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A Brief Review on Novel Approaches in Mucoadhesive/ Bioadhesive Drug Delivery Systems

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ABSTRACT
The current article focuses on the mucoadhesive drug delivery system, which may be designed to allow for prolonged retention at the site of application while also providing a controlled rate of drug release for improved therapeutic outcome. The adhesion of two materials, at least one of which is a mucosal surface, is commonly defined as mucoadhesion. Dosage forms applied to mucosal surfaces may benefit drug molecules that are not amenable to oral administration, such as those that undergo acid degradation or extensive first-pass metabolism. A dosage form's mucoadhesive ability is determined by a number of factors, including the nature of the mucosal tissue and the physicochemical properties of the polymeric formulation. Based on the literature, this review article aims to provide an overview of the various aspects of mucoadhesion, mucoadhesive materials, factors affecting mucoadhesion, evaluating methods, and finally various mucoadhesive drug delivery systems (buccal, nasal, ocular, gastro, vaginal, and rectal).

Keywords: Bioadhesive, Transmucosal, Oral Administration, Mucoadhesion, Prolonged Retention

I. INTRODUCTION

Many various formulations, including sprays, pills, mouthwashes, gels, pastes, and patches, are already utilized for administration into and/or across the oral mucosa, however there are significant obstacles for researchers studying innovative delivery approaches to overcome.[1-2]

Any bond produced between two biological surfaces or between a biological and a synthetic surface is referred to as bioadhesion. The term bioadhesion is used to describe the adhesion between polymers, either synthetic or natural, and soft tissues or the gastrointestinal mucosa in the case of bioadhesive medication delivery. The word mucoadhesion can be used interchangeably with bioadhesion when the binding is established using mucus. Buccal delivery refers to the administration of a medication through the mouth cavity's buccal mucosal membrane lining. Unlike oral drug administration, which creates a hostile environment for pharmaceuticals, particularly proteins and polypeptides, due to acid hydrolysis and the hepatic first-pass effect, buccal mucosal lining provides a considerably softer environment for drug absorption.[3]

MUCOADHESION

The term ioadhesion can be defined as a state in which two materials, at least one of which is iological in nature, are held together for an extended period of time by forces between the faces.[4]

In biological systems, bioadhesion can be classified into 3 types:

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

Type 2 : Cell adhesion to culture dishes, for example, and bio-film formation on prosthetic devices and inserts are examples of biological phase adhesion to an artificial substrate.

Type 3 : Adhesion of an artificial material to a biological substrate, such as the adhesion of synthetic hydrogels to soft tissues or sealants to dental enamel.[5]

The term bioadhesion in drug delivery refers to the attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue or the mucus coat on a tissue's surface. When an adhesive attaches to a mucus coat, the phenomenon is known as mucoadhesion. Mucoadhesion was defined by Leung and Robinson as the interaction of a mucin surface with a synthetic or natural polymer. Mucoadhesion should not be confused with bioadhesion; in bioadhesion, the polymer is attached to the biological membrane, whereas

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mucoadhesion is used when the substrate is a mucus membrane.[6]

Hydrocolloids are thought to adhere to mucosa after being hydrated because the synthetic polymer molecules become more freely mobile and are able to align adhesive sites with those of the substrate. Adhesive strength was found to decrease as the level of hydration increased, because mucoadhesive bonds became overextended. It is proposed that the polymer's ability to form hydrogen bonds is important in this effect, which may highlight the well-documented mucoadhesive properties of polymers with numerous carboxyl groups, such as carbopol and polycarbophil. However, the increased ionisation of the polymer's swelling properties may result in a reduction in mechanical strength and, as a result, a reduction in mucoadhesive properties. According to mucoadhesion theories, the most efficient mucoadhesive polymers have physiochemical properties that are similar to those of the mucus substrate.

