International Journal of
Science, Architecture, Technology and Environment

Review on Buccal Mucoadhesive Drug Delivery System in the Human Body

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Abstract

Considering its ease of administration, the oral cavity is a preferred place for pharmaceutical distribution. This approach enables the delivery of medications both mucosally (local effect) and transmucosally (systemic effect). The goal in the first case is to achieve a site-specific release of the drug on the mucosa, whereas in the second case, the drug is absorbed through the mucosal barrier and into the systemic circulation. The primary obstacles that drugs confront when administered bucally are the narrow absorption area and mucosal barrier properties. Other obstacles to consider include the oral cavity's superior physiological clearance processes, which move the formulation away from the absorption site. Using new materials with mucoadhesive, enzyme inhibitory, and permeation-enhancing properties, to overcome these limitations, researchers are exploring innovative drug delivery technologies that increase patient compliance and promote closer contact between the drug and the absorption mucosa. This overview covers the benefits and downsides of buccal medication delivery, including the anatomy of the oral mucosa, drug permeation mechanisms, current formulation design, and improvements in buccal delivery methods.

Keywords: Buccal delivery, Mucoadhesive, Permeation enhancers, Formulation design

1. Introduction

The oral route is the most widely used mode of drug delivery, yet many medications are not properly absorbed because of substantial pre-systemic clearance in the liver, which reduces bioavailability. This has prompted the investigation of alternate medication delivery channels, including transmucosal routes (nasal, rectal, vaginal, ophthalmic, and oral). (Senel S, Ikinci G, Kas S, Yousefi-Rad A, Sargon MF, HIncal AA. Chitosan films and hydrogels of chlorhexidine gluconate for oral mucosal delivery. Int. J. Pharm. 2000;193:197–203. doi: 10.1016/s0378-5173(99)00334-8.)

The buccal mucosa stands out as a viable choice due to its accessibility, smooth muscle, immobility, and suitability for controlled-release formulations. It also provides direct access to the systemic circulation, avoiding gastrointestinal and hepatic processing, resulting in greater bioavailability. (Vamshi Vishnu Y, Chandrasekhar K, Ramesh G, Madhusudan Rao Y. Development of Mucoadhesive Patches for Buccal

Administration of Carvedilol. Current Drug Delivery. 2007;4:27–39. doi: 10.2174/156720107779314785.)
However, buccal distribution has limitations, such as lower membrane permeability than the sublingual route, a smaller absorption surface area, and the possibility of drug loss due to saliva secretion and swallowing. There are also concerns regarding choking and discomfort while eating or drinking.
Despite these disadvantages, the benefits of buccal drug administration, combined with recent advances, make it an attractive field of future research, particularly for adhesive drug delivery systems. (Guo JH. Investigating the surface properties and bioadhesion of buccal patches. J. Pharm. Pharmacol. 1994;46:647–650. doi: 10.1111/j.2042-7158.1994.tb03875.x.)

2. Oral cavity anatomical and physiological features

Light microscopy shows distinct maturation patterns in the epithelium of the human oral mucosa, varying by cavity region.

The oral mucosa consists of three unique layers: epithelium, basement membrane, and connective tissues. The epithelium lines the mouth cavity, which is supported by a basement membrane and connective tissues. depicts the cross-sectional area of the buccal mucosa, depicting several cell layers. (Harris D, Robinson JR. Drug delivery via the mucous membranes of the oral cavity. J. Pharm. Sci. 1992;81:1–10. doi: 10.1002/jps.2600810102)

The epithelium, which protects the tissues beneath, is divided into

1. Nonkeratinized area in the mucosal lining of the soft palate, the ventral surface of the tongue, the floor of the mouth, alveolar mucosa, vestibule, lips, and cheeks
2. Keratinized epithelium occurs in the hard palate and non-flexible areas of the oral cavity. Epithelial cells, which develop from basal cells, mature, change shape, and grow in size as they move to the surface.

(Harris D, Robinson JR. Drug delivery via the mucous membranes of the oral cavity. J. Pharm. Sci. 1992;81:1–10. doi: 10.1002/jps.2600810102)

The buccal epithelium is a non-keratinized tissue with a thickness of around 500800-μ in humans, dogs, and rabbits. The term 'buccal' is wrongly used to denote that the buccal epithelium lacks the tight connections found in intestinal and nasal mucosae, but does have gap junctions, desmosomes, and hemidesmosomes, which are loose intercellular links. (Shojaei AH, Chang RK, Guo X. Systemic drug delivery via the buccal mucosal route. J. Pharm. Technol. 2001;25(6):70–81)

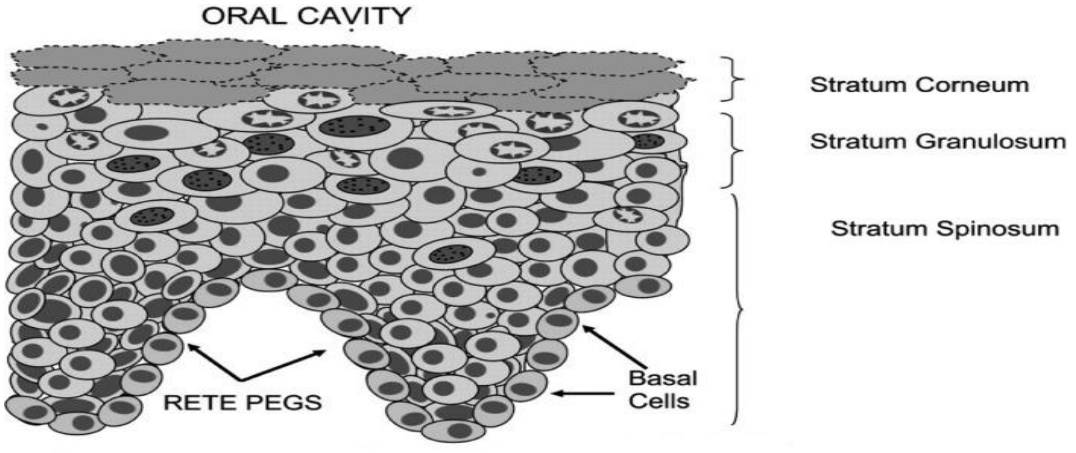

Figure 1: Cross section area of buccal mucosa

3. Permeability

The oral mucosa is a slightly leaky epithelia that sits between the epidermis and the intestinal mucosa. The buccal mucosa is considered to be 4-4000 times more permeable than the epidermis. The large range in this reported number indicates that there are significant variances in permeability between different parts of the oral cavity due to the unique structures and functions of the various oral mucosae. In general, the permeability of the oral mucosae decreases in the following order: sublingual, buccal, and palatal. (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. doi: 10.1023/a:1015802427428)

The rank order of these tissues is established by their relative thickness and degree of keratinization, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized. (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. doi: 10.1023/a:1015802427428)

The oral mucosa's permeability barrier is believed to be caused by intercellular material composed of "membrane coating granules" (MCG). MCGs arise when cells differentiate and merge with the plasma membrane at the apical surface, discharging their contents into the upper one-third of the epithelium's intercellular gaps. (Gandhi RB, Robinson JR. Oral cavity as a site for bioadhesive drug delivery. Adv. Drug Deliv.Rev. 1994;13:43–74.)

