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Review Article

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A REVIEW ON BUCCAL MUCOADHESIVE DRUG DELIVERY SYSTEM

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ABSTRACT

Purpose of this review is to compile the recent literature with special focus on various aspects of Buccal drug delivery system that gaining significance place among novel drug deliveries. Buccal drug delivery system is a novel drug delivery system. bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. Buccal mucosa is the preferred site for both systemic and local drug action. The mucosa has a rich blood supply and it relatively permeable. In Buccal drug delivery systems mucoadhesion is the most important element so various mucoadhesive polymers have been utilized in different dosages form. Various bioadhesive dosages form such as Chewing gum, tablets, Patches, Hydrogel, Thiolated tablets. In this review article the Anatomy of mucosa, advantages, disadvantages, polymers, and evaluations of the Buccal drug delivery has been discussed.

KEYWORDS: Anatomy of Oral Mucosa, Buccal, Mucoadhesive Polymer, Permeation, Dissolution.

INTRODUCTION

Anatomy and Physiology of ducal mucosal membrane

The oral mucosa is composed of an outermost layer called stratified squamous epithelium and below a basement membrane; a lamina propria followed by the sabmucosa as the inner most layer. It also contains many sensory receptors including the taste receptors of the tongue. The blood epithelium is classified as nonkeratinized tissues .It is penetrated by tall and conical shaped connective tissues. These tissues which are refer to as lamina propria, consist of colagen fibers a supporting layer of connective tissues, blood vessel and smooth muscles. The epithelium may consist of a single layer (stomach, small and large intestine, bronchi) or multiple layers.[1-2]

The upper layer contains goblet cells, which secrete mucus components directly onto the epithelial surface. Specialized glands producing components of the mucous layer may also be located beneath the epithelium. Very responsible for gelatinous structure, cohesion, and antiadhesive properties. Mucin consist of three dimensional network with large number of loops. The main functions of the mucus are to protect and lubricate the supporting epithelial layer. In the gastrointestinal tract, the mucus facilitates the movement of food boluses along the digestive canal and protects the epithelium from harmful influences due to intrinsic peristaltic movements and proteolytic enzymes. The components of the mucus secreted onto the surface of the eye by goblet cells adhere tightly to the glycocalyx of corneal-conjunctival epithelial cells, protecting the epithelium from damage and facilitating the movement of the eyelids.[3-4]

It is estimated that the permeability of the Buccal mucosa is 4-4000 times greater than the skin. There are considerable differences in permeability between different region of the oral cavity because of diverse structures and functions of the different oral mucosa.[5]

Mucus

The epithelial cells of Buccal mucosa are surrounded by the intercellular ground substance called mucus with the thickness varies from 40 µm to 300 µm. Mucus is composed chiefly of mucins and inorganic salts suspended in water. Mucins are a family of large, heavily glycosylated proteins composed of oligosaccharide chains attached to a protein core.

Role of mucus

1. Made up of proteins and catbohydrates.
2. Cell –cell adhesion.
3. Lubrication.
4. Bio adhesion of mucoadhesive drug delivery system.[6]

Saliva

A constant flowing down of saliva within the oral cavity makes it very difficult for drugs to be retained for a significant amount of time in order to facilitate absorption in this site.

Role of Saliva

1. Protective fluid for all tissues of the oral cavity.
2. Continuous mineralization of the tooth enamel.
3. To hydrate oral mucosal dosage forms[7-8]

Functions of oral cavity

1. It helps in chewing, mastication and mixing of food stuff.
2. It is Helps to lubricate the food material and bolus.
3. To identify the ingested material by taste buds of the tongue.
4. To initiate the carbohydrate and fat metabolism.
5. As a portal for intake of food material and water.
6. To aid in speech and breathing process.[9-10]

The mucoadhesive drug delivery system includes the following:

1. Buccal drug delivery systems.
2. Sublingual drug delivery systems.
3. Rectal drug delivery systems.
4. Vaginal drug delivery systems.
5. Ocular drug delivery systems.
6. Nasal drug delivery systems.

1. Buccal drug delivery, consisting of the administration through the Buccal mucosa, mainly composed of the lining of the cheeks.
2. Sublingual drug delivery, consisting of the administration through the membrane of the ventra surface of the tongue and the floor of the mouth.
3. Local drug delivery, consisting of the administration through all areas other than former two regions.

These site differs anatomically in their permeability to drugs, the rate of drug delivery, and ability to maintain a delivery system for a time required for drug release out of the delivery apparatus and into the mucosa.

