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Review On Oral Mucosal Drug Delivery System

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Abstract:Oral mucosal drug delivery systems have emerged as an effective alternative for delivering drugs into the body. They avoid issues like the liver breaking down drugs before they can work. This method offers better absorption and a faster effect. The oral mucosa, which has a rich supply of blood vessels, is a good surface for both local and systemic delivery. However, several challenges exist. Limited permeability, the breakdown of drugs by enzymes, and continuous saliva production can hinder how well drugs are absorbed and retained. Recent developments in mucoadhesive polymers and penetration enhancers have greatly improved the effectiveness of oral mucosal systems. These advances allow for controlled and targeted delivery of various therapeutic agents. This review discusses the physiology of the oral cavity, theories and mechanisms of mucoadhesion, factors that affect drug delivery, and the latest developments in formulation technologies aimed at enhancing therapeutic effectiveness.

Index Terms-Buccal delivery, Mucoadhesive polymers, Permeation enhancers, Formulation design.

I. INTRODUCTION

Perhaps the most popular method of medicine delivery among patients and physicians is the oral route. According to our current knowledge of the physiological and biochemical aspects of absorption and metabolism, many medications cannot be administered efficiently by the traditional oral route because they undergo extensive pre-systemic clearance in the liver after administration, which frequently results in a lack of a meaningful relationship between membrane permeability, absorption, and bioavailability . Poor oral availability and challenges with parenteral delivery fueled interest in investigating alternate delivery methods for these medications. As a result, more absorptive mucosae are thought to be viable drug delivery sites.

When it comes to systemic action, transmucosal drug delivery routes—that is, the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavities—offer clear advantages over peroral administration. Because of its superior accessibility, smooth muscular expanse, and relative immobility, the buccal mucosa is one of the several transmucosal channels that can be used to administer controlled release dosage forms.[1]

II. PHYSIOLOGY OF ORAL CAVITY

The gastrointestinal tract's first reception area is the mouth cavity. It is surrounded by the cheeks on the side, the floor of the mouth on the bottom, and the hard and soft palates on top. It stretches from the mouth opening to the throat. The tongue is at the bottom, whereas the teeth are in the front. The mouth cavity has a number of salivary glands that produce mucus and saliva. Additionally, the oral papillae have unique neuroanatomical structures called taste buds.

The mucous membrane, also known as the mucosa, is a membrane that borders the cavities in the body and covers the surface of internal organs. It has mucous covering it . In addition to isolation, the mucosa of the human body plays a major role in transport and, to a lesser degree, immune defense against infections. The buccal, sublingual, gingival, palatal, and labial mucosa make up the oral mucous membrane. [2]

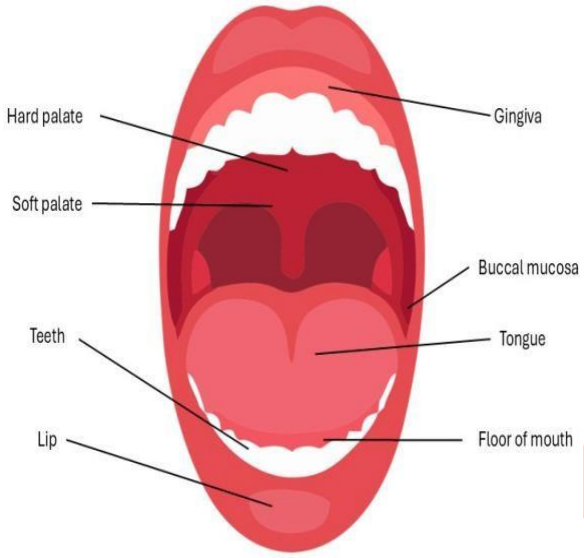

Figure.1.Physiology of oral cavity[2]

III. THEORIES OF MUCOADHESION

The phenomena of mucoadhesion has been explained by six ideas. Mucoadhesion is the relationship between a mucoadhesive substance and polymer and mucosal layer, and these ideas explain different stages of two substrate contact. These theories are put out as follows:

1.THEORY OF WETTING

This idea postulates that a mucoadhesive polymer penetrates the absorbent surface's imperfections, hardens, and causes the mucosa to adhere. By measuring the contact angle, one can ascertain the affinity toward the surface.

