ejpmr, 2021,8(10), 475-483

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEMS: A REVIEW

Vikash Dahiya[1], Dr. Saroj Jain[1], Dr. Seema Rohilla[1]*

Department of Pharmaceutics, Hindu College of Pharmacy, Sonepat.

***Corresponding Author: Dr. Seema Rohilla**

Department of Pharmaceutics, Hindu College of Pharmacy, Sonepat.

Article Received on 20/08/2021 **Article Revised on 09/09/2021** **Article Accepted on 30/09/2021**

ABSTRACT

Owing to the ease of administration, the oral route is an attractive site for drug liberation. The oral route is helpful to produce mucosal (by achieving a site-specific release of drug on mucosa) and transmucosal drug administration (by absorbing drug through mucosal barrier to reach in systemic circulation). The limited absorption area and barrier properties of mucosa are main obstacles of buccal route. This article highlighted the anatomical structure of oral mucosa, advantages and limitations of buccal drug delivery, mechanisms of drug permeation through oral mucosa and formulation consideration for buccal drug delivery system.

KEYWORDS: Transmucosal, Buccal drug delivery, Obstacles, Site-specific, Permeation, Oral mucosa.

INTRODUCTION

Oral route is most commonly employed route of drug administration. Although different routes are used for drugs adminsteration due to flexibility in dosage form design and patient compliance but oral route is preferred.[1] The popularity of oral route is attributed to ease of administration, patient acceptance, accurate dosing, cost effective manufacturing methods and generally improved shelf-life of product.[2]

There are several techniques of conventional drug delivery system where tablets, capsules, pills, liquids, are used as drug carrier. Among them, solid formulations do not require sterile conditions and are therefore, less expensive to manufacture.[3] Drug delivery via the membrane of the oral cavity can be subdivided as follows.

1. **Sublingual delivery** - In this the drug is administered via sublingual mucosa (membrane present at ventral surface of tongue and floor of mouth) to systemic circulation.
2. **Buccal delivery** – In this the drug is administered via buccal mucosa (lining of cheek) to systemic circulation.
3. **Local delivery**- This route is used especially for the treatment of oral cavity, principally for ulcers, fungal conditions.

ADVANTAGES OF BUCCAL DRUG DELIVERY SYSTEM

Drug administration via oral mucosa offers several advantages[4-5] which are given below:

1. Ease of administration.
2. Termination of therapy is easy.
3. Permit localization of drug to oral cavity for a prolonged period of time.
4. Can be administered to unconscious patients.
5. Offers an excellent route for systemic delivery of drugs with high first pass metabolism, thereby offering greater bioavailability.
6. A significant reduction in dose can be achieved thereby reducing dose dependent side effects. Drugs which are unstable in the acidic environment are destroyed by enzymatic or alkaline environment of intestines can be administered by this route.
7. Drugs which show poor bioavailability via oral route can be administered conveniently.
8. Offers a passive system for drug absorption and does not require any activation.
9. Presence of saliva ensures relatively less amount of water for drug dissolution unlike in case of rectal and transdermal routes.
10. Rapid systemic absorption.
11. This route provides an alternative for the administration of various hormones, narcotic analgesic, steroids, enzymes, cardiovascular agents, etc.
12. The buccal mucosa is highly amalgamated with blood vessels and offers a greater permeability than skin.
13. It allows for the local modification of tissue permeability, inhibition of protease activity or reduction in immunogenic response. Thus, relative use of therapeutic agents like peptides, protein and ionized species can be achieved.
14. Therapeutic concentration of the drug can be achieved more rapidly.

LIMITATIONS OF BUCCAL DRUG ADMINISTRATION

Drug administration via this route has certain limitations[6-7] which are given below.

1. Drug, which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odour, cannot be administered by this route.
2. Drugs, which are unstable at buccal pH, cannot be administered by this route.
3. Drugs can be administered only with small dose by this route.
4. Only those drugs, which are absorbed by passive diffusion, can be administered by this route.
5. Eating and drinking may become restricted.
6. There is possibility that patient can swallow the tablet.
7. Over hydration may lead to formation of slippery surface and structural integrity of formulation may get disrupted by this swelling and hydration of bio adhesive polymers.