This barrier is located at the outermost 200μm of the superficial layer. Tracers with large molecular weights, such as horseradish peroxidase and lanthanum nitrate, are commonly utilized in permeation investigations. (Gandhi RB, Robinson JR. Oral cavity as a site for bioadhesive drug delivery. Adv. Drug Deliv.Rev. 1994;13:43–74.)

When the tracers when applied to the epithelial surface, they only penetrate the outermost layer or two cells. When applied to the submucosal surface, they penetrate up to, but not through, the epithelium's outermost cell layers.
(Collins LMC, Dawes C. The surface area of the adult human mouth and thickness of the salivary film covering the teeth and oral mucosa. J. Dent. Res. 1987;66:1300–1302. doi: 10.1177/00220345870660080201)

According to these findings, it appears that flattened surface cell layers are the primary barrier to permeation, whereas higher isodiametric cell layers are more permeable.In both keratinized and non-keratinized epithelia, the limit of penetration was the level at which MCGs could be observed close to the epithelial cells' surface plasma membranes.Since the same result was achieved in both keratinized and non-keratinized epithelia, keratinization is unlikely to play a substantial role in barrier function. (Lee JW, Park JH, Robinson JR. Bioadhesive-based dosage forms: the next generation. J. Pharm. Sci. 2000;89:850–866. dAlur HH, Johnston TP, Mitra AK. Peptides and Proteins: Buccal Absorption. In: Swarbrick J, Boylan J.C, editors. Encyclopedia of Pharmaceutical Technology. 3. Vol. 20. New York: Marcel Dekker Inc. ; 2001. pp. 193–218. oi: 10.1002/1520-6017(200007)89:7<850::AID-JPS2>3.0.CO;2-G)

The components of MCGs in keratinized and non-keratinized epithelia differ, however. The MCGs of keratinized epithelium consist of lamellar lipid stacks, whereas the non-keratinized epithelium possesses non-lamellar MCGs. (Philip T, Jane H, Jeffrey F, Michael F. Buccal micronucleus cytome biomarkers may be associated with Alzheimers disease. Mutagenesis. 2007;22(6):371–379. doi: 10.1093/mutage/gem029.)

In keratinized epithelia, MCG lipids comprise sphingomyelin, glucosylceramides, ceramides, and other nonpolar lipids. In non-keratinized epithelia, cholesterol esters, cholesterol, and glycosphingolipids are the primary MCG lipid components. (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. pp.

1–25)

Aside from the MCGs, the basement membrane may offer some resistance to permeation; nonetheless, the outer epithelium is still thought to be the rate-limiting phase in mucosal penetration. The basement membrane is not dense enough to exclude even moderately big molecules. (Rathbone MJ, Tucker IG. Mechanisms, barriers and pathways of oral mucosal drug permeation. Adv. Drug Del. Rev. 1993;13:1–22)

4. Permeability barrier of the oral mucosa

The oral mucosa's permeability barrier is mostly owing to intercellular components formed from what are known as'membrane coating granules' (MCGs). An intracellular lipid part is bundled in membrane-coated granules (MCGs), which migrate to the cell's apical surface where their membranes fuse with the cell membranes and the lipid content is extruded into the extracellular environment. (Squier CA, Eady RA, Hopps RM. The permeability of epidermis lacking normal membrane-coating granules: an ultrastructural tracer study of Kyrle-Flegel disease. J. Invest. Dermatol. 1978;70:361–364. doi: 10.1111/1523-1747.ep12543565)

Cultured oral epithelium without MCGs has been shown to be permeable to chemicals that ordinarily do not enter it. Tracer molecules of different sizes did not enter the membrane during permeation studies. When tracer molecules were placed sub-epithelially, they went across the intercellular space. (Robinson JR, Yang X. Absorption enhancers. In: Swarbrick J, Boylan JC, editors. Encyclopedia of Pharmaceutical Technology. Vol. 18. New York: Marcel Dekker, Inc.; 2001. pp. 1–27)

This penetration limit reflects the level of MCGs measured. Both keratinized and non-keratinized epithelia show a comparable pattern, showing that epithelial keratinization does not play a substantial role as a penetration barrier. (Jacobsen J, Bjerregaard S, Pedersen M. Cyclodextrin inclusion complexes of anti mycotics intended to act in the oral cavity-drug supersaturation, toxicity on TR 146 cells and release from a delivery system. Eur. J. Pharm. Biopharm. 1999;48(3):217–224. doi: 10.1016/s0939-6411(99)00043-0)

Enzymatic degradation is another factor that reduces drug permeability across the buccal epithelium. Saliva contains considerable amounts of esterases, carbohydrases, and phosphatases but no proteases. However, multiple proteolytic enzymes have been discovered in the buccal epithelium. (Nielsen HM, Rassing MR. TR146 cells grown on filters as a model of human buccal epithelium. Permeability enhancement by different pH value, different osmolarity value and bile salts. Int. J. Pharm. 1999;185:215–225. doi: 10.1016/s0378-5173(99)00165-9)

Endopeptidases and carboxypeptidases have been observed to be absent from the surface of swine buccal mucosa, with aminopeptidase serving as the primary enzymatic barrier to peptide medication delivery. (Squier CA, Kremer MJ, Wertz PW. Continuous flow mucosal cells for measuring in vitro permeability of small tissue samples. J. Pharm. Sci. 1997;86:82–84. doi: 10.1021/js9602047)

Buccal tissue contains plasma membrane-bound peptidases N and A, as well as cytosolic aminopeptidase B. These are some of the hurdles to medication entering the systemic circulation. (Gu JM, Robinson JR, Leung SHS. Binding of acrylic polymers to mucin/epithelial surfaces: structure- property relationships. Crit. Rev. Ther. Drug Carr. Syst. 1998;5:21–67)

5. Penetration enhancers

To build penetration enhancers with enhanced efficacy and a lower toxicity profile, it is necessary to understand the interaction between enhancer structure, effect caused in the membrane, and mechanism of action. However, the efficiency of an enhancer is determined by the drug's physicochemical qualities, the nature of the vehicle, and other drug-specific excipients that must be safe and non-toxic, pharmacologically and chemically inert, non-irritant, and non-allergenic. One of the key problems of buccal medication delivery is poor flux, which leads to reduced drug bioavailability. (Lueßen HL. Mucoadhesive polymers in peroral

peptide drug delivery. Influence of mucoadhesive excipients on the proteolytic activity of intestinal enzymes. Eur. J. Pharm. Sci. 1996;4:117–128.)

