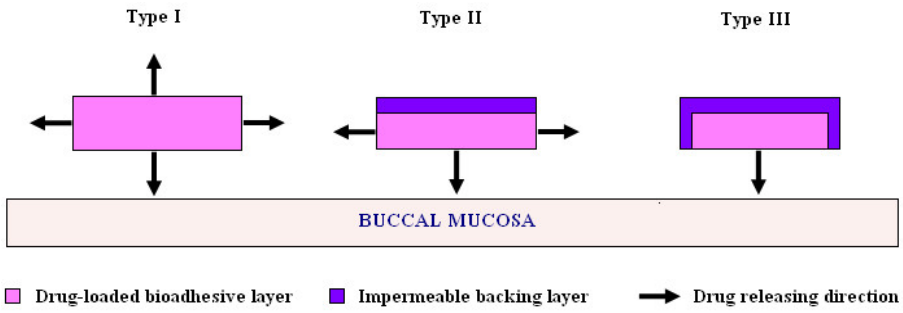


Fig 2: Design of buccal mucoadhesive dosage forms

Mucoadhesive Buccal Tablets

The purpose of the buccal tablet is absorption of the drug through the lining of the mouth. Buccal tablets can be most easily held between the gum and cheek. Various drugs have been investigated for their delivery through the buccal mucosa in a mucoadhesive buccal tablet form.

Factors Affecting Mucoadhesion

The muco-adhesion of a drug carrier system to the mucous membrane depends on the below mentioned factors**.**

1. Polymer based factors:Molecular weight of the polymer, Concentration of polymer used, Flexibility of polymer chains, Swelling factor, Stereochemistry of polymer,2. Environment related factors:pH at polymer substrate interface, Applied strength, Contact time, 3. Physiological factors:Mucin turnover rate, Diseased state

Method Of Preparation Of Mucoadhesive Buccal Tablets

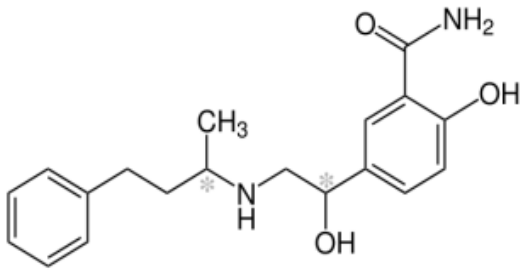
The design of mucoadhesive was mainly do ne by three processes namely wet granulation process, dry granulation process and direct compression process. From this the wet granulation process was the most widely used and most general method of tablet preparation. Its popularity is due to the greater probability that the granulation will meet all physical requirements for the compression of good tablets. The dry granulation process explained as when the tablet ingredients are sensitive to moisture and are unable to withstand elevated temperatures during drying and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules. This method is known as dry granulation or pre-compression method or the double compression method. Finally the third method was direct compression method in this method of tablet manufacturing the all ingredients such as drug, diluents, binders, lubricants and other required excipients and chemicals are weighed individually then mixed and blended together for some time period and then directly compressed into a compact mass. This process was the most preferred method of tablet manufacturing because of it is the cheapest and fastest direct method of tablet production.

Evaluation of Mucoadhesive Buccal Tablets

The prepared mucoadhesive buccal tablets should be evaluated for various physical and chemical evaluation parameters. The physical evaluation parameters mainly involves tablet appearance, hardness test which provide a measure tablet strength to the tablet, friability gives an indication of the tablets ability to resist abrasion on handling during packaging, thickness gives size of the tablet, weight variation also carried out for similarity in weight of same tablets. After doing these physical evaluation tests the chemical evaluation comes which are explained as drug content for demonstrating actual amount of drug present in individual tablet, swelling index and surface pH of tablet also checked, *in vitro* release study demonstrate the release pattern of drug in the medium. *Ex vivo* permeation of buccal tablets through the excised sheep buccal mucosal membrane was studied using modified Keshary Chien (K-C) type of diffusion cell, the *ex vivo* residence time for buccal tablet was determined using a locally modified USP disintegration apparatus, the FTIR interpretation checks the drug excipients interaction for suitable dosage form and the stability study also done for long time storage of the tablets. The important evaluation factor for the buccal tablet was the *in vitro* mucoadhesive strength of the tablet was measured on a modified physical balance employing the method described by Gupta et al using sheep buccal mucosa as model mucosal membrane and the results are obtained in grams.

