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A BRIEF REVIEW ON BUCCAL DRUG DELIVERY SYSTEM: ADVANTAGES, LIMITATIONS, AND IMPACT ON HEALTHCARE SYSTEM

Mohit and Md. Sadique Hussain*

School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, 144411, Punjab, India.

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***Corresponding Author**
Md. Sadique Hussain
School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, 144411, Punjab, India.

ABSTRACT

Delivery of pharmaceutical formulations is approaching a revolutionary change where rising numbers of new drug delivery technologies are being used and are active therapeutically. The discovery and development of medical formulations is presently concentrated on the improvement of therapeutic drugs to be aimed at the targeted location or place to reduce total dissemination in the host. For the administration of the desired drug, buccal area of an oral cavity is desirable aim to resolve the limitation of conventional drug administration. Problems involving the presystemic metabolism and drug depletion in digestive tract can be prevented by mouth administration of the drug. Buccal drug delivery system is a novel method of drug delivering system which have various benefits involving oral administration. The duration of placement of the pharmaceutical formulations at the recommended site could be extended. The structures are in direct contact with both the absorbing surface and the mucus membrane thus enhance the medicinal effects of administered medicine. Besides having many advantages, buccal drug delivery system has few disadvantages such as buccal supply are comparatively limited areas and considerable medication loss could be cause by salivary movement and swallowing. Moreover, in future, the field of oral drug distribution is the need for secure and convenient buccal permeation absorption boosters.

KEYWORDS: Novel drug delivery, Buccal drug delivery, Improved efficacy, Oral delivery, Targeted location.

INTRODUCTION

The oral approach is the appropriate one for patients and the safest way of delivering medication to circulatory system. The failure to monitor and identify the process in the gastrointestinal tract (GIT) has been nevertheless hampered by administration by oral route of almost all the medicines in traditional dosage forms.[1] Buccal Drug Delivery System (BDDS) has been studied as an advance drug delivery approach instead of using and following traditional drug administration routes.[2] Drug side-effects can be greatly reduced and drug delivery in a proper manner can be achieved at intended site through BDD.[3,4] The delivery of medicines by buccal mucosa (BM) has attracted great interest because of its convenient availability.[5]

Various developments have been made in Bucco-adhesive drug delivery to overcome certain issues (first pass metabolism, poor bioavailability) with commonly used dosage forms. Ascanio Sobrero for the very first time worked on BM in 1847 for drug delivery, since then many research and development have been done in the field.[6] At the BM region, various distinct cells are present such as stratum basale, lamina propria, and stratum filamentosum etc.[7] For controlled drug release (CDR), BM is the perfect location for drug absorption,, extended retention time and ideal drug release.[8–11] Inner cheek region is edged by BM region and buccal formulations positioned for local and systemic therapy in the middle of gums and buccal pouch.[12] Unlike different parts of mouth cavity, BM cavity is keratinized having 50.2 cm^2 surface area and multiple cell layers as stratified epithelia. The girth of the BM cavity is about 500-800µm with some variations for (please revise sentence) invaginations (Table 1).[13] The above features make BM cavity a best route for diffusion of low-molecular-weight molecules. The absorption of molecules also relies on their interaction with cell membrane and dosage form.[14,15] Active pharmaceutical ingredients (API) and hydrophilic polymer together aggregately are used for Buccoadhesion (clarify the term) for better bioavailability of drugs.[16] BDDS has several benefits constituting effortless approach for administration and patient compliance. Enzyme activity is also restricted because mucosa and smooth muscle are somewhat static thus drug administration has appropriateness for CDR.[17–21] Using BDDS, local and systemic medications can be administered via BM: compounds with 40-2000 partition coefficient and pka 2-10 are ideally absorbed.[22]

Various drug compounds(barbiturates) and enzymes (papain and trypsin) (can be given via buccal route).[23] Sublingual route is not contemplated to be perfect for prolonged release

administration because of interference during chewing etc. Contrarily, BDDS can have prolonged duration of drug administration with saliva attenuated adhesive polymer without sublingual administration difficulties.[23,24] Administration via buccal or sublingual route can help avoid concentration of drug compound because of pre-systemic metabolism. Degradation & metabolism of dosage form in GIT can be nullified in case of systemic administration.[7,25] For mucosal delivery of drugs, novel bio-adhesive formulations are developed in recent years. For example, mucoadhesive polymers are required to overcome limitations like mastication and to withstand saliva.[24] The buccal route also provides possible pathways for absorption of complex, high-molecular-weight polysaccharides, oligonucleotides, hydrophilic and unstable proteins, and the traditional small molecules of medicines. The oral cavity is being utilized for local and systemic intake of medicines.[26] Research and development in pharmaceutical sciences is shifting towards advancement in novel drug delivery system rather than developing the new chemical entities.

