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REVIEW ARTICLE

CURRENT STATUS OF BUCCAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Buccal mucosa is the preferred site for both systemic and local drug action. The mucosa has a rich blood supply and it relatively permeable. The buccal region of the oral cavity is an attractive target for administration of the drug of choice, particularly in overcoming deficiencies associated with the latter mode of administration. Problems such as first-pass metabolism and drug degradation in the gastrointestinal environment can be circumvented by administering the drug via the buccal route. Moreover, rapid onset of action can be achieved relative to the oral route and the formulation can be removed if therapy is required to be discontinued. It is also possible to administer drugs to patients who unconscious and less co-operative. In buccal drug delivery systems mucoadhesion is the key element so various mucoadhesive polymers have been utilized in different dosages form. Mucoadhesion may be defined as the process where polymers attach to biological substrate or a synthetic or natural macromolecule, to mucus or an epithelial surface. When the biological substrate is attached to a mucosal layer then this phenomenon is known as mucoadhesion. The substrate possessing bioadhesive polymer can help in drug delivery for a prolonged period of time at a specific delivery site. Both natural and synthetic polymers are used for the preparation of mucoadhesive buccal patches. However, this review article provides a current status of buccal drug delivery of patches (films) along with formulation development and characterization of mucoadhesive buccal patches.
Keywords: Buccal, Mucoadhesive Polymer, Buccal formulations, Buccal patch

INTRODUCTION

Bioadhesive drug delivery formulations were introduced in 1947 when gum tragacanth was mixed with dental adhesive powder to apply penicillin to the oral mucosa. In recent years delivery of therapeutic agents via Mucoadhesive drug delivery system has become highly interesting. Certain drugs have lack of efficacy due to decreased bioavailability, GI intolerance, unpredictable and erratic absorption or pre-systemic elimination of other potential route for administration. The recent development in the drug delivery has intensified the investigation of mucosal drug delivery. Such route includes oral, buccal, ocular, nasal and pulmonary routes[1,2]. Mucoadhesive drug delivery systems are delivery systems, which utilized the property of bioadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting a drug to particular region of the body for extended period of time[3]. The ability to maintain a delivery system at a particular location for an extended period of time has great appeal for both local as well as systemic drug bioavailability[4].

Among the various routes of drug delivery, the oral route is perhaps the one mostly preferred by patients and clinicians. Based on our current understandings of biochemical and physiological aspects of absorption and metabolism, many drugs, cannot be delivered effectively through the conventional oral route, because after administration are subjected to pre-systemic clearance extensively in liver, which often leads to a lack of significant correlation between membrane permeability, absorption, and bioavailability[5]. Difficulties associated with parenteral delivery and poor oral availability promoted the impetus for exploring alternative routes for the delivery of such drugs. Consequently, other absorptive mucosae are considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavities) offer distinct advantages over peroral administration for systemic effect. Among the various transmucosal routes, buccal mucosa has an excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of controlled release dosage forms. Additionally, buccal drug delivery has a high patient acceptability compared to other non-oral transmucosal routes of drug administration. Direct access to the systemic circulation through the internal jugular vein avoids acid hydrolysis in the gastrointestinal (GI) tract and bypasses drugs from the hepatic first pass metabolism leading to high bioavailability. Moreover, rapid cellular recovery of the buccal mucosa is other advantage of this route[6]. Disadvantages of drug delivery by this route are the low permeability of the buccal membrane[7], specifically when compared to the sublingual membrane [8], and a smaller surface area.

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Buccal administration of drugs provides a convenient route of administration for both systemic and local drugs actions[9]. Over the last two decades mucoadhesion has become of interest for its potential for localized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining a formulation an intimate contact with the absorption site (e.g. buccal cavity[10] .Recently various Mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels, have recently been developed. However, buccal patch offer greater flexibility and comfort than adhesive tablets. In addition, a patch can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva. Buccal route of drug delivery provides direct access to the systemic circulation through the jugular vein by passing the hepatic first pass metabolism leading to high bioavailability.[11] The term bioadhesion is typically used to describe the adhesion between polymer either synthetic or natural to soft tissue.

