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A REVIEW OF MUCOSAL DRUG DELIVERY- INNOVATION AND APPLICATION

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ABSTRACT

Mucosal drug delivery systems have emerged as a pivotal approach in pharmacotherapy, offering advantages such as bypassing first-pass metabolism and enhancing bioavailability. Recent innovations in this field include the development of Nano-formulations, biodegradable polymers, and targeted delivery mechanisms, which improve drug absorption through mucosal surfaces such as the oral, nasal, and rectal mucosa. These advancements not only facilitate the administration of a wide range of therapeutics, including peptides, vaccines, and small molecules, but also enhance patient compliance by providing non-invasive delivery options. This review explores the latest breakthroughs in mucosal drug delivery technologies, their mechanisms of action, and their clinical applications, highlighting their potential to revolutionize treatment paradigms in various therapeutic areas, including respiratory diseases, gastrointestinal disorders, and systemic vaccinations.

KEYWORDS: Anatomy of oral cavity, Mucoadhesion, Theories of mucoadhesion, Factors, Evaluation test.

1. INTRODUCTION

Mucosal drug delivery is considered one of the most convenient, simple, and cost-effective methods for administering drugs in the human body. Mucosal membranes are present in various areas, including the respiratory tract, eyes, female genital tract, and gastrointestinal (GI) tract, all of which are exposed to the external environment.[1]

Adhesion refers to the process of joining or sticking two opposing tissue surfaces together. In physics, it is described as "the molecular force of attraction at the interface between dissimilar materials, which acts to hold them together.[2] Bio-adhesion refers to the process of binding or adhering two materials, one of which is of biological origin. Essentially, it involves the adhesion of excipients or synthetic materials to biological tissues. In some cases, both materials may be biological, such as the attachment of microbes to the gut, which can be either beneficial (symbiotic) or harmful (infectious).[3]

When adhesion occurs on the surface of the mucosal lining, it is referred to as muco-adhesion. The mucosal layer is crucial as it acts as a semipermeable barrier, facilitating the exchange of nutrients and gases while preventing the entry of most bacteria and pathogens.[4]

Recent advancements have highlighted the use of biocompatible materials and novel drug carriers, such as lipid-based systems and polymeric nanoparticles, which facilitate targeted delivery and controlled release. Additionally, the integration of mucoadhesive agents enhances retention time at the absorption site, further optimizing drug uptake.[5]

2. OBJECTIVE

- Analysing Mechanisms: Understanding the mechanisms of drug absorption through various mucosal membranes.
- Evaluating Formulations: Assessing different formulation strategies, including nanoparticles, bioadhesive polymers, and smart delivery systems.
- Exploring Applications: Identifying potential therapeutic applications and benefits, such as improved bioavailability and reduced side effects.
- Addressing Challenges: Highlighting the challenges in mucosal drug delivery, including permeability issues and formulation stability.

3. ADVANTAGES OF MUCOSAL DRUG DELIVERY[6]

- Drug is protected from dehydration in the acidic environment in GIT.

- Quicker onset of action because of the mucosal surface.
- Enhanced patient adherence and simplicity of medication delivery.
- Excellent penetrability and quick absorption because of enormous blood supply.
- Additionally, swift cellular recovery and healing of the local area.
- Pain-free administration of the medication.
- Decreased frequency of dosing.
- Shorter treatment period.
- Better patient compliance.
- Drug release for prolonged duration of time.
- Drug absorption occurs by passive diffusion.
- Sustained drug delivery.

4. DISADVANTAGE OF MUCOSAL DRUG DELIVERY[7]

- Drug might dissolute due to continuous secretion of saliva.
- Only low-dose medications can be administered.
- Medications that are absorbed through passive diffusion can be administered.
- Ocular formulations cause uneasiness and blurring.
- Some these drugs may have bitter or unpleasant taste, odour and colour.
- Eating and drinking may become restricted.
- Drugs, which are unstable at buccal PH, cannot be administered by this route.

5. ANATOMY AND PHYSIOLOGY OF ORAL CAVITY[8]

5.1 Oral cavity

The oral cavity is covered by mucous membranes with a total surface area of 200 cm². It consists of several distinct regions.

1) The floor of mouth (sublingual)
2) The buccal area (Cheeks)
3) The gums (gingival)
4) The palatal region. (Hard palate and soft palate).