ANATOMY AND NATURE OF 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.[8]

Oral cavity (Fig. 1) is that area of mouth delineated by lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions,

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

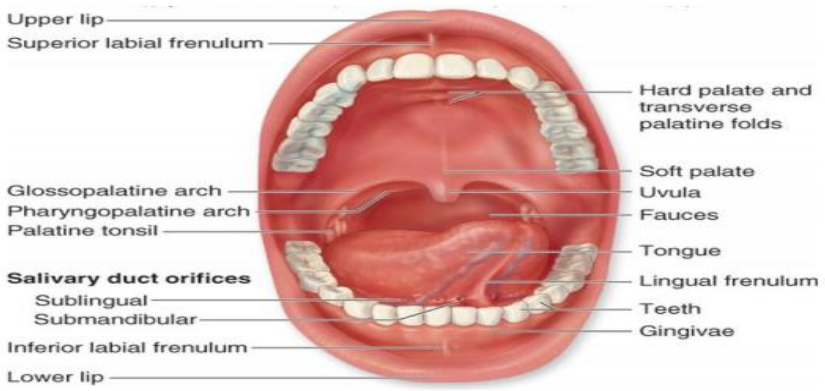

Fig. 1: Structure of Buccal Cavity.

The drug administered via oral mucosa gain access to systemic circulation through a network of arteries and capillaries. The major artery supplying blood to oral cavity is external carotid artery. The venous backflow goes through branches of capillaries and veins and finally taken up by the jugular vein.[9] The secretions in oral cavity include saliva, crevicular fluid and mucus. From that, Saliva is a complex fluid containing organic and inorganic materials. It is produced by three pairs of major glands (parotid, submandibular and sublingual) each situated outside the oral cavity and in minor salivary glands situated in 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 type of stimulus used, duration and length of exposure, glands stimulated, the age and sex of individual and their health status. The average resting flow rate for whole saliva is 0.3 ml/ min (range 0.1-0.5 ml/min). For stimulated saliva the average flow rate is 1.7 ml/min (range 1.1 to 3.0 ml/min). 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, and globulin, mucinand enzymes [lysozyme and amylase (ptyalin). The crevicular fluid is secreted from the gingival glands of oral cavity. Mucus 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. The mucin glycoprotein, MG1 consists of several disulphide-linked subunits containing a protein core with 4-16 oligosaccharide side-chain units. Its molecular size is over 1000 KDa. A small mucin glycoprotein, MG2 has a molecular weight of 200-250 KDa and consists of a single peptide chain with 2-7 oligosaccharide side-chain units. The glycoprotein of mucus has amphoteric properties and therefore capable of buffering small amounts of either acids or alkalies. The mucus however acts as a potential barrier to drug penetration. The oral cavity is a portal for intake of food material and water, to bring chewing, mastication and

mixing of food stuff, then for lubrication of food material and formation of bolus, for the identification of ingested material by taste buds of tongue, to carry out initiation of carbohydrate and fat metabolism and absorption of catabolic products thereafter metabolism and lastly it has slight antisepsis of ingested material and within oral cavity by saliva (Fig. 2).[10]

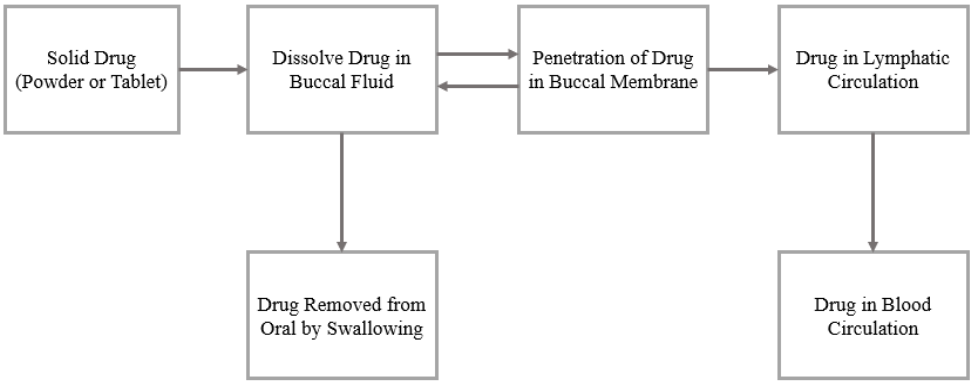

Fig. 2: Schematic representation of absorption kinetics of drugs administered via buccal route.

ORAL MUCOSA

The mucosa that lines the oral cavity may be divided into three types according to their function as.

Masticatory mucosa: It includes the mucosa around teeth and on hard palate. These regions have keratinized epithelium.

Lining mucosa: It include the mucosa over the lips, cheeks, fornix, lower part of tongue, bottom of oral cavity and soft palate. These regions have non-keratinized epithelium.

Specialized mucosa: It covers the dorsum of tongue with highly keratinization.