In instances when bond is formed between mucus membrane and polymer the term mucoadhesion is used. Mucus membrane is one, in which the goblet cells are present for the secretion of mucus which is composed of glycoprotein mucin. Buccal mucosa presents a relatively smooth and immobile surface for the placement of Mucoadhesive dosage form. The amount of drug that can be incorporated is limited by the size limitation of the buccal dosage form. In general, a drug with a daily requirement of 25 mg or less is suitable for buccal delivery. Drug with short half-life, requiring sustained or controlled release showing poor aqueous solubility and which is sensitive to enzymatic degradation, may be successfully delivered across the buccal mucosa. Buccal delivery system is found to be the most promising because buccal mucosa itself provides a protecting covering for the underlying tissues acting as a physical barrier against toxins and microorganism[12,13]. Buccal delivery system provides easy administration thereby increasing patient compliance. Drug is easily administered and extinction of therapy in emergency can be facilitated .It can be administered in unconscious and trauma patients .Large contact surface of the oral cavity contributes to rapid and extensive drug absorption. Because of the high permeability and rich blood supply transport via the sublingual route results in a rapid onset of action[14].

Mucoadhesive buccal drug delivery system[15, 16]

Drug delivery via the mucosal membrane of the oral cavity can be divided into following:

- Sublingual delivery: - Drug administration via sublingual mucosa to the systemic circulation.
- Buccal delivery: - Drug administration via buccal mucosa to the systemic circulation.
- Local delivery: - Drug administration via bioadhesive sytem either to the palate or the cheek.

ADVANTAGES OF MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEM[17-22]

Mucoadhesive via buccal route offers following advantages: -

- Ease of drug administration and termination of drug action can be easily accomplished.
- Permits localization or retention of the drug to the specified area of oral cavity for extended period of time.
- Bypass hepatic first pass metabolism.
- Drugs with poor bioavailability owing to the high first pass metabolism can be administered conveniently.
- Ease of drug administration to unconscious patients.
- Water content of saliva is being capable to ensure drug dissolution.

Limitation of buccal drug administration[17-22]

There is certain limitation via drug administered through buccal route: -

- Drugs with ample dose are often difficult to be administered.
- Possibility of the patients to swallow the tablets being forgotten.
- Eating and drinking may be restricted till the end of drug release.
- This route is unacceptable for those drugs, which are unstable at pH of buccal environment.
- This route cannot administer drugs, which irritate the mucosa or have a bitter or unpleasant taste.
- Limited surface area is available for absorption.

BUCCAL PATCHES ARE OF TWO TYPES [23]

(a)In matrix type-The drug is homogeneously dispersed in hydrophilic or lipophilic polymer matrix and the medicated polymer is then moulded into medicated disc with a defined surface area.

(b)In reservoir type-The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to in the mouth and to prevent drug loss.

BIOADHESION [24, 25, 26]

'Bioadhesive' is defined as a substance that is capable of interacting with biological material and being retained on them or holding them together for extended period of time. Bioadhesive are classified into three types.

- Bioadhesion between biological layers without involvement of artificial materials. Cell diffusion andcell aggregation are good examples.
- Bioadhesion can be represented by cell adhesion into culture dishes or adhesion to a variety of substances including metals, woods and other synthetic materials.
- Adhesion of artificial substances to biological substrate such as adhesion of polymer to skin or other soft tissue.

MECHANISM OF BIOADHESION [27, 28, 29]

For bioadhesion to occur, three stages are involved:

- An intimate contact between a bioadhesive and a membrane either from a good wetting of the bioadhesive and a membrane or from the swelling of bioadhesive.
- Penetration of the bio-adhesive into the tissue takes place.
- Inter penetration of the chains of the bioadhesive with mucous takes place. Low chemical bonds can then settle.

The bonding between the mucus and the biological substance occurs chiefly through both physical and chemical interactions results from enlargement of the adhesive material and chemical bonds due to electrostatic interaction, hydrophobic interactions, hydrogen bonding and dispersion forces.

