IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
January 2024 Vol.:30, Issue:1

Buccal Drug Delivery System – An Updated Overview

IJPPR
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An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Meena. S*, Daisy Chellakumari. S, Amarnath. S, Akilandeshwari. V, Mahalakshmi. A, Kokila. E

Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai- 600 003, Tamil Nadu, India.

Submitted: 20 December 2023
Accepted: 25 December 2023
Published: 30 January 2024

ijppr.humanjournals.com

Keywords: Novel drug delivery, Buccal drug delivery, Buccal absorption, Bio-adhesion, By- pass first-pass metabolism.

ABSTRACT

Buccal drug delivery has invariably overcome the major drawbacks of oral drug delivery – first-pass metabolism and reduced bioavailability of dosage form. Buccal dosage forms release the drug into the systemic circulation directly. This has reduced the required dose of the drug for achieving the therapeutic effect and protect the drug from adverse environments of varying pH throughout the GI tract. Buccal delivery can be utilized for local as well as systemic effects. This delivery systems, when made bucco-adhesive is more suitable for pediatrics, geriatrics, non-cooperative and unconscious patients. This review describes briefly about overview of oral mucosa, mechanism of buccal absorption, bio-adhesion, basic components of buccal drug delivery system, approaches of buccal delivery, recent developments and patented formulations, and commercial and clinical trials of mucoadhesive formulations.

INTRODUCTION:

Owing to the advances and progress made by the buccal drug delivery system about treatment of diseases and thereby enhancing the quality of life, it has gained considerable interest as a major participant in Pharma industry. In 1947, the Buccal Drug Delivery System was introduced for the administration of Penicillin to the oral mucosa through dental adhesive powder mixed with Gum tragacanth [1,2]. Among various drug delivery systems, the oral approach is best convenient and safety way of delivering medication covers a wider patient group from Pediatrics to Geriatrics. But some drug has low bioavailability in oral administration there undergo hepatic metabolism or some are GI degradation, unpredictable and erratic absorption. To overcome this problem to deliver drugs systemically via an alternate route of administration such as intranasal, buccal, sublingual, pulmonary or transdermal.

Delivery of drugs via the absorption mucosa in various easily accessible body cavities like ocular, nasal, rectal, vaginal and oral cavities offer distinct advantages over per – oral administration. [First pass metabolism, poor bioavailability] The delivery system which utilized the property of bio-adhesion of certain polymers, become adhesive on hydration is known as the mucoadhesive drug delivery system. This delivery system includes the following:

- ✓ Buccal Drug Delivery System
- ✓ Rectal Drug Delivery System
- ✓ Sublingual Drug Delivery System
- ✓ Nasal Drug Delivery System
- ✓ Ocular Drug Delivery System
- ✓ Vaginal Drug Delivery System [3]

A buccal drug delivery system involves the administration of the desired drug through the buccal mucosal membrane lining in the oral cavity. Buccal mucosa is the best trans mucosal route for local and systemic medication among the available options. Because of presence of immobile mucosa and plain smooth muscle -buccal route become good accessibility for administration. For controlled release, the buccal mucosa is the perfect location for extended retention time for drug absorption [4,5].

ORAL MUCOSAL SITE: [6,7]

Within the oral mucosal cavity, the delivery of drugs is classified into three categories.

