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A REVIEW ON MUCOADHESIVE DRUG DELIVERY

Raghavarapu Hemanth Kumar*[1], J. N. Suresh Kumar[1], Sravan Kumar Pudota[1]

[1]*Department of Pharmaceutics, Narasaraopet Institute of Pharmaceutical Sciences, Narasaraopet, Guntur, Andhra Pradesh, India.

ABSTRACT

The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Because after oral administration many drugs show first-pass metabolism, which leads to a lack significant correlation between membrane permeability, absorption, and bioavailability. Difficulties associated with parenteral delivery and poor oral bioavailability provides alternative route for delivery of such drugs. These include routes such as pulmonary, ocular, nasal, rectal, buccal, sublingual, vaginal, and transdermal. Among the varies transmucosal routes the mucosal lining of the oral cavity offers some distinct advantages.

KEYWORDS

Buccal region, Mucosal membrane, Oral administration, Sublingual, Transmucosal and Transdermal.

Author for Correspondence:

Raghavarapu. Hemanth Kumar,

Department of Pharmaceutics,

Narasaraopet Institute of Pharmaceutical Sciences,

Narasaraopet, Guntur, Andhra Pradesh, India.

Email: hemanthkumar506@gmail.com

INTRODUCTION[1]

The term bio adhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. In case of bio adhesive drug delivery, the term bio adhesion is used to describe the adhesion between polymers, either synthetic or natural and soft tissues or the gastrointestinal mucosa. In cases where the bond is formed with the mucus the term mucoadhesion may be used Synonymously with bio adhesion. Mucoadhesion can be defined as a state in which two components, of which one is of biological origin

are held together for extended periods of time by the help of interfacial forces. Generally speaking, bio adhesion is an term which broadly includes adhesive interactions with any biological or biologically derived substance, and mucoadhesion is used when the bond is formed with a mucosal surface[2-10]. Mucoadhesive drug delivery systems includes the following

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

Formulation Design

Buccal adhesive drug delivery systems with the size 1-3 cm^2 and a daily dose of 25 mg or less are preferable. The maximal duration of buccal delivery is approximately 4-8 h[11].

Buccal Adhesive Polymers

A polymer is a molecule made up of a chain of repeating units which are chemically bonded together. Adhesives are substances which are used to glue things together. A polymer adhesive is a synthetic bonding substance made from polymers and is considered to be stronger, more flexible and have greater impact resistance than other forms of adhesives. The term is derived from the Greek words: polys meaning many, and meros meaning parts. Bio adhesive polymers should possess certain physicochemical features including hydro philicity, numerous hydrogen bond-forming groups, flexibility for interpenetration with mucus and epithelial tissue, and visco-elastic properties[12].

Ideal Characteristics

1. Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
2. Should have good spread ability, wetting, swelling and solubility and biodegradability properties.
3. pH should be biocompatible and should possess good viscoelastic properties.
4. Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.
5. Should possess peel, tensile and shear strengths at the bio adhesive range.
6. Polymer must be easily available and its cost should not be high.
7. Should show bio adhesive properties in both dry and liquid state.
8. Should demonstrate local enzyme inhibition and penetration enhancement properties.
9. Should demonstrate acceptable shelf life.
10. Should have optimum molecular weight.
11. Should possess adhesively active groups.
12. Should have required spatial conformation.
13. Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.
14. Should not aid in development of secondary infections such as dental caries.

Physiological Considerations

Physiological considerations such as texture of buccal mucosa, thickness of the mucus layer, its turn over time, effect of saliva and other environmental factors are to be considered in designing the dosage forms[13]. Saliva contains moderate levels of esterases, carbohydrases, and phosphatases that may degrade certain drugs. Although saliva secretion facilitates the dissolution of drug, involuntary swallowing of saliva also affects its bioavailability. Hence development of unidirectional release systems with backing layer results high drug bioavailability.

Permeation Enhancers

Substances that help to promote drug permeation through the buccal epithelium are referred to as penetration enhancers, permeation promoters or absorption enhancers[14]. The chemicals used as penetration enhancers ideally should be safe and non-toxic, pharmacologically and chemically inert, non-irritant, and non-allergenic[15]. Penetration enhancers can be divided into many categories according to their structure, mechanism of action, and the type of drugs whose permeation they enhance. Most of the compounds used as buccal mucosal penetration enhancers are the ones generally used to compromise barrier function. Different types of permeation enhancers are shown in the Table No.1.