BIOADHESIVE POLYMER

The first step in the development of buccoadhesive dosage forms is the selection and Characterization of appropriate bio adhesive polymers in the formulation. Bio adhesive polymers play a major role in buccoadhesive drug delivery systems of drugs. Polymers are also used in matrix devices in which the drug is embedded in the polymer matrix, which control the duration of release of drugs[30] .Bio adhesive polymers are from the most diverse class and they have considerable benefits upon patient health care and treatment[31]. The drug is released into the mucous membrane by means of rate controlling layer or core layer. Bio adhesive polymers which adhere to the mucin/ epithelial surface are effective and lead to significant improvement in the oral drug delivery[32].

AN IDEAL POLYMER FOR BUCCOADHESIVE DRUG DELIVERY SYSTEMS SHOULD HAVE FOLLOWING CHARACTERISTICS[33]

It should be inert and compatible with the environment.

- The polymer and its degradation products should be non-toxic absorbable from the mucous layer.
- It should adhere quickly to moist tissue surface and should possess some site specificity.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The polymer should be easily available in the market and economical.
- It should allow easy incorporation of drug in to the formulation.

CRITERIA FOLLOWED IN POLYMER SELECTION

- It should form a strong non covalent bond with the mucine/epithelial surface.
- It must have high molecular weight and narrow distribution.
- It should be compatible with the biological membrane.

Table1: Bio adhesive polymers in pharmaceutical applications[34]

Criteria	Categories	Examples
Sources	Semi natural/ Natural	Agarose, chitosan, gelatin, Hyaluronic acid, Various gums (guar gum, xanthan, gellan, carragenan, pectin and sodium alginate).
	Synthetic	**Cellulose derivatives:** [CMC, thiolated CMC, NaCMC, HEC, HPC, HPMC,MC.]
		Poly(acrylic acid)-based polymers: [CP, PC, PAA, polyacrylates, poly(methyl vinyl ether-co-methacrylic acid), poly(2- hydroxy ethyl methacrylate),poly(acrylic acidco-ethyl hexyl acrylate), poly(methacrylate), poly(isobutylcyanoacrylate), copolymer of acrylic acid and PEG].
		Others: polyoxyethylene, PVA, PVP, thiolated Polymers.

BACKING MEMBRANE

Backing membrane plays a major role in the attachment of bioadhesive devices to the mucus membrane. The materials used as backing membrane should be inert, and impermeable to the drug and penetration enhancer. Such impermeable membrane on buccal bioadhesive patches prevents the drug loss and offers better patient compliance. The commonly used materials in backing membrane [35] include carbopol, magnesium stearate, HPMC, HPC, CMC, polycarbophil etc .

PERMEATION ENHANCERS:

Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. Selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other Excipients. Table 2

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Table 2: Examples of permeation enhancers with mechanism [34]

Category	Examples	Mechanism(s)
Surfactants and Bile Salts	Surfactants and Bile Salts, Sodium dodecyl sulphate, Sodium lauryl sulphate, Polysorbate 80	Acting on the components at tight junctions Increasing the fluidity of lipid bilayer membrane;
Fatty Acids	Oleic acid, Cod liver oil, Capric acid, Lauric acid	Increasing the fluidity of lipid bilayer membrane.
Polymers and Polymer Der.	Chitosan, Trimethyl chitosan Chitosan-4- thiobutylamide	Increasing the fluidity of lipid bilayer membrane; Increased retention of drug at mucosal surface.
Others	Ethanol, Azone, Octisalate, Padimate, Menthol	Acting on the components at tight junctions; Increasing the fluidity of lipid bilayer membrane

MANUFACTURING METHODS OF BUCCAL PATCHES/ FILMS:

Manufacturing processes involved in making mucoadhesive buccal patches/films, namely solvent casting, hot melt extrusion and direct milling.

Solvent casting: In this method, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry[36].