Table 1: Surface Area & thickness of Oral Cavity Membranes.

Oral cavity membrane	Structure	Surface area (cm^2)	Thickness (µm)	Blood Flow ($ml.min^{-1}.cm^{-2}$)
Buccal mucosa	non-keratinised	50.2	500-800	2.40
Gingival mucosa	Keratinised	--	200	1.47
Palatal	Keratinised	20.1	250	0.89
Sublingual mucosa	non-keratinised	26.5	100-200	0.97

Drugs can be delivered throughout oral mucosa into three distinct forms:

a) Sublingual delivery of medications: the administration across the layer of the tongue's front surface and the floor of mouth
b) Buccal supply: composed primarily of the lining of the cheeks and the BM membrane.
c) Local delivery of drugs: consisted of administration in all places apart from those 2 previous zones.

These sites are bodily different in their drug penetration, delivery rate and ability to sustain a delivery mechanism for a specific time period to release drugs out of the supplies and into the mucous membrane.[27]

Ideal Characteristics of Buccal Drug Delivery

An ideal BDDS should have following characteristics:

- Well moisturized, soluble and biodegradable.
- Polymer and its decaying derivatives should be harmless and free from leaching toxins.

- Should have good adhesive properties and mechanical strength.
- Bio-adhesive set should be ductile and have firmness.
- Polymer should be readily accessible and cost-effective.
- Should demonstrate both dry and liquid bio-adhesive properties.
- If inhibition and penetration properties in local enzymes are shown, they should have adhesively active groups.
- Molecular weights should be optimal.
- Must indicate acceptable shelf-life.
- Spatial confirmation is necessary.
- Should havegood bonding nature.
- Should stick for few hours to the attachment site.
- Subject to controlled release of the medication.
- Should have unidirectional drug release into the mucosa.
- Should effectively enhance absorption rate and duration of medication.
- Should not irritate patient or trigger any discomfort.
- Should not affect basic processes such as speaking and drinking.[28,29]

ADVANTAGES AND DISADVANTAGES OF BUCCAL DRUG DELIVERY

Advantages

- Administration is effortless.
- Drug administration can be possible even in unconscious patients.
- Dosage side effects are few to no (Sentence can be resynthesized).
- Drugs with first pass metabolism are conveniently delivered through this route and have increased bioavailability.
- Various compounds which are easily degraded in the gastric environment like highly acidic or caustic surroundings, can be given via this way.
- Local administration of drug is also suitable for extended time.
- Buccal mucosa provides better permeability than the skin.
- In contrast to rectal and transdermal routes there is greater volume of water as saliva for dissolution of drug in buccal route.
- This route offers better bioavailability of drugs than oral route (or use better terminology).which shows inferior bioavailability with oral route.[16,30]

Disadvantages

- Drugs having unpleasant taste or irksome to mucosal cavity cannot be given by this route.
- Buccal route is not suitable for large doses (please specify whether in size or amount).
- Surface area is small and absorption area is relatively smaller.
- Continuous saliva secretion results in drug dilution.
- Eating greatly interferes drug administration through this way. Drugs having risk of destabilization at Buccal pH cannot be given by this way.[9,31–33]

Anatomy of Buccal Mucosa

The oral mucosa consists of an exterior sheath known as stratified squamous epithelium and lamina propria backed up by the sub-mucosa as an innermost sheath. There are several sensory receptors consisting of tongue taste receptors. The epithelium of the blood is referred to as without keratinous tissue. The tissues known as lamina propria consist of collagen fibers, which protect the connective tissue sheet, blood vessels and smooth muscles.[34] Buccal cavity membrane is classified into masticatory, lining as well as specialized mucosa. Masticatory mucosa consists of keratinized tissues, while lining mucosa consist of non-keratinized tissues lining the floor of mouth, lips and cheeks etc. In the oral cavity, different thickness and varied composition of non-keratinized and keratinized tissues are present, whereas mouth surface area is 50% composed of keratinized tissue and 30% is inhabited by non-keratinized tissues.[35]