Table 1: Penetration enhancer and their mechanism of action

Category	Examples	Mechanism of action
Surfactants	Anionic: Sodium lauryl sulfate Cationic: Cetyl pyridinium chloride Nonionic: Poloxamer, Brij, Span, Myrj, Tween	Perturbation of intercellular Lipids and protein domain integrity
Bile salts	Sodium glycocholate, Sodium tauro deoxycholate, Sodium tauro cholate	Perturbation of intercellular Lipids and protein domain integrity
Fatty acids	Oleic acid, Caprylic acid, Lauric acid, Lyso phosphatidyl choline, Phosphatidyl choline	Increase fluidity of phospholipid domains
Cyclodextrins	α, β, γ, Cyclodextrin, methylated β –cyclodextrins	Inclusion of membrane Compounds
Chelators	EDTA, Citric acid, Sodium salicylate, Methoxy salicylates	Interfere with Ca^{+}
Positively charged Polymers	Chitosan, Trimethyl chitosan	Ionic interaction with negative charge on the mucosal surface
Cationic Compounds	Poly-L-arginine, L-lysine	Ionic interaction with negative charge on the mucosal surface

6. Mechanism of permeation enhancers

6.1. Changing mucus rheology

Mucus generates a viscoelastic layer of varied thickness, which influences drug absorption. Furthermore, saliva coating the mucus layers reduces absorption. Some permeation enhancers reduce mucus viscosity, allowing saliva to cross the barrier. (Jacobsen J, Bjerregaard S, Pedersen M. Cyclodextrin inclusion complexes of anti mycotics intended to act in the oral cavity-drug supersaturation, toxicity on TR 146 cells and release from a delivery system. Eur. J. Pharm. Biopharm. 1999;48(3):217–224. doi: 10.1016/s0939-6411(99)00043-0)

6.2. Increase in the fluidity of lipid bilayer membrane

The intracellular route is the most commonly accepted mode of drug absorption through the buccal mucosa. Some enhancers disrupt intracellular lipid packing through interactions with either lipid or protein components. (Nielsen HM, Rassing MR. TR146 cells grown on filters as a model of human buccal epithelium. Permeability enhancement by different pH value, different osmolarity value and bile salts. Int. J. Pharm. 1999;185:215–225. doi: 10.1016/s0378-5173(99)00165-9)

6.3. Action on the components at tight junctions

Some permeation enhancers work on desmosomes by disrupting and/or interacting with its components, which are a prominent component at tight junctions. (Ahuja RP, Khar JA. Mucoadhesive drug delivery systems. Drug Dev. Ind. Pharm. 1997;23:489–515)

6.4. Overcoming the enzymatic barrier

Buccal permeation enhancers work by blocking the numerous peptidases and proteases found in the buccal mucosa, thereby breaking down the enzymatic barrier. Changes in membrane fluidity also affect enzymatic activity indirectly. (Khanvilkar K, Donovan MD, Flanagan DR. Drug transfer through mucus. Adv.

Drug Del. Rev. 2001;48(2-3):173–193. doi: 10.1016/s0169-409x(01)00115-6.)

6.5. Increase in thermodynamic activity of drug

Some permeation enhancers affect the partition coefficient of the medication, hence increasing its solubility. This leads to higher thermodynamic activity, which improves medication absorption. (Clark MA, Hirst BH, Jepson MA. Lectin mediated mucosal delivery of drugs and microparticles. Adv. Drug Del. Rev. 2000;43(2-3):207–223. doi: 10.1016/s0169-409x(00)00070-3)

7. Enzyme inhibitors

Coadministration of medicine with enzyme inhibitors is another technique for improving buccal absorption of pharmaceuticals, particularly peptides. Enzyme inhibitors such aprotinin, bestatin, puromycin, and bile salts stabilize protein therapeutics through numerous means, including changes in enzyme activity, peptide or protein structure, and reduced susceptibility. (Savage DC. Microbial ecology of the gastrointestinal tract. Annu. Rev. Microbiol. 1977;31:107–133. doi: 10.1146/annurev.mi.31.100177.000543)

In addition, several mucoadhesive polymers, such as polyacrylic acid and chitosan derivatives, have been shown to suppress enzyme activity even when not present in the buccal mucosa. Polyacrylic acid (carbomer) is particularly capable of binding key enzyme cofactors such as calcium and zinc causing enzyme autolysis and loss of activity through conformational changes. (Sanford BA, Thomas VL, Ramsay MA. Binding of staphylococci to mucus in vivo and in vitro. Infect. Immun. 1989;57:3735–3742. doi: 10.1128/iai.57.12.3735-3742.1989)

Furthermore, the chemical modification of chitosan (a cationic polymer) with EDTA yields polymer conjugate chitosan-EDTA, a highly effective inhibitor of metallopeptidases such as carboxypeptidase. Recent research has shown that polymer derivatization with thiol groups on poly (acrylates) or chitosans improves polymer enzyme inhibitory capabilities. (Bernkop-Schnürch A, Gabor F, Szostak M, Lubitz W. An adhesive drug delivery system based on K99-fimbriae. Eur. J. Pharm Sci. 1995;3:293–299.)

8. Solubility modifier

Although buccal distribution increases the bioavailability of hepatically metabolized drugs, the drug's poor solubility in saliva may hinder release from the device and uptake by the buccal mucosa. Cyclodextrins increase pharmaceutical absorption and bioavailability by solubilizing and delivering it through the buccal mucosa, particularly for weakly water soluble medications. (Roldo M, Hornof M, Caliceti P, Bernkop-Schnürch A. Mucoadhesive thiolated chitosans as platforms for oral controlled drug delivery: synthesis and in vitro evaluation. Eur. J. Pharm. Biopharm. 2004;57:115–121. doi: 10.1016/s0939-6411(03)00157-7.)

Buccal tablets comprising hydroxypropyl-β-cyclodextrin-felodipine complex and hydroxylpropyl methyl cellulose release felodipine in a sustained and complete manner, with increased buccal permeability. Hydroxypropyl-β-cyclodextrin's ability to form a complex with felodipine enhances drug solubility, dissolution rate, and permeability. (Jinsong H, Paul WSH. Buccal Delivery Systems. Drug dev. Ind. Pharm. 2003;29:821–832. doi: 10.1081/ddc-120024178)

Polymeric formulations with inclusion complexes are effective for transmucosal drug administration, providing prolonged release and improved permeability. Imidazole antimycotics (including miconazole and clotrimazole)are commonly used to treat fungal infections in the oral cavity. (Giunchedi P, Juliano C, Gavini E, Cossu M, Sorrenti M. Formulation and in vivo evaluation of chlorhexidine buccal tablets prepared using drug-loaded chitosan microspheres. Eur. J. Pharm. Biopharm. 2002;53:233–239. doi: 10.1016/s0939-6411(01)00237-5)

Due to their low water solubility and high lipophilicity, they were slowly released from lipophilic chewing gum bases. Adding hydroxypropyl-β-cyclodextrin to chewing gum enhances drug release. (Vamshi Vishnu Y, Ramesh G, Chandra Sekhar K, Bhanoji Rao ME, Madhusudan Rao Y. Development and in vitro evaluation of buccoadhesive carvedilol tablets. Acta Pharm. 2007;57:185–197. doi: 10.2478/v10007-007-0015-7)

9. Drug absorption pathway

Drug transport through the buccal mucosa occurs via two primary pathways: transcellular (intracellular) and paracellular (intercellular).Studies with microscopically visible tracers such as small proteins and dextrans indicate that the primary pathway for large molecules across stratified epithelium is through intercellular spaces, where there is a barrier to penetration due to superficial layer intercellular substance modifications. (Huang Y, Leobandung W, Foss A, Peppas NA. Molecular aspects of muco-and bioadhesion: tethered structures and site-specic surfaces. J. Control. Rel. 2000;65(1-2):63–71. doi: 10.1016/s0168-3659(99)00233-3)

It is widely acknowledged that the lipid matrix of the extracellular space plays a significant role in the barrier function of the paracellular route, particularly when substances like peptides are hydrophilic and have a large molecular weight. (Ceschel GC, Maffei P, Borgia SL, Ronchi C. Design and evaluation of buccal adhesive Hydralazine HCL tablets. Int. J. Pharm. 2002;238:161–170)