2 THEORY OF ADSORPTION:

This theory states that adhesion results from the interaction of the mucus substrate and adhesive polymer via two distinct kinds of chemical bonding, which includes Van der Waals forces and Hbonding. The force between the two surfaces' atoms is what causes their adhesion after first coming into contact.

3 THEORY OF ELECTRONICS:

According to this idea, two surfaces' interactions are significantly influenced by variances in their electrical structures. The arrangement Electrons are transferred between the polymer and the mucous membrane to form bonds. An electrical double-layer creates the attraction force between the polymer and the mucosal surface.

4.THEORY OF MECHANICAL:

According to this theory, two surfaces adhere to one another because a mucoadhesive fluid fills the rough surface. This action has a significant impact on mucoadhesion mechanisms, even though anomalies expand the interface's surface area.

5. THEORY OF FRACTURE:

This hypothesis states that there is a relationship between the force required to separate two surfaces and the force that creates their bond of adhesion.

The following calculation uses this assumption to calculate the force needed to separate the polymer from the mucus: $\sigma = \sqrt{(E^{*}\varepsilon)/L}$, where L is the critical length of the crack, E is the Young's modulus of elasticity, ε is the energy of fracture, and σ is the fracture strength.

6. THEORY OF DIFFUSION:

The concentration gradient and the duration of the polymer chain's penetration into the glycoprotein network serve as the foundation for the diffusion theory of the mucous. Diffusion is a reciprocal process. One is the development of an interpenetration layer, and the other is the attainment of effective adhesion, which happens when the thickness of the interpenetration layer reaches between 0.2 and 0.5 µm. A concentration gradient, the molecular weight of sticky macromolecules, hydrodynamic size, mobility, flexibility, and the length of the polymer chains are some of the variables that affect how this layer forms. [3]

IV. MECHANISM OF MUCOADHESION

An interfacial phenomena known as mucoadhesion occurs when two materials come into contact; one of these materials may be artificial, such mucoadhesive polymer, and the other may be the mucinlayer .The interfacial forces of attraction hold mucosal tissue together. The term "mucoadhesive" refers to an artificial material that can interact with mucous membranes and keep them in place or hold them together for a long time. Generally speaking, there are two steps in the adhesion process, which are listed below:

Contact stage: An intimate wetting between the mucoadhesive and mucous membrane takes place during this stage when the mucoadhesive substance makes contact with the mucus membrane.The mucus found in the mucosal membrane acts as a mucoadhesive.

Consolidation stage: The mucoadhesive substance is linked to the mucus membrane by various physicochemical factors of attraction, producing a long-lasting mucoadhesion. We refer to this as the consolidation stage. The mucoadhesion process is finished after these two phases. [4]

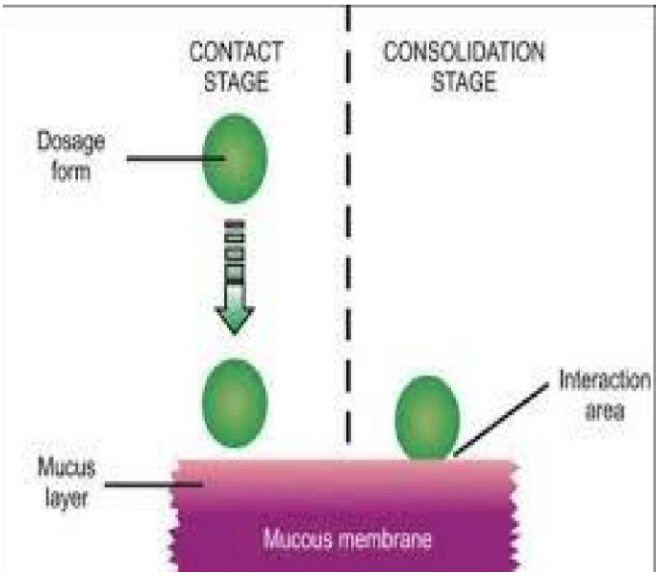

Figure2.[4]