Epithelium of buccal mucosa is not keratinized, consisting of squamous stratified epithelium. Lamina propria is a connective tissue overlie with several cell layers. Connective tissue layer is differentiated from epithelium by basement membrane. Tonofilament as huge amount of protein is present in most of the layers.[36] According to five major regions in the oral cavity, oral mucosa can be distinguished into:

- The floor of the mouth (sublingual region)
- The buccal mucosa (cheeks)
- The gum (ginigiva)
- The palatal mucosa
- The inner side of the lips.[37]

NOVEL BUCCAL DOSAGE FORMS

Tablets, films, patches and powders are few of the novel buccal dosage formulations which are briefly discussed below.

Buccal mucoadhesive tablets

These are basically dry formulations, which are required to be dampened before allowing to be in proximity with buccal mucosa. For instance, a two layered tablet, having adhesive matrix hydroxypropyl cellulose layer and with an internal center of cocoa butter including insulin and sodium glycocholate.[38]

Patches and films

Two laminations are present in the buccal patches along with aqueous adhesive polymeric solution which is embedded over not permeable backing sheath structure, which gets split into the needed oval structure. Zilactin is a unique muco-adhesive film constituting solution of organic acids, alcohol and hydroxypropyl cellulose. Film can remain as is when used on buccal mucosa region upto 12 hours.[38]

Semi-solid formulations

Gels and ointments which are available in bio-adhesive forms do not have much patient compliance as that of solid mucco bio-adhesive dosage forms and mostly all dosage forms are utilized for locally delivering drug. Orabase is a gel based oral formulation which can remain on site for 15-150 mins.[38]

Powders

As sprinkled on to the rat's BM, powdered form of HPC and beclomethasone show a substantial improvement in residency time compared with oral solution, and 2.5 percent beclomethasone is stored on BM for more than four hours.[38]

TYPES and STRUCTURE OF BUCCAL DOSAGE FORMS

Two types of buccal Dosage form are matrix type and reservoir type:

a. Matrix type: the patch configuration is matrix-configured with medication, adhesive and mixed components.

b. Reservoir type: The configuration of the buccal patch involves a drug cavity and different components of the adhesive in a reservoir system. An impermeable back-up is implemented

to avoid drug degradation, to avoid deformation and breakdown in mouth and to monitor drug distribution.[39]

The buccal mucoadhesive dosages can be divided into 3 structural forms (Figure), already mentioned below.

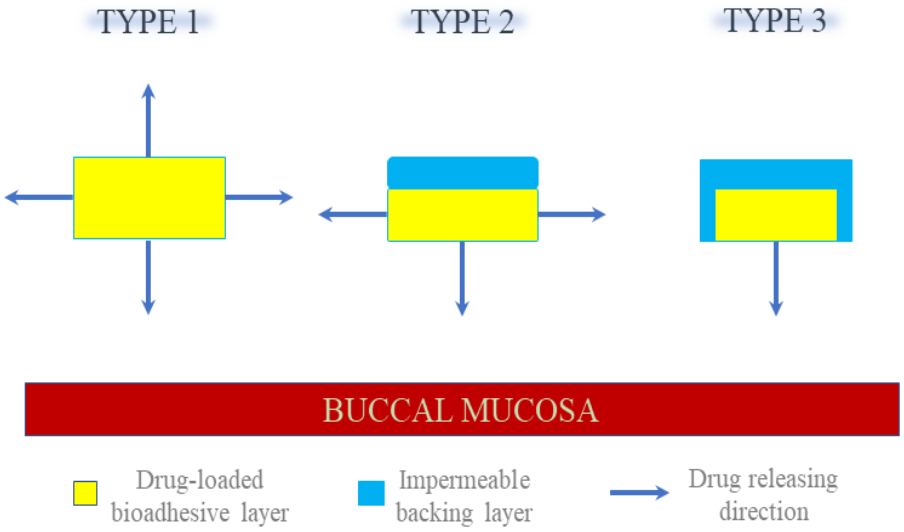

Figure 1: Kinds of buccal mucoadhesive dosage form.