ADVANTAGES[7-8]

- Extends the dosage form's residence time at the site of absorption.
- Avoiding first-pass metabolism
- Increased residence time improves absorption and thus the therapeutic efficacy of the drug.
- Excellent accessibility
- Rapid absorption due to abundant blood supply and high blood flow rates
- Increased drug bioavailability as a result of avoiding first pass metabolism
- The drug is protected from degradation in the GIT's acidic environment.
- Increased patient compliance and ease of medication administration
- The mucosal surface allows for a faster onset of action.

THEORIES OF MUCOADHESION:

Electronic theory[9]

It is predicated on the idea that mucoadhesive and biological materials have opposing electrical charges. When both materials come into contact, electrons are transferred, resulting in the formation of a double electronic layer at the interface, where the attractive forces within this electronic double layer determine the mucoadhesive strength.

Adsorption theory[10]

According to this theory, the mucoadhesive device adheres to the mucous after contact due to surface force acting between atoms on both surfaces. This force generates a secondary chemical interaction, such as van der Waals and hydrogen bonds, electrostatic attraction, or hydrophobic interactions.

Wetting theory [11]

The wetting theory applies to liquid systems and describes a liquid's affinity to maintain contact with a surface. The contact angle, for example, can be used to determine this affinity. The general rule is that the lower the contact angle, the greater the affinity. Contact angle must be zero or close to zero for adequate spreading and complete wetting of liquid.

The difference between the surface energies γB and γA and the interfacial energy γAB, as indicated in equation

(Equation 1)

$$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB}$$

The greater the individual surface energy of mucus and device concerning the interfacial energy, the greater the adhesion work, WA, i.e., the greater the energy needed to separate the two phases

(Equation 2)

$$W_A = \gamma_A + \gamma_B - \gamma_{AB}$$

Diffusion theory

The dissemination theory depicts the interpenetration of polymer and mucin chains to a sufficient depth to form a semi-permanent adhesive bond .The adhesion force is thought to increase with the level of penetration of the polymer chains. The diffusion coefficient, flexibility and nature of the mucoadhesive chains, mobility, and contact time all influence the penetration rate. According to the literature, the depth of interpenetration required to form an effective bioadhesive bond is in the range of 0.2-0.5 m. The contact time can be used to calculate the interpenetration depth of polymer and mucin chains, and Db is the diffusion coefficient of the mucoadhesive material in the mucus.

(Equation 3) $l = (tD_b)^{1/2}$

The adhesion strength of a polymer is reached when the penetration depth is proportional to the length of the polymer chain. For diffusion to occur, the components involved must have high mutual solubility, which means that both the bioadhesive and the mucous have comparable chemical structures—the greater the structural similarity, the stronger the mucoadhesive bond.

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Mechanical theory[12]

According to this theory, adhesion occurs as a result of the used mucoadhesive liquid filling irregularities on a rough surface. Furthermore, such irregularity increases the interfacial area available for interactions, assisting in energy scattering and can be considered the most important phenomenon of the process. It is implausible that the mucoadhesion process is the same in all cases, and thus it cannot be described by a single theory. To identify the critical process variables, all theories are relevant. The mechanisms that regulate mucoadhesion are also influenced by the formulation's intrinsic properties and the environment in which it is used. Polymer inherent factors include molecular weight, concentration, and chain flexibility.

Fracture theory[13]

This may be the most commonly used theory in studies on the mechanical estimation of mucoadhesion. It differs from previous theories in that it relates adhesive strength to the forces required for detachment of the two involved surfaces following adhesion. It investigates the force required to separate two surfaces after adhesion has been established. In rupture tests, this force, Sm, is frequently determined by the ratio of the maximal detachment force, Fm, and the total surface area, A0, involved in the adhesive

$$s_m = \frac{F_m}{A_0}$$

interaction. (Equation 4)

The fracture force, SJ, which is equivalent to the maximal rupture tensile strength, Sm, in a single component uniform system is proportional to the fracture energy (GC) for Young's module (E) and the critical breaking length (c) for the fracture site, as described in the following equation. (Equation 5)

$$s_f \sim \left(\frac{g_c E}{c}\right)^{1/2}$$

$$g_c = W_r + W_i$$

The reversible adhesion work, Wr (energy required to produce new fractured surfaces), and the irreversible adhesion work, Wi (work of plastic deformation caused by the removal of a proof tip until the adhesive bond is disrupted) can be used to calculate fracture energy (GC), which is expressed as units of fracture surface (Af). (Equation 6)