Mechanisms of Action

Due to its relative complexity, the process of mucoadhesion cannot be described by just one of the theories. In considering the mechanism of mucoadhesion, a whole range of scenarios for *in-vivo* mucoadhesive bond formation are possible

In the study of adhesion generally, two steps are identified, which have been adapted to described the interaction between mucoadhesive materials and a mucous membrane [16,17]. The mechanism shows in Figure No.1 and 2.

Step-1: contact stage: An intimate contact (wetting) occurs between the mucoadhesive and mucous membrane.

Step-2: consolidation stage: various physicochemical interaction occur to consolidate and strengthen the adhesive joint, leading to prolonged adhesion.

Muco/Bio Adhesion

Adhesion is defined as the state in which surfaces are held together by interfacial forces, which may consist of valence forces interlocking action, or both. The term Bio adhesion is used to describe adhesion between two materials where at least one of the materials is of the biological origin. In case of Bio adhesive drug delivery system, Bio adhesion often refers to adhesion between the excipients of the formulation and biological tissue. Mucoadhesive drug delivery systems utilize the property of certain water-soluble polymers, which become adhesive on hydration and hence can be used for targeting a drug to a particular region of body for an extended period of time[18, 19].

THE MUCOADHESION INTERACTION

Chemical bonds: the molecule must bond across the interface for adhesion to occur. These bonds can arise in the following ways[20].

1. Ionic bonds
2. Covalent bonds
3. Hydrogen bonds
4. Vander wall bonds
5. Hydrophobic bonds
6. Hydrogen bonding
7. Disulphide bridging
8. Hydration forces
9. Electrostatic double-layer forces
10. Steric forces.

Theories of Bio Adhesion

There are various general theories of adhesion, which have been adapted for investigation of mucoadhesion[21-23].

Adsorption theory

According to this theory, after an initial contact between two surfaces, the material adheres because of surface forces. Two types of chemical bonds resulting from these forces can be distinguished:

I. Primary chemical bonds of covalent nature which are undesirable in Bio adhesion because there high strength may result in permanent bond.

II. Secondary chemical bonds having many different forces of attraction, including electrostatic force, Vander-wall forces, hydrogen and hydrophobic bonds.

Diffusion theory

According to this theory, polymer chains and the mucus mix to a sufficient depth to form a semi-permanent bond. The depth of interpenetration depends on the diffusion coefficient and time of contact. This diffusion coefficient depends on the molecular weight between cross-links and decreases significantly as the cross linking density decreases.

Electronic theory

According to this theory, an electronic transitions occurs upon contact of adhering surfaces and due to differences in there electronic structure. This is proposed to result in the formulation of an electrical double layer at the interface with subsequent adhesion due to attractive forces.

Mechanical theory

According to this theory, adhesion arises from an interlocking of a liquid adhesive into irregularities on a rough surface. However, rough surfaces provide an increase area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are thought to be more important in adhesion process than a mechanical effect.

Wetting theory

This theory is predominantly applicable to liquid and solid Bio adhesive systems. It analyses adhesive and

contact behavior in terms of the ability of liquid or paste to spread over biological system.

Various theories exist, but it is clear that all the mechanisms of adhesion require high intimate contact between the polymer and mucin and expanded network in both substances favours strong adhesion. Although these theories have provided some insight, no single theory has been successful in explaining the muco adhesion phenomenon, this is due to the fact that in actual process a number of factors are involved simultaneously.

Methods to Study Mucoadhesion

The evaluation of muco adhesive properties is fundamental to the development of novel Bio adhesive drug delivery system. Measurement of the mechanical properties of a Bio adhesive material after interaction with a substrate is one of the most direct ways to quantify the Bio adhesive performance. Testing is essential for the development, quantification, processing and proper use of the Bio adhesive. Several methods have been developed for the determination of Bio adhesive bond strength. These tests are also important during the design and development of Bio adhesive controlled release system as they ensure compatibility, physical and mechanical stability, surface analysis, and Bio adhesive strength[24].