MECHANISM OF BUCCAL ABSORPTION

Paracellular and transcellular are the two main routes of oral mucosa for transportation of (Figure 2). Permeates may concurrently use these pathways, but the physicochemical properties of the diffusion normally favor one path over another. Dependent on the hydrophilic properties of intercellular spaces and cytoplasm, the lipophilic compounds are of poor solubility. However, plasma membrane is lipid loving in nature, and due to low partition coefficient, hydrophilic solutes would have trouble entering the membrane. Intercellular regions are thus the greatest barrier to lipophilic compound permeation, and the plasma membrane is main transport obstruction for water repelling compounds. The solute permeation can require a combination of both routes because an oral epithelium is stratified.[40]

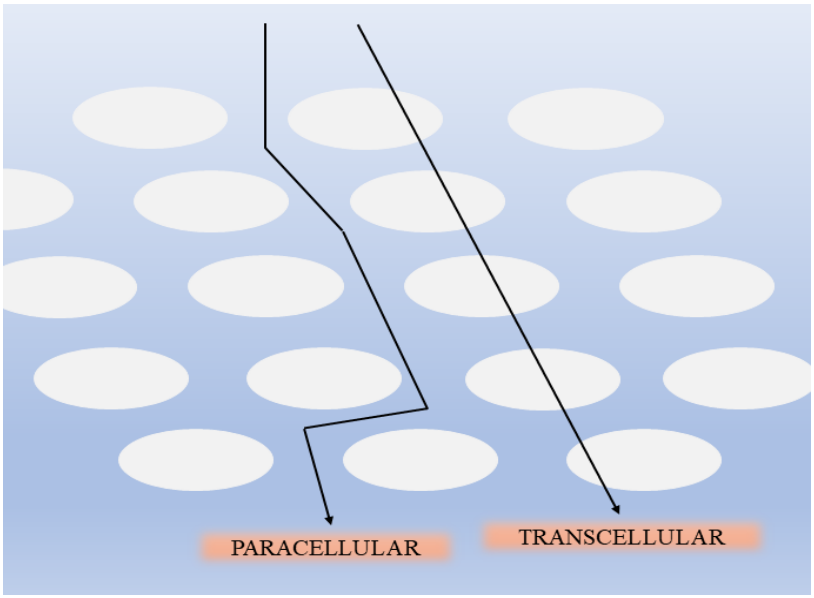

Figure 2: Diagrammatic representation of pathways for drug delivery via oral cavity mucosa.

FACTORS AFFECTING BUCCAL ABSORPTION

Table 2: Various permeation enhancers utilized in buccal drug delivery.[41]

Class of permeation enhancers	Examples
Bile salts	Sodium deoxycholate, sodium glycocholate, sodium glycodeoxycholate, sodium taurocholate, sodium taurodeoxycholate
Chelators	citric acid, EDTA, methoxy salicylates, sodium salicylate
Fatty acids	capric acid, lauric acid, lysophosphatidylcholine, methyloleate, Oleic acid, phosphatidylcholine.
Inclusion complexes	Cyclodextrins
Non-surfactants	Unsaturated cyclic ureas.
Surfactants	Polyoxyethylene, sodium lauryl sulphate
Others	Sulfoxides, polysorbate 80, dextran sulfate, cyclodextrin, azone.

Oral cavity is a dynamic medical supply area, since both interdependent and independent variables lessen the absorbed density at the absorption location.[42] Three main factors influencing buccal absorption are:

i. Membrane Factors

ii. Environmental Factors such as saliva, salivary glands and movement of buccal tissues.

- Saliva
- Salivary Gland
- Movement of buccal tissues

iii. Formulation related factors including molecular size, partition coefficients, pH, and pKa.

Approaches To Increase Absorption In Buccal Drug Delivery

i. Permeation Enhancers

One of the key barriers to the uptake of medication is the epithelium that line the BM. Substances which allow oral permeation are known as absorption enhancers. Most absorption enhancers have been developed to improve drug absorption, increase effectiveness, and minimize the drug toxicity. The collection and effectiveness of an enhancer relies therefore on the physicochemical characteristics of the drug, the administration site and the type of the vehicle etc.[34] (Table 2) defines the various classes of permeation enhancers and their examples.

