

Development of Buccal Adhesive Controlled Release Tablets

Ashok Baban Shimple, Amit Vilasrao Pondakule

Student , Associate Professor

Dattakala College of Pharmacy Bhigwan

ABSTRACT

Lercanidipine hydrochloride (LER) is a third generation dihydropyridine calcium channel antagonist. The present study was undertaken to develop and evaluate a buccal drug delivery system of Lercanidipine Hydrochloride (LER) with the objective of improving its bioavailability and therapeutic efficacy. Lercanidipine Hydrochloride is a third-generation dihydropyridine calcium channel blocker widely used in the management of hypertension due to its high selectivity for vascular smooth muscle cells. The drug is conventionally administered orally at a dose of 10–20 mg daily; however, its therapeutic effectiveness is limited by poor oral bioavailability (10–20%), extensive first-pass hepatic metabolism, food-dependent absorption, and significant inter- and intra-patient variability. The buccal route was selected as a promising alternative owing to its rich vascularization, ease of administration, and ability to bypass hepatic first-pass metabolism. Delivery of Lercanidipine Hydrochloride through the buccal mucosa is expected to enhance systemic drug availability, reduce dose requirements, and provide a more predictable plasma concentration profile. Furthermore, controlled drug release through buccal delivery may help maintain therapeutic drug levels for extended periods, thereby improving patient compliance and treatment outcomes.

The study involved the formulation of buccal dosage forms of Lercanidipine Hydrochloride using suitable mucoadhesive polymers and excipients. The prepared formulations were evaluated for various physicochemical parameters including appearance, thickness, weight uniformity, drug content, surface pH, swelling behavior, and mucoadhesive strength. In vitro drug release studies were performed to assess the controlled-release characteristics of the formulations. Drug–excipient compatibility studies and other characterization techniques were employed to ensure formulation stability and integrity. The developed buccal formulations are expected to provide controlled and prolonged drug release while avoiding extensive hepatic metabolism. The study aims to establish an effective buccal delivery system for Lercanidipine Hydrochloride that enhances bioavailability, improves therapeutic performance, reduces dosing variability, and offers a patient-friendly alternative to conventional oral dosage forms.

KEYWORDS:-

Lercanidipine, Bioadhesive, Controlled Release, Mucoadhesive Strength, Swelling Index, Bioavailability, Sodium Alginate, Hydroxy Methylcellulose.

INTRODUCTION

The oral route of drug delivery is traditionally the most preferred route of systemic drug administration by physicians and patients. Oral route offers distinct advantages over other conventional drug delivery routes like topical and parenteral. However, per oral administration of certain drugs have disadvantages such as unpredictable and erratic absorption, GI intolerance, incomplete absorption, degradation of drug in GI contents and pre systemic metabolism resulting in reduced bioavailability. Parental route of drug administration is the only established route that overcomes the drawbacks associated with orally less efficient or inefficient drugs. However, parental formulations are costly, have least patient compliance, and self administration is difficult. Consequently, over the last decade, there has been a particular interest in investigating other absorptive mucosae as potential sites for systemic delivery of drugs. Transmucosa route of drug delivery (i.e., the mucosal linings of the

nasal, rectal, vaginal, ocular and oral cavity) offer distinct advantages over per oral administration for systemic and local drug delivery¹. Major advantages of transmucosal routes include possible bypass of first pass effect and avoidance of metabolism/degradation of drug within the GI tract.²

The sublingual route is the most widely studied of the oral transmucosal routes. The sublingual mucosa has good permeability resulting in quick onset of action and higher bioavailability for many drugs. Moreover, this route is convenient, accessible, and generally well accepted. Sublingual dosage forms create a very high drug concentration in the sublingual region before the drug is systemically absorbed across the mucosa. Even though the sublingual mucosa is relatively more permeable than the buccal mucosa, it is not suitable for oral transmucosal controlled delivery of drug.³

The sublingual region lacks an expanse of smooth muscle or immobile mucosa and is constantly washed by a considerable amount of saliva. This makes retention of delivery system a difficult proposition. Due to its high permeability and rich blood supply, the sublingual route is capable of producing a quick onset of action making it appropriate for drugs with short delivery period requirements with infrequent dosing regimen as in case of nitroglycerine tablets⁴.