Three distinctive layers of oral mucosa are epithelium, basement membrane and connective tissues. The oral cavity is lined with epithelium, below which lies supporting basement membrane. The basement membrane is in turn supported by connective tissues. The epithelial cells originating from basal cells after maturing increase in size and change their shape while moving towards the surface. The thickness of buccal epithelium in humans, dogs and rabbits has been determined to be approximately 500-800 µm. The basement membrane forms a distinctive layer between connective tissues and epithelium to provide adherence that functions as a mechanical support for epithelium (Fig. 3).[11]

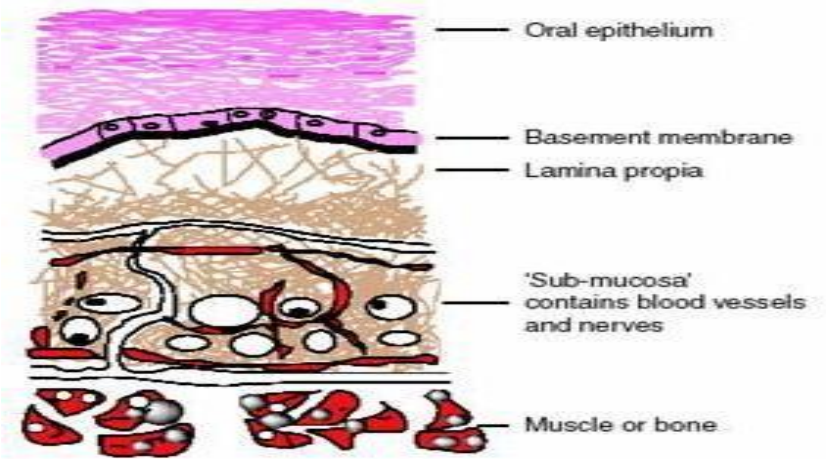

Fig. 3: Structure of buccal mucosa.

BIOCHEMISTRY OF ORAL MUCOSA

Protein present in all layers of oral mucosal membranes in the form of filaments, called keratins with molecular sizes of 40-70 Kda. Keratinized and non- keratinized tissues of varying thickness and composition are found in oral cavity. Keratinized and non-keratinized tissues occupy about 50% and 30% respectively of total surface area of the mouth. The keratinized and non-keratinized epithelia are differentiated merely by the molecular size of existing keratins (Table 1). Cells of non-keratinized epithelia contain lower molecular weight protein while those in keratinized epithelia contain mainly higher-molecular weight keratins. The lipid content of the cells varies between tissues.[12]

Table 1: Composition and state of keratinization of various tissues of oral mucosa.

Tissue	State of Keratinization	Composition
Buccal mucosa	Non-keratinized	Few neutral, but mainly polar lipids, particularly cholesterol sulphate and glucosylceramides
Sublingual mucosa	Non-keratinized	
Gingiva mucosa	Keratinized	Neutral lipids i.e., ceramides
Palatal mucosa	Keratinized	

MECHANISMS INVOLVED IN DRUG ABSORPTION ACROSS THE ORAL MUCOSA

The drugs cross biological lipid membranes via passive diffusion, facilitated diffusion, active transport and pinocytosis mechanisms. Small water-soluble molecules may pass through, small water filled pores. Drugs and nutrients cross the oral mucosa through passive diffusion (Fig. 4). Passive diffusion involves the movement of a solute from a region of high concentration in mouth to a region of low concentration within buccal tissues. Further diffusion then takes place into the venous capillary system, with drug eventually reaching the systemic circulation via jugular vein. The physicochemical characteristics of a drug are very important for this diffusion process.[13]

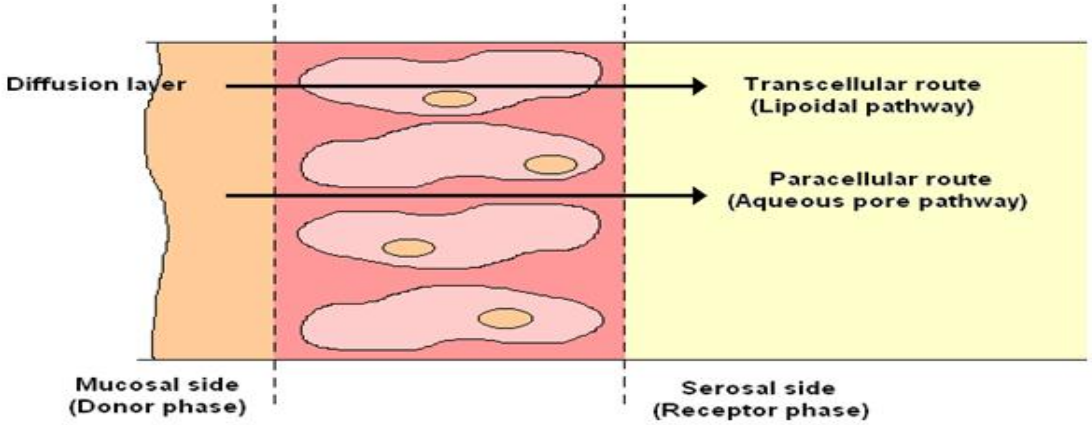

Fig. 4: Drug absorption pathways across buccal mucosa.

