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EXPLORING MUCOSAL PATHWAYS FOR DRUG DELIVERY: FROM DESIGN TO CLINICAL APPLICATIONS

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ABSTRACT

Mucoadhesion is defined as, the attachment of two materials, at least one of which is a mucosal surface, is frequently referred to as mucoadhesion. Mucoadhesive dosage forms can be made to allow for extended retention at the application site, resulting in a regulated rate of drug release for better therapeutic results. Drug molecules that are not suitable to the oral route, such as those that undergo acid degradation or substantial first-pass metabolism, may benefit from the application of dosage forms to mucosal surfaces. A number of variables, such as the type of mucosal tissue and the physicochemical characteristics of the polymeric formulation, affect a dosage form's capacity to adhere to mucosal tissue. The ability of a dosage form to stick to mucosal tissue depends on several factors, including the kind of mucosal tissue and the physicochemical properties of the polymeric formulation.

KEYWORDS: Substantial first pass metabolism, mucosal tissue, retention, Polymeric formulation, Chemo embolization.

INTRODUCTION

Bioadhesion and Mucoadhesion

The situation in which two materials, at least one of which is biological in nature, are kept together for a long time by interfacial forces is known as bio adhesion. Three categories of bio adhesion exist in biological systems.

Type 1: adhesion between two biological phases, such as wound healing and platelet aggregation.

Type 2: Cell adhesion to culture dishes and biofilm formation on prosthetic devices and inserts are examples of type 2 adhesion, which occurs when a biological phase adheres to an artificial substrate.

Type 3: refers to the adherence of an artificial substance to a biological substrate, such as the adherence of sealants to dental enamel or synthetic hydrogels to soft tissues.[1]

Stages of muco adhesion

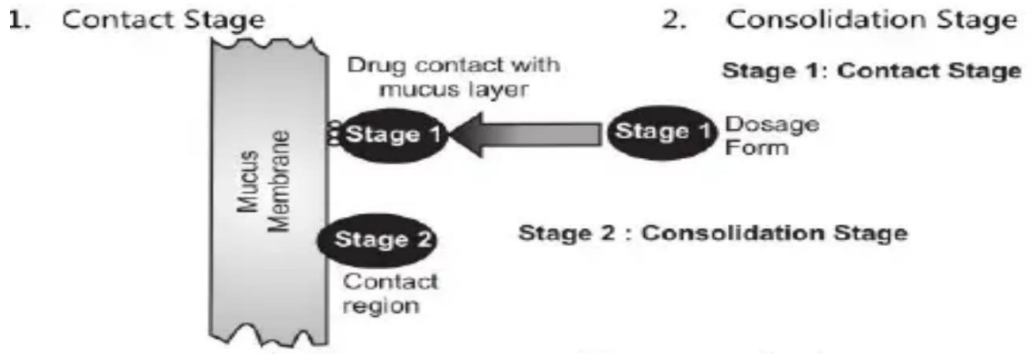

Fig no-1: Stages of muco adhesion.

In the context of drug delivery, bio adhesion refers to the attachment of a drug carrier system to a designated biological site. A tissue's mucous layer or epithelial tissue can both be considered the biological surface. The phenomenon is known as mucoadhesion if the adhesive attachment occurs to a mucus coat. Leung and Robinson, defined mucoadhesion as the interaction of a natural or synthetic polymer with a mucin surface. Bio adhesion and mucoadhesion are not the same thing. In bio adhesion, the polymer is affixed to the biological membrane, whereas mucoadhesion is utilized when the substrate is a mucus membrane.

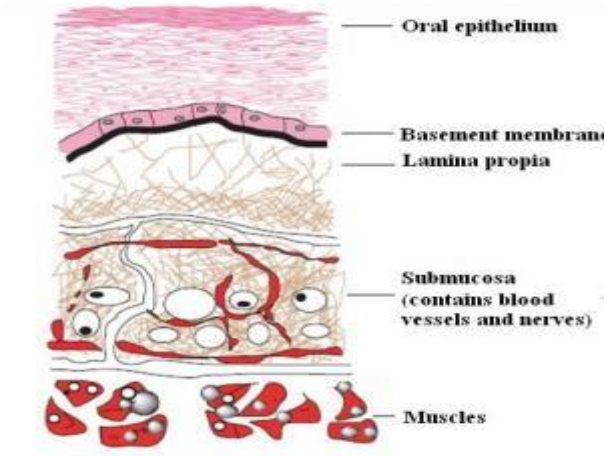

Fig no - 2: General structure of mucous layer.