1.1 Structure and Environment of Buccal Mucosa

The primary role of the buccal mucosa, like skin, is to protect underlying structures from foreign agents. The surface of buccal mucosa consists of a stratified squamous epithelium which is separated from the underlying connective tissue (lamina propria and submucosa) by a continuous layer of extracellular material called basement membrane⁵. This stratified squamous epithelium consists of differentiating layers of cells (keratinocytes) which change in size, shape, and content as they travel from the basal region to the superficial region. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers. There are approximately 40–50 cell layers in epithelium, resulting in a buccal mucosa of 500 - 800 Km thickness⁶.

The permeability of the buccal mucosa is greater than that of the skin, but less than that of the intestine. The simple columnar epithelium covering the small intestine provides less resistance to drug transfer than the stratified squamous epithelium covering the skin and buccal mucosa accounting for higher permeability of intestine. Buccal mucosa although structurally similar to skin, is either less or not keratinized and hence more permeable.

The composition of oral epithelium also varies depending on the site in the oral cavity. The mucosae of areas subject to mechanical stress (the gingivae and hard palate) are keratinized similar to the skin. The mucosae of the soft palate, sublingual and buccal regions are non-keratinized. The keratinized epithelia are relatively impermeable to water because of high proportion of lipids like ceramides and acylceramides in them. Non-keratinized epithelia, such as the sublingual and the buccal mucosa do not contain acylceramides and only have small amounts of ceramide⁷. They also contain small amounts of other polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia hence it can be said that presence of lipids like ceramides and acylceramides in epithelium is associated with barrier function of mucosa. A gel like secretion known as mucus, which contains mostly water insoluble glycoproteins covers the entire buccal cavity. Mucus is bound to the apical cell surface and acts as a protective layer to the cells⁸. It is composed of several components such as proteins, enzymes, electrolytes and nucleic acids. The composition of mucus varies based on the origin of the mucus secretion in the body.

1.1.1 Barriers to penetration across buccal mucosa

The upper one-third to one-quarter of the buccal epithelium has been attributed for its barrier function. Experimental evidence for this was first demonstrated with the topical application of horseradish peroxidase to the oral mucosa of monkeys, rabbits and rats, where the protein was unable to penetrate deeper than the

top 1–3 cell layers. When injected subepithelially, horseradish peroxidase was found within connective tissue and the intercellular spaces of the epithelium, till the region where the membrane-coating granules (MCG's) first appear⁹. This suggested that the permeability barrier of buccal mucosa may be attributed to the materials extruded from membrane-coating granules. To ensure that this region was also the barrier to permeation of smaller molecules, the experiments were repeated using smaller molecules (lanthanum salts), and the results obtained were identical.

The role of MCG's in the barrier properties of buccal mucosa was further confirmed by good permeability of tissues (junctional epithelium) lacking these granules to tracers like horseradish peroxidase. Similar results were obtained when these tracers were applied topically to keratinized oral epithelium in tissue culture¹⁰. Since these cultured tissues lacked MCG's. It became evident that the permeability barrier of oral mucosa could be attributed to contents extruded from the MCG's into the epithelial intercellular spaces.

MCG's have been reported to extrude lipids (mainly ceramides and acylceramides) into the intercellular spaces mainly responsible for barrier function of buccal mucosa. It is believed that the barrier of non-keratinized oral epithelium is also composed of lipid material, since treatment of oral mucosa with chloroform/methanol mixtures resulted in a reduced barrier function¹¹. To verify the chemical nature of these lipids, various regions of porcine oral cavity were separated, and the lipids present in each region were extracted and identified by thin-layer chromatography. The keratinized palatal and gingival mucosae contained high quantities of ceramides and cholesterol, and a low proportion of cholesterol esters and glycosylceramides. Whereas, the non-keratinized buccal and sublingual mucosae showed higher proportion of polar phospholipids, cholesterol esters and minimal amounts of ceramides. Histochemical staining suggested that polar lipids were localized in intercellular spaces of the non-keratinized oral epithelium. Therefore, the intercellular lipids of non-keratinized regions of the oral cavity are more polar in nature than the intercellular lipids of keratinized regions. This difference in chemical nature of the lipids has been reported to contribute to the differences in permeability observed between these mucosae¹².