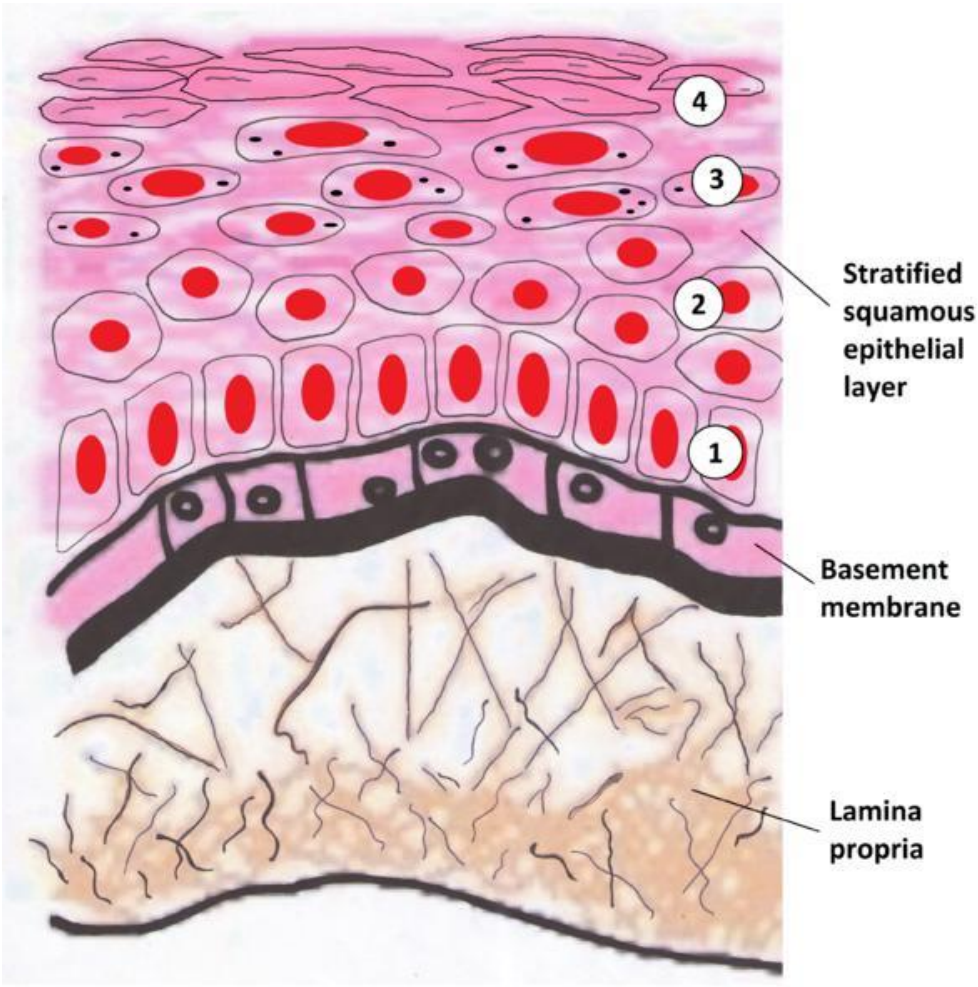
- ❖ Buccal delivery
- ❖ Sublingual delivery
- ❖ Local delivery

Buccal delivery: Buccal delivery is the administration of drugs via the buccal mucosa to the systemic circulation.

Sublingual delivery: Sublingual delivery is the administration of the drug via the sublingual mucosa to the systemic circulation.

Local delivery: which is drug delivery into the oral cavity.

OVERVIEW OF ORAL MUCOSA: [1,8,9]



The oral mucosal thickness varies depending on the site. Buccal mucosa – 500-800µm. Hard and soft palates, floor of the mouth, ventral tongue, Gingival- 100-200µm. It is composed of an outermost layer of stratified squamous epithelium, a lamina propria followed by the submucosa as the innermost layer. The total surface area of the oral cavity is 100cm^2. The oral mucosa protects the body from external influences such as the entry of potentially dangerous substances.

The mucosa of the gingival and hard palate is keratinized like the epidermis contains neutral lipids like ceramides and acyl ceramides which are relatively impermeable to water. The mucosa of the soft palate, the sublingual, and the buccal regions are not keratinized contain only small amounts of ceramides.

MUCUS COMPOSITION: [8,10,11,12]

The epithelial cells of buccal mucosa are surrounded by mucus with a thickness about 40-300mm. Mucus – translucent, viscid secretion secreted by goblet cell.

COMPOSITION:

- Water -95%
- Glycoprotein & lipid -0.5- 5%
- Mineral salt – 1%
- Free proteins -0.5-1%

FUNCTIONS:

1. Cell-cell adhesion
2. Lubrication
3. Bio-adhesion
4. Protective
5. Barrier

IDEAL CHARACTERISTICS OF BDDS: [1,8,9,10,11,12]

- Should have good adhesive properties.
- Should have good mechanical strength.
- A buccal adhesive system facilitates the rate and extent of drug absorption.
- The system should have well moisturized, soluble and biodegradable.
- Should not aid in development of secondary infections such as dental caries.