The elastic module of the system (E) is related to the stress (s) and to the shear (e) by Hooke's law:

(Equation 7)

$$E = \left[\frac{\sigma}{\varepsilon}\right]_{\varepsilon \to 0} = \left[\frac{F/A_0}{\Delta l / l_0}\right]_{\Delta l \to 0}$$

In equation 7, the stress is the ratio between force (F) and area (A0), and shear is given by the ratio between the variety of system thickness (Dl) and the original thickness (l 0).

One criticism of this analysis is that the system under consideration must have known physical dimensions and be made of a single, uniform material. In this case, the equation should be expanded to include elastic dimensions and modules for each component. Furthermore, it must be considered that adhesion failure will occur at the bioadhesive interface. Nonetheless, it has been demonstrated that the rupture rarely occurs at the surface, no matter how close it is, or at the most vulnerable point, which can simply be the interface itself, the mucus layer, or the hydrated region of the mucus, as shown in. Because the fracture theory is primarily concerned with the force required to isolate the parts, it does not take into account the interpenetration or diffusion of polymer chains. As a result, it is appropriate for use in calculations for rigid or semi-rigid bioadhesive materials with polymer chains that do not penetrate the mucus layer.

FACTORS AFFECTING MUCOADHESION

The mucoadhesion of a drug carrier system to the mucous membrane is determined by the factors listed below.

Polymer Based Factors

1. Molecular weight of the polymer, polymer concentration in the polymer chain.
2. Polymer Swelling Factor Stereochemistry.

Physical Factors

- pH at the polymer substrate interface, application strength, and contact time.

Physiological Factors

- Mucin turnover rate diseased state.[14]

IDEAL MUCO POLYMER CHARACTERSTICS

The formulation contains a mucoadhesion promoting agent or polymer, which aids in the adhesion of the active pharmaceutical ingredient to the oral mucosa. When in contact with saliva, the agent may exhibit additional properties such as swelling, which promotes disintegration. As previously stated, various physical and chemical exchanges can affect polymer/mucus adhesion;

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therefore, the polymer should be carefully selected with the following properties in mind.[15]

- The polymer must have a high molecular weight of at least 100.00 to promote adhesiveness between the polymer and mucus.[16]
- Long chain polymers-chain length must be sufficient to promote interpenetration but not so long that diffusion becomes a problem.[17]
- High viscosity
- Degree of cross linking- it influences chain mobility and resistance to dissolution
- In the presence of water, highly cross-linked polymers swell and retain their structure. Swelling promotes controlled drug release and increases polymer/mucus interpenetration. However, as cross linking increases, chain mobility decreases, reducing muco adhesive strength.Spatial conformation[17]
- Polymer chain flexibility promotes polymer interpenetration within the mucus network.[18]
- Polymer concentration-an optimum concentration is required to promote muco adhesive strength. It is, however, dependent on the dosage form. The adhesive strength of a solid dosage form increases as the polymer concentration increases. However, in the case of semisolid dosage forms, there is an optimum concentration beyond which the adhesive strength decreases.[19]
- Optimum hydration- excessive hydration leads to decreased mucoadhesive strength due to formation of a slippery mucilage
- High applied strength and initial contact time
- It should non toxic, economic, biocompatible preferably biodegradable

POLYMERS USED FOR MUCOADHESIVE DRUG DELIVERY[20]

PAA derivatives carbomer- carbopol noveon-polycarbophil[21]

These are acrylic acid polymers that have been cross-linked with polyalkenyl ethers or divinyl glycol. They are made from primary polymer particles ranging in size from 2 to 6 microns. Each primary particle is made up of a network structure of polymer chains linked together by cross links. Carbopol polymers, pemulen polymers, and noveon polymers are all cross linked. When exposed to a pH of 4.0 to 6.0, they swell up to 1000 times their original volume to form a gel; the glass transition temperature is approximately 105°C. Because of the presence of a carboxylate group and a pKa of 6.0 to 0.5, repulsion between the negative charges occurs, causing swelling and thus increased mucoadhesive strength of the polymer.