The lipid solubility and molecular weight of the diffusant alter the buccal mucosa's absorption capacity. Some medications are absorbed more effectively through the buccal mucosa when the pH of the carrier is lower, and less effectively when the pH is raised. (Nakane S, Kakumoto M, Yukimatsu K, Chien YW. Oramucosal delivery of LHRH: pharmacokinetic studies of controlled and enhanced transmucosal permeation. Pharm. Dev. Technol. 1996;1:251–259. doi: 10.3109/10837459609022593)

In general, peptide medicines are expected to permeate the buccal epithelium via paracellular passive diffusion. Recently, it was revealed that medications with a monocarboxylic acid residue might be transported into systemic circulation from the oral mucosa via their carriers. (Perioli L, Ambrogi V, Rubini D, Giovagnoli S, Ricci M, Blasi Pand RC. Novel mucoadhesive buccal formulation containing metronidazole for the treatment of periodontal disease. J. Control. Rel. 2004;95:521–533. doi: 10.1016/j.jconrel.2003.12.018)

Several in vitro and in vivo models have been used to examine oral mucosal permeability and the efficiency of penetration enhancers. The permeability of oral mucosa has been determined using a variety of diffusion cells, including continuous flow perfusion chambers, Ussing chambers, Franz diffusion cells, and Grass-Sweetana. (Han RY, Fang JY, Sung KC, Hu OYP. Mucoadhesive buccal disks for novel nalbuphine prodrug controlled delivery: effect of formulation variables on drug release and mucoadhesive performance. Int. J. Pharm. 1999;177:201–209. doi: 10.1016/s0378-5173(98)00343-3)

Cultured epithelial cell lines were also in vitro model was designed to explore drug transport and metabolism at biological barriers, as well as to understand the potential mechanisms of action of penetration enhancers. Recently, the TR146 cell culture model has been proposed as a useful in vitro model of human buccal mucosa for permeability and metabolism investigations using enzymatically labile pharmaceuticals, such as leu-enkefalin, intended for buccal administration. (Yong CS, Jung JH, Rhee JD, Kim CK, Choi HG. Physicochemical characterization and evaluation of buccal adhesive tablets containing omeprazole. Drug Dev.Ind.Pharm. 2001;27:447–455. doi: 10.1081/ddc-100104320)

10. Formulation design for buccal delivery

Conventional dosage forms for mucosal and transmucosal administration cannot ensure therapeutic drug levels in the mucosa and circulation due to physiological removal of the oral cavity (washing effect of saliva

and mechanical stress), which takes the formulation away from the mucosa, resulting in a very short exposure time and unpredictable distribution of the drug at the site of action/absorption.

To achieve therapeutic activity, it is required to extend and improve the contact between the active material and the mucosa. (Celebi N, Kislal O. Development and evaluation of a buccoadhesive propranolol tablet formulation. Pharmazie. 1995;50:470–472)

To meet the therapeutic requirements, formulations for buccal administration should contain: mucoadhesive agents, to maintain intimate and prolonged contact of the formulation with the absorption site; penetration enhancers, to improve drug permeation across mucosa (transmucosal delivery) or into deepestlayers of the epithelium (mucosal delivery), enzyme inhibitors that protect the medicine from destruction by mucosal enzymes, and solubility modifiers that increase the solubility of poorly soluble pharmaceuticals. (Jain NK. Controlled and Novel Drug Delivery, 1 st edition, published by CBS Publishers and Distributors, New Delhi. 1997; 52-81)

11. Buccoadhesive polymers used in the oral cavity

The primary benefits of bioadhesive systems include increased residence duration of the drug-containing device in the oral cavity and drug localization in a specific region. Electronic, adsorption, wetting, diffusion, and fracture theories have all contributed to understanding the bioadhesion process. In general, bioadhesive polymers must have strong hydrogen bonding groups, strong anionic or cationic charges, a high molecular weight, chain flexibility, and surface energy features that promote spreading over the mucus layer. (Patel KV, Patel ND, Dodiya HD, Shelat PK. Buccal bioadhesive drug delivery system: an overview. Ind. J. of Pharma. & Bio. Arch. 2011; 2(2): 600-609.

In general, sticky polymer sources should be natural or synthetic, water-soluble or insoluble, charged or uncharged polymers. Examples of modern bioadhesive buccal polymers are described below. Polymers classed as nonspecific bioadhesives are considered first-generation bioadhesive. Duration of bioadhesion is mostly governed by the rapid turnover of the mucus layer. Saliva secretion, food intake, local pH, and the makeup of delivery systems all have a significant impact on bioadhesion. (Shojaei AH. A systemic drug delivery via the buccal mucosal route. Pharm. Tech. 2001: 70-81.)

Table 2: Mucoadhesive polymers in buccal delivery system.

Criteria	Category	Examples
Source	Semi-natural/natural	Agarose, chitosan, gelatin
		Hyaluronic acid
		Various gums (guar, hakea, xanthan, gellan, carragenan, pectin, and sodium alginate)
	Synthetic	Cellulose derivatives
		[CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC]
		Poly(acrylic acid)-based polymers
		[CP, PC, PAA, copolymer of acrylic acid and PEG]
		Others
		PVA, PVP, thiolated polymers
Aqueous solubility	Water-soluble	CP, HEC, HPC (water<0 38C), 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

12. Investigation on the buccal drug delivery system

Many researchers have created buccal medication delivery systems on a laboratory scale for local or systemic activities. They're broadly divided into

(i) Solid buccal adhesive dosage forms

(ii) Semi-solid buccal adhesive dosage forms

(iii) Liquid buccal adhesive dosage forms. Buccal mucoadhesive dosage forms can also be categorized into three types on the basis of geometry. (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.)

Type I is a single-layered device with multidirectional medication release. This sort of dosage form has high medication loss due to swallowing. (Patel RS, and Poddar SS. Development and characterization of mucoadhesive buccal patches of salbutamol sulphate, Curr. Drug Deliv., 2009, 6, 140-144.)

In type II devices, an impermeable backing layer is applied on top of the drug-loaded bioadhesive layer, resulting in a double-layered device that prevents drug leakage from the top surface of the dosage form into the oral cavity. (L. Mucoadhesive chitosan/gelatin films for buccal delivery of Propranolol hydrochloride, Carbohydrate Polymers xxx (2011) xxx– xxx)

Type III is a unidirectional release device that causes minimum medication loss since the medicine is released from the side next to the buccal mucosa. This can be accomplished by covering all surfaces of the dosage form except the one in contact with the buccal mucosa. (Furtado S, Bharath S, Basavaraj BV, Abraham S, Deveswaran R and Madhavan V. Development of chitosan based bioadhesive bilayered patches of Metoprolol tartarate, Inter. J.Pharm. Sci. Rev. and Res., 2010, 4(3), 198-202.)

The device should be designed so that the swelling rate of the bioadhesive polymer is optimum to ensure long-term bioadhesion and regulated or sustained medication release. (Nafee NA, Ahmed N, Ismail BFA, Mortada LM. Design and characterization of mucoadhesive buccal patches containing Cetylpyridinium chloride, Acta. Pharm., 2003, 53, 199–212)

13. Types of buccal dosage

13.1. Solid buccal adhesive dosage form

These are dry formulations that achieve bioadhesion by dehydrating the local mucosal surface.