- Should not affect basic processes such as eating, speaking, and drinking.

ADVANTAGES:

- Drug is easily administered and withdrawal of therapy in an emergency can be facilitated.
- Drugs can be administered even in unconscious and trauma patients.
- Buccal mucosa is relatively permeable with a rich blood supply, vigorous in comparison to the other mucosal tissues.
- Buccal drug delivery system increasing the bioavailability of orally administered drugs bypasses the first pass metabolism.
- The buccal mucosa is relatively large surface area contributes to rapid and extensive drug absorption.
- Controlled release API combined with increased residence time may lead to a lesser frequency of administration.

DISADVANTAGES:

- Drugs that are unstable in buccal pH cannot be administered.
- A bitter taste or unpleasant taste cannot be administered.
- Eating and drinking are restricted.
- Occurrence of local ulcerous effects due to prolonged contact of the drug.
- Lack of a good model for in vitro screening to identify drugs suitable for such administration.

STRUCTURE AND DESIGN OF BUCCAL DOSAGE FORM: [1,8,11]

1.TYPE -I [MULTIDIRECTIONAL]: This device has a single layer with multiple directions of drug release.

DIS.AD: Significant drug loss due to swallowing.

2. TYPE – II [BI- LAYERED]: Double layered device preventing drug loss by an impermeable backing layer superimposed on top of the drug-loaded bio-adhesive layer.

3.TYPE-III [UNIDERECTIONAL]: Drug released from only one side to the buccal mucosa so the drug loss is minimal.

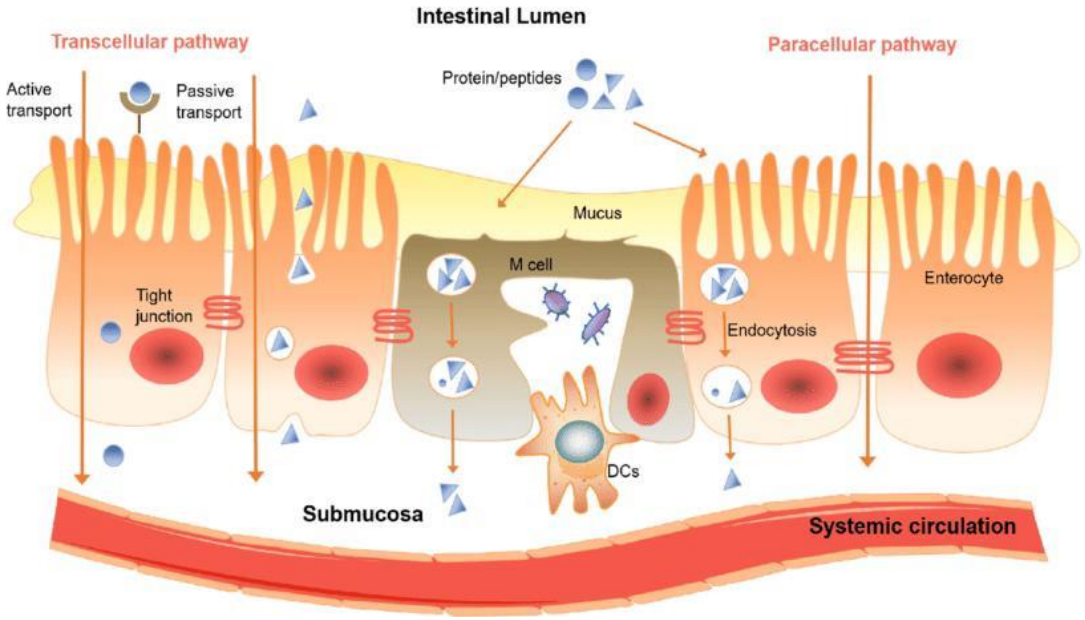
BUCCAL ABSORPTION: [1,11-19]

Drug absorption via buccal mucosa known as buccal absorption produce systemic and local effect.