Enzymatic degradation is another barrier to drug permeability across buccal mucosa. Saliva contains moderate levels of esterases, carbohydrases, and phosphatases and several other proteolytic enzymes like aminopeptidase¹³. To reach systemic circulation, drugs must overcome this enzymatic barrier. However, this enzymatic barrier is less effective than the GI enzymatic barrier.

1.1.2 Mechanisms of drug permeation

The cellular organization of buccal epithelia is that of stratified squamous epithelium. The epithelial cells are surrounded by a relatively hydrophilic intercellular matrix. The intercellular spaces of the epithelia are also filled with polar lipids because of extrusion of contents from the membrane-coating granules¹⁴. The lipophilic cell membranes of the epithelial cells are thus surrounded by relatively polar intercellular lipids on the outside and a hydrophilic aqueous cytoplasm on the inside. Consequently, the existence of hydrophilic and lipophilic regions in the oral mucosa has led majority of researchers to postulate existence of two routes of drug transport through the buccal mucosa namely paracellular (between the cells) and transcellular (across the cells). The lipophilic drugs penetrate mainly through the more lipophilic transcellular route, while the less lipophilic paracellular route, characterized by loosely packed polar intercellular lipids, is the principle route for absorption of hydrophilic drugs. The major route of drug penetration is dependent upon the physicochemical properties of the drug molecule. Generally, both the routes co-exist for all the drugs but the predominant route is the one with least resistance¹⁵.

Sometimes absorption is reported to be by the mechanism of endocytosis where the drug molecules are engulfed by the cells. Active transport mechanism has not been reported in literature but acidic stimulation of the salivary glands, with accompanying vasodilatation, facilitates absorption and uptake into the circulatory system¹⁶.

Literature suggests that most compounds actually traverse the buccal mucosa via the paracellular route. Few lipophilic compounds (like glycosylceramides) have been histochemically shown to be located in the intercellular spaces of buccal mucosa. The significance of paracellular route in buccal permeation was further substantiated by presence of tracer compounds (horseradish peroxidase and lanthanum salts) in intercellular spaces, when applied to the oral mucosa of rabbits, rats, and monkeys¹⁷. The paracellular route was also found to be the major route of permeation for water, ethanol, cholesterol, and thyrotropin releasing hormone. Confocal Laser Scanning Microscopy has also been used to determine the route of transport of fluorescently labeled dextrans, and it was shown that these hydrophilic macromolecules also penetrated the oral mucosa via the paracellular route¹⁸.

The permeability of ionizable drugs across buccal mucosa is believed to follow the pH-partitioning theory characteristic of passive diffusion. Studies have been carried out on lidocaine and nicotine to find out effect of ionization on permeation through buccal mucosa and the results were found to be in accordance with pH partition hypothesis. It is generally believed that increasing non-ionized fraction of ionizable drugs could favor drug penetration through the transcellular route.

1.2 General Considerations in Formulation Design

The limited area for placement of buccal drug delivery system seriously limits the device size and hence the amount of drug that can be loaded onto the device. Generally, a device with the size of 1–3 cm² and a daily dose of 25 mg or less is preferred for buccal delivery¹⁹. Various factors that should be considered for designing a formulation for transmucosal delivery of drugs through buccal route are discussed in subsequent sections.