V. ADVANTAGES :

Prolonged residence time, enhanced therapeutic efficacy, quick absorption, avoiding first pass metabolism, accelerating commencement of action, reducing enzymatic degradation, superior accessibility, and cost-effectiveness are just a few of the many benefits of oral mucoadhesive drug administration.

There are further benefits.

- Because of its high vascularization, the buccal mucosa has a plentiful blood supply, making it easy for drugs to pass through.
- Increases the dose form's duration of stay at the absorption site.
- The mucosal surface helps to obtain a quicker onset of action.
- The medication avoids the first pass effect by entering the systemic circulation directly.

Presystemic excretion in the gastrointestinal tract is avoided; it is easily accessible; and because the injection pain is eliminated, patient compliance is improved.

- rapid and thorough medication absorption is facilitated by the oral cavity's surface making large contact. Vomiting and nausea are largely prevented.[5]

VI. DISADVANATAGES:

- The buccal membrane has a smaller surface area and lower permeability, particularly in comparison to the sublingual membrane. The membranes' overall surface area of the

Of the 170 cm2 oral cavity that can be used for medication absorption, about 50 cm is made up of non-keratinized tissues, such as the buccal membrane.

- Constant salivary flow (0.5-2 l/day) causes the medication to be diluted later.
- Swallowing saliva may also result in the involuntary removal of the dose form and the loss of any dissolved or suspended medication .
- These are a few issues with the buccal drug delivery mechanism as it now exists.[4]

VII. FACTORS AFFECTING MUCOADHESION:

1. HYDROPHILICITY:

Many hydrophilic functional groups, including carboxyl and hydroxyl, are present in bioadhesive polymers. These groups enable the substrate to form a hydrogen bond, which causes swelling in aqueous conditions and maximizes the exposure of possible anchor sites. Furthermore, swollen polymers contain the greatest space between their chains, which increases chain flexibility and facilitates effective substrate penetration.

2. MOLECULAR WEIGHT:

Higher molecular weight polymers prefer entanglements, while low molecular weight polymers favor interpenetration of polymer molecules. The type of polymer determines the ideal molecular weight for maximum mucoadhesion; bioadhesive forces rise up to 100,000 with the molecular weight of the polymer. There is no more gain at this point.

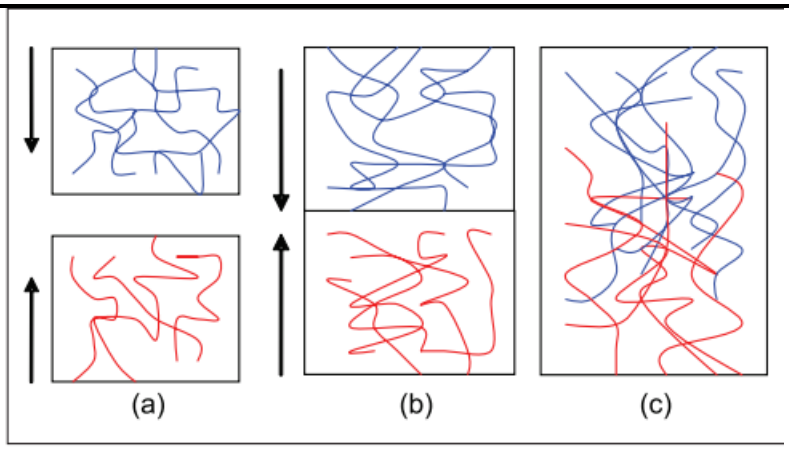

figure3.[6]