The permeability barrier property of oral mucosa is predominantly due to intercellular materials derived from the so-called 'membrane coating granules' (MCGs). MCGs are spherical or oval organelles that are 100-300 nm in diameter and found in both keratinized and non-keratinized epithelia. These organelles have also been referred to as small spherically shaped granules corpusula, small dense granules, small lamellated bodies, lamellated dense bodies, keratinosomes, transitory dense bodies and cementsomes. MCGs are found near the upper, distal or superficial border of cells and a few occur near the opposite border.[14] They discharge their contents into the intercellular space to ensure epithelial cohesion in superficial layers and this discharge forms a barrier to the permeability of various compounds.[15] Another barrier to drug permeability across buccal epithelium is enzymatic degradation. Saliva contains moderate levels of esterase, carbohydrates and phosphatases.[16] Walker et al. reported that endopeptidases and carboxypeptidases were not present on the surface of porcine buccal mucosa, whereas aminopeptidases appeared to be the major enzymatic barrier to buccal delivery of peptide drugs.[17]

FORMULATION CONSIDERATIONS

For buccal drug delivery, it is cardinal to prolong and augment the contact between API and mucosa to obtain desired therapeutic effect. Buccal adhesive drug delivery systems with the size 1-3 cm^2 and a daily dose of 25 mg or less are preferable. The maximal duration of buccal delivery is approximately 4-6 h 25. Mucoadhesives are synthetic or natural polymers that interact with the mucus layer covering the mucosal epithelial surface and main molecules constituting a major part of mucus. The list of mucoadhesive polymers used in buccal drug delivery is shown in Table 2.[18] The concept of mucoadhesives has alerted many investigators to the possibility that these polymers can be used to overcome physiological barriers in long-term drug delivery. The new generation of mucoadhesive polymers can adhere directly to cell surface, rather than to mucus. They interact with the cell surface by means of specific receptors or covalent bonding. The incorporation of L-cysteine into thiolated polymers and target-specific, lecithin-mediated adhesive polymers are examples of such polymers. These classes of polymers helped in delivery of wide variety macromolecules, and create possibilities for specific drug-receptor interactions and improved targeted drug delivery.[18-21]

Table 2: List of mucoadhesive polymers used in buccal delivery.

Criteria	Categories	Examples
Source	Semi-natural/natural	Agarose, chitosan, gelatin, Hyaluronic acid, Various gums (guar, hakea, xanthan, gellan, carrageenan , pectin, and sodium alginate)
	Syenthetic	Cellulose derivatives (CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, methylhydroxyethylcellulose)
		Poly(acrylic acid)-based polymers [CP, PC, PAA, polyacrylates, poly(methylvinylether-co-methacrylic acid), poly(2-hydroxyethyl methacrylate), poly(acrylic acid-co-ethylhexylacrylate), poly(methacrylate), poly(alkylcyanoacrylate), poly(isohexylcyanoacrylate), poly(isobutylcyanoacrylate), copolymer of acrylic acid and PEG
		Others Poly(N-2-hydroxypropyl methacrylamide) (PHPMAm), polyoxyethylene, PVA, PVP, thiolated polymers
Aqueous solubility	Water-soluble	CP, HEC, HPC (water < 38oC), HPMC (cold water), PAA, sodium CMC, sodium alginate
	Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC
Charge	Cationic	Aminodextran, chitosan, dimethylaminoethyl (DEAE)-dextran, trimethylated chitosan
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum
	Non-ionic	Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP, scleroglucan
Potential bioadhesive forces	Covalent	Cyanoacrylate
	Hydrogen bond	Acrylates [hydroxylated methacrylate, poly(methacrylic acid)], CP, PC, PVA
	Electrostatic interaction	Chitosan

The mechanism of mucoadhesion involved uniform distribution of mucoadhesive over the substrate to initiate close contact and hence increase surface contact, promoting the diffusion of its chains within mucus (Fig. 5). This generates the attractive and repulsive forces and, for a mucoadhesive to be successful, the attractive forces must be dominated. Each step can be facilitated by the nature of dosage form and how it is administered. The main theories on mucoadhession are briefly described in table 3.