Direct milling: In this, patches are manufactured without the use of solvents. Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the resultant material is rolled on a release liner until the desired thickness is achieved. The backing material is then laminated as previously described.[37] While there are only minor or even no differences in patch performance between patches fabricated by the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues[38].

Hot melt extrusion of films: In hot melt extrusion blend of pharmaceutical ingredients is molten and then forced through an orifice to yield a more homogeneous material in different shapes such as granules, tablets, or films. Hot melt extrusion has been used for the manufacture of controlled release matrix tablets, pellets and granules, as well as oral disintegrating films.

Solid dispersion extrusion:

In this immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means of dies.

Semisolid casting:

In the semisolid casting method firstly a solution of water soluble film forming polymer is prepared .The resulting solution is added to a solution of acid insoluble polymer (cellulose acetate phthalate, cellulose acetate butyrate) which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained. Finally the gel mass is casted in to films or ribbons using heat controlled drums. Thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble forming polymer should be 1:4.

Rolling method:

In this rolling method solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on rollers and cut in to desired shapes and sizes.

EVALUATIONS OF BUCCAL PATCH:

Surface pH: Buccal patches are left to swell for 2 hrs on the surface of an agar plate. The surface pH is measured by means of a pH paper placed on the surface of the swollen patch.[39-40]

Thickness measurements: The thickness of each film is measured at five different locations (centre and four corners) using an electronic digital micrometer[41].

Swelling study: Buccal patches are weighed individually (designated as W1), and placed separately in 2% agar gel plates, incubated at 37°C ± 1°C, and examined for any physical changes. At regular 1- hr time intervals until 3 hours, patches are removed from the gel plates and excess surface water is removed carefully using the filter paper [42]. The swollen patches are then reweighed (W2) and the swelling index (SI) are calculated using the following formula.

$SI= (W2-W1)/W1\times 100.$

Folding endurance: The folding endurance of patches is determined by repeatedly folding 1 patch at the times without breaking[43].

Thermal analysis study: Thermal analysis study is performed using differential scanning calorimeter (DSC).

Morphological characterization: Morphological characters are studied by using scanning electron microscope (SEM).

Permeation study of buccal patch: The receptor compartment is filled with phosphate buffer pH 6.8, and the hydrodynamics in the receptor compartment is maintained by stirring with a magnetic bead at 50 rpm. Samples are withdrawn at predetermined time intervals and analyzed for drug content [44].

In vitro drug release: The United States Pharmacopeia (USP) XXIII-B rotating paddle method is used to study the drug release from the bilayered and multilayered patches. The dissolution medium consisted of phosphate buffer pH 6.8. The release is performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal patch is attached to the glass disk with instant adhesive material. The disk is allocated to the bottom of the dissolution vessel. Samples (5 ml) are withdrawn at

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predetermined time intervals and replaced with fresh medium. The samples filtered through whatman filter paper and analyzed for drug content after appropriate dilution. The in-vitro buccal permeation through the buccal mucosa (sheep and rabbit) is performed using Keshary-Chien /Franz type glass diffusion cell at 37°C± 0.2°C. Fresh buccal mucosa is mounted between the donor and receptor compartments. The buccal patch is placed with the core facing the mucosa and the compartments clamped together.

Ex-vivo mucoadhesion time: The ex-vivo mucoadhesion time performed after application of the buccal patch on freshly cut buccal mucosa (sheep and rabbit). The fresh buccal mucosa is tied on the glass slide, and a mucoadhesive patch is wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the buccal mucosa by applying a light force with a fingertip for 30 secs. The glass slide is then put in the beaker, which is filled with 200 ml of the phosphate buffer pH 6.8, is kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate is applied to simulate the buccal cavity environment, and patch adhesion is monitored for 12 hrs. The time for changes in color, shape, collapsing of the patch and drug content is noted[45].