(a) Schematic representation of the diffusion theory of bioadhesion. Blue polymer layer and red mucus layer before contact; (b) Upon contact; (c) The interface becomes diffuse after contact for a period of time

3.CROSS LINKING AND SWELLING:

The degree of swelling is negatively correlated with the cross-link density.[25] Flexibility and hydration rate increase with decreasing cross-link density, but mucoadhesion improves with increasing polymer surface area. A polymer with a low degree of cross-linking is preferred in order to attain a high degree of swelling. However, a slippery mucilage that is easily taken from the substrate occurs when there is an excessive amount of moisture and swelling.[26] The use of adhesion promoters, such as free polymer chains and polymers grafted onto the premade network, into the formulation of cross-linked polymers can improve their mucoadhesion.

3. SPACIAL CONFORMATION:

In addition to chain length or molecular weight, a polymer's spatial conformation is crucial. Their adhesive strength is comparable to that of polyethylene glycol (PEG), which has a molecular weight of 200,000, even though dextrans has a high molecular weight of 19,500,000. Unlike PEG polymers, which have a linear conformation, dextran's helical structure may conceal several adhesively active groups, which are principally responsible for adherence.

4. PH

The adherence of bioadhesives with ionizable groups might be affected by the pH at the contact between the bioadhesive and substrate. Polyanions with carboxylic acid functions make up a large number of bioadhesives utilized in medication delivery. More ionization will occur if the local pH is higher than the polymer's pK, and more unionization will occur if the pH is lower. The poly(acrylic acid) family of polymers has an approximate pKa of 4 to 5. Around pH 4–5, these polymers have their highest adhesive strength, which progressively diminishes beyond pH 6.

5. DRUG/ CONCENTRATION:

The concentration of the drug or excipient may affect mucoadhesion. The effect of propranolol hydrochloride on the adherence of Carbopol® hydrogels, a mildly cross-linked poly(acrylic acid) polymer, was investigated by BlancoFuente [28]. Because of an increase in elasticity brought on by the complex formation between the medication and the polymer, the author showed greater adhesion when the amount of water in the system was limited. The complex precipitated out when there was a lot of water present, which slightly reduced the adhesive quality. Mucoadhesion to pig cheek tissue was considerably enhanced by raising the content of toluidine blue O (TBO) in Gantrez®-based mucoadhesive patches (poly(methylvinylether/maleic acid).[29] The cationic drug and anionic copolymer's electrostatic interactions were thought to be the cause of the patches' enhanced internal cohesiveness.

7.OTHER FACTORS:

The initial force of application may have an impact on mucoadhesion.Increased interpenetration and strong bioadhesive strength are the results of higher forces. Additionally, the swelling and interpenetration of polymer chains increase with the first contact time between the bioadhesive and substrate. Mucoadhesion can also be impacted by physiological factors. Both the presence of a bioadhesive device and illness conditions can influence the pace of mucus turnover. Furthermore, depending on the body site and whether a local or systemic disease is present, the type of surface that is exposed to the bioadhesive formulation might differ greatly.[6]

VIII. RECENT APPLICATIONS IN ORAL MUCOSAL DRUG DELIVERY SYSYTEM:

Many medications whose oral administration results in low bioavailability can benefit from oral mucoadhesive drug delivery.

Drug administration that is quickly broken down by the oral mucoadhesive offers the benefits of low enzymatic activity and high accessibility. Previously, periodontal disorders were treated with hydrophilic polymers such as SCMC, HPC, and polycarbophil; however, the current trend is moving toward the efficient application of these systems for the delivery of proteins, peptides, and polysaccharides.

High patient compliance is another benefit of the buccal cavity. A first-generation mucoadhesive paste called Orabase has been utilized as a barrier system for oral ulcers. Tablets have also been developed, however semisolids are easier to administer.