MECHANISM OF BUCCAL ABSORPTION:

The epithelial cells of the oral mucosa were closely compacted on the top quarter to one-third of the epithelium form the main barrier for penetration. Oral epithelium is not a uniform hydrophobic barrier. The epithelial cell membrane is lipophilic in nature. So, lipophilic drugs are more readily absorbed. Drug transport across the buccal mucosa can take place for it to reach the local and systemic circulation by two pathways.

- Transcellular route
- Paracellular route



Transcellular route: Drug permeation through the epithelial cells involves transport across the apical cell membrane. It is also known as an intracellular pathway. The primary transport mechanism of non-ionic species is passive transport across the lipid membrane. Lipophilic compounds molecules predominantly undergo trans-cellular transport.

Paracellular route: Drug permeation through the epithelial cells involves transport through in between the epithelial cells. It is the primary route for hydrophilic compounds because it is difficult to penetrate the lipophilic cell membrane. Hence it preferred intercellular space.

Limitations: limited surface area in the intercellular space.

FACTORS AFFECTING BUCCAL ABSORPTION: [1,11,12,20,21]

a) The permeability of the oral mucosa
b) Physicochemical characteristics of the drug.
c) Environmental factors.

a) Permeability of the oral mucosa: Buccal mucosa permeability is 4-4000 times greater than that of the skin. A wide range of considerable differences in permeability between different regions of the oral cavity Oral mucosa decreases in the order of sublingual greater than buccal and buccal greater than palatal. This is based on the relative thickness and degree of keratinization of these tissues. Absorptive membrane thickness, blood supply, Enzyme content, and cell renewal will all contribute to reducing the rate and amount of drug entering the systemic circulation.

b) Physio-chemical characteristics of the drug:

i) Molecular weight: ions are low penetrate than molecules. Smaller molecules more rapidly penetrate than larger molecules.

ii) Degree of ionization: The pH of saliva is on an average of 6.4. pKa of the drug plays an important role in absorption. If the pKa is greater than 2 for an acid and pKa less than 10 for a base adequate absorption occurs.

iii) Lipid solubility: For optimal drug absorption the partition coefficient between 40-2000 is necessary.

c)Environmental factors: saliva- in the lining of buccal mucosa the saliva is thin-coated and is called film. The thickness, composition, and movement of the film affect the rate of buccal absorption.

Movement of buccal tissues- in the oral cavity buccal region shows fewer active movements. The mucoadhesive polymer is to be incorporated to keep dosage for longer periods to withstand tissue movement during easting drinking and speaking.

METHODS TO INCREASE DRUG DELIVERY VIA BUCCAL ROUTE [17,21,22]

i) PERMATION ENHANCERS: In the BDDS one of the key barriers is epithelium that line in the buccal mucosa. Delivering the high molecular weight compounds, such as protein & peptide generally exhibit low buccal absorption rates. To overcome the barrier a substance is incorporated to the drug which allow buccal permeation are known as absorption enhancers. Most absorption enhancers have been developed to improve drug absorption, increase effectiveness and minimize drug toxicity. The most common absorption enhancers are fatty acids, bile salts and surfactants such as sodium dodecyl sulfate.

ii) PRODRUGS: Nalbuphine and naloxone are the bitter drug administered to dogs via the buccal mucosa cause excess salivation and swallowing shows low bioavailability. To overcome this nalbuphine and naloxone are administered as prodrug shows comparatively high bioavailability no adverse effects are produced.