1.2.1 Physiological factors

Constant flow of saliva and mobility of the involved tissues challenge drug delivery to the oral cavity. The residence time of drugs delivered to the oral cavity is very short, in the range of 5–10 min. Consequently, mucoadhesive formulations are used to overcome this problem. These formulations contain a mucoadhesive polymer which helps in retention of delivery system at site of absorption or action for a longer duration. They also provide a means to confine and maintain high local concentrations of the drug to a defined and relatively small region of the mucosa in order to minimize loss to other regions and limit potential side effects.

The mucus layer covering the buccal mucosa is necessary for bioadhesive systems. Apart from being a physical barrier to drug permeation, because of its short turnover time mucus prevents long term bioadhesion and sustained drug release. Moreover, the presence of bioadhesive polymers on a mucous membrane might alter the turnover of mucin. The maximum duration of delivery however should not exceed reported mucin turnover rate of 12–24 h in humans²⁰. The maximum duration for buccal drug delivery is usually limited to approximately 6–8 h, since eating and drinking may require dosage form removal. Faster turnover rate of buccal mucosa (3–8 days) also continuously affects its permeability characteristics.

1.2.2 Pathological factors

Many diseases affect the thickness of the buccal epithelium, its turnover rate and mucin turnover rate resulting in alteration of the barrier properties of the mucosa and affecting the performance of mucoadhesive drug delivery systems. Some diseases or treatments may also influence the secretion and properties of the mucus and saliva²¹. A change at the mucosal surface due to these pathological conditions complicates the application and retention of bioadhesive delivery device. Therefore, understanding the nature of mucosa under relevant disease conditions is necessary for designing an effective buccal delivery system. In addition, drugs with the potential of changing physiological conditions of the oral cavity are unsuitable for buccal delivery. Cancer patients often develop oral candidosis and a substantial decrease in salivary flow after irradiation treatment. The bioadhesive buccal tablet containing miconazole has been shown to be effective in treatment of oral candidosis, but its efficacy was substantially influenced by low saliva secretion in cancer patients.

123 Pharmacological factors

A buccal dosage form may be designed for systemic or local action. For local action, the residence time and local concentration of the drug in the mucosa are important considerations. For a systemic effect, the amount of drug transported across the mucosa into the circulatory system is an important factor²⁰.

124 Pharmaceutical/ Physicochemical factors

The drug must be released from the delivery system and should permeate through buccal mucosa (if necessary) to exert its pharmacological action. Poor drug solubility in saliva significantly retards drug release from the dosage form and hence leads to poor drug absorption. Cyclodextrins have been used to solubilize and increase the absorption of poorly water-soluble drugs delivered via buccal mucosa. Apart from these hemispherical characteristics required for desirable drug release and absorption, organoleptic properties of the drug or the delivery device are of utmost importance as buccal delivery systems are exposed to a highly developed sensory organ. Some excipients are generally incorporated to enhance the effectiveness and acceptability of the dosage forms. Selection of formulation excipients is a very important consideration, since acidic compounds can stimulate the secretion of saliva, which enhances not only drug dissolution, but also drug loss by involuntary swallowing. Addition of a separate additive for each function could complicate and enlarge the dosage form, which might be problematic for buccal applications. Therefore, additives with multiple functions need to be selected¹².

Important additives that can be incorporated into the delivery system are permeation enhancers, polymers that retard the drug release (when controlled or sustained delivery of drug is desirable) and polymers that help in retaining the delivery system for prolonged duration time at the site of application by mucoadhesion. In the next few sections, permeation enhancers and mucoadhesive polymers will be dealt with in detail.

14 Buccal Permeation Study

Prior to formulating a buccal delivery system for a drug, buccal absorption/permeation studies must be conducted to determine the feasibility of this route of administration for the candidate drug. The developed delivery systems should also be evaluated for drug permeation to establish safety and efficacy. These studies involve methods that would examine in vitro and/or in vivo buccal permeation profile and absorption kinetics of the drug.