Mucosal adhesion mechanisms

The mechanisms behind the mucoadhesion process between

Three steps can be used to characterize mucosa and hydrogels:

The polymer wets and swells to provide close contact with the biological tissue.

The bio adhesive polymer chains' penetration and tangling with the mucin and polymer chains, and

Weak chemical connections are formed between entangled chains.

Theories

a) Electronic theory

Involves the flow of electrons between the mucoadhesive polymer and the mucin glycoprotein network, resulting in the creation of an electric double layer at the muco adhesive interface. As an illustration, consider the interaction of the negatively charged mucosal surface with the positively charged polymer chitosan, which becomes sticky when hydrated and allows for close contact between a dosage form and the absorbing tissue.

b) Wetting Theory

It states that a liquid's affinity for the substrate surface increases with a smaller contact angle between the liquid and the substrate surface. The liquid may function as an adhesive between the substrate surfaces if two of these surfaces come into touch with one another while the liquid is present.

c) Adsorption Theory

This hypothesis states that the material adheres after initial contact between two surfaces due to surface force between the atoms on the two surfaces. Primary covalent chemical links and secondary chemical bonds with a variety of other forces of attraction, such as electrostatic forces, Vander Walls forces, and hydrogen and hydrophobic bands, are the two types of chemical bonds that arise from these forces.

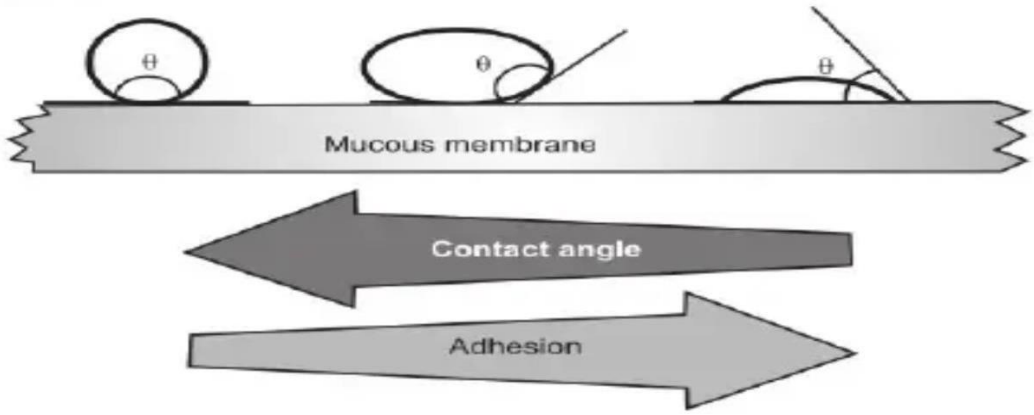

Figure 3: Adsorption theory.

(d) Diffusion Theory

This theory states that a semi-permanent adhesive bond is formed when the mucus and polymer chains mix deeply enough. The period of contact and the diffusion coefficient determine how deeply the polymer chain enters the mucus.

(e) Mechanical Theory

Describes how liquid adhesives diffuse into the surface imperfections and microcracks of the substrate to generate an interlocking structure that promotes adherence.

(f) Cohesive Theory

Asserts that molecular interactions between like molecules are the primary cause of bioadhesion occurrences. According to the aforementioned hypotheses, bioadhesion can be roughly divided into two groups.

Chemical: Electronic and adsorption theories.

Physical: Wetting, diffusion and cohesive theory.

Two phases can be distinguished in the adhesion process. The first stage, sometimes referred to as the contact stage, is when the mucoadhesive polymer and mucous membrane moist. This is followed by the consolidation stage, which is when the physicochemical interactions occur.[2]

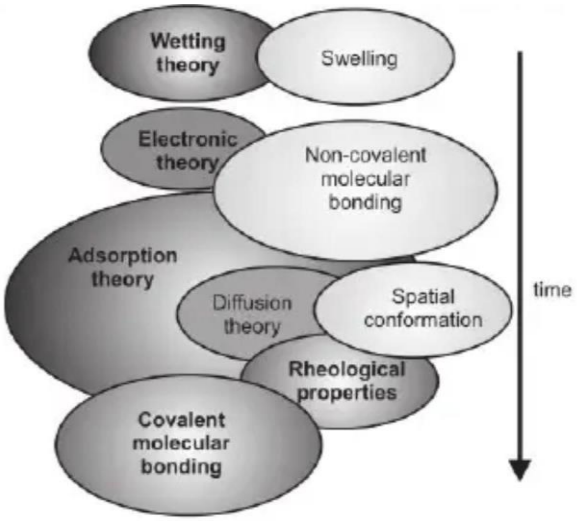

Figure 4: Theory of mucoadhesion.

