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Review Article

A Brief Review on Bucco-adhesive Drug Delivery System

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Abstract

The buccal region within the mucosal cavity of the mouth provides an alternative route over an oral drug administration for systemic as well as local drug delivery. As the buccal mucosa has an abundant blood supply and is relatively permeable, it can be considered as most accessible and desired location for both local and systemic drug delivery. The buccal method for medication delivery greatly helps in avoiding issues in the gastrointestinal environment, such as increased first-pass metabolism and medication degradation. Bucco-adhesive systems offer varieties of advantages such as convenience in administration and termination of therapy in case of emergency, higher patient compliance, better bioavailability, rapid absorption, etc. This current review highlights the bucco-adhesive drug delivery system, its advantages and limitations, mechanisms and theories of mucoadhesion, different bucco-adhesive dosage forms, and bioadhesive polymers. It also highlights the current status on mucoadhesive drug delivery methods for the buccal cavity or bucco-adhesive systems.

Keywords: Bioadhesion, mucoadhesion, bucco-adhesive drug delivery system, oral mucosa, first-pass metabolism, bioadhesive polymers.

INTRODUCTION

The phenomenon in which two materials are attached with each other for a prolonged period of time due to interfacial forces where one material is at least of biological nature are known as bioadhesion. It simply means the adherence/ attachment of any drug delivery system to a particular biological surface. Epithelial tissue or the mucous layer are examples of biological surfaces. The adhesive attachment if it happens with a mucus layer then it can be known as mucoadhesion[1]. Mucoadhesive drug delivery system are those system which basically utilizes the bioadhesion property of certain polymers which on hydration become adhesive and therefore can be used to target a drug at a particular region of the body for a prolonged period of time[2]. There are several areas like the respiratory tract, the gastro-intestinal tract, eye, ear, nose, etc. lined by mucous membrane where any bioadhesive system can attach or adhere.

The mucoadhesive delivery system can be classified based on their route of application as follows[3]:

1. Buccal drug delivery system
2. Ocular drug delivery system
3. Nasal drug delivery system
4. Gastrointestinal drug delivery system
5. Rectal drug delivery system
6. Vaginal drug delivery system

The mucoadhesive delivery system has several advantages like prevention of first pass metabolism, better bioavailability, specific tissue targeting, rapid onset of action, elimination of enzymatic degradation, etc. Basically, it can be considered as a possible option for both systemic as well as local drug distribution. Among these, oral mucosa is perhaps the most convenient and preferred route for drug delivery[4].

The delivery of drug over the mucosa of the mouth can be classified into three types[5]:

1. Sublingual delivery- involves delivery of drug via the Ventra surface of the tongue and the floor of the mouth's mucosal membrane.

2. Buccal delivery- involves the delivery of drug via means of the mucosal membrane lining the cheeks i.e. buccal mucosa.

3. Local delivery- involves delivery of drug inside the oral cavity.

The buccal mucosa present in the mouth cavity is highly vascularized with an abundant blood supply and is relatively permeable. Moreover, it bypasses first pass metabolism and prevents pre-systemic GI tract degradation[6].

MECHANISM OF MUCOADHESION

Basically, mucoadhesion is the phenomenon in which two materials, one which may be artificial substance like polymer for mucoadhesion and other material the mucin layer lining

the mucosal tissue are adhered together for prolonged period of time with the aid of interfacial forces.

The process of mucoadhesion, generally involves two stages:

1. Contact stage
2. Consolidation stage

Contact stage- An intimate bond between the mucoadhesive substance and the mucous membrane take place when they come in contact with each other during this stage.

Consolidation stage- The attachment of mucoadhesive material to the mucous membrane by different physicochemical forces of attraction cause a prolong and deep intimate adhesion and is called as consolidation stage[7].

THEORIES OF MUCOADHESION[8]

There are several theories of mucoadhesion which are as follows:

a. Electronic theory- As the mucoadhesive and biological materials both carry opposite electrical charges, so on coming in contact with each other, transfer of electrons takes place at the interface which results in the formation of double electronic layer. These attractive forces determine the mucoadhesive strength.

b. Adsorption theory- Initial contact between mucus and mucoadhesive polymer results in the formation of chemical bonds i.e., primary and secondary bonds (covalent and non-covalent).

c. Wetting theory- The ability of bioadhesive polymer to spread over the biological surface is described in this theory. Here, the angle of contact between the two surfaces is measured. The wettable polymers exhibit optimal adhesion to epithelial surfaces.

d. Diffusion theory- The penetration of mucin and polymer chains to a suitable depth creates a semi-permanent adhesive bond which is necessary for the components to have good mutual solubility for diffusion to take place.

e. Fracture theory- The amount of force needed to separate the polymer from the mucus is measured. This theory is based on the measurement of mechanical strength of mucoadhesion.

f. Mechanical theory- In this theory, adhesion occurs when mucoadhesive liquid fills the irregularities present on a rough surface.