The buccal and sublingual are the commonly used routes for producing local or systemic effects.

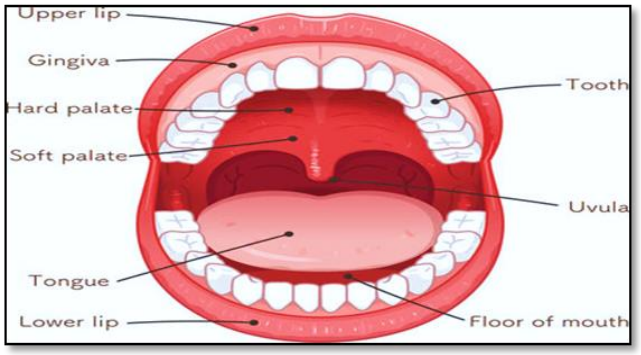

Fig. 1: Anatomy of oral cavity.[9]

5.2 Oral mucosa

The oral mucosa has layers: stratified squamous epithelium, basement membrane, lamina propria, and submucosa. The epithelium's basal layer is mitotically active. The buccal mucosa is 40–50 cell layers thick, while the sublingual epithelium is thinner. Oral mucosa permeability decreases as follows: sublingual > buccal > palatal, due to differences in thickness and keratinization. Sublingual mucosa is thin and non-keratinized, buccal is thicker and non-keratinized, and palatal is keratinized with intermediate thickness.[10]

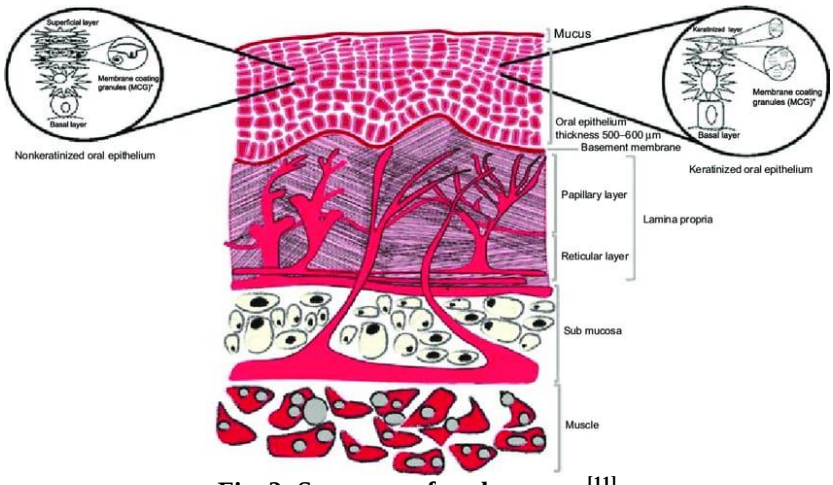

Fig. 2: Structure of oral mucosa.[11]

The oral mucosa is relatively impermeable due to intercellular materials from Membrane Coating Granules (MCGs), found in both keratinized and non-keratinized epithelium. In keratinized epithelium, MCGs contain lamellar lipid stacks, including sphingomyelin, glucosylceramides, ceramides, and non-polar lipids. Non-keratinized epithelium has non-lamellar MCGs with cholesterol esters, cholesterol, and glycosphingolipids. These MCGs release lipids into intercellular spaces, ensuring cohesion and slowing the movement of hydrophilic substances.[12]

6. MUCOUS COMPOSITION[13,14]

The oral mucus is generally secreted by various glands of oral cavity that are sublingual gland, parotid gland, and other salivary glands. The mucus is a translucent gel secreted by goblet cell or by special exocrine glands with the mucus cells.

Table 1: composition of mucosa.

Components	Percentage
Water	95%
Glycoprotein's and lipids	0.5-5%
Minerals salts	1%
Free proteins	0.5-1%

Mucus glycoproteins are the high molecular proteins that contain attached oligo-polysaccharide units. The mucus contains following oligosaccharide units.

- L-fructose
- D-galactose
- N-acetyl-D-glucosamine
- N-acetyl-D-galactose amine.

7. STAGES OF MUCOADHESION[15]

Mucosal drug delivery systems rely on mucoadhesion to enhance the retention and effectiveness of drugs administered via mucosal surfaces. The stages of mucoadhesion in this context typically include

- **Contact stage:** The mucoadhesive material comes into close proximity with the mucus layer, enabling interactions that are necessary for adhesion.