[i]. BUCCAL TABLET

Tablets have been the most extensively studied dosage type for buccal medication administration. In recent years, several bioadhesive buccal tablet formulations have been created using the direct compression approach for both local and systemic drug delivery. They are intended to deliver the medicine either unidirectionally through the buccal mucosa or multidirectionally into the saliva. (Das R., Effective mucoadhesive buccal patches: wound healing activity of curcumin & centella asiatica extract compared to rhegf, Inter. J. Pharm. and Pharm. Sci., 2001, 3(1), 97-100.)

Alternatively, the dosage form may have an impermeable backing layer to ensure that the medicine is given unidirectionally. The disadvantages of buccal tablets may include patient tolerability (mouth feel, taste, and discomfort) and the nonubiquitous diffusion of the medicine within saliva for local treatment. (Patel VM, Prajapati BG and Patel MM. Design and characterization of chitosan-containing mucoadhesive buccal patches of Propranolol hydrochloride, Acta. Pharm., 2007, 57, 61–72.)

It is crucial to highlight the probable problems that youngsters and the elderly may face by using sticky tablets, such as possible discomfort caused by the material applied to the mucosa, with the possibility of dose separation from the mucosa, ingestion, and subsequently adhering to the esophageal wall. (Manasa B, Gudas GK, Sravanthi N, Madhuri RA, Lavanya Y and Pranitha C. Formulation and evaluation of mucoadhesive buccal patches of Resperidone. J Chem. and Pharm. Res., 2010, 2(4), 866-872.)

A typical bioadhesive formulation of this type includes a bioadhesive polymer (such as polyacrylic acids or cellulose derivatives), either alone or in combination, incorporated into a matrix containing the active agent and excipients, and possibly a second impermeable layer to allow unidirectional drug delivery. (Patel RS, and Poddar SS. Development and characterization of mucoadhesive buccal patches of salbutamol sulphate, Curr. Drug Deliv., 2009, 6,140-144)

[ii]. BIOADHESIVE MICRO/NANOPARTICLES

Bioadhesive micro/nanoparticles provide the same benefits as tablets, but due to their physical qualities, they can make intimate contact with a larger mucosal surface. These are commonly given as an aqueous suspension, mixed into a paste or ointment, or applied as aerosols. Particulates have the benefit of being quite tiny and hence more likely to be tolerated by patients. (Deshmane SV, Channawar MA, Chandewar AV, Joshi UM andN Biyani K. Chitosan based sustained release mucoadhesive buccal patches containing Verapamil HCL, Inter. J. Pharm. and Pharm. Sci.,2009, 1(1), 216-229.)

Bioadhesive polymeric microparticles of carbopol, polycarbophil, chitosan, or Gantrez will stick to porcine esophageal mucosa, with polyacrylic acid particles displaying better mucoadhesive strength during tensile testing experiments. However, in elution investigations, particles of chitosan or Gantrez were seen to remain on mucosal tissue for longer durations of time. (Kumar DS, Reddy KS, Tiwari AM and Dey S. Design and evaluation of buccal patches of lornoxicam, Inter. J. Pharm. and Bio.Sci., 2010,1(4), 587-596.)

It's been reported. The application of nanoparticles for local delivery to the oral mucosa has been documented. In a proof-of-concept study, two types of nanoparticles were investigated: solid lipid nanoparticles incorporating either idarubicin or BODIPY®FL C12 as model fluorescent probes, and polystyrene nanoparticles (Fluo-Spheres®). (Shidhaye SS, Saindane NS, Sutar S and Kadam V. Mucoadhesive bilayered patches for administration of Sumatriptan succinate,Pharm. Sci. Tech., 2008, 9(3), 909- 916.)

The results showed that OSCC cells assimilated solid lipid nanoparticles. The observed penetration of nanoparticles through the epithelium and basement membranes into the underlying connective tissue raised the prospect of oral transmucosal nanoparticle delivery for systemic treatment. Monti and colleagues created an atenolol-containing microsphere using Poloxamer 407 and tested the formulation in vivo in rabbits against a commercial tablet formulation as a reference. (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)

After administering the microsphere formulations,The atenolol concentration remained greater than the reference tablet throughout the elimination phase, indicating a prolonged release profile from the microspheres. Furthermore, despite a reduced drug dose, the absolute bioavailability of microsphere formulations was higher than that of reference tablets, implying that atenolol microparticles may reduce the dose via oral transmucosal delivery. (Wise Donald L, Handbook of Pharmaceutical controlled release technology: 255-265)

Liposomes are one of the possibilities for medications that are poorly soluble and hence cannot be administered adequately through a solid dosage form. For example, silamyrin liposomal buccal administration demonstrated steady-state penetration via a chicken buccal pouch for 6 hours, which was greater than free drugpowder.

Microparticles are smaller than tablets, therefore they are less likely to produce local discomfort at the location of Adhesion and the unpleasant sense of a foreign object inside the mouth cavity are decreased. (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.)

[iii]. BIOADHESIVE WAFERS

The delivery system is made up of a composite wafer having adhesive surface layers and an antibacterial, biodegradable, and matrix polymer bulk layer. A conceptually unique periodontal drug delivery system designed to treat microbial infections associated with periodontitis has been described. (Jain N.K., Controlled and novel drug delivery; 65-75; 371-377.)

[iv]. BIOADHESIVE LOZENGES

A sluggish release. Bioadhesive lozenges have the potential to prolong drug release while improving patient compliance. Bioadhesive lozenges can be used to administer medications that act in the mouth, such as antimicrobials, corticosteroids, local anesthetics, antibiotics, and antifungals. A bioadhesive lozenge has been reported as a method of delivering antifungal medicines into the mouth cavity. (Edgar W.M., Saliva: its secretion, composition and functions, Br. Dent. J, 1992; 172:305-312)

The brief residence period at the site of absorption of these bioadhesive lozenges, which is determined by the size and type of formulation, plus the fact that they disintegrate within 30 minutes limits the total amount of medicine that may be administered. The dissolution or disintegration of lozenges is often controlled by the patient, i.e. how hard they suck the unit. (Indian Journal of Pharmaceutical Science, July-Aug. 2004; 66 (4):371-536:556-562.)

Increased sucking and saliva production leads to uncontrolled swallowing.Drug loss occurs throughout the digestive tract. As a result, absorption and bioavailability in solid dose forms vary significantly between and within individuals. Also, these systems are incapable of providing unidirectional drug release. The continuous release of saliva is another significant impediment to the performance of such dosage forms.

(Savage D.C., Microbial ecology of the gastrointestinal tract, Annu.Rev. Microbiol.,1977; 31:107– 133.)

13.2. Semisolid dosage form

(i) . MEDICATED CHEWING GUMS

Though medicated chewing gums make it difficult to accurately control the dose supplied, they do have some advantages as drug delivery methods, particularly in the treatment of oral cavity illnesses and nicotine replacement therapy. Some commercial items are available on the market. Stay Alert®, a caffeine chewing gum, was recently designed to alleviate tiredness. It is absorbed more faster and has equivalent bioavailability to the capsule formulation. Nicotine chewing gums (such as Nicorette® and Nicotinell®) have been advertised as smoking cessation aids. (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.)