Measurement of mechanical properties: Mechanical properties of the films (patches) include tensile strength and elongation at break is evaluated using a tensile tester. Film strip with the dimensions of 60 x 10 mm and without any visual defects cut and positioned between two clamps separated by a distance of 3 cm. Clamps designed to secure the patch without crushing it during the test, the lower clamp held stationary and the strips are pulled apart by the upper clamp moving at a rate of 2 mm/sec until the strip break. The force and elongation of the film at the point when the strip break is recorded. The tensile strength and elongation at break values are calculated using the formula.

T = m x g/ b x t Kg/mm2

Where,

M - is the mass in gm, g - is the acceleration due to gravity 980 cm/sec 2, B - is the breadth of the specimen in cm, T - is the thickness of specimen in cm Tensile strength (kg/mm2) is the force at break (kg) per initial cross- sectional area of the specimen (mm2).

Weight variation- The three disks of 1cm2 was cut and weight individually on electronic balance for weight variation test and the average weights were calculated. The test was done to check the uniformity of weight and thus check the batch to batch variation.[cls]

Thickness- Thickness of the patch was measured by using vernier callipers with atleast count 0.001mm.The thickness uniformity was measured at five different points and average reading was taken.

Buccal absorption test

A method [46] for the measurement of the developed a method to measure the kinetics of the drug absorption by swirling a 25 ml sample of the test solution for 15 min by human volunteers followed by the expulsion of the solution. The amount of the drug remaining in the expelled volume is then determined to assess the amount of drug absorbed. The drawbacks of this method are inability to localize the drug solution within a specific site of the oral cavity, accidental swallowing of a portion of the sample solution and the salivary dilution of the drug.

Modified beckett's test

The test has been modified [47] by addition of phenol red as a marker for drug dilution by saliva secretion as well as for accidental swallowing of the drug solution. The 'Schurmann and Turner Test' has also been modified[48] by taking a small sample of the solution in the oral cavity every few minutes, without removal of the residual solution. In this way he was able to study kinetics of the absorption in a single test for 15–20 minutes.

CONCLUSION

Buccal adhesive systems offer innumerable advantages in terms of accessibility, administration and withdrawal, retentivity, low enzymatic activity, economy and high patient compliance. Buccal region provides a convenient route of administration for both local and systemic drug actions. Buccal adhesive systems offer innumerable advantages in term of accessibility, administration and withdrawal, retentivity, low enzyme activity, economy and high patients compliance. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. Adhesions of these drug delivery devices to mucosal membranes lead to an increased drug concentration gradient at the absorption site and therefore improve bioavailability of systemically delivered drugs. In addition, buccal adhesive dosage forms have been used to target local disorders at the mucosal surface (e.g., mouth ulcers), to reduce the overall required dosage and minimize side effects that may be caused by systemic administration of drugs. Investigations are continuing beyond traditional polymer networks to find other innovative drug transport systems. Currently solid dosage forms, liquids, spray and gels applied to oral cavity are commercially successful. The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides.

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CONFLICT OF INTEREST

The authors have no conflicts of interest with regards to the content of this review article.