- **Consolldation stage:** This is when the adhesive interactions are established. The mucoadhesive materials are activated by moisture**.**

8. THEORIES OF MUCOADHESION[16,17]

Many theories have been suggested to explain the complex process of mucoadhesion. Each theory is important in describing how mucoadhesion works. Initially, the adhesive may wet the mucus layer, followed by the diffusion of the adhesive polymer into the mucus. This can create breaks in the layers, leading to either electronic transfer or simple adsorption, which ultimately results in mucoadhesion. Additionally, the contact angle and the duration of contact are crucial factors in this process.

- **Electronic Theory**

This theory proposes that electron transfer takes place across the adhesive interface and the contacting surfaces. This leads to the formation of an electrical double layer at the interface, creating a set of attractive forces that help maintain the connection between the two layers.

- **Wetting Theory**

Wetting theory is one of the oldest theories of adhesion, mainly relevant for liquid or low-viscosity mucoadhesive systems. According to this theory, adhesion occurs due to interfacial energy. The adhesive penetrates the surface irregularities of the substrate, hardening to anchor itself. The affinity between the adhesive and substrate can be assessed by measuring the contact angle; generally, a lower contact angle indicates greater affinity. For optimal spread ability, the contact angle should be close to zero.

- **Diffusion Theory**

Adhesion occurs when polymer chains diffuse across an adhesive interface, driven by a concentration gradient, forming a semi-permanent bond with mucus. The extent of penetration depends on the diffusion coefficient, influenced by polymer molecular weight, and decreases with higher cross-linking density.

- **Absorption theory**

According to the adsorption theory, after the initial contact between two surfaces, the material adheres due to surface forces acting between the atoms of both surfaces.

Two significant types of chemical bonds can form as a result of these interactions
(1) Primary chemical bonds.
(2) Secondary chemical bonds.

- **Fracture Theory**

This is the most widely accepted theory for explaining mucoadhesion. It examines the force needed to separate two surfaces after they have adhered.

9. FACTORS AFFECTING MUCOADHESION

9.1 Physiological Factors

- **Mucin Turnover:** The mucus layer is continuously renewed. This limits the time mucoadhesives can stay attached, even if their bonding strength is high.

- **Disease State:** Diseases (e.g., common cold, gastric ulcers, infections) alter the structure and properties of mucus, affecting mucoadhesive performance.

- **Rate of Renewal of Mucoadhesive Cells:** Different types of mucosa have different renewal rates, affecting the consistency and duration of mucoadhesion.

- **Tissue Movement:** Movements such as eating, speaking, and gastrointestinal peristalsis can disrupt

the mucoadhesive bond, especially in gastro-retentive drug delivery.

- **Concomitant Diseases:** Secondary illnesses (e.g., altered gastric secretion, fever, inflammation) can change mucus properties, impacting mucoadhesion.

9.2 Environmental Factors

- **pH of Polymer-Mucus Interface:** pH affects both the mucus and polymer surface, influencing adhesion strength. Hydration and electrostatic interactions vary with pH changes.
- **Applied Strength:** Applying pressure during the initial contact helps increase mucoadhesive strength by improving interpenetration between polymer and mucus.
- **Initial Contact Time:** Longer initial contact time allows for better swelling and interpenetration of polymer chains, enhancing adhesion strength.
- **Moistening:** Adequate moisture allows the polymer to spread over the surface, increasing the mobility and interpenetration of polymer and mucin molecules.
- **Swelling:** Swelling of the polymer matrix allows for better adhesion, but excessive swelling may reduce bioadhesion.
- **Selection of Model Substrate Surface:** Handling and treatment of biological substrates are critical as changes can affect experimental results.