14.1 In vitro methods

Most of the in vitro studies reported for examining drug transport across buccal mucosa have used buccal tissues from animal models and Franz Type diffusion cell¹⁶. Animals are sacrificed immediately before the start of an experiment. Buccal mucosa with underlying connective tissue is surgically removed from the oral cavity, after which the connective tissue is carefully removed and the buccal mucosal membrane is isolated. The membranes are then stored in ice-cold (4°C) buffer until mounted between a diffusion cell for the in vitro permeation experiments.

The major issue in these in vitro models is the viability and integrity of the dissected tissue. The dissected tissue needs to be preserved properly as this directly affects the results of the study. There are no standard means by which the viability or the integrity of the dissected tissue can be assessed. Have studied tissue viability by monitoring ATP levels in rabbit buccal mucosa. Using ATP levels as an indicator for tissue viability is not an accurate measure, as they reported that a 50% drop in the tissue ATP concentration did not result in change of tissue permeability. Therefore, a decrease in ATP levels does not assure a drop in permeability characteristics of the tissue. The most meaningful method to assess tissue viability is the actual permeation experiment itself. If the drug permeability does not change during the course of the study under specific experimental conditions of pH and temperature, then the tissue is considered to be viable.

15 Importance of Buccaladhesion/ Bioadhesion

The term bioadhesion can be defined as the attachment of a synthetic or natural macromolecule to mucus and/or an epithelial surface. In general it is defined as adherence of a polymeric material to a biological surface (bioadhesion) or to a mucosal surface (mucoadhesion).

15.1 Theories of buccaladhesion

The mucus layer covering mucosal surfaces is composed primarily of mucins. Mucins are highly glycosylated glycoproteins with a large peptide backbone and oligosaccharide side chains. Their protein backbone is characterized by the presence of repeating sequences rich in serine, threonine and proline residues. As a result, mucins are negatively charged at physiological pH. Mechanisms of polymer attachment to mucosal surfaces are not yet fully understood. However, certain theories of bioadhesion have been proposed. It has been postulated that mucoadhesion might occur via physical entanglement and/or chemical interactions, such as electrostatic, hydrophobic, hydrogen bonding, and Van der Waals interactions.

Five theories have been suggested to play a major role in bioadhesion, namely, adsorption, diffusion, electronic, fracture and wetting theories. In the adsorption theory, primary and secondary chemical bonds of the covalent and non-covalent (electrostatic and Van der Waals forces, hydrogen, and hydrophobic bonds) type are formed upon initial contact between the mucus and the polymer¹⁸.

15.2 Buccaladhesive tablets formulations

Tablets have been the most commonly investigated dosage form for buccal drug delivery. Buccal tablets are small, flat or oval; with a diameter of approximately 5–8 mm. Buccal tablets get hydrated and adhere to the mucosa. They are retained in position until drug dissolution and/or release is complete. Successive tablets can be applied to alternate sides of the mouth. The major drawback of buccal bioadhesive tablets is their lack of physical flexibility, leading to poor patient compliance for long-term and repeated use.

Bioadhesive tablets are usually prepared by direct compression, but wet granulation techniques can also be used.

Tablets intended for buccal administration by insertion into the buccal pouch may dissolve or erode slowly³². Multilayered tablets can also be prepared by sequentially adding and compressing the ingredients layer by layer. If necessary, the drug may be formulated in certain physical states, such as microspheres, prior to direct compression in order to achieve some desirable properties like enhanced activity and prolonged drug release¹⁵.