The term bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. In case of bioadhesive drug delivery, the term bioadhesion is used to describe the adhesion between polymers, either synthetic or natural and soft tissues or the gastrointestinal mucosa.[11-12]

Advantages of buccoadhesive drug delivery

1. Drug is easily administered and extinction of therapy in emergency can be facilitated.
2. Drugs bypass first pass metabolism so increases bioavailability.
3. Some drugs that are unstable in acidic environment of stomach can be administered by Buccal delivery.
4. Drug degradation in harsh gastrointestinal environment can be circumvented by administering the drug via Buccal route.
5. Drug absorption can be terminated in case of emergency.
6. Better patient compliance-ease of drug administratio n.
7. Rapid cellular recovery.
8. Rapid absorption of drug is possible dueto largae surface area of Buccal mucosa.[13-14]

Limitations of buccoadhesive drug delivery

1. Drugs which are unstable at Buccal pH cannot be administered.
2. Drugs which have a bitter taste or unpleasant taste or an obnoxious odor or irritate the mucosa cannot be administered by this route.
3. 3Eating and drinking may be restricted.
4. Possibility of the patient to swallow the tablet.
5. Only drug having small dose is given by this drug delivery.6. Dosage form may be dislodged.[15]

Mechanism of Buccal Absorption

For bioadhesion to occur, three stages are involved:

1. An intimate contact between a bioadhesive and a membrane either from a good wetting of the bioadhesive and a membrane or from the swelling of bioadhesive.
2. Penetration of the bio-adhesive into the tissue takes place.
3. Inter penetration of the chains of the bioadhesive with mucous takes place. Low chemical bonds can then settle.

The Following theories explained about mechanisam of bioadhesion

1. Wetting theory.
2. Diffusion theory.
3. Adsorption theory.
4. Fracture theory.
5. Absorption theory
6. Electronic theory[16-17]

Structure and Design of Buccal Dosage Form

Buccal Dosage form can be of;

1. Matrix type: The Buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together.

2. Reservoir type: The Buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss. Buccal absorption: Buccal absorption leads systemic or local action via Buccal mucosa. [18]

Basic components of Buccal drug delivery system

The basic components of Buccal drug delivery system are

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

1. Drug substance

Before formulating mucoadhesive drug delivery systems, one has to decide whether the intended, action is for

rapid release/prolonged release and for local/systemic effect. The selection of suitable drug for the design of buccoadhesive drug delivery systems should be based on pharmacokinetic properties. The drug should have following characteristics. The conventional single dose of the drug should be small. The drugs having biological half-life between 2-8 hrs are good candidates for controlled drug delivery. Tmax of the drug shows wider-fluctuations or higher values when given orally. Through oral route drug may exhibit first pass effect or presystemic drug elimination. The drug absorption should be passive when given orally.[19-20]

Polymers used for mucoadhesive drug delivery

A short list of mucoadhesive polymers is given below:

(1) Synthetic polymers

(a) Cellulose derivatives (methylcellulose, ethylcellulose, hydroxy-ethylcellulose, Hydroxyl propyl cellulose, hydroxy propyl methylcellulose, sodium carboxy methylcellulose.
(b) Poly (acrylic acid) polymers (carbomers, polycarbophil).
(c) Poly (hydroxyl ethyl methyl acrylate).
(d) Poly (ethylene oxide).
(e) Poly (vinyl pyrrolidone).
(f) Poly (vinyl alcohol).

(2) Natural polymers

(a) Tragacanth.
(b) Sodium alginate.
(c) Karaya gum.
(d) Guar gum.
(e) Xanthan gum.
(f) Lectin.
(g) Soluble starch.[21]

Ideal Characteristics of Muco Polymer

Polymer should be carefully selected with the following properties in mind.
1) Polymer must have a high molecular weight upto 100.00 or more.
2) Long chain polymers-chain length must be long enough.
3) High viscosity.
4) Degree of cross linking.
5) Spatial conformation.
6) Flexibility of polymer chain
7) Concentration of the polymer.
8) Charge and degree of ionization.
9) Optimum hydration.
10) Optimum pH.
11) High applied strength and initial contact time.
12) It should non toxic, economic, biocompatible preferably biodegradable.[22-23]

Novel mucoadhesive polymers

A new class of hydrophilic pressure sensitive adhesives h as been developed by corium technologies. Complex have been prepared by non-covalent hydrogen bonding cross linking of a film forming hydrophilic polymer with a short chain plasticizer having reactive OH groups at chain ends. Tomato lectin showed that it has binding.