DRUG PROFILE

Name: Labetatol
Description: Blocker of both alpha- and beta-adrenergic receptors that is used as an antihypertensive.
Structure:



Chemical Formula: $C_{19}H_{24}N_2O$,
Molecular weight: 328.40 g/ mol
Mechanism of Action: Labetalol HCl combines both selective, competitive, alpha-1-adrenergic blocking and nonselective, competitive, beta-adrenergic blocking activity in a single substance. The principal physiologic action of labetalol is to competitively block adrenergic stimulation of β-receptors within the myocardium (β1-receptors) and within bronchial and vascular smooth muscle (β2-receptors), and α1-receptors within vascular smooth muscle. This causes a decrease in systemic arterial blood pressure and systemic vascular resistance without a substantial reduction in resting heart rate, cardiac output, or stroke volume, apparently because of its combined α- and β-adrenergic
Uses: Labetalol is used to treat high blood pressure (hypertension). It helps to prevent strokes, heart attacks, and kidney problems.
Materials And Equipments: Compression Machine- Rimetek mini press-II, Mechanical Sieve Shaker- Retsch , Germany, Tap Density Tester- Electrolab, Mumbai, Disintegration Tester- Electrolab, Mumbai, Hardness Tester- Pfizer, Friabilator- Electrolab, Hyd, Thickness Tester- Sams Techno Mumbai, Dissolution Apparatus USP II- Lab India, Disso 8000.
Materials And Suppliers: Labetalol- AR chemicals, Sodium alginate- AR chemicals, Xanthan gum- AR chemicals, Ethylcellulose- AR chemicals, Lactose- AR chemicals, Microcrystalline cellulose- AR chemicals, Magnesium Stearate- AR chemicals, Talc- AR chemicals.

METHODOLOGY

Preformulation Studies

Physical properties like, The color, odour, taste of the drug were recorded using descriptive terminology.Solubility studies:Solubility study of Labetalol was performed in Water, 0.1 N HCl , pH 6.8 phosphate buffer. Determination of melting point: Melting point of Labetatol was determined by capillary method.

Table 1: Standard values of precompression parameters

S. No	Angle of repose (^{0})	Carr's index(%)	Hausner's ratio	Properties
1	25-30	5-12	1.00-1.11	Free Flowing
2	30-35	12-16	1.12-1.18	Good
3	35-40	18-21	1.19-1.25	Fair
4	40-55	23-35	1.35-1.45	Poor
5	55-65	33-38	1.46-1.59	Very poor
6	>65	>40	>1.60	Extremely poor

Drug excipients compatibility studies: Drug excipients compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in HDPE bags and LDPE bags. Glass vials were exposed to 600 C and 400C/75 %RH for 4 weeks and LDPE bags were exposed to 400C±75 %RH for 4 weeks. Samples were observed periodically for any physical change.
Preparation of standard curve of Labetalol:
*Preparation of 6.8 phosphate buffer:*28.80 gm of Disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen phosphate in 1000 ml of water.
Preparation of standard curve of Labetatol in 6.8 pH : For the standard graph, Labetatol 10 mg was accurately weighed and dissolved in 10ml of 6.8 phosphate buffer. From the stock solution (1mg/ml), different concentration of Labetatol viz, 1, 2, 3, 4 and 5 mcg/ml were prepared and made up to volume with distilled water. The absorbance's, which were found.
Drug-excipients compatibility study: The compatibility of drug and formulation components is important prerequisite for formulation development. It is therefore necessary to confirm that the drug does not interact with excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