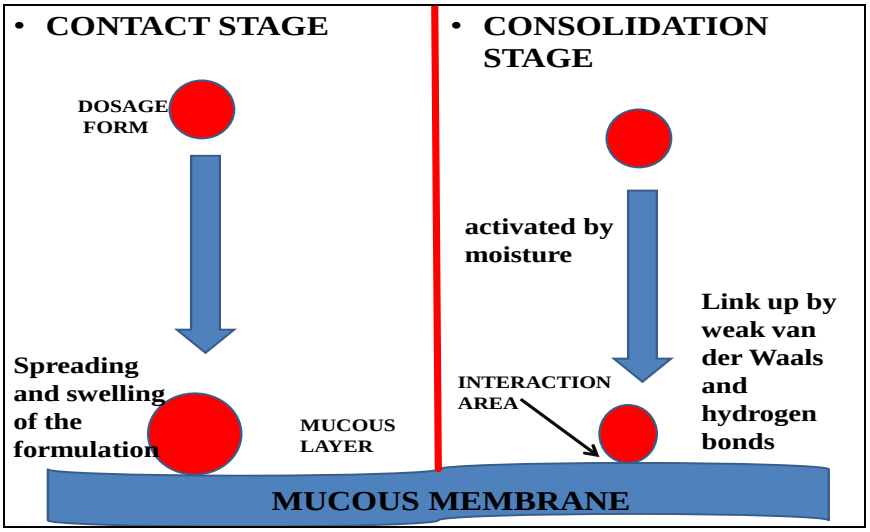

Fig. 5: Mechanism of mucoadhesion.

Table 3: Theories on mucoadhesion.

Theory	Mechanism of bioadhession[19-21]
Adsorption theory	Surface force resulting in chemical bonding.
Mechanical theory	Adhesion arises from an interlocking of liquid adhesive into irregularities on the rough surface.
Wetting theory	Ability of bioadhesive polymer to spread and develop intimate contact with the mucous membrane.
Diffusion theory	Physical entanglement of mucin strands and flexible polymer chains.
Fracture theory	Analyses the maximum tensile stress developed during attachment of the transmucosal DDS from the mucosal surface.
Electronic theory	Attractive electrostatic forces between glycoprotein mucin network and the bioadhesive material.

ENZYME INHIBITORS

Enzyme inhibitors, such as aprotinin, bestatin, puromycin and some bile salts stabilize protein drugs by different mechanisms, including affecting the activities of enzymes, altering the conformation of peptides or proteins and/or rendering the drug less accessible to enzymatic degradation.[22-23] Circular dichroism studies suggest that Ca^{2+} depletion, mediated by the presence of some mucoadhesive polymers, changes the secondary structure of trypsin, and initiates a further autodegradation of enzyme.[24]

PENETRATION ENHANCERS

Penetration enhancers are the substances, which increase the buccal mucosal membrane permeation rate (Table 4). They show their effects by following mechanisms.

i. **Changing mucus rheology**: They act by reducing the viscosity of mucus and saliva overcomes this barrier.
ii. **Increase in thermodynamic activity of drugs:** Some permeation enhancers alter the partition coefficient of the drug there by increase solubility and thermodynamic activity that leads to better drug absorption.
iii. **Action on the components at tight junctions**: Desmosomes is the main component at the tight junctions. Some permeation enhancers act by disturbing or interacting with the components of the desmosomes.
iv. **Increase in fluidity of lipid bilayer membrane**: They disturb the intracellular lipid packing by interaction with either lipid or protein components. Changes in membrane fluidity indirectly affect the enzymatic activity.
v. **Overcoming the enzymatic barrier:** The buccal permeation enhancer acts by inhibiting the various peptidases and proteases present within buccal mucosa, thereby overcoming the enzymatic barrier.

Although most penetration enhancers were originally designed for purposes other than absorption enhancement, a systemic search for safe and effective penetration enhancers must be a priority in drug delivery.[25] With the rapid development of biotechnology, more and more protein, peptide, and nucleotide drugs are becoming available, most of which have low membrane-absorption characteristics due to a large size with high molecular weight, domains of different hydrophobicity, irregular shapes, and delicate structures easily inactivated. These drugs are unable to cross membrane barriers in therapeutic amounts and thus research into penetration enhancers becomes ever more important.[26, 19-21]

Table 4: Different penetration enhancers with their mechanism of action.