REFERENCES

1. Jain NK. Controlled and Novel Drug Delivery. 1st edition, published by CBS Publishers and Distributors, New Delhi; 1997. P .52-81.
2. Patel KV, Patel ND, Dodiya HD, Shelat PK, Buccal bioadhesivedrug delivery system: an overview, Ind. J. of Pharma. & Bio. Arch, 2011; 2(2): 600-609.
3. Shojaei AH. A systemic drug delivery via the buccal mucosal route. Pharm. Tech. 2001. P. 70-81.
4. Verma S, Kaul M, Rawat A, Saini S, An overview on buccal drug delivery system Ind. , J.Pharm. Sci. Res. 2011, 2(6): 1303-1321.
5. Harris D, Robinson JR. Drug delivery via the mucous membranes of the oral cavity, J. Pharm. Sci.1992, 81: 1–10.
6. Shojaei AH, Chang RK, Guo X, Systemic drug delivery via the buccal mucosal route, J. Pharm. Technol. 2001, 25(6): 70–81.
7. Rojanasakul Y, Wang LY, Bhat M, Glover DD, Malanga CJ, Ma JKH, The transport barrier of epithelia: a comparative study on membrane permeability and charge selectivity in the rabbit, Pharm. Res.1992, 9: 1029–1034.
8. Gandhi RB, Robinson JR, Oral cavity as a site for bioadhesive drug delivery, Adv. Drug Deliv. Rev, 1994, 13: 43–74.
9. Kurosaki Y, Kimura T, Regional variation in oral mucosal drug permeability: Crit Rev , Ther Drug Carrier Syst, 2000, 17: 467–508.
10. Giradkar KP, Design development and in vitro evaluation of bioadhesive dosage form for buccal route, International Journal of Pharma Research & Development, 2010, 2: 21-23.
11. Shidhaye SS, Mucoadhesive bilayered patches for administration of sumatriptan, AAPS Pharm Sci Tech. 2009, 9(3): 909-916.
12. Elkayam, R., Friedman, M., Stabholz, A., Soskolne, A.w., Sela, M.N., and Golub, L., Sustained release device containing minocycline for local treatment of periodontal disease, J. Control. Rel., 1988, 7: 231-236.
13. Tripathi K. D. In Essential of medical pharmacology, 6th ed. Jaypee Brothers Medical Publishers, New Delhi. 2001. P. 519-35.
14. Chhote Lal Singh, Namita Srivastava, Munish Garg Monga, Amit Singh. A review: buccal buccoadhesive drug delivery system, World J Pharm Sci, 2014, 2 (12): 1803-1807.
15. Squier CA, Wertz PW, Structure and function of the oral mucosa and implications for drug delivery. In: Rathbone M.J, editor. Oral mucosal drug delivery. Marcel Dekker; 1996. P. 1–25.
16. Sevda Senel, Mary Kremer, Katalin Nagy , Christopher Squier, Delivery of bioactive peptides and proteins across oral (Buccal) Mucosa, Current Pharmaceutical Biotechnology, 2001, 2, 175-186.
17. A.J. Hoogstraate, Diffusion rates and transport pathways of FITC-labelled model compounds through Buccal Epithelium, Proc Int Symp Contr Rel. Bioact Mater. (1993), 20, 234–235.
18. Gandhi Pankil A, Patel K.R, Patel M.R, Patel N.M, A review article on muccoadhesive buccal drug delivery system, Inter. J. of Pharm. Res. Development, 2011, 3(5), 159-173.
19. Prajapati V, Bansal M., Sharma P.K, Mucoadhesive buccal patches and use of natural polymer in its preparation, A Review Inter J of Pharm Tech Res, 2012, 4(2), 582-589.
20. Puratchikody A, Prasanth V.V, Mathew S.T., Kumar B.A, Buccal drug delivery past, present and future: A Review, Inter J of Drug Delivery, 2011, 3, 171-184.
21. Narasimha R. R, Sindhu R. K, Swapna D, Konasree S.D, Swathi E, Formulation and evaluation of rapidly dissolving buccal patches, Int J Pharm. Bio Sci., 2011, 1(3): 145-159.
22. Venkatalakshmi R., Yajaman S., Madhuchudana Chetty C., Sasikala C., Varma M, Buccal drug delivery using adhesive polymeric patches, Inter J of Pharm Sci Res, 2012, 3(1): 35-41.
23. Nazila SM, Montakarn C, Thomas PJ, The use of mucoadhesive polymers in buccal drug delivery, Advanced Drug Delivery Reviews, 2005, 57, 1666–1691.
24. Gandhi BR, and Robinson JR, Bioadhesion in drug delivery, Ind. J. Pharm. Sci. 1988, 50, 145−152.
25. Boddupalli BM, Mohammad ZNK, Nath RA, Banji D, mucoadhesive drug delivery system an overview, J. Adv. Pharm. Tech. Res., 2010, 1(4), 381-387.
26. Gandhi SD, Priyanka RP, Rahul U, Tambawala T, Shah MA, Mucoadhesive drug delivery systems-An unusual maneuver for site specific drug delivery system, An Int. J .Pharm. Sci. ISSN, 0976-7908,2013, 851-871.
27. Satheesh Madhav NV, Ashok KS, Pragati S, Kuldeep S, Orotransmucosal drug delivery systems: A review, Journal of Controlled Release, 2009, 140, 2–11.
28. M. E. Aulton. Pharmaceutics the science of dosage form Design 2nd edition. Harcourt publishers Limited. 2002. P. 198-200.
29. Steward A , The Effect of enhancers on the buccal absorption of hybrid (BDBB) alpha interferon, Int. J. Pharm, 1994, 104: 145– 149.
30. Deirdre Faye Vaughan, Pharmacokinetics of Albuterol and Butorphanol administered intravenously and via a Buccal Patch, A thesis submitted to the office of graduate studies of Texas A&M University in partial fulfillment of the requirements for the degree of Master of Science, May 2003
31. Yajaman S., Bandyopadhyay A.K., Buccal bioadhesive drug delivery - A promising option for orally less efficient drugs, Journal of Controlled Release, 2006;114: 15–40.
32. Indian Journal of Pharmaceutical Science, July-Aug. 2004; 66 (4): 371-536:556-562.
33. N. G. Raghavendra Rao, B. Shravani, Mettu Srikanth Reddy, Overview on buccal drug delivery systems, J. Pharm. Sci. & Res., 2013 , 5(4): 80 – 88.
34. B.J. Aungst and N.J. Rogers, Site dependence of absorption- promoting actions of Laureth-9,Na Salicylate,Na2EDTA, and Aprotinin on rectal, nasal,