(ii) . ADHESIVE GEL

Adhesive gels can transfer medications to the buccal mucosa for sustained release. Gel-forming bioadhesive polymers contain cross-linked polyacrylic acid, which has been utilized to stick to mucosal surfaces for extended periods of time and allow regulated drug release at the site of absorption. The development of a unique, hydrogel-based, bioadhesive, intelligent response system for controlled drug release has been disclosed. (Kumar M et al, Design and in vitro evaluation of mucoadhesive buccal films containing Famotidine, International journal of pharmacy and pharmaceutical sciences, 2010, 2, 3. 9.)

This method incorporated multiple desirable characteristics into a single formulation: a poly (hydroxyethyl methacrylate) layer as a barrier, poly (methacrylic acid-g-ethylene glycol) as a biosensor, and poly (ethylene oxide) to promote mucoadhesion. Gel formulations' disadvantages include their inability to deliver a calibrated dose of medicine to the location, which limits their applications drugs with a restricted therapeutic window. (Semalty M et al, Development of mucoadhesive buccal films of Glipizide, International journal of pharmaceutical sciences and nanotechnology, 2008, 1(2).)

[iii].BUCCAL PATCHES / FILM

Patches are laminates made up of a bioadhesive surface for mucosal adhesion, an impermeable backing layer, and a drug-containing reservoir layer from which the drug is delivered in a regulated fashion. To administer medications straight to a mucosal membrane, flexible films or patches have been made using the solvent casting or hot melt extrusion techniques. They have an advantage over lotions and ointments in that they can administer a precise dosage of medication to the area. (Zhang.J et al, 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)

13.3. Liquid dosage form

These are medication suspensions or solutions in appropriate aqueous media. Several mouthwashes and mouth fresheners that are commercially available for this purpose are antibacterial, and these kinds of dosage forms are typically used to exert local action into the oral cavity. (Goudanavar PS et al, Formulation and In-vitro evaluation of mucoadhesive buccal films of Glibenclamide, Der pharmacia lettre,2010, 2 (1),382-387.)

These liquid dose forms have two drawbacks: they can distribute comparatively uncontrolled dosages of medication across the oral cavity and are not easily kept or targeted to the buccal mucosa. Chitosan exhibits the strongest binding among the diverse array of polymer solutions, with methylcellulose, gelatin, carbopol, and polycarbophil following closely after. (Choudhary A et al, Formulation and characterization of carvedilol buccal mucoadhesive patches, www.ijrps.pharmascope.org, 2010,1(4), 396-401.)

The buccal surface can be coated with viscous liquids as a protective layer or as a means of delivering medications to the mucosal surface. Artificial saliva solutions that are kept on mucosal surfaces are used to treat dry mouth apply lubricant. Sodium CMC is a bioadhesive polymer found in these solutions. (Kamel AH et al, Micromatricial metronidazole benzoate film as a local mucoadhesive delivery system for treatment of periodontal diseases, AAPS pharm sci tech, 2007, 8 (3), 75.)

14. Challenges in buccal drug deliver development

Systemic medication distribution in the oral cavity is complicated by variables such as pH, fluid volume, enzyme activity, and mucosal permeability. In order for the drug to enter the bloodstream, it must first pass through the mucosal layers and then be released to the intended location (such as the buccal or sublingual region) by drug delivery systems. (Gandhi RE and Robinson JR, Bioadhesion in Drug Delivery, Indian J. Pharm. Sci, 1988, 50 (May/- June),145–152.)

Saliva, which is secreted by the main and minor salivary glands, is essential to the oral environment because it helps with digestion, lubricates the mouth, and controls pH. Saliva's tiny volume (approximately 1.1 ml in the mouth) can impede drug absorption because of "saliva washout" from continuous flow, even if it offers a suitable water-rich environment for drug release. (Sanzgiri YD et al, Evaluation of Mucoadhesive Properties of Hyaluronic Acid Benzyl Esters, Int.J.Pharm, 1994, 107, 91–97.)

Regional differences exist in the oral mucosa's permeability, with keratinized epithelia (such the hard palate and gingiva) having less more permeable than non-keratinized epithelia (such the sublingual and buccal regions). The intercellular substances known as membrane-coating granules (MCGs), which restrict permeability, are primarily responsible for the mucosa's barrier function. (Park K and Robinson JR, Bioadhesive Polymers as Platforms for Oral Controlled Drug Delivery, Method to Study Bioadhesion, Int. J.Pharm., 1984,19, 107–127 .)

But because they are more porous, the buccal and sublingual mucosa are perfect for medication transport. The oral mucosa is far more porous than the skin, and drugs diffuse passively through it via either paracellular or transcellular channels. (Zhang. J et al, 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.)

15. Advantages

1. Medication is not exposed to the stomach's harmful acidic environment.

2.Quick start of action

3.Without initially going through the liver, the medication enters the general circulation.

4.Compared to other non-oral routes, the buccal medication delivery has a high patient acceptance rate.

5.Reduce the number of times a medicine is administered

6.An increase in patient adherence

7.Extended duration of drug release

8.Close contact with the absorbing membrane results in a maximum absorption rate.

9.It is simple to deliver and remove medication under unfavorable circumstances.

10.It is best to use the oral cavity because it is easy to assess.

(Bottenberg P, Cleymaet R, Muynek CD, Remon JP, Coomans D, Slop D. Development and testing of bioadhesive, fluoride containing slow-release tablets for oral use. J. Pharm. Pharmacol. 1991;43:457–464. doi: 10.1111/j.2042-7158.1991.tb03514.x)

16. Disadvantages

1. It is not possible to deliver medications that are unstable at the buccal pH.

2. This method cannot be used to administer medications that irritate the mucosa, have an unpleasant taste, or have an offensive odor.

3. Only a modest dose of the necessary drug can be given.

4. Restrictions may be placed on eating and drinking.

5. Unsuitable for youngsters.

6. In cases of illness, it cannot be administered.

7. Constant buccal membrane secretion, particularly in contrast to the sublingual route.

8. In particular, the buccal membrane has low permeability in contrast to the sublingual route.

(Khurana R, Ahuja A, Khar RK. Development and evaluation of mucoadhesive films of miconazole nitrate. Indian J. Pharm. Sci. 2000;60:449–453.)

DESIGN OF BUCCAL DOSAGE FORM

Matrix type

The medication, adhesive, and additives are all combined in the matrix-designed buccal patch. Drugs are released by bi-directional patches into the mouth and mucosa. MUCOADESIVE MATRIX + DRUG

(Shivanand K, Raju SA, Nizamuddin S, Jayakar B. In vivo bioavailability studies of sumatriptan succinate buccal tablets. DARU J. Pharm. Sci. 2011;19(3):224–230.)

Reservoir type

A cavity in the reservoir-system buccal patch holds the medication and additives apart from the adhesive.

In order to prevent drug loss and minimize patch deformation and disintegration while in the mouth, impermeable backing is used to regulate the direction of drug delivery.