ORAL MUCOSA

The oral mucosa has three distinctive layers namely the epithelium, connective tissue and basement membrane[9]. The stratified squamous epithelium coated with mucus is found on the outermost layer of oral mucosa. The thickness of epithelium is about 40-50 cell layers thick[10].

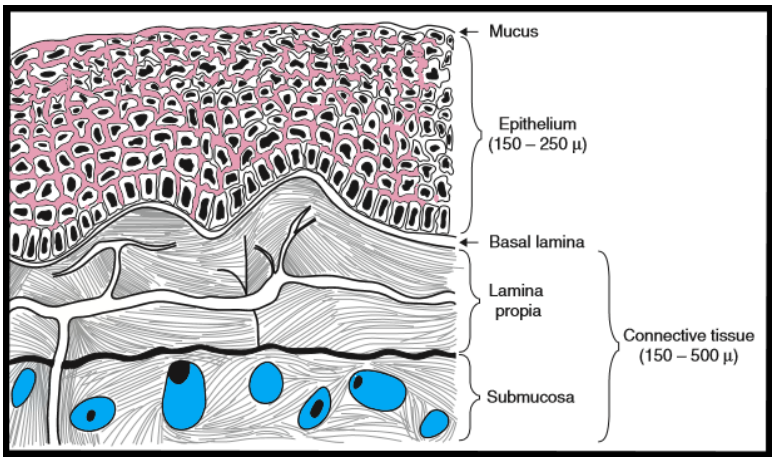

Figure 1: Structure of buccal mucosa[11]

The basement membrane, lamina propia, and submucosa lie underneath the epithelium. The mucosa of the mouth can be classified into five types based on the different oral cavity areas[12]:

1. The mouth's floor (sublingual region)
2. The mucosa of the buccal cavity (cheeks)
3. The gum (gingiva)
4. The palatal mucosa
5. The lips from the inner side.

The mucosae of buccal, sublingual and soft palate are non-keratinized whereas the mucosae of hard palate and gingivae are keratinized. The non-keratinized epithelia have more permeability than keratinized epithelia[13]. Buccal mucosa permeability is believed to be 4-4000 times higher than skin permeability. Oral mucosa's permeability is in order as sublingual>buccal>palatal which depends mainly on keratinization level and relative thickness[14]. The thickness of buccal mucosa is 500-800mm and the thickness of sublingual region i.e., the ventral tongue, the hard palate, the soft palate, and the gingivae is 100-200mm[15].

BUCCAL DRUG DELIVERY SYSTEM

Buccal drug delivery system is defined as the delivery of a medication to the systemic circulation via the buccal mucosa, which is the lining of the cheek. Buccal route is suitable for administration of hydrophilic oligonucleotides and polysaccharides, as well as large unstable proteins. It is used as the mostly desired site for systemic as well as local medication delivery[16]. The buccal mucosa coats the inside of the cheek and to treat systemic and local diseases, a buccal dosage form should be inserted in the mouth between the upper gingiva and the cheek[17]. This system is considered as a possible alternative to drug administration as it has more advantages over peroral routes. Buccal mucosa avoids enzymatic decomposition in gastrointestinal tract and first-pass metabolism of drug as the buccal mucosa are highly vascularized with an abundant blood supply and is relatively permeable which allows drug to be absorbed directly into the systemic circulation[18]. The buccal cavity has short

residence time caused by excessive salivation and swallowing, therefore developing a suitable bioadhesive system is necessary that stick to the buccal mucosa for a prolonged period of time[19]. Bucco-adhesive drug delivery systems are those system in which the drugs are administered in the oral cavity's buccal mucosa[20]. Bucco-adhesive drug delivery system are suitable for drugs having short half-lives, poor permeability and solubility, susceptible to enzymatic decomposition and drug that require sustained effect. The administration of medication using this system is completely safe and easy and the dosage form can be removed any time required in case of emergency[21].

ADVANTAGES OF BUCCO-ADHESIVE DRUG DELIVERY SYSTEM[22]

1. Avoids first pass metabolism and hence offers greater bioavailability.
2. Allows drug localization for a prolonged period of time.
3. Provides convenience for administration and termination of therapy in case of emergency.
4. Can be easily administered to unconscious patient.
5. It is possible to obtain significant dose decrease.
6. Drugs that are likely to be unstable in acidic or in an alkaline condition of stomach and intestine or drug that are susceptible to enzymatic degradation can be administered.
7. Drug absorption take place by passive diffusion.
8. Better patient compliance or acceptance.
9. Provides sustained delivery of drug.
10. Rapid onset of action.

LIMITATIONS OF BUCCO-ADHESIVE DRUG DELIVERY SYSTEM[23]

1. Drugs that irritate oral mucosa, have odor and bitter taste, are unpalatable cannot be administered.
2. Drugs that are unstable at buccal pH cannot be administered.
3. Drugs with a low dosage need can be given.
4. Excess salivation may cause swallowing of drug.
5. Drugs that are absorbed through passive diffusion can be administered.
6. Food and liquid consumption may not be convenient.
7. Accidental swallowing of formulation by patients is possible.