Classification	Examples	Mechanism
Surfactants	**Anionic**: Sodium lauryl sulfate, Sodium laurate **Cationic**: Cetylpyridinium chloride **Nonionic**: Poloxamer, Brij, Span, Myrj, Tween **Bile salts**: Sodium glycodeoxy cholate, sodium glycocholate, sodium taurodeoxycholate, sodium taurocholate, Azone	Perturbation of intercellular lipids, protein domain integrity
Chelators	EDTA, sodium citrate Polyacrylates	Interfere with Ca^{2+}
Positively charged polymers, Cationic compounds	Chitosan, trimethyl chitosan, Poly-L-arginine, L-lysine	Ionic interaction with negative charge on the mucosal surface
Cyclodextrins	α-, β, γ-cyclodextrin, methylated β-cyclodextrins	Inclusion of membrane compounds
Fatty acids	Oleic acid, caprylic acid	Increase fluidity of phospholipids domains

SOLUBILITY MODIFIERS

Solubilization of poorly water-soluble drugs by complexation with cyclodextrins and delivering via the buccal mucosa is advantageous in increasing drug absorption and bioavailability.[27] For example the release of felodipine from buccal tablets comprising hydroxypropyl-β-cyclodextrin-felodipine complex and hydroxylpropyl methyl cellulose and is a complete but sustained release of drug associated with an enhanced buccal permeation. These results could be attributed to the ability of hydroxypropyl-β-cyclodextrin to form a complex with felodipine, resulting in an increase in apparent drug solubility, dissolution rate and permeability.[20-21]

TYPES OF BUCCAL DRUG DELIVERY SYSTEM

For delivery of drug through buccal route several mucoadhesive dosage forms have been reported because of the presence of a smooth and relatively immobile surface for placement of a mucoadhesive dosage forms. The buccal region appears to be more suitable for sustained delivery of therapeutic agents using a mucoadhesive system. The various types of buccal drug delivery system are explained as follows.

1. Buccal patches/films

Patches are laminates consisting of an impermeable backing layer a drug containing reservoir layer from which the drug is released in a controlled manner and a bioadhesive surface for mucosal attachment. Two

methods used to prepare adhesive patches include solvent casting and direct milling. In solvent casting method, the intermediate sheet from which patches are punched is prepared by casting solution of drug and polymers onto a backing layer sheet and subsequently allowing the solvents to evaporate. In the direct milling method, formulation constituents are homogenously mixed and compressed to desired thickness and patches of predetermined size and shape are then cut or punched out. An impermeable backing layer may also be applied to control the direction of drug release, prevent drug loss and minimize deformation and disintegration of device during application period.

2. Buccal gels and ointments

Such semisolid dosage forms have the advantage of easy dispersion throughout oral mucosa. Poor retention of gels at the site of application has been overcome by using bioadhesive formulations. Certain bioadhesive polymers undergo a phase change from a liquid to a semisolid; this change enhances viscosity which results in sustained and controlled release of drugs. Hydrogels are also promising dosage forms which are formed from polymers that are hydrated in an aqueous environment and physically entrap drug molecules for subsequent slow release by diffusion or erosion. These dosage forms provide an extended retention time, adequate drug penetration as well as high efficacy and patient acceptability.[28-33]

3. Buccal tablets

Buccal tablets are small, flat, and oval shaped dosage form. Buccal mucoadhesive tablets allow for drinking and speaking without major discomfort. They adhere to the mucosa and are retained in position until dissolution or release is complete. These tablets can be applied to different sites in the oral cavity including palate, mucosa lining, cheek as well as between lip and gum. These tablets are usually prepared by direct compression but wet granulation techniques can also be used. Multi-layered tablet may be prepared by sequentially adding and compressing the ingredients layer by layer. Some newer approaches use tablets that melt at body temperature.[34]

MARKETED PRODUCTS

Marketed formulations or formulations under research in clinical trials for buccal drug delivery are listed in table 5.[35, 19-21]

Table 5: List of marketed formulations of buccal delivery system.

Brand name	Active ingredient	Dosage form	Company
Striant SR	Testosterone	Tablet	Ardana Bioscience Ltd
Buccastem	Prochlorperazine	Tablet	Reckitt Benkiser Plc
Suscard	Glyceryl trinitrate	Tablet	Forest Laboratories
Isordil (Wyeth)	Isosorbide dinitrate	Tablet	Globus Remedies Ltd
Aphtach	Triamcinolone acetonide	Tablet	Teijin Ltd
Nicorette	Nicotine	Tablet	Leo Pharmaceuticals
Cyclo-Diol SR	Androdiol	Tablet	Ergo Pharm
	Desmopressin	Tablet	Columbia Laboratories Inc.
PIOLOBUC	Pilocarpine	Tablet	Cytokine Pharma Sciences
Cyclo-Nordiol SR	Norandrodiol	Tablet	Ergo Pharm
Tementil	Prochlorperazine	Tablet	Rhone-Poulenc Rorer
Subutex	Buprenorphine HCl	Tablet	Reckitt Benckiser
Metandren	Methyltestosterone	Tablet	Ciba-Geigy
Temesta Expidet	Lorazepam	Tablet	Wyeth Pharma
Seresta Expidet	Oxazepam	Tablet	Ceuticals

PATENTED FORMULATIONS

Some patented formulations of mucoadhesive buccal drug delivery system are shown in table 6.