BIBLIOGRAPHY

1. Shojaei, A.H., Buccal mucosa as a route for systemic drug delivery: a review. *J. Pharm. Pharm. Sci.*, 2018; 1, 15-30.
2. Soyani, A.P., Chien, Y.W., Systemic delivery of peptides and proteins across absorptive mucosae. *Crit. Rev. Ther. Drug Carrier Syst.*, 2016; 13, 174-184.
3. Langoth, N., Kalbe, J., Bernkop-Schnurch, A., Development of buccal drug delivery systems based on a thiolated polymer. *Int. J. Pharm.*, 2023; 252, 141-148.
4. Lehr, C.M., Lectin-mediated drug delivery: the second generation of bioadhesives. *J. Control. Release*, 2020; 65, 19-29.
5. Chen, L., Hui-Nan, X., Xiao-Ling, L., In vitro permeation of tetramethylpyrazine across porcine buccal mucosa. *Acta Pharmacol. Sin.*, 2022; 23, 792-796.
6. Dal Negra, R., Turco, P., Pomari, C., Trevisan, F., Calcitonin nasal spray in patients with chronic asthma: a double-blind crossover study versus placebo. *Int. J. Clin. Pharmacol. Ther. Toxicol.*, 2021; 29, 144-146.
7. Dowty, M.E., Knuth, K.E., Robinson, J.R., Enzyme characterization studies on the rate-limiting barrier in rabbit buccal mucosa. *Int. J. Pharm.*, 2022; 88, 293-302.
8. Du, X., Squier, C.A., Kremer, M.J., Wertz, P.W., Penetration of N-nitrosornicotine (NNN) across oral mucosa in the presence of ethanol and nicotine. *J. Oral Pathol. Med.*, 2020; 29, 80-85.
9. Gandhi, R.B., Robinson, J.R., Oral cavity as a site for bioadhesive drug delivery. *Adv. Drug Deliv. Rev.*, 2024; 13, 43-74.
10. Gurney, R., Meyer, J.M., Peppas, N.A. Bioadhesive intraoral release systems: design, testing and analysis. *Biomaterials*, 2024; 5, 336-340.

11. Kast, C.E., Bernkop-Schnurch, A., Thiolated polymers–thiomers: development and invitro evaluation of chitosan–thioglycolic acid conjugates. *Biomaterials*, 2021; 22, 2345-2352.
12. Langoth, N., Kalbe, J., Bernkop-Schnurch, A. Development of buccal drug delivery systems based on a thiolated polymer. *Int. J. Pharm.*, 2023; 252, 141-148.
13. Lee, J.W., Park, J.H., Robinson, J.R., Bioadhesive based dosage forms: the next generation. *J. Pharm. Sci.*, 2020; 89, 850-866.
14. Nicolazzo, J.A., Reed, B.L., Finnin, B.C., Assessment of the effects of sodiumdodecyl sulfate on the buccal permeability of caffeine and estradiol. *J. Pharm. Sci.*, 2024; 93,431-440.
15. Nicolazzo, J.A., Reed, B.L., Finnin, B.C., Enhancing the buccal mucosal uptake and retention of triamcinolone acetonide. *J. Control. Release*, 2025; 105, 240-248.
16. Rathbone, M.J., Tucker, I.G., Mechanisms, barriers and pathways of oral mucosal drug permeation. *Adv. Drug Deliv. Rev.*, 2023; 13, 1-22.
17. Shojaei, A.H., Buccal mucosa as a route for systemic drug delivery: a review. *J. Pharm. Pharm. Sci.*, 2018; 1, 15-30.
18. Squier, C.A., Cox, P., Hall, B.K., Enhanced penetration of nitrosonornicotine across oral mucosa in the presence of ethanol. *J. Oral Pathol.*, 2016 ; 15, 276-279.
19. Squier, C.A., Cox, P.S., Wertz, P.W., Downing, D.T., The lipid composition of porcine epidermis and oral epithelium. *Arch. Oral Biol.*, 2017 ; 31, 741-747.
20. Tanaka, M., Yanagibashi, N., Fukuda, H., Nagai, T., Absorption of salicylic acid through the oral mucous membrane of hamster cheek pouch. *Chem. Pharm. Bull.*, 2020; 28, 1056-1061.
21. Tengamnuy, P., Mitra, A.K., Bile salt-fatty acid mixed micelles as nasal absorption promoters of peptides. I. Effects of ionic strength, adjuvant composition, and lipid structure on the nasal absorption of [D-Arg2] Kyotorphin. *Pharm. Res.*, 2020;7,127-133.

Copyright & License:

© Authors retain the copyright of this article. This work is published under the Creative Commons Attribution 4.0 International License (CC BY 4.0), permitting unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.