Tablets can be multilayered systems with a mucoadhesive agent or matrix devices. To prevent the salivary gland's clearing mechanism, the tablet is kept beneath the upper lip. This is how buccostem, an adhesive antiemetic pill that contains prochlorperazine, is often given.

Three types of buccalmucoadhesive dose forms can be distinguished: A single-layer apparatus with a multidirectional medication release. A double-layered device that prevents loss from the top surface of the dosage form into the oral cavity is made by placing an impermeable backing layer on top of a drug-loaded bioadhesive layer.

The medicine is exclusively released from the side next to the buccal mucosa via a unidirectional release device. [7]

IX. TYPES OF PENETRATION ENHANCERS: □

- Bile salts □
- Fatty acids and their Salts Esters □
- Azones□
- Surfactants □
- Complexing Agents □
- Co-solvents □
- Miscellaneous □

1. BILE SALTS :

Bile salts are steroids that bind together in water and have characteristics similar to those of surfactants. Their physiological function is to emulsify dietary lipids.

moving through the intestinal wall to facilitate the digestion and absorption of fat. Bile salts have been widely used to improve drug absorption through a variety of epithelia and are used as permeation enhancers. Through a number of processes, such as protein denaturation and extraction, tissue swelling, enzyme inactivation, solubilization and micellar entrapment of intercellular lipids, membrane fluidization, reverse membrane micellation, and the extraction of lipids or proteins from the cell wall, they are thought to act on both the transcellular and paracellular pathways.

2. FATTY ACIDS AND THEIR SALTS AND ESTERS:

Cod liver oil extract, oleic acid, and lauric acid serve as examples of fatty acids, while sodium laurate and various fatty acid salts represent the other category. Glycerylmonostearate, diethylene glycol monoethyl ether, and numerous sucrose fatty acid esters illustrate sodium caprate and its derivatives. These compounds typically exhibit limited solubility in water and are characterized by their lipophilic properties. Due to their "kinked" molecular configuration resulting from the double bond within the hydrocarbon chain, unsaturated fatty acids such as oleic acid decrease lipid organization and enhance fluidity in the skin. They are also expected to have a similar effect on the oral mucosa.

3. AZONES:

Azone, also known as laurocapram, is widely used to improve transdermal penetration and has also been used to give drugs buccal. It is a surfactant that is lipophilic. in the natural world. In a keratinized hamster cheek pouch model, pre-application of an Azone emulsion improved salicylic acid penetration in vivo. Azone has also been used to enhance the absorption of octreotide and some hydrophobic substances.

4. SURFACTANTS:

Other surfactants include benzalkonium chloride, laureths, polysorbates, sodium dodecyl (lauryl) sulfate, and Brijs. These are mostly soluble in water and capable of forming micelle interactions in aqueous solution. They are thought to improve transbuccalpermeability through a process akin to that of bile salts, which includes tissue swelling, protein denaturation, lipid extraction, and enzyme inactivation. Although sodium dodecyl sulfate is said to significantly improve absorption, it may potentially cause mucosal injury. Porcine buccal tissue has been used to assess the impact of sodium dodecyl sulfate on the in vitro buccal permeability of caffeine and estradiol.

5. COMPLEXING AGENTS:

Complexing Agents: Sodium edetate and cyclodextrins are examples of complexing agents. Enzymatically altered starches known as cyclodextrins create rings of six to eight units. The ring's inside surface is non-polar, whereas its external surface is polar. Therefore, by creating inclusion complexes, the cyclodextrin's core can be utilized to transport water-insoluble molecules in an aqueous environment. Two distinct hydrophilic cyclodextrin derivatives, 2-hydroxypropyl β-cyclodextrin and poly βcyclodextrin, were found to be effective in facilitating the buccal absorption of steroidal hormones. It has also been reported how cyclodextrins (5%) affect interferon buccal absorption. It has been observed that chelators including sodium citrate, EDTA, and polyacrylic acids improve absorption by interfering with calcium ions.