There are different ways through which penetration enhancers do better absorption like:

- Mucus Rheology Transition
- Enhance lipid two-layer membrane fluidity
- working on the constituents at compact junctions
- Through eliminating the blockade to enzymes
- Increased drug thermodynamic behavior[43]

ii. Enzyme inhibitors

Another approach to boost buccal incorporation of medications especially peptides is to arrange medications with enzyme inhibitors. Protein medicines are stabilized by various processes including changes in the action of enzymes, changes in the shape of peptides or proteins, and/or making the medication less available to enzyme depravity by enzyme inhibitors such as aprotinin, bestatin, and certain bile-salts.[18]

iii. Prodrugs

Nalbuphine and naloxone bitter medications were used to make excess salivation and swallowing in dogs by oral mucous membranes. Consequently, the drug was improperly bioavailable. The prodrug uses of nalbuphine and naloxone has not had an adverse impact, with bioavailability of 35% to 50%, which is usually 5% or less, greatly enhancing the oral bioavailability.[38]

Bioadhesion or Mucoadhesion

The term bio-adhesion (also known as mucoadhesion) described by Longer and Robinson as the attachment to the mucus and/or the surface of the synthetic or natural macromolecule. The general concept of polymer adherence to the biological (bio-adhesive) or mucosal

(mucoadhesive) surfaces still exists. A bio-adhesive is defined as a compound that can collaborate with and hold on biological material for an continued span of time.[44]

Mechanism of Mucoadhesion

The adhesion mechanism of some macromolecules to a mucous tissue surface is not yet well understood. To begin proximate contact and thereby maximizing superficial contact, the mucoadhesive must be distributed over the substrate surface, which facilitates the spread of their chains in the mucus. Attraction and repulsion forces exist and the attraction forces must prevail for a mucoadhesive to succeed. The essence of the dosage type and the way it is delivered can encourage each phase. There is also usually a two-step mechanism of mucoadhesion that is.[45]

1) The contact stage

Between both the mucous membrane and the mucoadhesive there is an intimate wetting. In certain cases, these two surfaces can be merged physically, e.g. inside the oral cavity, oculum or vagina, and preserved.[46]

2) The consolidation stage

The adhesive joints are mixed and tougher with various physicochemical interactions, which contribute to lifelong adherence. Mucoadhesive materials adhere to stable dry surface areas most intensely when they are moisturizing, allowing for an efficient freezing of mucoadhesive molecules, conforming to the surface shape and binding mostly by hydrogen, and a weaker van der Waal bonding method.[46]

Intimate relation (Figure 3), accompanied by bond formation between the polymeters and the membrane. The attachment primarily occurs from the entanglement of the adhesive substance and the expanded mucus chain, by physical as well as mechanical bands. The mucoadhesive materials are activated by humidity in the consolidation phase. Moisture plasticizes the mechanism so that the mucoadhesive molecules free themselves and attach with the hydrogen bonds through a weak van der Waals.[27,45]

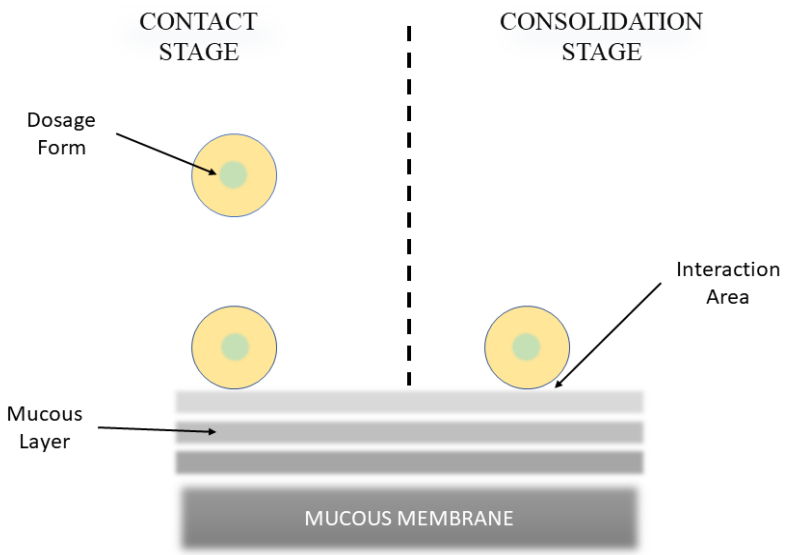

Figure 3: The two steps involved in the Mucoadhesion Process.