TRANSMUCOSAL PERMEABILITY

"Transmucosal permeability" refers to a drug's ability to cross mucosal barriers and reach the bloodstream. This is an important consideration for developing novel drug delivery systems, especially for drugs that must take effect quickly or that are poorly absorbed when taken orally. The mouth cavity, nasal passages, vaginal area, and gastrointestinal system are among the bodily parts that include mucosal membranes. Each type of mucosa has unique properties that influence drug absorption. For instance, the nasal mucosa is ideally suited for the administration of drugs due to its high vascularization, which allows them to swiftly reach the bloodstream.

Transmucosal permeability is influenced by the following significant factors:

- The physicochemical characteristics of the medication: The drug's molecular weight, solubility, and lipophilicity can all have a significant impact on its ability to cross mucosal barriers. In general, molecules that are smaller and more lipophilic have better permeability.
- Methods of Formulation: There are several formulation strategies that can be used to enhance transmucosal drug delivery. These include the use of permeation enhancers—substances that temporarily dissolve the mucosal barrier—liposomes, nanoparticles, gels that can help with drug absorption, and more.
- Mucosal Surface Features: The composition and organization of the mucosal surface may affect drug absorption. For example, strong bonds between epithelial cells may limit permeability, while their disintegration may enhance drug absorption.
- Physiological Factors: pH, temperature, and the presence of enzymes can all affect the stability and absorption of drugs. For instance, the permeability and ionization state of the medication may be impacted by the somewhat acidic pH of the nasal cavity.

- Delivery Route: Different transmucosal delivery routes (such as nasal, buccal, and sublingual) have different absorption characteristics. Sublingual administration of medications can increase their bioavailability by avoiding first-pass metabolism.[3-10]

Table 1: List of Oraltransmucosal dosage forms available in market.

Brand name	Active drugs	Uses	Manufacturer	Dosage form
Loramyc	Miconazole lauriad	Oropharyngeal candidiasis	Bioalliance Pharma	Buccal tablet
Lauriad	Acyclovir	Herpes labialis	Bioalliance Pharma	Buccal tablet
Onsolis	Fentanyl citrate	Opioid analgesic	Meda Pharmaceuticals, Inc.	Buccal soluble film
BEMA	Buprenorphine	Opioid analgesic	Biodelivery Sciences International, Inc.	Buccal soluble film
Actiq	Fentanyl citrate	Opioid analgesic	Wolters Kluwer Health	Lozenge on a stick
Fentora	Fentanyl citrate	Opioid analgesic	Wolters Kluwer Health	Buccal tablet
Sublimaze	Fentanyl citrate	Opioid analgesic	Wolters Kluwer Health	Injection
ACT fluoride rinse	Fluoride topical	Anticavity	Cerner Multum, Inc.	Oral solution
Amantadine oral solution USP	Amantadine hydrochloride	Antiviral	Qualitest Pharmaceuticals	Oral solution
Rapamune	Sirolimus	Hepatic impairment	Wyeth Pharmaceuticals	Oral solution
Nicoderm CQ	Nicotine	Smoking cessation agent	Pfizer	Oral patch
Anadrol-50	Androgen	Hormonal agent	Thomson Healthcare Products	Oral patch
Nitrocot	Nitroglycerin	Anti-angina	Thomson Healthcare Products	Sublingual tablet
Buprenorphine HCl sublingual tablets (CIII)	Buprenorphine hydrochloride	Opioid analgesic	Roxane Laboratories	Sublingual tablet
Saphris	Asenapine maleate	Schizophrenia, bipolar disorder	Catalent UK Swindon Zydis Ltd.	Sublingual tablet
Gelclair	Glycyrrhetinic acid/povidone/ sodium hyaluronate	Relieve mouth pain and irritation	Wolters Kluwer Health	Oral gel
Gel-kam	Fluoride	Anticavities	Cerner Multum, Inc.	Oral gel

Table 2: Permeability enhancers used in transmucosal drug delivery.