6. CO SOLVENTS :

Water-miscible solvents like ethanol and propylene glycol are examples of cosolvents. Utilizing automobiles that improve absorbency has been taken into account for transdermal drug delivery and could also be beneficial for buccal delivery. They function by altering the drug's thermodynamic activity in solution, raising its concentration, enhancing passive diffusion, and easing the drug's partition into the membrane.

7. MISCELLANEOUS:

One phospholipid that can be extracted from soybeans or egg yolk is lecithin (phosphatidylcholine). It is offered for sale in high purity for therapeutic applications and has been applied to improve insulin absorption in vivo. In vitro, it has also been demonstrated that the antibiotic sodium fusidate, a steroid with a chemical structure resembling bile salts, enhances insulin penetration. It has been demonstrated that chitosan, a polysaccharide comprising glucosamine and acetylglucosamine units, has the ability to increase penetration. Because they temporarily widened the mucosa's tight connections, chitosan solutions and gels were discovered to be efficient absorption enhancers.[8]

X. MECHANISTIC APPROACHES OF MUCOADHESIVE DRUG DELIVERY SYSTEM :

Mucoadhesion can be explained by a few general theories, including mechanical theory, electrical theory, adsorption theory, wetting theory, scattering theory, and part theory. A combination of all the potential theories aids in the clarification of a few frameworks pertaining to mucoadhesion. The wetting idea is clarified when the estimation outline winds up noticeably swelling and spreading over the organic liquid. Next, connections may form inside the organic liquid polymer interface due to the movement of electric charges (electronic theory) (adsorption conjecture). Then, according to the scattering theory, the polymer and protein chains diffuse and capture together, creating additional holding (adsorption and electronic theories) for a longer link. These frameworks can therefore be divided into two groups: contact stageThese frameworks can therefore be divided into two groups: the union stage and the interaction stage.These frameworks can therefore be divided into two groups: the union stage and the interaction stage.[9]

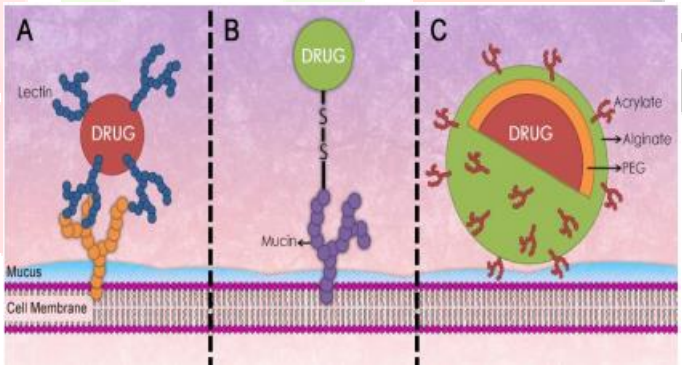

Figure4.[9]
Mechanistic approach in Mucoadhesive delivery system into the tissue/surface of the mucous membrane

XI. CONCLUSION

Oral mucosal drug delivery systems offer a promising way to administer drugs effectively and in a way that patients find acceptable. They can avoid first-pass metabolism, improve bioavailability, and provide controlled release. This makes them valuable for both systemic and local treatments. Ongoing research into mucoadhesive materials, permeation enhancers, and new formulation methods has broadened the types of drugs that can be delivered through this route. There are still some challenges, including drug taste, mucosal irritation, and limited dose capacity, but technological improvements continue to tackle these issues. Future developments in biocompatible polymers and smart delivery systems are likely to increase the clinical potential of oral mucosal drug delivery.

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4. .Review on Mucoadhesive Drug Delivery System with Special Emphasis on
Buccal Route: An Important Tool in Designing of Novel Controlled Drug
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