(Mortazavi SA, Aboofazeli R. Preparation and in vitro assessment of various mucosa-adhesive films for buccal delivery. DARU J. Pharm. Sci. 2000;8(1-2):9–18)

17. Evaluation of buccal tablets

1. Establishing the duration of residence

2. Studies on penetration

3. Studies on swelling

4. Studies on release rates

5. Study of toxicity and irritation

6. Measurements of bioadhesion.

7. Uniformity of folding endurance content

8. Surface pH: 1% agar solution for two hours, followed by one minute of equilibrium

(Tucker IG. A method to study the kinetics of oral mucosa of drug absorption from solutions. J. Pharm. Pharmcol. 1988;40:679–683. doi: 10.1111/j.2042-7158.1988.tb06994.x)

18. Buccal formulations marketed

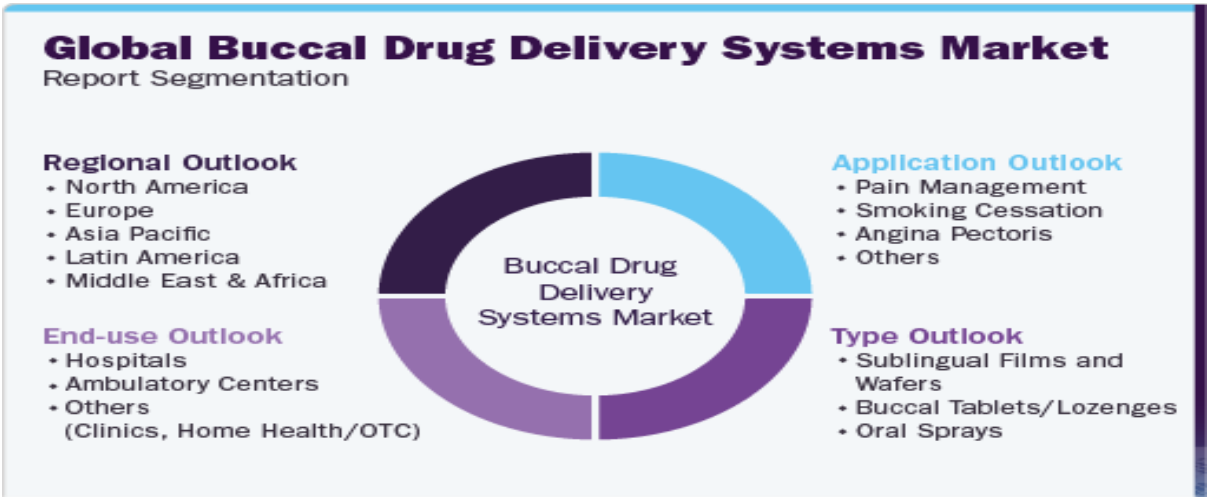

Figure 2: Global buccal drug delivery systemsin market

Manufacturer	Product	Present status
Generex Biotechnology Corporation	Insulin Buccal Spray	
	ORALGEN (US)	Commercially available
	ORALIN (Canada)	Clinical Trials Completed
	Heparin Buccal Delivery System	Clinical Trials Completed
	Fentanyl Buccal Delivery Systems	
Columbia Laboratories Inc.	Testosterone Buccal Tablet (Straint)	Commercially available
	Desmopressin Buccal Tablet	Commercially available
Ergo Pharm	Androdiol Buccal Tablets (Cyclo-Diol SR)	Commercially available
	Norandrodiol Buccal Tablets (Cyclo-Nordiol SR)	Commercially available
Cytokine Pharma Sciences Inc.	Pilocarpine Buccal Tablet (PIOLOBUC)	Commercially available
Britannia Pharmaceuticals Ltd	Prochlorperazine Buccal Tablet (Buccastem)	Commercially available
Pharmax Limited	Glyceryl Trinitrate (Suscard Buccal Tablet)	Commercially available

Cephalon, Inc.	Oral Transmucosal Fentanyl Citrate Solid Dosage Form (ACTIQ)	Commercially available
Wyeth Pharma	Lorazepam Buccal Tablets (Temesta Expidet)	Commercially available
Ceuticals	Oxazepam Buccal Tablets (Seresta Expidet)	Commercially available
IVAX Corporation	Estrogen Buccal Tablet	Under Phase III clinical trials
Regency Medical research	Vitamins Trans Buccal Spray	Commercially available
Leo Pharmaceuticals	Nicotine Mucoadhesive Tablet (Nicorette)	Commercially available
	Nicotine Chewing Gum (Nicotinell)	Commercially available
Teijin Ltd.	Triamcinolone acetonide(Aftach)	Commercially available
Rhone-Poulenc Rorer	Prochlorperazine Bioadhesive Buccal Tablet (Tementil)	Commercially available
Reckitt Benckiser	Prochlorperazine Bioadhesive Buccal controlled release Tablet (Buccastem)	Commercially available
Reckitt Benckiser	Buprenorphine HCl Tablets (Subutex)	Commercially available
Reckitt Benckiser	Buprenorphine HCl & Naloxone HCl (Suboxane)	Commercially available
Ciba-Geigy	Methyltestosterone Buccal Tablets (Metandren)	Commercially available

Table 3: Commercial formulations or formulations in clinical studies designed for buccal delivery.

19. Recent advances in buccal drug delivery system

Vaccination has improved life expectancy, particularly in children, and significantly lessened the effect of infectious diseases. The route of administration is one of the most important elements influencing the efficiency of vaccinations, especially mucosal vaccines. (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. doi: 10.1111/j.2042-7158.1978.tb13185.x)

The majority of vaccines are administered by intrusive techniques, such as injections, which may not adequately protect the mucosa but cause systemic immune responses. Effective mucosal vaccines, on the other hand, have the ability to elicit systemic and local immune responses. (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.)

In order to address mucosal barriers and improve immune protection, nanocarrier systems including liposomes and polymeric nanoparticles are being investigated for mucosal vaccination administration. In the future, treating infectious diseases could be greatly enhanced by combining mucosal delivery with nanocarriers. (Obaidat R.M., Bader A., Al-Rajab W., Sheikha G.A., Aiman A. Obaidat. Preparation of Mucoadhesive Oral Patches Containing Tetracycline Hydrochloride and Carvacrol for Treatment of Local Mouth Bacterial Infections and Candidiasis. Sci Pharm. 2011; 79(1):197–212.)

The formulation, composition, and general therapeutic uses of buccal drug delivery systems (BDDS) have significantly improved in recent years.Bypassing the first-pass metabolism, increasing bioavailability, and offering a quick onset of action are just a few benefits of these systems. Some of the most significant developments in BDDS are listed below:

(Alagusundaram M., Chetty C.M., Dhachinamoorthi D.Development and evaluation of novel-trans-buccoadhesive films of famotidine. J. Adv. Pharm. Tech. Res. 2011; 2(1): 17-23)

1. Nanotechnology in Buccal Drug Delivery

- Nanoparticles and Nanocarriers: Drug stability, permeability, and controlled release are improved by the use of nanoparticles, such as liposomes, niosomes, and solid lipid nanoparticles. By enhancing drug absorption through the buccal mucosa, these nanocarriers can guarantee increased bioavailability and more targeted therapeutic effects.
- Nanostructured Buccal Films:To improve the drug's residence time and guarantee sustained release, polymeric nanoparticles are used in the design of these films. They can reduce the need for frequent dosing by providing a more reliable and regulated drug administration.