THEORIES OF BIOADHESION

Several theories are present to elaborate experimental information formed around the bio-adhesion course. Unluckily, every hypothetical model cannot explain the wide dimension of cooperation that include bio-adhesive bond. However, 5 prominent hypothesis can be differentiated.[29,47]

i. **Wetting theory:** This hypothesis is largely appropriate to liquid bio-adhesive systems and examines adhesive and proximity conduct in reference to a liquid or a mush to expand over a biological system.

ii. **Diffusion theory:** As per diffusion hypothesis, polymeric series & mixture of mucus to such an extent to form a semi-permanent adhesive bond. precise extent till which the polymer chain series pierce the mucus relies on diffusion coefficient & contact span. Further, diffusion coefficient, relies on the value of molecular mass between cross links and reduces considerably as the cross-linking density reduces.

iii. **Electronic theory:** In this hypothesis, electronic transfer happens during proximity of an adhesive polymer and mucus glycoprotein connections due to distinctions in their electronic structure. This leads to making of an electronic bilayer at the interface adhesion happens because of attractive forces across the double membrane.

iv. **Fracture theory:** This hypothesis of adhesion is associated with splitting of 2 surfaces following adhesion. The fracture strength equals the adhesive intensity.

v. **Adsorption theory:** As per these hypothesis, following the primary association in middle of 2 surfaces, the components adhere due to surface forces playing role in middle of the

atoms in the 2 surfaces. Two kinds of chemical bonds like primary covalent and secondary chemical bonds are implicated in the adsorption method.

Factors Influencing Mucoadhesion

The mucoadhesion of a drug carrier to the membrane depends on the factors described below[48]

i. Polymer based variables

- Molar mass.
- Concentration of polymer used
- Swelling factor
- Polymer stereochemistry

ii. Environmental variables

- Applied force
- Duration of proximity

iii. Physiological variables

- Mucin turnover rate
- Sickness conditions

Recent Developments In Buccal Drug Delivery Systems

Strong interest have been seen in recent years in creating alternative bio-adhesive formulations for the mucus supply of medications to resolve the restriction. Advancements have been suggested for distributing peptides through the oral route in BDDS such as buccal spray lipophilic gel, and phospholipid vesicles. Some authors suggested specifically the use of glyceryl monooleate as buccal medicament carrier in cubic and lamellar liquid crystalline phases for peptides.[49] A new formulation of liquid aerosol has been made in last decaderecent years (Oralin).[50] Phospholipids deformable vesicles have recently been produced for insulin delivery in the oral cavity.[51]

In disease control and management, vaccines have long been made and used against bacterial infections has greatly improved lifespan particularly of children around the globe. Parallelly, variety of conditions have seen that may challenge efficacy of vaccines to provide sufficient mucosal safety. The path of delivery and the rate of antigen's absorption by immune cells (macrophages and dendritic cells) are two main factors that affect efficacy of mucosal

vaccines. Many vaccines are currently delivered via the parenteral route or via other intrusive pathways.[52] In future, vaccines may play a vital role in prevention of infectious diseases through use of combined technological methods such as nanocarriers delivered through BDDS. Various commercially available formulation for BDDS is listed in Table 3.

Table 3: Commercially Available Formulations Intended for Buccal Drug Delivery System.