Permeability enhancer	Active drug	Attributes
n-Butyric acid and *n*-butanol	Acyclovir	Increase the permeability of acyclovir through buccal mucosa
n-Butyric acid and *n*-butanol	Propranolol	Increase the permeation of propranolol through buccal mucosa
Dextran	Octreotide, LHRH insulin and IFN	Large molecular weight hydrophilic polymers significantly increase the permeation of hormones
Sodium deoxycholate and sodium lauryl sulfate	Salicylic acid	Increase the permeability of salicylic acid across rabbit buccal mucosa
Sodium glycocholate, Sodium lauryl sulfate	Insulin	Increase in insulin bioavailability from about 0.7% (without permeation enhancer) to 26 – 27% in the presence of sodium glycocholate (5% w/v) and sodium lauryl sulfate (5% w/v)
Sodium deoxycholate and sodium glycocholate	Insulin	Increase the buccal absorption of insulin

Considerations for buccal drug delivery system formulation

Properties of Drugs

A. Properties of Physico chemicals

Solubility: To guarantee availability at the absorption site, the medication must be adequately soluble in saliva. Solubility may be improved by methods such as co-solvents, inclusion complexes (such as with cyclodextrins), and salt production.

Lipophilicity: To pass the buccal membrane, a substance must have optimal lipophilicity (log P between 1-3). In contrast to highly lipophilic medications, which may stay in the membrane, too hydrophilic drugs have little permeability.

Molecular Weight: For improved mucosal absorption, medications having a molecular weight less than 500 Da are favoured.

pKa and Ionisation: Non-ionized drugs are better absorbed through the mucosa. To keep the medication in the proper ionisation state, formulation must take into account the pH of saliva, which ranges from 5.5 to 7.0.

Stability: At buccal pH, the medication must be stable and not be broken down by salivary enzymes such amylases and esterases.

B. Bio Pharmaceutical Properties

Permeability: Is necessary to use permeation enhancers, such as fatty acids, bile salts, or surfactants, for drugs that have low permeability.

Drugs with minimal dose requirements: (e.g., less than 25 mg/dose) are more suitable for buccal systems because of the restricted surface area and volume of saliva that they can hold.

Protein Binding: Excessive protein binding may impede the absorption of free drugs.

Design of Formulation

A. Dosage Forms

Often small and manageable, mucoadhesive buccal tablets: are made for either unidirectional or bidirectional release.

Buccal films and patches: enable regulated drug delivery and are more comfortable, flexible, and thin.

Gels and ointments: are ideal for localised action and are simple to apply. Although they can have limited retention periods, powders and sprays are useful for quick commencement of action.

B. Mucoadhesive Polymers

That Stick Mucosa Polymers stick to the buccal mucosa, extending the residence time. Popular options consist of:

Natural polymers: include pectin, alginate, and chitosan.

Synthetic Polymers: Polyvinyl alcohol (PVA), carbopol, and hydroxypropyl methylcellulose (HPMC).

Functional groups (such as carboxylic or hydroxyl groups), molecular weight, and polymer viscosity all affect how strong is the adhesive.

Enhancers of Permeation: Increase drug penetration by altering the fluidity of membranes or lowering barrier resistance. As examples, consider:

Bile salts: Sodium Taurocholate,

Fatty acids: linoleic and oleic acids. Polysorbates

Surfactants: sodium lauryl sulphate

Chelating agent: EDTA is a chelating agent that momentarily breaks down tight connections.

Excipients Plasticizers: such as glycerol and PEG, increase the films' comfort and flexibility. Sweeteners and flavouring agents: such as menthol, aspartame, and saccharin, can cover up offensive flavours.

Stabilisers: Include buffers or antioxidants (like BHT and BHA) that keep the pH stable.

Release Modifiers: Polymers such as PVP or HPMC for continued or regulated medication.

Physiological Factors

A. Properties of Mucosa Thickness: Compared to keratinised tissues like gingiva, buccal epithelium (500–800 µm) permits improved permeability.

Vascularization: Rapid systemic medication absorption is ensured by a rich blood supply.

Enzymatic Barrier: Enzyme inhibitors must be included in the formulation since salivary enzymes can break down some medications, such as peptides.

B. Saliva Volume: Drugs may be diluted and washed away by saliva. This effect is lessened by using mucoadhesive materials.

Flow Rate: The drug's residence time may be shortened by increased flow, such as that caused by irritation.