MUCOADHESIVE POLYMERS

While developing a buccal drug delivery system, mucoadhesive plays a vital role so that there can be in increase in the duration of the dosage form's stay at the desired site. These may be water soluble and water insoluble polymers. These polymers form a close contact with mucosal surface as soon as they come in contact with moist surface of mucin layer[24].

The popularity of mucoadhesive drug delivery system have been increasing day by day and with that, vast numbers of polymers are being designed and developed recently such as acrylated polymers, chitosan, cellulose derivatives, alginates, etc. are the most widely used[25].

Mucoadhesive polymers attach to the mucin epithelial surface and may be classified into three categories:

1. Sticky polymers that attribute their mucoadhesion to their stickiness when put in water.
2. Polymers that are predominantly electrostatic in nature and attach through nonspecific, non-covalent interactions (although hydrogen and hydrophobic bonding may be significant).
3. Polymers that attach to a particular receptor location on a tile self-surface[26].

Ideal Mucoadhesive Polymer Characteristics[27] -

1. It must be non-toxic and non-absorbable by the gastrointestinal tract.

2. It must not irritate the mucous membrane.

3. It should create a strong non-covalent connection with the epithelial mucin layer.

4. It should attach to most tissues quickly and have some site specificity.

5. It must allow the drug to be easily incorporated and shouldn't obstruct its release.

6. During storage or the shelf life of the dosage form, the polymers must not degrade.

7. The cost of the polymer should not be prohibitively high in order for the produced dosage form to stay competitive.

DIFFERENT BUCCO-ADHESIVE DOSAGE FORMS[28]

Bucco-adhesive dosage forms may be divided into three distinct categories:

a. Solid dosage form- includes tablets, lozenges, bioadhesive wafers, etc.

b. Semisolid dosage form- includes chewing gums, adhesive gels and ointments, patches and films, etc.

c. Liquid dosage form- includes mouth washes, mouth spray, mouth fresheners, etc.

Among these dosage forms, only few have been successful into reaching the market.

CURRENT STATUS

Mucoadhesive drug delivery systems are globally gaining popularity and nowadays more scientists and researchers are working on the design and development of new devices related to adhesion. Vast numbers of new formulations are coming up day by day and their demands are on the rise. Mucoadhesive preparations and the use of peptides as drug are one the example of such new developments. Mucoadhesive drug delivery systems available in the market include Oralone tablet (Triamcinolone acetonide), Susadrin tablet (Nitroglycerin), Buccostem tablet (Prochlorperazine maleate), Salcoat powder sprays (Beclomethasone dipropionate), Rhinocort powder spray (Budesonide) and Sucralfate (Aluminum hydroxide). However, only few formulations currently have been able to make it to the market so far but by looking at its increasing popularity, more new formulations types could be expected in the coming years[29].

Table: List of some of the marketed buccal products[30]

PRODUCT NAME	DRUGS	DOSAGE FORM	MANUFACTURER
Buccastem	Prochlorperazine	Tablet	Reckitt Benckiser
Suscard	Glyceryl trinitrate	Tablet	Forest laboratories
Aphtach	Triamcinolone acetonide	Tablet	Teijin Ltd
Straint SR	Testosterone	Tablet	Ardana Bioscience Ltd
Zolpimist	Zolpidem	Spray	NovaDel Pharmaceuticals
Coralan	Hydrocortisone sodium succinate	Pellets	Celltech Pharma Ltd
Corsodyl	Chlorhexidine Hydrocortisone sodium succinate	Gel	GlaxoSmithKline
Subutex	Buprenorphine HCl	Tablet	Reckitt Benckiser
Actiq	Fentanyl citrate	Lozenge	Cephalon
Nicorette	Nicotine	Chewing gum	GSK Consumer Health
Nitrostat	Nitroglycerine	Tablet, Spray	Pfizer Pharmaceuticals
Suboxone	Buprenorphine hydrochloride-naloxone HCl	Tablet	Reckitt Benckiser
Sativex	Cannabis-derived	Spray	GW Pharmaceuticals, PLC

CONCLUSION

Buccal regions provide a convenient route for both local and systemic delivery of drugs. Bucco-adhesive systems offers several advantages over other delivery systems such as easy administration and withdrawal of delivery system, higher patient compliance, prevention of first-pass metabolism, cost effectiveness and so on. It allows for close contact between the dosage form and the buccal cavity. and ensures longer residence time which offers prolonged drug release. Many new developments and works are still going on all around the world on mucoadhesive buccal drug delivery system. The future direction of bucco-adhesive drug delivery system lies in vaccine formulation and delivery of small proteins and peptides.

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The authors report no conflicts of interest in this review work.

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