Table 6: Patented formulations of mucoadhesive buccal drug delivery system.

Patent	Titles	Patentees	References
WO2006105615A1	Buccal delivery system	Ernest Alan Hewitt, Richard James Stenlake	[36]
US20090263476A1	Composition of Rapid Disintegrating Direct Compression Buccal Tablet	Christopher N. Jobdevairakkam, Vikram Katragadda	[37]
US20020142042A1 P1383479A2EP138	pH-sensitive mucoadhesive film-forming gels and wax-film composites suitable for topical and mucosal delivery of molecules	Russell Mumper, Michael Jay	[38]
US8529939B2	Mucoadhesive drug delivery devices and methods of making and using thereof	David B. Masters, Eric P. Berg	[39]

US9320721B2	Mucoadhesive patch with opposite ratios of nonionic and anionic hydrocolloids in adhesive and backing layer	Ulrike Vollmer	[40]
EP3173067A1	Mucoadhesive buccal in situ gel formulation	Ayca Yildiz Pekoz, Yildiz ozsoy Erginer, Derya Arslan	[41]
EP2509586A1	Mucoadhesive buccal tablets for the treatment of orofacial herpes	Pierre Attali, Dominique Costantini, Caroline Lemarchand	[42]

CONCLUSION

Buccal drug delivery holds a great promise for 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. The buccal route of administration has significant advantages for systemic drug delivery. It is an effective alternative to traditional oral route, especially when fast onset of action is required. In addition, it is also useful for the drugs that undergo high hepatic clearance or degradation in the gastrointestinal tract, and for patients that have swallowing difficulties. Thus, buccal adhesive systems offer innumerable advantages in terms of accessibility, administration and withdrawal, retentivity, low enzymatic activity, economy and high patient compliance. 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. Efforts have to be made to develop standardized *in vitro* and *ex vivo* biological models that allow one to characterize and compare different material and formulation in terms of their capability to promote drug absorption via the buccal route.

ACKNOWLEDGEMENT

Declared none.

REFERENCES

1. Notari R, Biopharmaceutics and Clinical Pharmacokinetics, An Introduction, 3rd Ed., Marcel Dekker Inc. New York, 1980; 152-154.
2. Vinay K, Prajapati SK, Girish CS, Mahendra S, Neeraj k. Sustained release matrix type drug delivery system. IRJP, 2012; 1(3): 934-960.
3. Kumar V, Sharma A, Sharma A, Joshi G, Dhillon V. Recent Advances in Novel Drug Delivery System for Delivery of Anti- Hypertensive Drugs. Int J D D Res, 2011; 3(1): 252-259.
4. Shojaei HA. Buccal mucosa as a route for systemic drug delivery: A Review. J Pharm Sci, 1998; 1(1): 15-30.
5. Haris D, Robinson JR. Buccal drug delivery via the mucous membranes of the oral cavity. J Pharm Sci, 1992; 81(1): 1-9.
6. Gorahowski TT. Principles of anatomy and physiology. 7thed. Edited by Gerad J. Tor- Tora and Sandro Reynolds Gorahowski: Harpet Collins College Publishers, 1992; 770-774.
7. Ross &Wilson. Anatomy & physiology in health and illness. 9thed. Edited by Anne Waugh and Allison Goraw: Churchill Livingstone Edinburgh Publishers, 2001; 289-293.
8. Chatterjee CC. Human physiology. 10thed. Calcutta: Medical Allied Agency, 1985; 427-434.
9. Pramod KTM, Shivakumar HG and Desai KG. Oral transmucosal drug delivery systems. Indian Drugs, 2004; 41(2): 63-67.
10. Chen YS, Squier CA. The ultra structureof the oral epithelium. In: J. Meyer, CA. Squier, SJ. Gerson (eds.), The structure and function of oral mucosa, Pergamon Press, Oxford, 1984; 7-30.
11. James S. Bioadhesivedrug delivery systems. 1st ed. New York: Marcel Dekker Inc, 1999; 541-562.
12. Jain NK. Controlled and novel drug delivery. 1st ed. New Delhi: CBS Publishers & Distributors, 1997; 52-81.
13. Hayward AF. Membrane-coating granules. Int Rev Cyt, 1979; 59: 97-127.
14. Squier CA, Eady RA, Hopps RM. The permeability of epidermis lacking normal membrane-coating granules: an ultra structural tracer study of Kyrle-Flegel disease. J Invest Dermatol, 1978; 70: 361-364.
15. Robinson JR, Yang X. Absorption enhancers. In: J. Swarbrick, JC. Encyclopedia of pharmaceutical technology. New York: Marcel Dekker Inc, 2001; 18: 1-27.
16. 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.
17. Walker GF, N. Langoth, A. Bernkop- Schnurch. Peptidase activity on the surface of the porcine buccal mucosa. Int J Pharm, 2002; 233: 141-147.
18. Miller N.S. *et al*., The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Deliv Rev, 2005; 57: 1666-1691.
19. Verma S, Kaul M, Rawat A and Saini S. An Overview on Buccal Drug Delivery System. IJPSR, 2011; 2(6): 1303-1321.
20. Chinna Reddy P, Chaitanya KSC, Madhusudan Rao Y. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. DARU J Pharma. Sci, 2011; 19(6): 385-