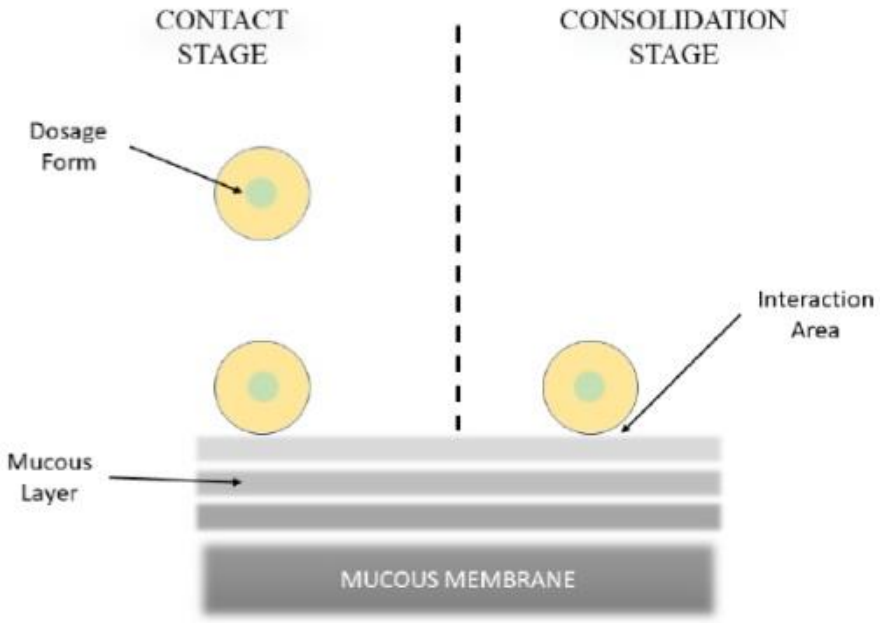
BIOADHESION: [11,12,23,24]

Longer and Robison described the term bio-adhesion (also known as muco-adhesion). Bio-adhesion is defined as a substance that can adhere to the biological tissues.

MECHANISM OF ADHESION:

The mechanism of bio-adhesion is a two steps process,

- ✓ The contact stage
- ✓ The consolidation stage



Step 1 The contact stage: initial contact between two surface polymers of the drug and the mucus surface. Then wetting & swelling of the polymer these two surfaces are merged physically.

Step:2 The consolidation stage: interpenetration of bio-adhesive polymer in mucus membrane the attachment primarily occurs from the entanglement of the adhesive substances and the expanded mucus chain, Then the formation of secondary bonds due to non-covalent interaction.

THEORIES OF ADHESION: [1,8,9,10,11,12,]

1.Wetting theory: this theory describes the affinity to the surface in order to spread over it. The wetting theory applies to liquid systems. The affinity is measured by the techniques is contact angle. Lower the contact angle – greater the affinity. The contact angle should be equal or close to zero to provide adequate spread ability.

2. Diffusion theory: Diffusion theory describes the interpenetration of polymer chains and the mucus to a sufficient depth to create a semi-permanent adhesive bond. The exact depth to which the polymer chains penetrate the mucus depends on the diffusion co-efficient and the contact time. It is believed that the adhesion force increases with the degree of penetration of the polymer chains.

3. Electronic theory: According to this theory, electronic transfer leading to the building of a double electronic layer at the interface, where the attractive forces within this electronic double layer determines the mucoadhesive strength.

4. Adsorption theory: After an initial contact between two surfaces. Two types of chemical bonds such as primary covalent and secondary chemical bonds (including electronic forces, Vander Waals force and hydrophobic bons) are involved in adsorption process.

5. Fracture theory: the second most accepted theory explaining the force required to detach two surfaces that have undergone adhesion. Such force is called as tensile stress or fracture strength.

FACTORS AFFECTING BIO-ADHESION / MUCOADHESION: [1,8-12,14,25]

POLYMER RELATED FACTORS:

i) Molecular weight
ii) Concentration of polymer
iii) Flexibility of polymer chains
iv) Swelling.

ENVIRONMENTAL FACTOR:

i) pH
ii) Contact time
iii) Applied strength

PHYSIOLOGICAL FACTORS:

i) Mucin turnover
ii) Disease state

POLYMER RELATED FACTORS:

i) Molecular weight:
   - ✓ For successful muco-adhesion, At-least 1,00,000 molecular weights.
   - ✓ Buccal adhesiveness increases with increasing molecular weight.

ii) Concentration of polymer:
   - ✓ More concentrated buccal -adhesive dispersion retained on mucus membrane for longer period of time.

iii) Flexibility of polymer chains:

- ✓ As water-soluble polymers become cross-linked, the mobility of individual polymer chain decreases.