and buccal insulin, Delivery Pharm Res. 1988, 5 (5), 305–308.
35. Savage D.C., Microbial ecology of the gastrointestinal tract, Annu. Rev. Microbiol.,1977, 31, 107– 133.
36. Aungst BJ and Rogers NJ, Site dependence of absorption- promoting actions of Laureth , Na Salicylate, NaEDTA, and Aprotinin on rectal, nasal, and buccal insulin, Delivery Pharm. Res,1988, 5 (5), 305–308.
37. Muzib Y.I., Kumari K.S. Mucoadhesive buccal films of glibenclamide : Development and evaluation, Int J Pharma Investig [serial online] 2011. 25 Sep 2012. http://www.jpionline.org/text.asp?2011/1/1/42/767 28 (2nd sept. 2012).
38. Singh G, Gokulan, P.D, Kinikar D, Kushwah M. http://www.pharmatutor.org/articles/developmentevaluation-of-mucoadhesive-buccal-films-of glibenclamide?page=0,2.
39. Zhang. J , An in vivo dog model for studying recovery kinetics of the buccal mucosa permeation barrier after exposure to permeation enhancers apparent evidence of effective enhancement without tissue damage, Int. J. Pharm, 1994, 101,15–22.
40. Goudanavar PS, Formulation and in-vitro evaluation of mucoadhesive buccal films of Glibenclamide, Der pharmacia lettre, 2010, 2 (1),382-387.
41. Giradkar KP, Design development and in vitro evaluation of bioadhesive dosage form for buccal route, International journal of pharma research & development, 2010, 2 ,17-21.
42. Leung SS and J.R. Robinson, Polymer structure features contributing to mucoadhesion II, J. Contr. Rel, 1990, 12, 187–194.
43. Gandhi RE and Robinson JR, Bioadhesion in drug delivery, IndianJ. Pharm. *Sci*, 1988, 50 (May/-June),145–152.
44. Beckett AH, Triggs EJ. Buccal absorption of basic drugs and its application as an in vivo model of passive drug transfer through lipid membranes, J. Pharm. Pharmacol. 1967, 19, 31S–41S.
45. Schurmann W, Turner P. A., membrane model of human oral mucosa as derived from buccal absorption and physicochemical properties of beta blocking drugs atenolol and propranolol, J. Pharm. Pharmcol,1978, 30, 137–147.
46. Tucker IG. A method to study the kinetics of oral mucosa of drug absorption from solutions, J. Pharm. Pharmcol, 1988, 40, 679–683.

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