(Jain S.K., Jain A., Gupta Y., Kharya A. Design and developement of muccoadhesive buccal films bearing progesterone. Pharmazie. Feb 2008; 63(2):129-1)

2. Mucoadhesive and Bioadhesive Polymers

- Bioadhesive Polymers: .The creation of polymers that lengthen the drug's retention period at the buccal mucosa and improve absorption is the result of advancements in mucoadhesive technology. Even when saliva is present, modern polymers like polycarbophil, chitosan, and carbopol are now more successful in enhancing adherence.
- Crosslinked Polymers: The mechanical characteristics and drug release profiles of bioadhesive polymers are enhanced by crosslinking. The medication release from these crosslinked formulations is regulated and prolonged.

(Yang TZ. Phospholipid deformable vesicles for buccal delivery of insulin. Chem. Pharm. Bull. 2002;50:749–753. doi: 10.1248/cpb.50.749.)

3. Mucoadhesive Tablets and Films

- Fast-Dissolving Films and Tablets: Recent advancements in oral disintegrating or fast-dissolving films have improved the usability of buccal medication delivery. When these systems come into contact with saliva, they dissolve quickly, allowing for fast medication absorption and preventing gastrointestinal breakdown.
- Multi-layered Tablets: These tablets address the requirement for multi-drug therapy, such as those involving cardiovascular or central nervous system medications, by enabling the release of various pharmaceuticals in a regulated order.

(Modi G. Evolving role of oral insulin in the treatment of diabetes using a novel rapidmist system. Diabetes MetabRes. Rev. 2002;18:38–42. doi: 10.1002/dmrr.208.)

4. Lipophilic and Hydrophilic Drug Formulations

- Enhanced Lipophilic Drug Delivery: Nowadays, lipid-based carriers like micelles or emulsions

provide a superior way to introduce lipophilic drugs—which usually have limited solubility—into buccal systems. This makes them more soluble and makes absorption easier.

- Hydrophilic Drugs and Buccal Gels:A wider range of pharmacological uses in buccal delivery are made possible by new formulations that use hydrophilic drug carriers, such as gels and hydrogels, to boost the solubility and release rate of hydrophilic medicines.

(Luker K. Single-screw extrusion and screw design. In: Ghebre- Sellassie I, Martin C, editors. Pharmaceutical extrusion technology. Drugs and the pharmaceutical sciences. Vol. 133. Newyork: Marcel Dekker; 2003. pp. 39–68)

5. Stratified Delivery and Controlled Release

- Patches and Reservoir Systems:Patches are designed to distribute medication over time in a controlled manner. With a few modifications, these systems can maintain a therapeutic drug level.
- Reservoir Systems: Drug reservoir systems use a gel or matrix to contain the active ingredient and allow for controlled release at predetermined rates. They ensure that medication is supplied consistently, without highs and lows.

(Repka MA, Sridhar T, Sampada BU, Sunil Kumar B, McGinity JW, Martin C. Pharmaceutical applications of Hot-Melt Extrusion: Part I. Drug Dev. Ind. Pharm. 2007;33:909–926. doi: 10.1080/03639040701498759.)

6. Biodegradable and Eco-Friendly Materials

BDDS uses natural polymers such as alginate, chitosan, and guar gum, which are not only biocompatible but also environmentally friendly. These materials are currently often utilized in films, patches, and tablets.

(Mohamed MI, Mortada ND. Development and characterization of a buccoadhesive dosage form of terbutaline sulphate. J.Pharm. Sci. 2000;16:69–81.)

7. Targeted and Smart Drug Delivery

- Smart Systems: These systems respond to environmental cues like pH, temperature, or enzyme activity to release medications in a controlled way. This is especially useful for the delivery of medications that require precise release profiles for maximum therapeutic impact.
- Targeted Buccal Delivery:• Current research focuses on targeting medications to specific oral tissues or locations. This can be accomplished by improving medication formulations' targeting qualities, such as utilizing ligands that bind to specific receptors on the mucosal surface.

(Li C, Bhatt PP, Johnston TP. Transmucosal delivery of oxytocin to rabbits using a mucoadhesive buccal patch. Pharm.Dev.Tech. 1997;2:265–274. doi: 10.3109/10837459709031446)

8. Recent Applications

- CNS Drugs:The buccal route is gaining popularity for delivering central nervous system (CNS) medications as it bypasses the blood-brain barrier and provides speedier start of action. Buccal versions of opioids, anti-epileptics, and Parkinson's medications, for example, are being studied.
- Hormonal Therapy: Hormonal medicines, such as testosterone and estradiol, have been successfully designed for buccal distribution to address disorders including hypogonadism and menopause, as the quick absorption through the buccal mucosa avoids first-pass metabolism in the liver.

(Anders R, Merkle HP. Evaluation of laminated muco-adhesive patches for buccal drug delivery. Int. J. Pharm. 1989;49:231–240)

9. Patient-Centric Approaches

- Patient Compliance: Discrete, user-friendly buccal dose forms such thin films, lozenges, and dissolving tablets have greatly increased patient compliance. These formulations are especially beneficial for children, the elderly, and people who have difficulty swallowing.
- Personalized Drug Delivery: Personalized buccal medication delivery devices are crucial for managing chronic diseases.

(Save T, Shah UM, Ghamande AR, Venkatachalam P. Comparative study of buccoadhesive formulations and sublingual capsules of nifedipine. J. Pharm. Pharmacol. 1994;46(3):192–195. doi: 10.1111/j.2042-7158.1994.tb03776.x.)

10. Regulatory and Commercial Developments

Regulatory Advancements:The FDA and other regulatory agencies have issued recommendations on buccal medication products to ensure their safety, efficacy, and stability. With the growing interest in non-invasive drug administration, buccal systems are projected to gain approval and commercial traction.

(Nafee NA, Ismail FA, Nabila V, Boraie LM. Mucoadhesive buccal patches of miconazole nitrate: in vitro/ in vivo performance and effect of ageing. Int. J. Pharm. 2003;264:1–14. doi: 10.1016/s0378-5173(03)00371-5.)

20. CONCLUSION

Buccal adhesive systems provide numerous benefits in terms of accessibility, administration and withdrawal, retentivity, low enzymatic activity, cost-effectiveness, and high patient compliance. Adherence of these drug delivery devices to mucosal membranes results in an enhanced drug concentration gradient at the absorption site, which improves the bioavailability of systemically given medicines.

Furthermore, buccal adhesive dose forms have been utilized to address local problems at the mucosal surface (e.g., mouth ulcers), reducing overall dosage and minimizing side effects associated with systemic drug administration. Beyond standard polymer networks, researchers are looking for new ways to carry drugs.

In the current global context, scientists are investigating ways to construct buccal adhesive systems using various approaches to improve the bioavailability of drugs are administered orally by manipulating formulation tactics such as the presence of pH modifiers, enzyme inhibitors, permeability enhancers, etc. The future of buccal adhesive drug delivery is in vaccine formulations and the delivery of tiny proteins/peptides.

Another key consideration is the in vitro and ex vivo methodologies used to evaluate the efficacy of materials and dosage forms. Efforts should be undertaken to create standard in vitro and ex vivo biological models that allow for the characterization and comparison of various materials and formulations in terms of their capacity to increase medication absorption via the buccal route.

Declaration of Conflicting Interests

The authors declare no potential conflicts of interest with respect to the research, authorship and publication of this article.

Funding

The author received no financial support for the research, authorship and publication of this article.

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