C. Buffering and pH Drug ionisation and solubility are impacted by salivary pH. Buffers are frequently used in formulations to maintain the ideal pH environment for medication release and absorption.

Absorption and Release of Drugs

A. Kinetics of Release Immediate Release: Ideal for medications that need to start working right away. Drug particles are layered or embedded in rate-controlling matrices to provide controlled release.

B. Mechanism of Absorption: The main mechanism is passive diffusion. If necessary, enhancers or nanoparticles could help with active transport. Drug loss into the oral cavity is prevented by unidirectional release systems.

Consistency and Harmony

A. Stability of the Body For solid dose forms: such as buccal pills and patches, moisture resistance is crucial. During storage, formulations must be able to withstand deformation or disintegration.

B. Stability of Chemicals: Protective excipients, such as desiccants or packaging that is resistant to light, are necessary for drugs that are susceptible to hydrolysis, oxidation, or photodegradation

C. Compatibility Testing: To guarantee compatibility, drug-excipient interactions need to be assessed using methods like FTIR or DSC.

Acceptability of Patients Taste Masking

In order to ensure patient compliance with bitter medications, sweets or flavouring agents must be added.

Comfort: The device should stay in place without irritating the user or making it difficult to swallow or speak.

Usability: The formulation ought to be simple to apply, take off, and use without the need for medical supervision.

Manufacturing and Regulatory Aspects

Scalability: The manufacturing procedure needs to be effective and repeatable. Testing for stability, medication release profile, and mucoadhesion strength are all part of quality control.

Regulatory Compliance: All safety, effectiveness, and quality requirements set forth by regulatory bodies such as the FDA or EMA must be met by the formulation.

Advantages of mucosal drug delivery system

These systems allow the developing of contact in-between the dosage forms and the mucosa

(muco adhesion/bio adhesion)

- High drug concentration can be maintained at the absorptive surface for a prolonged period.

- Dosage forms can be immobilized specifically at any part of the oral mucosa, buccal mucosa, sublingual or gingival mucosa, etc.

DISADVANTAGES OF MUCOSAL DRUG DELIVERY SYSTEM

- Small mucosal surface for contact.
- Lack of flexibility of dosage forms.
- Difficult to achieve high drug release rates required for some drugs.

APPLICATIONS OF MUCOADHESIVE MICROSPHERES

- The distribution of vaccines to prevent diseases like diphtheria, hepatitis, influenza, pertussis, ricin toxoid, and birth control. There are several advantages to using microspheres for vaccine delivery, including improved antigenicity via adjuvant action, antigen stability, and control of antigen release.
- Passive targeting of leaky tumor arteries and active targeting of tumor cells and antigens via intravenous or intraarterial injection.
- Chemoembolization is an endovascular procedure that involves targeted arterial embolization of a tumor and the local administration of a chemotherapeutic drug either simultaneously or afterward. Theoretically, the advantage of such embolization is that, in addition to providing arterial occlusion, it will result in sustained therapeutic levels of chemotherapeutics in the tumor locations.
- Imaging: The application of microspheres for targeting has been extensively studied as an extension of chemoembolization. Numerous cells, cell lines, tissues, and organs can be imaged using radiolabeled microspheres. The particle size range of the microspheres is an important factor to take into account while imaging particular regions.
- Topically porous microspheres: Micro sponges are porous microspheres with the particle size range of 5 to 300 µm and a multitude of interconnected spaces. These tiny sponges, which have the ability to absorb a variety of active substances, including essential oils, emollients, and perfumes, are employed as topical carriers.
- Surface-modified microspheres: To modify carriers' patterns of body distribution and protect them against phagocytic clearance, a variety of methods have been employed to modify the carriers' surface properties.

CONCLUSION

In conclusion, the mucosal drug delivery system is a practical way to deliver therapeutic substances since it can circumvent the gastrointestinal tract, increase bioavailability, and provide localized or systemic pharmacological effects. Since these systems can be designed for multiple channels, including the nasal, oral, buccal, vaginal, and ophthalmic, they offer versatility in treating a range of disorders. Fewer side effects, improved patient compliance, and the potential for a controlled and extended drug release are among the advantages. However, issues with drug permeability, mucosal irritation, and the need for innovative delivery methods to increase efficacy remain. Continued research and development in biomaterials, formulation methods, and understanding of mucosal barriers will likely improve the functionality and clinical application of these systems making them an increasingly important tool in modern pharmacotherapy.

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