Table 2: Formulation of buccal tablets of Labetalol

Ingredients(mg)	L1	L2	L3	L4	L5	L6	L7	L8
Labetalol	50	50	50	50	50	50	50	50

Sodium alginate	100		50	25	75	30	70	40
Xanthan gum	-	100	50	75	25	70	30	60
Ethylcellulose	100	100	100	100	100	100	100	100
Lactose	44	44	44	44	44	44	44	44
Talc	2	2	2	2	2	2	2	2
Magnesium Stearate	3	3	3	3	3	3	3	3
Saccharine	1	1	1	1	1	1	1	1
Total wt	300	300	300	300	300	300	300	300

Preparation method

Different tablet formulations were prepared by direct compression method. The formulations are composed of polymers. All powders were passed through 100-mesh sieve. The microcrystalline and the polymer were mixed uniformly. Drug was added to the polymers and blended for 20 min. The resulting powder were mixed with magnesium Stearate and talc in polyethylene bag for 10 min. The lubricated powder were compressed using 10mm punch (single punch tablet machine) in to tablets. The total weight of tablet was kept at 200 mg.Post compression parameters: thickness, hardness, friability, content uniformity, swelling index were done

In- Vitro *Release study*

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 100 rpm. The dissolution medium consisted of 900 ml of Standard buffer 0.1 N HCL for 2 hr and followed by pH 6.8 period of time. Temperature maintained at 37±5.The sample of 1ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 1 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask, and make the volume with buffer. The diluted samples were assayed at 300 nm against reagent blank.

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile.

The prepared Labetalol buccal tablets were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2^{o}c and refrigerator 2-8^{o}c for a period of 90 days.

RESULTS

Preformulation Studies

A. Physical characteristics a. Colour-white, odour-characteristics, taste-Bitter, and appearance: Crystal powder

b. Melting point determination: Drug: Labetatol reported M.P195-196^{0}c observed M.P-195^{0}c

c.Determination of solubility: The solubility of the Labetatol was determined and found to be freely soluble in water.

Preparation of standard curve of Labetatol

Standard curve of Labetalol was determined by plotting absorbance V/s concentration at 300nm. Using solution prepared in pH 6.8 at 300 nm. And it follows the Beer's law. The R ^{2} value is 0.997.

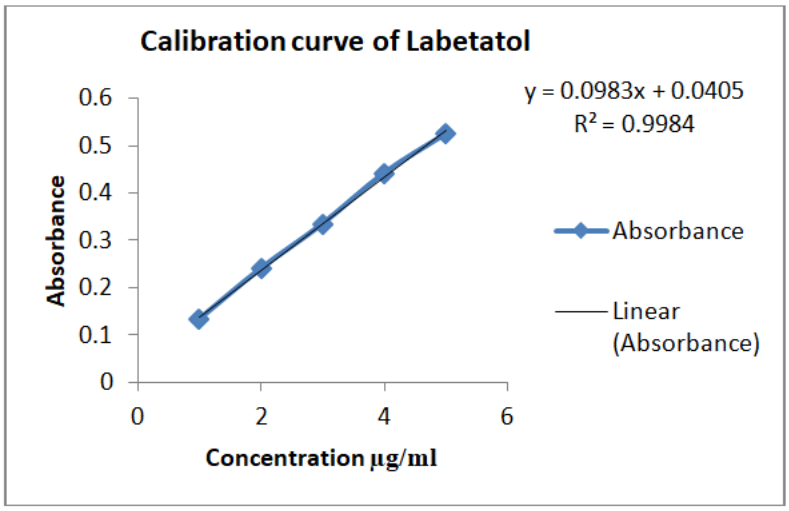


Fig 3: Calibration curve of Labetalol

Evaluation of Pre Compression Parameters

Table 3: Evaluation of Precompression parameters

S.no	Formulations	Angle of repose (^{0})	Bulk density g/ml	Tapped density g/ml	Compressibility index	Hausner's ratio
1	F-1	29	0.396	0.485	18.35	1.22
2	F-2	30	0.398	0.489	18.60	1.22
3	F-3	27	0.401	0.491	18.32	1.22
4	F-4	31	0.390	0.486	19.75	1.24
5	F-5	28	0.394	0.489	19.42	1.24
6	F-6	30	0.389	0.484	19.62	1.24
7	F-7	29	0.391	0.485	19.38	1.24
8	F-8	28	0.395	0.484	18.38	1.22

Bulk density and tapped density for the formulations were in the range of 0.389-0.401g/cc. The angle of repose for the formulations was found to be in the range of 27^o to 31^o. Compressibility index and Hauser's ratio were in the range of 18.32 to 19.62 % and 1.22 to 1.24.