Manufacturer	Product	Application
Cephalon, Inc.	Oral Transmucosal Fentanyl Citrate Solid Dosage Form (ACTIQ)	Cancer pain management
Columbia Laboratories Inc.	Desmopressin Buccal Tablet	Control increased thirst and too much urination, and helps prevent dehydration
Ergo Pharm	Norandrodiol Buccal Tablets (Cyclo-Nordiol SR)	Dietary supplement
Generex Biotechnology Corporation	Insulin Buccal Spray	Type-2 diabetes
Leo Pharmaceuticals	Nicotine Mucoadhesive Tablet (Nicorette)	Smoking cessation aid used to control nicotine withdrawl symptoms and cravings associated with quitting of smoking
Pharmax Limited	Glyceryl Trinitrate (Suscard Buccal Tablet)	Treatment of angina
Reckitt Benckiser	Buprenorphine HCl & Naloxone HCl (Suboxane)	Treatment of opioid addiction
Rhone-Poulenc Rorer	Prochlorperazine Bioadhesive Buccal Tablet (Tementil)	Used to treat nausea, vomiting, dizziness due to various causes including migraine
Teijin Ltd.	Triamcinolone acetonide (Aftach)	Treatment of various skin diseases (dermatitis, allergy, eczema etc)
Wyeth Pharmaceuticals	Lorazepam Buccal Tablets (Temesta Expidet)	Treatment of anxiety disorders, trouble sleeping

Patents For Oral Transmucosal Administration

Diverse scientific work on the advancement of transmucosal supply has established many types of dosage such as pills, lozenges, gel, patches, films, and microspheres. The goods sold commercially are primarily pills and lozenges. Few firms have been able to produce fast release profile drugs and therapeutic reaction patches and films. The table 4 displays the list of oral transmucosal patents.[53]

Table 4: Patents on buccal patches/films.

Inventors	Title of the work	Patent number
Garry L Myres, Samuel D Hilbert, Bill J Boone, B. Arlie Borge, Pradeep Sanghvi, Madhusudhan Hariharan	Sublingual and buccal film compositions	US20110033542A1
Stephen mayer, Greg Slominski, Christopher E F	Orally administrable films	US20100063110A1
Stephen mayer, Greg Slominski, Christopher E F, Nicole Ouis	Multi - zone films	US20100266669A1
Meir haber, Throdis Kristmundsdottir, Skuli Skulason	Orally administrable films and preparation thereof	US8840935B2
Richard T Clark, Maurice E Durschlag	Oral/Buccal transmucosal delivery ways for electrolyte compositions including xylitol	US20080152695A1
James E Biegajski	Film bandage for mucosal administration of actives	US20070172515A1
Richard C Fuisz	Two Phase mucoadhesive composition	US20070298087A1
Joachim Moormann, Klaus Optiz, Hans-Rainer Hoffmann	Oral formulations of desoxypeganine and thereof	US20070155774A1
Tina Rademacher	Transmucosal form of administration with reduced mucosal irritation	WO2005000263A1
Kenneth Widder, Warren Hall, Kay Olmstead	Transmucosal delivery of proton pump inhibitors	US20040006111A1
Horst George Zerbe, Jian-Hwa Guo, Anthony Serino	Water soluble film for oral intake with immediate wettability	US20020127190A1
Michael A Repka, Staci l Repka, James W Mcginity	Bio adhesive hot-melt extruded film for topical and mucosal adhesion applications and drug delivery and process for preparation and thereof	US6375963B1

CONCLUSION

The need for drug delivery systems researches always try to figure out and adopt modern techniques who have more efficacy and advantages. From an economic and public safety standpoint it is expensive and often seriously harmful to look for ways to prescribe injectable drugs. In reference to approachability, administration, removal, retainability, low enzyme activity, budgetary and greater patient satisfaction, BDDS offer countless advantages. Adhering to mucosal membranes of these drug supply which causes an escalated medication concentration gradient on the absorbing location and thus improves the bioavailability of the medications supplied systemically. By adding a mass of the most recent molecules owing to the disclosure of drugs, BDDS is becoming more and more essential.

Multiple-dosing formulations need also to be cheaper and better bioavailable. Enhanced ways of opioid release by transmucosal and transdermal methods can be very useful because discomfort associated with parenteral drug control mechanisms can be completely prevented by these pathways. The distribution of BDDS is promising for more research directed at the systemic supply of inefficient buccal medicines and an enticing and viable substitute for the non-intrusive supply of potent peptide and protein medicinal molecules. Multiple-dosing formulations need also to be cheaper and better bioavailable.

CONFLICT OF INTEREST

Declared none.

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