Factors affecting drug delivery via Buccal route.[10]

Oral cavity is a complex environment for drug delivery as there are many interdependent and independent factors which reduce the absorbable concentration at the site of absorption.

1. Membrane Factors.

2. Environmental Factors.
A. Saliva.
B. Salivary glands.
C. Movement of Buccal tissues.

3. Formulation related factors:
A. Molecular size.
B. Partition coefficient.
C. pH.
D. pKa.[22]

Methods to improve drug delivery via Buccal route

1. Absorption enhancers.
2. Pro drugs.
3. PH.

Different dosage forms of Buccal route

a. Buccal tablets

These are solid dosage forms prepared by the compression of powder mixes that can be placed into contact with the oral mucosa and allowed to dissolve or adhere depending on the type of excipients incorporated into the dosage form. They can deliver drug multidirectionally into the oral cavity or to the mucosal surface.

b. Buccal gels and ointments

Semisolid dosage forms usually include gels, creams and ointments, which are applied topically into the mucosal surface for either local or systemic effects. These typically contain a polymer and drug plus any required excipient dissolved or suspended as a fine powder in an aqueous or non-aqueous base. Hydrogels can also be used in semi-solids for drug delivery to the oral cavity.

c. Buccal Patches/Films

These dosage forms are usually prepared by casting a solution of the polymer, drug and any excipients (such as a plasticiser) on to a surface and allowing it to dry. Patches can be made 10-15 cm2 in size but are more usually 1-3 cm2 with perhaps an ellipsoid shape to fit comfortably into the centre of the Buccal mucosa.

d. Buccal sprays

Generex biotechnologies have been introduced insulin spra. This technology is being used to develop a formulation for Buccal delivery of insulin for the treatment of type-1 diabetes Buccal spray delivers a mist of fine droplets onto mucosal membrane probably on to mucin layer. e. g. Estradiol sprays [23-24]

In vitro in vivo evaluations of buccal mucoadhesive drug delivery system[23,24,25,26]

1. Moisture absorption studies for Buccal patches

The moisture absorption studies for the Buccal patches give an indication about the relative moisture absorption capacities of polymers and an idea whether the Buccal patches maintain their integrity after absorption of moisture. Moisture absorption studies have been performed in 5% w/v agar in distilled water, which while hot was transferred to petri plates and allowed to solidify. Then six Buccal patches from each formulation were selected and weighed.

Buccal patches were placed in desiccator overnight prior to the study to remove moisture if any and laminated on one side with water impermeable backing membrane. Placed on the surface of the agar plate and incubated at 37°C for 2 hrs in incubator. The patches were weighed again and the percentage of the absorbed moisture was calculated using the formula:

% Moisture absorbed = Final weight – Initial weight×100Initial weight

2. Swelling and erosion studies for Buccal tablets

Swelling and erosion studies for Buccal tablets were determined gravimetrically in phosphate buffer, of pH 6.6. The tablets were attached to pre-weighed glass supports using a cyanoacrylate adhesive sealant. The supports with tablets were immersed into the phosphate buffer at $37.^{0}$C. At pre-determined time intervals, the devices were removed from the media, blotted with tissue paperto remove excess water, and weighed. After determination of the wet weight, the tablets were dried at 40°C until constant mass.

3. Determination of tensile strength

Tensile stress is also termed Maximum Stress or Ultimate Tensile Stress. The resistance of a material to a force tending to tear it apart, measured as the maximum tension the material can withstand without tearing. Tensile strength can be defined as the strength of material expressed as the greatest longitudinal stress it can bear without tearing apart. As it is the maximum load applied in breaking a tensile test piece divided by the original cross-sectional area of the test piece, it is measured as Newtons/sq.m.

4. Colloidal gold staining method

Park proposed the colloidal gold staining technique for the study of bioadhesion. The technique employs red colloidal gold particles, which were adsorbed on mucin molecules to form mucin–gold conjugates, which upon interaction with bioadhesive hydrogels develops a red color on the surface. This can be quantified by measuring at 525 nm either the inte `nsity on the hydrogel surface or the conjugates.