Evaluation of Post Compression Parameters

Table 4: Results for Post parameters

S.no	Formulations	Thickness (mm)	WeightVariation (mg)	Friability (%)	Hardness (kg/cm^2)	Drug content	Swelling Index
1	F-1	2.93	300	0.49	4.10	78.52	42.25
2	F-2	2.93	299	0.47	4.19	81.38	58.46
3	F-3	2.90	300	0.51	4.21	86.23	56.05
4	F-4	2.99	299	0.52	4.18	81.85	61.15
5	F-5	2.99	298	0.60	4.20	79.25	59.02
6	F-6	3.0	300	0.62	4.17	82.21	58.96
7	F-7	2.97	299	0.58	4.15	83.28	59.65
8	F-8	3.10	301	0.57	4.16	79.49	61.45

Drug Release Studies

Table 5: Dissolution profiles of Labetalol buccal tablets

Time(hr)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	12.34	13.43	19.68	14.21	12.12	11.28	12.85	17.96
2	22.43	28.9	27.84	25.31	27.52	26.59	23.75	25.31
3	36.54	35.93	38.59	38.12	35.62	36.09	37.34	30.18
4	40.92	42.78	47.03	43.24	42.65	44.53	46.79	45.21
5	52.56	50.87	58.43	52.96	53.12	55.46	54.68	56.15
6	66.34	62.46	69.59	63.25	67.56	65.35	69.85	65.78
7	78.96	75.64	79.63	75.28	73.98	78.25	77.90	73.96
8	86.26	84.62	90.26	89.55	87.36	89.99	88.58	87.90

We selected F-3 as best formulation as it showed total drug release in 8 hr as sustained manner than all other formulations.

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-3 after 3 Months. Parameters quantified at various time intervals were show.

Table6: Results of stability studies of optimized formulation F-3

Formulation Code	Parameters	Initial	1 Month	2 Month	3 Month	Limits as per Specifications
F-3	250C/60%RH% Release	90.26	90.24	90.18	90.11	Not less than85 %
F-3	300C/75%RH% Release	90.26	90.23	90.15	90.09	Not less than85 %
F-3	400C/75%RH% Release	90.26	90.19	90.12	90.07	Not less than85 %

SUMMARY & CONCLUSION

The present study was mainly based upon the "Development and characterization of Labetalol Buccal tablets" by direct compression method. The double layered structure design was expected to provide drug delivery in an unidirectional fashion to the mucosa and to avoid loss of drug due to washout by saliva, release drug immediately to produce a prompt pharmacological action and remain in oral cavity and provide a sustained release of enough drug over an extended period of time. A total of ten formulations of buccal tablets of Labetalol were prepared and evaluated for biological, physical and mechanical parameters. The blends were also evaluated for various pre compression parameters. Bulk density and tapped density for the formulations were in the range of 0.389-0.401g/cc. The angle of repose for the formulations was found to be in the range of 27º to 31º. Compressibility index and Hauser's ratio were in the range of 18.32 to 19.62 % and 1.22 to 1.24. According to work plan, the tablets were evaluated for their thickness, hardness, friability, weight variation, swelling index, surface pH, in vitro drug release. The appearance of buccoadhesive tablets was smooth and uniform on physical examination. The hardness of prepared tablets of Labetalol was found to be 4.10-4.21 kg/cm^2. The thickness and weight variation were found to be uniform as indicated by the low values and were found to be in the range of 2.97-3.10 mm and 298-301mg respectively. Friability values less than 1% indicate good mechanical strength to withstand the rigors of handling and transportation. The calibration curve was constructed having regression value of 0.998. Compatibility studies were performed and it was observed that all the ingredients used were compatible with the drug. Formulation F3 results showed within limits and 99.8% drug release was found in 8hr .So, formulation (F3) was taken as optimized formulation. Accelerated stability studies were performed for this batch. Assay and Dissolution studies were performed for the optimized formulation (F-3) at different time intervals. The formulation F3 containing sodium alginate and xanthan gum was found to be promising, which showed 90.26 % drug within 8h.