The test methods can be classified into two major categories:

1. *In vitro/Ex vivo* methods
2. *In vivo* methods

***In vitro/Ex vivo* methods**

The in vitro methods are based on the measurements of either tensile stress or shear stress.

Methods based on measurement of tensile strength

In these methods the force required to break the adhesive bond between a model membrane and the test polymer is measured.

Tensinometer

This instrument consists of two jaws from flat glasses. The upper glass was fixed, but the lower glass had been mounted on a screw-elevating surface. The upper fixed glass was attached to a sensitive digital balance. Tablets from each formulations were suspended in water (pH 7) for 15 min. Then these adhesive tablets were located on the surface of lower glass and were elevated until they contact the surface of upper glass. The lower glass was then lowered until the tablet clearly was pulled free from the upper glass. The maximum tensile force needed to detach the jaws was recorded in gram/cm and mean values were calculated and recorded [25].

Modified balance method

Modified double beam physical balance was used as the Bio adhesion test apparatus. The right pan of the balance was replaced with lighter one and pan was prepared with the Teflon ring hanging by a number of metallic rings. A cylinder at whose base a tablet was attached was hung from this ring. The two sides of the balance were then balanced with a fixed weight on the right hand side. The mucus membrane was tied with mucosal side upward using a thread over a Teflon block. The block was then lowered into the jacketed beaker which was then filled with phosphate buffer such that buffer just reached the surface of the balance. The balance beam was raised by removing the fixed weight kept on the right side of the pan. This lowered the Teflon cylinder along with the tablet over the mucosa. The balance was kept in this position for a fixed time and then slowly increased on the right pan till the tablet separated from the mucus surface. The excess weight on right hand side gave the Bio adhesive strength of the tablet in grams. It was observed that assembly gave reproducible results and performed efficiently [26].

Buccal adhesive drug delivery system

Recent buccal mucoadhesive formulations prove to be an alternative to the conventional oral medications as they can be readily attached to the buccal cavity retained for a longer period of time and removed at any time. Mucoadhesive adhesive drug delivery systems using tablets, films, layered systems, discs, micro particles, ointments, wafers, lozenges and hydro gel systems has been studied by various research groups.

Buccal tablet is the tablet which dissolves when held between the cheek and gum, permitting direct absorption of the active ingredient through the oral

mucosa but tablets have some limitations such as size for tablet due to requirement for the dosage form.

Micro particles have more advantages than tablet. The physical properties of microspheres enable to make them closely contact with a large mucosal surface. They can also be delivered to less accessible sites like GI track and nasal cavity and they cause less local irritation at the site of adhesion but the success of these microspheres is limited due to their short residence time at site of absorption.

Wafers are a novel periodontal drug delivery system. This is used for the treatment of microbial infection.

Lozenges are used as topically within mouth including antimicrobials, corticosteroids, local anesthetics, antibiotics and antifungal. In lozenges multiple daily dosing is required because the release of drug in oral cavity is initially high and then rapidly decline to the sub therapeutic levels.

Buccal patches

These are flexible which deliver the drugs directly in to systemic circulation through mucos membrane thereby by passing the first pass effect. Buccal patch formulations are placed in the mouth between the upper gingivae (gums) and cheek to treat local and systemic conditions. Contact with digestive food of gastrointestinal tract is avoided which might be unsuitable for stability of many drugs. This is painless and without discomfort, precise dosage form and facilitates ease of removal without significant associated pain. Moreover it shows better stability, patient compliance; uniform and sustained drug release and above all easy and cheap methods of preparation which can be done with various commonly available biocompatible polymers.

An ideal buccal adhesive system must have the following properties[27-30]:

1. The drug release should be in a controlled fashion
2. Drug release should be in unidirectional way towards the mucosa
3. The rate and extent of drug absorption should be facilitated
4. Should not cause any irritation or inconvenience to the patient
5. Should not interfere with the normal functions such as talking, drinking etc
6. Should adhere to the site of attachment for a few hours.