Chitosan[22]

It is a cationic polymer (polysaccharide)[23], It is created when chitin is deactivated. Because of its good biocompatibility, biodegradability, and nontoxic nature, chitosan is gaining importance in the development of mucoadhesive drug delivery systems. It forms ionic bonds with the mucosa via the amino group and sialic acid residues. Newer second generation polymers

More site specific hence called cytoadhesives.

- Are least effected by mucus turn over rates.
- Site specific drug delivery is possible

Lectins[24]

Lectins are naturally occurring proteins that aid in the recognition of cells and proteins in biological systems. Lectins are a class of structurally diverse proteins and glycoproteins that bind to specific carbohydrate residues in a reversible manner. After binding to the cell, lectins can either stay on the cell's surface or be taken inside via endocytosis. As a result, they enable site-specific and controlled drug delivery. Lectins have many benefits, but they also have the disadvantage of being immunogenic.

Thiolated Polymers[25]

These are thiomers made from hydrophilic polymers like polyacrylates, chitosan, and deacetylated gallan gum. The presence of a thiol group prolongs residence time by promoting covalent bonds with cystiene residues in mucus. Because of their increased rigidity and cross-linking, disulphide bonds may also alter the mechanism of drug release from the delivery system.

Polyox WSRA[26]

The following properties are shared by a class of high molecular weight polyethylene molecular weight polyethylene oxide homo polymers:

- Water soluble.
- Hydrophilic nature
- High molecular weight.
- Functional group for hydrogen bonding.
- Biocompatible and non toxic.Can be formulated into tablets, films, gels, microcapsules, syrups.

NOVEL POLYMERS

- Tomato lectin demonstrated binding selectivity to the epithelium of the small intestine.27
- Shajaei and Li created and tested a co polymer of PAA and PEG monoethylether mono

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methacrylate (PAA-co- PEG) for optimal buccal adhesion.[28]
- Leleetal, investigated novel polymers of PAA complexed with PEGylated drug conjugate.[29]
- Corium Technologies has created a new class of hydrophilic pressure sensitive adhesives (PSA). Non-covalent hydrogen bonding cross linking of a film forming hydrophilic polymer with a short chain plasticizer with reactive OH groups at chain ends resulted in the formation of the complex.
- Alur et al. Studied the transmucosal sustained delivery of chlorphenazine maleate in rabbits using a novel natural mucoadhesive gum from hakea as an excipient in buccal tablets. The gum provided sustained release and sufficient mucoadhesion.[30]

RECENT APPLICATIONS IN AN ORAL MUCOADHESIVE DRUG DELIVERY

Oral mucoadhesive drug delivery has many applications for many drugs that have poor bioavailability and are rapidly degraded when administered orally. Oral mucoadhesive drug delivery has the advantages of high accessibility and low enzymatic activity.

Previously, hydrophilic polymers such as SCMC, HPC, and polycarbophil were used to treat periodontal diseases, but the trend is now shifting toward the effective use of these systems for the delivery of peptides, proteins, and polysaccharides.[31]

The buccal cavity has the added benefit of high patient compliance. Orabase, a first generation mucoadhesive paste, has been used as a mouth ulcer barrier system. Semisolids are more convenient to administer, but tablets have also been developed. Matrix devices or multilayered systems containing a mucoadhesive agent are examples of tablets. The tablet is kept under the upper lip to avoid the salivary gland's clearance mechanism. Buccostem, an antiemetic adhesive tablet containing prochloroperazine, is typically administered in this manner.[32]

METHODS OF EVALUATION

Mucoadhesive polymers can be evaluated by performing in vitro and in vivo adhesion strength tests.