CONCLUSION

The results of the present study indicate that buccoadhesive tablets of Labetalol with sustained drug release can be successfully prepared by direct compression method using natural polymers as mucoadhesive polymers and ethyl cellulose as backing layer.

The formulation F3 containing sodium alginate and xanthan gum was found to be promising, which shows an in vitrodrug release of 90.26 % in 8 h along with satisfactory results. From the above experimental results it can be concluded that mucoadhesive buccal tablets of Labetalol can be prepared by using different proportion & combination of Excipients and we selected F3 as best formulation based on dissolution profile and physical characteristics. Formulation (F3) showed total drug release in 8hr and showed fair flow properties when compared to other formulations. The formulations F3 followed Zero order kinetics.

REFERENCES

1. Jain NK. Controlled and novel drug delivery. 1st ed. New Delhi: CBS Publishers & Distributors; 1997: 52-81.
2. Patel VM, Prajapati BG, Patel MM. Formulation, evaluation and comparison of mucoadhesive buccal devices of propranolol hydrochloride. AAPS Pharm Sci Tech. 2007; 8(1): 1-8.
3. Shojaei HA. Buccal mucosa as a route for systemic drug delivery: A Review. J Pharm Sci. 1998; 1(1): 15-30.
4. David Haris, Robinson JR. Buccal drug delivery via the mucous membranes of the oral cavity. J Pharm Sci. 1992; 81(1): 1-9.
5. Tor-Tora Gorahowski. Principles of anatomy and physiology. 7th ed. Edited by Gerad J. Tor- Tora and Sandro Reynolds Gorahowski: Harpet Collins College Publishers; 1992: 770-774.
6. Ross & Wilson. Anatomy & physiology in health and illness. 9th ed. Edited by Anne Waugh and Allison Goraw: Churchill Livingstone Edinburgh Publishers; 2001: 289-293.
7. Chen YS, Squier CA. The ultra structure of the oral epithelium. In: J. Meyer, CA. Squier, SJ. Gerson (eds.), The structure and function of oral mucosa, Pergamon Press, Oxford. 1984: 7-30.
8. Swarbrick James. Bioadhesive drug delivery systems. 1st ed. New York: Marcel Dekker Inc; 1999: 541-562.
9. Robinson JR, Yang X. Absorption enhancers. In: J. Swarbrick, JC. Encyclopedia of pharmaceutical technology. New York: Marcel Dekker Inc; 2001; 18: 1-27.
10. Veuillez F, Kalia YN, Jacques Y, Deshusses J, Buri P. Factors and strategies for improving buccal absorption of peptides. Eur J Pharm Biopharm. 2001; 51: 93-109.
11. Walker GF, N. Langoth, A. Bernkop- Schnürch. Peptidase activity on the surface of the porcine buccal mucosa. Int J Pharm.

2002; 233: 141-147.
12. Wong CF, Yuen KH, Peh KK. Formulation and evaluation of controlled release Eudragit buccal tablets. Int J Pharm. 1999; 178: 11-22.
13. Rudnic EM, Schwartz JD. Oral solid dosage forms. In: Gennaro AR (editor). Remington: the science and practice of pharmacy. 20th ed. Lippincott Williams & Wilkins, Baltimore; 2000:858-859.
14. Roy S, Pal K, Anis A, Pramanik K, Prabhakar B. Polymers in mucoadhesive drug delivery system: A brief note. Designed Monomers Polymers 2009;12:483-95.
15. Kaelbe DH, Moacanin J. A surface energy analysis of bioadhesion. Polymer 1977;18:475-82. 15. Gu JM, Robinson JR, Leung S. Binding of acrylic polymers to mucin/ epithelial surfaces: Structure-property-relationship. Crit Rev The Drug Carrier Syst 1988;5:21-67.