ENVIRONMENTAL FACTOR:

i) pH

✓ For the degree of hydration pH of the medium is very important.

ii) Applied strength:

✓ Applied strength increases the adhesion strength.

iii) Initial contact time:

✓ Buccal adhesive strength increases as the initial contact time increases.

PHYSIOLOGICAL FACTORS:

i) Mucin turn over:

- ✓ To limit the residence time of the buccal adhesives on the mucus layer.
- ✓ Substantial amounts of soluble mucin molecules.

ii) Diseases states:

- ✓ The mucosa is damaged and would also be expected to change in permeability.

BASIC COMPONENTS OF BUCCAL DRUG DELIVERY: [1,8-12,14]

1. Drug substance
2. Bio-adhesive polymers
3. Backing membrane
4. Permeation enhancers.

1. Drug substance:

The choice of drug candidate depends on whether a rapid release/prolonged release and a local/systemic effect are intended. The selection of suitable drug for the design of buccal drug delivery system should be based on pharmacokinetic properties.

The drug should have the following characteristics:

- ❖ The drugs having biological half-life of 2-8 hrs.
- ❖ The conventional single dose of the drug should be small.
- ❖ Through oral route the drug may exhibit first-pass metabolism.

- ❖ The drug absorption should be passive when given orally.
- ❖ T-max of the drug shows wider fluctuations or higher values when given orally.

2. Bio-adhesive polymer:

The selection and characterization of appropriate bio-adhesive polymers in the formulation is the first step. Bioadhesive polymers play a major role in buccal adhesive drug delivery systems of drugs. The drug is embedded in the polymer matrix, which controls the duration of release of drug. An ideal polymer should have the following characteristics.

- ❖ It should be inert and compatible with the environment and biological membrane.
- ❖ The polymer should be easily available in the market and economical.
- ❖ It should adhere quickly to the tissue surface and should possess some site specificity.
- ❖ The polymer should be non-toxic and absorbable from the mucous layer.
- ❖ It should form a strong covalent bond with the mucin/ epithelial surface.

3. Backing membrane:

Backing membrane plays a major role in the attachment of bio-adhesive devices to the mucus membrane. The materials used should be inert, and impermeable to the drug and penetration enhancer. It prevents drug loss and offers better patient compliance.

Eg: HPMC, HPC, CMC etc.,

4. Permeation enhancers: Permeation enhancers are used to improve the release of the drug. They aid in the systemic delivery of the drug by allowing the drug to penetrate more readily into the tissues. The commonly used are CPC, polysorbate80, dimethyl formamide etc.,

APPROACHES OF BUCCAL DRUG DELIVERY SYSTEM: [26-52]

1. Non-attached drug delivery systems: includes fast dissolving tablet dosage forms, chewing gum, microporous hollow fibres. The local physiological environment greatly affects.

2. Bio-adhesive drug delivery systems: a) solid buccal adhesive dosage forms

b) semi-solid adhesive dosage forms

c) liquid buccal adhesive dosage forms.

a) Solid buccal adhesive dosage forms: they are dry formulations which achieve bio-adhesion via dehydration of the local mucosal surface.

Buccal tablets: For the buccal drug delivery system the most investigated dosage form is tablet. Buccal tablets are small, flat and oval-shaped dosage form. Buccal tablets are small, flat and oval shaped dosage form. Several bio-adhesive buccal tablet formulations have been developed by direct compression method either for local or systemic drug delivery. They soften, adhere to the mucosa and are retained in position until dissolution and /or release is complete. They are designed the drug can release the unidirectional or multi directional.

Microspheres, microparticles: microspheres, and microparticles provide comfortable sensation of a foreign object within the oral cavity. The local irritation caused by microspheres, microparticles at the site of adhesion is less.

Wafers: A wafer is a drug delivery system with surface layers of thin polymer films possessing adhesive properties.