403.
21. Miller SC, Donovan MD. Effect of poloxamer 407 gel on the meiotic activity of pilocarpine nitrate in rabbits. Int J Pharm, 1982; 12: 147-152.
22. Hao J and Heng PSW. Buccal delivery systems, Drug Dev. Ind. Pharm, 2003; 29: 821-832.
23. 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.
24. Luessen HL, Verhoef JC, Borchard G, Lehr CM, de Boer AG, Junginger HE. Mucoadhesive polymers in peroral peptide drug delivery: II. Carbomer and polycarbophil are potent inhibitors of the intestinal proteolytic enzyme trypsin, *Pharm Res*, 1995; 12: 1293-1298.
25. Pramod Kumar TM, Desai KG, Shivkumar HG. Mechanism of Buccal Permeation Enhancers. Indian J Pharm Educ, 2002; 36(3): 147-151.
26. Robinson JR, Yang X. Absorption enhancers, Encyclopedia of Pharmaceutical Technology: Swarbrick J, Boylan JC. Marcel Dekker, New York, 1999; 18: 1-27.
27. Chinna Reddy P, Sunil Kumar B, Ramesh G, Vamshi Vishnu Y, Michael AR, Madhusudan Rao Y. Role of cyclodextrin complexation in felodipine-sustained release matrix tablets intended for oral transmucosal delivery: *In vitro* and *ex vivo* characterization. Pharm. Dev. Tech, 2011; 1-12.
28. Puri V, Sharma A, Maman P, Rathore N, Singh I. Overview of Mucoadhesive Biopolymers for Buccal Drug Delivery Systems. Int J App Pharm, 2019; 11: 18-29.
29. Wong CF, Yuen KH, Peh KK. Formulation and evaluation of controlled release Eudragit buccal patches. Int J Pharm, 1999; 178: 11-22.
30. Kumar S, Haglund BO, Himmelstein KJ. In situ-forminggels for ophthalmic drug delivery. J Ocul Pharmacol, 1994; 10: 47-56.
31. Gurny R, Ryser JE, Tabatabay C, Martenet M, Edman P, Camber O. Precorneal residence time in humans of sodium hyaluronate as measured by gamma scintigraphy. Graefe Arch Clin Exp Ophthalmol, 1990; 228: 510-512.
32. Meseguer G, Gurny R, Buri P. Gamma scintigraphic evaluation of precorneal clearance in human volunteers and in rabbits. Eur J Drug Meta Pharma, 1993; 18: 190-194.
33. Martin L, Wilson CG, Koosha F, Uchegbu IF. Sustained buccal deliveryof the hydrophobic drug denbufylline using physically cross-linked palmitoyl glycol chitosan hydrogels. Eur J Pharm Biopharm, 2003; 55: 35-45.
34. 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.
35. Rossi S, Sandri G, Caramella CM. Buccal drug delivery: A challenge already won?, Drug Discov Today Technol, 2005; 2(1): 59-65.
36. Hewitt EA, Stenlake RJ. Buccal delivery system. WO2006105615A1(2006)
37. Jobdevairakkam CN, Katragadda V. Composition of Rapid Disintegrating Direct Compression Buccal Tablet. US20090263476A1 (2009)
38. Mumper R, Jay M. pH-sensitive mucoadhesive film-forming gels and wax-film composites suitable for topical and mucosal delivery of molecules. US20020142042A1 (2010)
39. Masters DB, Berg EP. Mucoadhesive drug delivery devices and methods of making and using thereof. US8529939B2 (2013)
40. Vollmer U. Mucoadhesive patch with opposite ratios of nonionic and anionic hydrocolloids in adhesive and backing layer. US9320721B2 (2016)
41. Pekoz AY, Erginer YO, Arslan D. Mucoadhesive buccal in situ gel formulation. EP3173067A1 (2018)
42. Attali P, Costantini D, Lemarchand C. Mucoadhesive buccal tablets for the treatment of orofacial herpes. EP2509586A1(2018)