9.3 Polymer-Related Factors

- **Molecular Weight:** Lower molecular weight polymers diffuse and penetrate more easily, enhancing adhesion, whereas high molecular weight polymers may entangle and hinder adhesion.
- **Concentration of Polymer:** Optimal concentration is crucial for effective mucoadhesion. Too low or too high concentrations reduce adhesive strength.
- **Flexibility of Polymer Chains:** Higher flexibility allows better interpenetration into the mucus layer, improving adhesion.
- **Spatial Conformation:** The shape of the polymer (e.g., helical or linear) affects adhesion. Helical conformations may shield active groups, reducing binding sites.
- **Swelling Capacity:** Proper swelling reveals bioadhesive sites for bonding, but excessive swelling can lower adhesion strength.
- **Hydrogen Bonding Capacity:** The presence of functional groups capable of forming hydrogen bonds is essential for strong mucoadhesion.
- **Crosslinking Density:** Higher crosslinking density reduces water diffusion, limiting swelling and penetration into the mucus, decreasing adhesion.
- **Charge:** Positively charged polymers typically show better mucoadhesion due to interaction with the negatively charged mucosal surface. Cationic polymers like chitosan are highly effective.

10. MECHANISM[18]

The mechanism of mucoadhesion is not fully understood and is complex. The mucoadhesive must spread over the surface to create close contact, which leads to both attractive and repulsive forces. Repulsive forces result from osmotic pressure, stemming from the interpenetration of electrical double layers, steric effects, and electrostatic interactions when surfaces or particles have opposite charges. The strength of these forces varies based on the particle type, the surrounding fluid, and the distance between the particle and the surface. For effective adhesion, particles need to overcome a repulsive barrier (potential energy barrier).

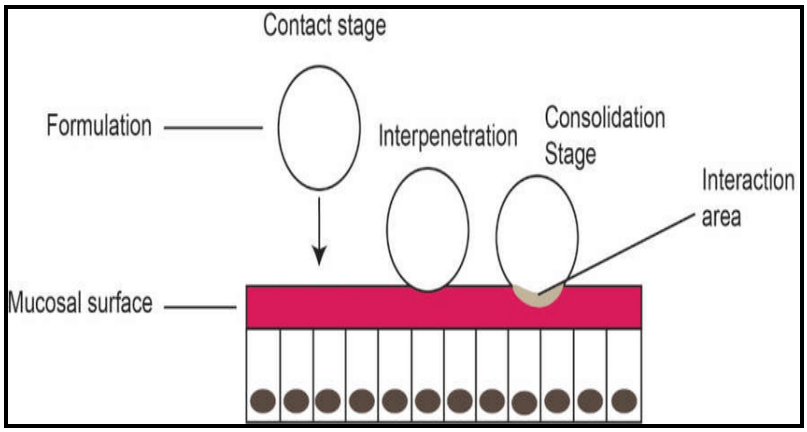

Fig. 3: Mechanism of mucoadhesion.

11. CLASSIFICATION OF MUCOSAL DRUG DELIVERY[19]

Classified based on various criteria, each focusing on different aspects of their design and application. Here's a comprehensive classification.

A. BY ROUTE OF ADMINISTRATION

- **Oral Mucosal Delivery**

- Sublingual (e.g., tablets, films)
- Buccal (e.g., lozenges, gels).

- **Nasal Delivery**

- Nasal sprays, powders, and gels.

- **Vaginal Delivery**

- Tablets, creams, gels, and rings.

- **Rectal Delivery**

- Suppositories and enemas.

B. BY FORMULATION TYPE

- **Solid Dosage Forms**

- Tablets, films, and powders.

- **Liquid Dosage Forms**

- Solutions and suspensions.

- **Semi-solid Dosage Forms**

- Gels and creams.

C. BY MECHANISM OF DRUG RELEASE

- **Immediate Release**

- Rapid release for quick action.

- **Sustained Release**

- Controlled release over an extended period.

- **Targeted Release**

- Specific release at particular sites within the mucosa.

D. BY COMPOSITION

- **Polymeric Systems**

- Use of natural or synthetic polymers for controlled release.

- **Lipid-based Systems**

- Liposomes and solid lipid nanoparticles.

- **Nano formulations**

- Nanoparticles and Nano carriers for enhanced bioavailability.

E. BY PHYSICAL STATE

- **Gels and Pastes**

- For prolonged contact and local delivery.

- **Sprays and Aerosols**

- For rapid and widespread distribution.

- **Films and Patches**

- For sustained release through adhesion to mucosal surfaces.

F. BY FUNCTIONALITY

- **Mucoadhesive Systems**

- Formulations designed to adhere to mucosal surfaces, increasing residence time.

- **Penetration Enhancers**

- Additives that facilitate drug absorption through mucosal barriers.