5. Direct staining method

It is a novel technique to evaluate polymer adhesion to human Buccal cells following exposure to aqueous polymer dispersion, both in vitro and in vivo. Adhering polymer was visualized by staining with 0.1% w/v of either Alcian blue or Eosin solution; and the uncomplexed dye was removed by washing with 0.25 M sucrose. The extent of polymer adhesion was quantified by measuring the relative staining intensity of control and polymer treated cells by image analysis. Carbopol 974 P, polycarbophil and chitosan were found to adhere to human Buccal cells from 0.10% w/w aqueous dispersions of these polymers.

Following in vivo administration as a mouthwash, these polymers persisted upon the human Buccal mucosa for at least one hour.

6. Shear stress method

The measurement of the shear stress gives an direct correlation to the adhesion strength. In asimple shear stress measurement based method two smooth, polished plexi glass boxes wereselected one block was fixed with adhesive araiditeon a glass plate, which was fixed onleveled table. The level was adjusted with the spirit level. To the upper block, a thread was tied and the thread was passed down through a pulley, the length of the thread from the pulley to the pan was 12cms. At the end of the thread a pan of weight 17gms was attached into which the weights can be added

7. Detachment force measurements

The Wilhelmy plate method is one of the traditional methods for the measurement of the force of adhesion of various bioadhesive dosage forms. The method involves the measurement of the dynamic contact angles and utilizes a microtensiometer and a microbalance. The CAHN dynamic contact angle analyzer is used for this purpose.

Wilhelmy plate method measures the bioadhesive force between the mucosal tissue and the polymer/dosage form attached to a metal wire and suspended into the microtensiometer.

i. Fracture strength: force per unit area required to break the adhesive bond.

ii. Deformation to failure: it is the distance required to move the stage before complete separation occurs.

8. Surface pH study: The surface pH study for Buccal tablets has to be done to investigate the possibility of any side-effect in vivo. An acidic or alkaline pH may irritate the Buccal mucosa, so the surface pH of tablet should be almost neutral. The tablets are allowed to swell by placing them in an agar plate for 2hr. The surface pH was measured by using a pH digital meter placed on the core surface of the swollen tablet. Bottenberg et.al used a combined glass electrode for the study. In this method the tablet was allowed to swell by placing it in contact with 1mL of distilled water (pH 6.5±0.05) for 2hrs at room temperature. The pH was determined by bringing the electrode into contact with the tablet surface and allowing the surface to equilibrate for 1minute.

9. *In-vitro* drug permeation study

Can be performed using Keshary-chien type glass diffusion cell at 37±0.2°C. The fresh pig Buccal mucosa (Buccal membrane closely resembles the human Buccal membrane in terms of structure and permeability) is to be mounted between donor and receptor compartments, the Buccal tablet is placed with the core facing the mucosa and the compartments are clamped together. The donor compartment is to be filled with 1mL of phosphate buffer pH6.8 and receptor compartment with phosphate buffer pH7.4, hydrodynamics between compartments is maintained with a magnetic bead at a uniform slow speed. The samples at pre-determined intervals of time are analyzed with the help of a U.V Spectrophotometer.

10. *In vitro* drug release studies

In-vitro release studies can be performed according to USP XXII type2 dissolution apparatus at suitable pH conditions. The temperature should be maintained at 37±0.5°C and the rotation speed of 100 rpm. Then 5ml of sample should be withdrawn at varioustime intervals and replenished with an equal volume of fresh dissolution media. The drug content in the sample can be analyzed spectrophotometrically at specific wavelength (nm).

10. *In vivo* tests

There is scant information available on the in vivo behavior of mucoadhesive formulations, especially in humans. applied gamma scintigraphy to analyse mucoadhesion in vivo of chitosan within the gastrointestinal tract. Pharmacokinetic study also performed.

11. Stability study in human saliva

The stability study of optimized bilayered and multilayered patches is performed in human saliva. The human saliva is collected from humans (age 18-50 y). Buccal patches are placed in separate Petri dishes containing 5 ml of human saliva and placed in a temperature controlled oven at 37°C±0.2°C for 6 h. At regular time intervals (0, 1, 2, 3, and 6 h), the dose formulations with better bioavailability are needed. [25-26]

CONCLUSION

Day bay day Buccal mucoadhesive drug delivery system getting popularity. The main objective of using bioadhesive systems orally would be achieved by obtaining a substantial increase in residence time of the drug for local drug effect and to permit once daily dosing. The natural mucoadhesive polymer as a carrier for Buccal drug delivery can be used to improve the health of all living things and to minimize the unwanted effect of synthetic polymers.Pharma researcher who are working on natural polymers should introduce new natural natural polymers in Bucco mucoadhesive drug delivery.

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