Bio-adhesive nanoparticles: due to their physical properties nanoparticles do not make intimate contact with the mucosal surface. Advantages over tablets are: bioavailability is higher than the tablets, do not cause irritation, patient acceptable, they are incorporated in the ointments or delivered by water suspension.

Lozenges: Bio- adhesive lozenges offers prolonged drug release with improved patient compliance.

b) Semi- solid buccal adhesive dosage forms:

Adhesive gels: Adhesive gels are used to deliver the drugs via buccal mucosa & allow sustained release. The gel-forming bio-adhesive polymer attached to the surface of mucosa by cross linking polyacrylic acid and at the site of absorption provide controlled release.

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 bio-adhesive surface for mucosal attachment. These are the most recently developed dosage forms for buccal administration. It may be preferred over tablets in-terms of flexibility and comfort. In addition, oral gels have relatively short residence time on the mucosa which are

easily washed away and removed by saliva. They are usually manufactured by a solvent casting method or hot melt extrusion technique.

c)Liquid buccal adhesive dosage forms: liquids used to coat buccal surface are viscous and serve as either protective agents or as drug vehicles for delivery of drugs on to the mucosal surface. Recently pharmaceutically acceptable polymers were used to improve the viscosity of products to aid their maintenance in the oral cavity.

RECENT DEVELOPMENTS IN BUCCAL DRUG DELIVERY SYSTEMS: [53-60]

In recent years strong interest has been seen in creating alternative bio-adhesive formulations for the mucus supply of drugs to resolve the restriction. Innovative drug delivery comprises use of lipophilic gel, buccal spray, and phospholipid vesicles to deliver peptides via the buccal route. The Glyceryl monooleate as buccal cure carrier in boxy and lamellar liquid crystalline phases for peptides. For insulin delivery in the oral cavity, phospholipid vesicles have been developed recently. Improve lifespan particularly children around the globe against infections vaccines have been made. Many vaccines are currently delivered via the parenteral route via other pathways. In future, vaccines may play a vital role in the prevention of infectious diseases delivered through buccal drug delivery system.

PATENTED ORAL BUCCAL ADHESIVE FORMULATIONS: [61]

ACTIVE INGREDIENT	PATENT NO. OR APPL.NO.	DOSAGE FORM	ROUTE OF ADMINISTRATION
Miconazole	022404	Tablet	Buccal
Fentanyl	N202788	Spray	Sublingual
Acyclovir	N203791	Tablet	Buccal
Naloxone	US 10617686B2	Liquid spray	Buccal
Zolpidem tartrate	A201509	Tablet	Sublingual
Desmopressin acetate	N022517	Tablet	Sublingual
Apomorphine Hydrochloride	US10888499	Film	Sublingual

A commercial and clinical trial of oral mucoadhesive formulations.

Active Ingredient	Dosage Form	Status
Asenapine	Wafer	Commercial
Triamcinolone	Paste	Commercial
Desmopressin	Tablet, Wafer	Commercial
Glyceryl trinitrate	Tablet, Spray	Commercial
Allergen extract	Wafer	Commercial
Insulin	Spray	Commercial
Vitamin B12	Tablet, Spray, Oral Liquid	Commercial
Montelukast	Film	Phase II
Apomorphine	Film	Phase II/III
Alprazolam	Tablet	Phase I/II/III Completed
Influenza vaccine	Oral Liquid	Phase I Completed

CONCLUSION:

In the past few years, researchers have been more concentrating in buccal drug delivery is becoming more and more popular because it does have significant merit like by-pass first-pass metabolism. Out of various drug delivery, buccal drug delivery is more permeable compare to others drug delivery and patient acceptability when compared to various transmucosal drug delivery systems like rectal, ocular, vaginal, etc., Researchers are continued the study in buccal drug delivery with the aim of systemic delivery of orally inefficient drugs and alternate for non- invasive delivery of peptide and protein drug molecules. Because buccal drug delivery is a promising area. For a prospective future in buccal drug delivery absorption enhancers is an important component for buccal permeation are need for safe and effective delivery.

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