G. BY THERAPEUTIC USE

- **Local Delivery**

- For localized treatment (e.g., antifungal, antiviral).

- **Systemic Delivery**

- For drugs intended for systemic circulation (e.g., hormones, vaccines).

12. INNOVATIONS IN MUCOSAL DRUG DELIVERY[20]

A. Nanotechnology and Nanocarriers

Nanotechnology has revolutionized mucosal drug delivery by allowing precise control over drug release and absorption. Nanoparticles, liposomes, micelles, and dendrimers are employed to improve drug stability, enhance permeability, and target specific cells or tissues.

- Nanoparticles
- Liposomes and Micelles.

B. Mucoadhesive Systems

Mucoadhesive polymers like chitosan, hyaluronic acid, and carbomers help keep drugs on the mucosal surface longer. They bond with mucin in mucus, improving contact time and drug absorption**.**

C. Hydrogels and Smart Polymers

Hydrogels are water-filled networks that can hold drugs and release them in response to changes like pH or temperature. They are great for controlled and steady drug delivery through mucosal surfaces.

D. Biologics Delivery

Delivering biologics such as peptides, proteins, and vaccines through mucosal routes is tough due to their sensitivity and size. New methods like enzyme inhibitors, permeation enhancers, and bioactive carriers (e.g., viral vectors) are helping to improve delivery.

E. Gene Delivery and RNA Therapeutics

Mucosal routes are being studied for gene therapy and RNA-based treatments. New delivery systems, including nanoparticles and lipid carriers, are promising for delivering tools like CRISPR or RNA treatments for cancer and genetic disorders.

F. Micro- and Nano-Needle Arrays

Microneedle arrays applied to mucosal surfaces allow for minimally invasive drug delivery, especially vaccines. These technologies improve drug penetration without much discomfort, providing a non-invasive alternative to injections.

13. APPLICATIONS OF MUCOSAL DRUG DELIVERY

A. Nasal Drug Delivery

The nasal mucosa has a lot of blood vessels, allowing for quick absorption of drugs. This makes it good for local treatments, like allergies, and systemic ones, like vaccines and pain relievers. It's also useful for delivering peptides and proteins, like insulin, since it avoids breakdown in the stomach.

B. Buccal and Sublingual Drug Delivery

These methods deliver drugs quickly, like nitroglycerin for heart pain. They skip first-pass metabolism, allowing fast absorption into the bloodstream, which is great for emergencies or ongoing treatments.

C. Pulmonary Drug Delivery

Inhalation is key for lung diseases like asthma and COPD. This method targets the lungs directly, giving quick relief. New tools like dry powder inhalers and smart inhalers help adjust doses.

D. Ocular Drug Delivery

These systems deliver drugs to the eye for treating conditions like glaucoma or infections. Using nanotechnology, like nanoemulsions and liposomal drops, improves how well drugs stay and work in the eye.

E. Vaginal and Rectal Delivery

These routes treat infections, deliver hormones, or allow drugs to avoid the digestive system. New mucoadhesive and extended-release forms help keep the drug active longer.

F. Vaccines and Immunotherapy

Mucosal vaccines are growing, especially for infections like flu and COVID-19. Oral or nasal vaccines provide a needle-free way to build local immunity.

G. Cancer Therapy

Mucosal delivery is being studied for treating cancers in the mouth, lungs, and colon. New nano-formulations can deliver drugs directly to tumors, reducing side effect.

14. CHALLENGES AND FUTURE DIRECTIONS

- **Mucosal Barriers:** Mucus can block drug absorption. Research is focused on better particles and sticky technologies to help drugs get through.
- **Patient Compliance:** While these methods are non-invasive, they need to be easy and comfortable for long-term use, like nasal sprays or buccal films.
- **Stability and Degradation:** Mucosal areas have enzymes that can break down drugs, especially biologics. New carriers and coatings are needed to keep drugs stable until they reach their target.

15. CONCLUSION

Mucosal drug delivery represents a rapidly evolving field with immense potential for improving therapeutic outcomes across various medical conditions. Innovations in nanotechnology, biologics delivery, and smart drug systems are paving the way for more efficient, targeted, and patient-friendly treatments. The future of mucosal drug delivery lies in overcoming current limitations, such as drug degradation and mucosal barriers, to fully harness its benefits in areas like vaccine delivery, cancer therapy, and gene therapeutics.

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