Table No.1: Provides an overview of some of the different chemical classes that have been used, with examples of materials and the proposed mechanisms of action[31-37]

Mucosal penetration enhancers and mechanisms of action

Classification	Examples	Mechanism
Surfactants	**Anionic:** sodium lauryl sulfate, sodium laurate **Cationic:** cetylpyridinium Chloride Nonionic: poloxamer, Brij, Span, Myrj, Tween **Bile salts:** sodium glycodeoxycholate, sodium glycocholate, sodium taurodeoxycholate, sodium taurocholate	Perturbation of intercellular lipids, protein domain integrity
Fatty acids	Oleic acid, caprylic acid	Increase fluidity of phospholipid Domains
Cyclodextrins	a-, b-, g-cyclodextrin, methylated b-cyclodextrins	Inclusion of membrane compounds
Chelators	EDTA, sodium citrate, Polyacrylates	Chelators EDTA, sodium citrate Interfere with Ca^{2+}
Positively charged polymers	Chitosan, trimethyl chitosan	Ionic interaction with negative
Cationic compounds	Poly-L-arginine, L-lysine	charge on the mucosal surface

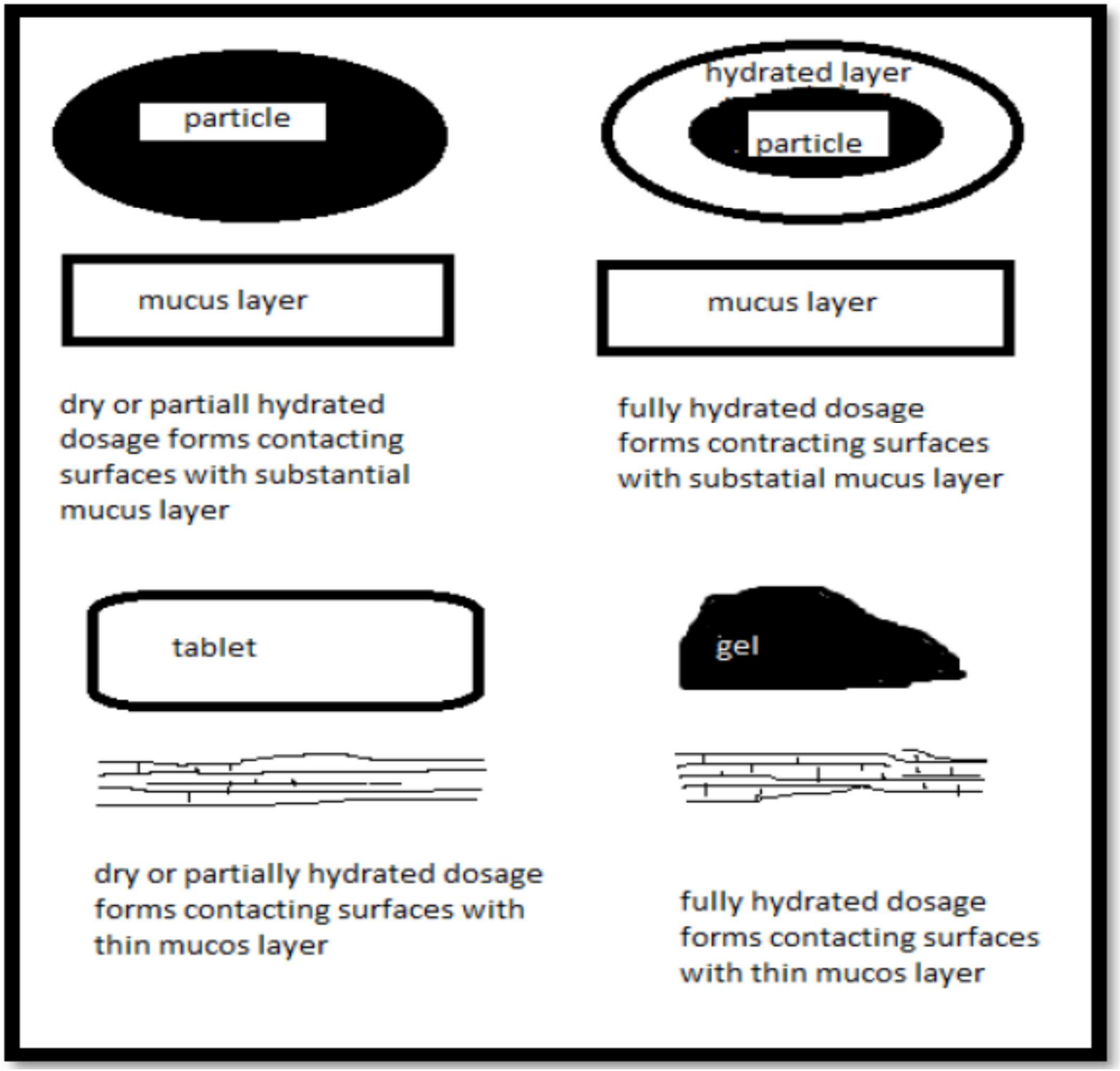

Figure No.1: Mechanism of Muco adhesion

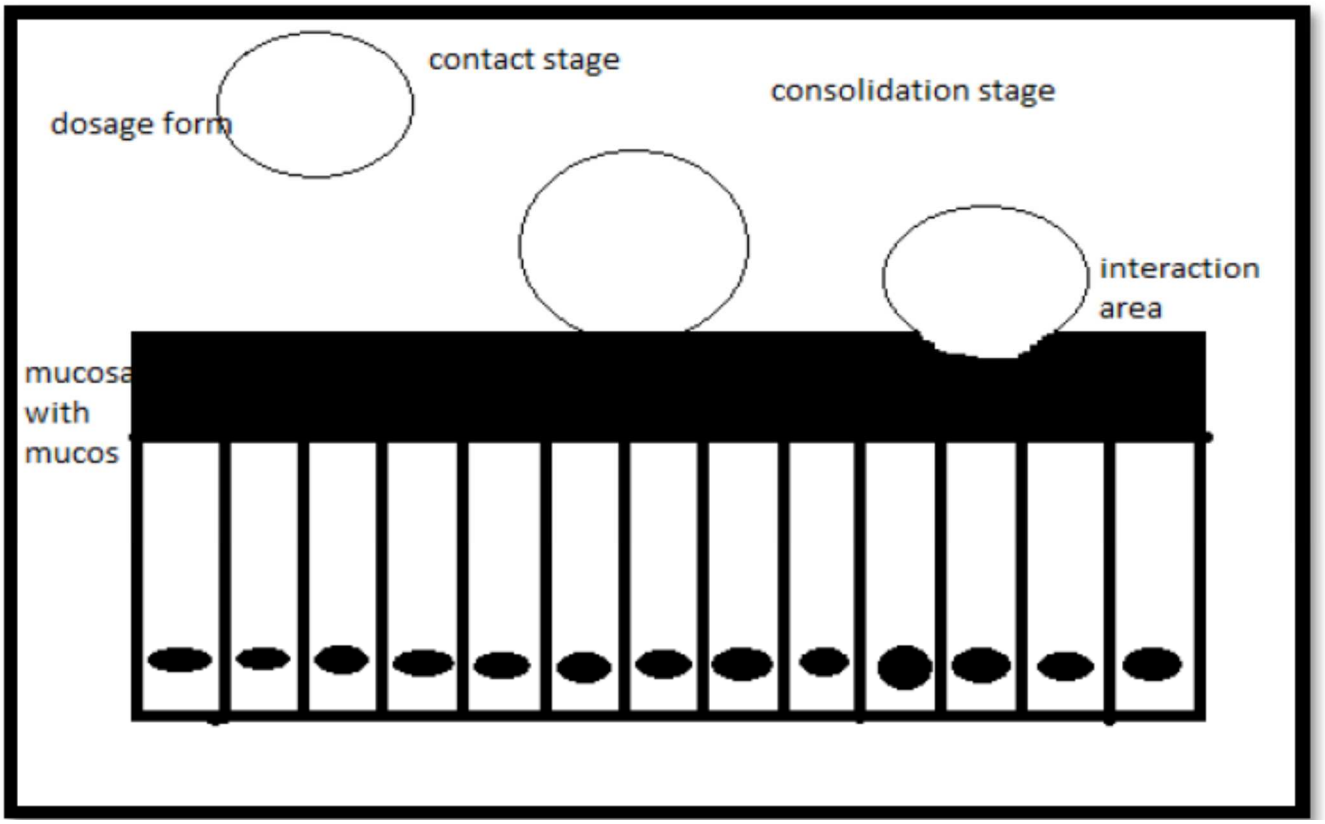

Figure No.2: Mechanism of Muco adhesion

CONCLUSION

The buccal mucosa offers several advantages over controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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