In Vitro Methods

The elucidation of the precise mechanisms of bioadhesion is emphasised. These are the methods.[33]

- Methods determining tensile strength
- Methods determining shear stress
- Adhesion weight method
- Fluorescent probe method
- Flow channel method
- Mechanical spectroscopic method
- Filling liquid film method
- Colloidal gold staining method
- Viscometer method
- Thumb method
- Adhesion number
- Electrical conductance
- Swelling properties
- In vitro drug release studies
- Muco retentability studies

In Vivo Methods

- Use of radioisotopes [34]
- Use of gamma scintigraphy
- Use of pharmacoscintigraphy
- Use of electron paramagnetic resonance (EPR) oximetry
- X ray studies
- Isolated loop technique

CURRENTLY USED FORMULATIONS

The table shows representative drugs with transmucosal dosage formers, as well as the type of release and manufacturer. Many novel formulations have advanced to various stages of development and approval, with varying degrees of manufacturing and marketing success.

a. Tablets[35]

For drugs such as nitroglycerin and fentanyl, lozenges, troches, and tablets for systemic delivery across the oral mucosa are currently commercially available. Tablets and lozenges dissolve into the saliva, utilising the entire surface area of the oral cavity for absorption.

b. Sprays[36]

Glyceryltrinitrate is a small molecule that can be quickly delivered across the sublingual oral mucosa using a spray to relieve angina. Generex Biotechnology Corporation has developed a RapidMistTM spray that can deliver large molecules such as insulin across the oral mucosa. To improve drug permeability across the buccal epithelium, the Generex Oral-lynTM spray employs micelles and generally recognised as safe GRAS-like surfactants as permeability enhancers.

c. Mouthwashes[37]

The majority of the current literature on mouthwashes and oral rinses focuses on their use in the local delivery of antimicrobial agents.

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Chlorhexidine gluconate is one such antimicrobial, with research supporting its use in the treatment of gingival and periodontal disease, caries, and as a prophylactic treatment for oral candidiasis in immunocompromised patients. The substantivity allows for a significant antibacterial effect up to 7 hours after using the mouth rinse.

d. Gels[38]

Since the 1980s, gels have been studied as a method of controlled drug delivery. The primary goal of bioadhesive controlled drug delivery is to locate a delivery device within the body in order to improve drug absorption in a site-specific manner. Bioadhesion is influenced by the biological environment's synergistic action, the properties of the polymeric controlled release device, and the presence of the drug itself. More than half of the therapeutic agents and vehicles being developed are still in the research and development stage (bioavailability, distribution, safety and adherence stages).

e. Pastes[39]

The use of pastes as a drug delivery vehicle is a controversial practise. Orabase® is a commercially available muco- adhesive paste that is available as a carrier alone or with 0.1 percent triamcinoloneacetonide (Kenalog in Orabase®) for treating immunologically mediated oral mucosal conditions. Liposomes have been studied as drug delivery carriers in both solution and paste form. According to one study, liposome-encapsulated corticosteroids applied topically in the form of a paste may improve symptom remission in the treatment of oral lichenplanus, and an anti-inflammatory paste containing amlexanox has been shown to accelerate healing of aphthous ulcers.

f. Patches[40]

Several patch systems designed to adhere to the oral mucosa and deliver drugs have been developed. There are three types of oro-adhesive patches: patches with a dissolvable matrix for drug delivery to the oral cavity; patches with a non-dissolvable matrix for drug delivery to the oral cavity; and patches with a non-dissolvable matrix for drug delivery to the oral cavity. These patches are more effective than solid forms such as tablets and lozenges in treating oral candidiasis and mucositis because they produce sustained drug release. During use, they slowly and completely dissolve, leaving nothing to be removed. Significant amounts of drug, however, will be lost to the oral cavity. As a result, they are better suited for delivering drugs more broadly into the oral cavity rather than the oral mucosa to which they are applied.

g. Wafers/Films[41]

Thin strips of polymeric films dissolve on the tongue in less than 30 seconds and deliver drugs (that can cross the permeability barrier) directly to the blood supply for rapid treatment of conditions such as impotence, migraines, motion sickness, pain relief, and nausea. Similar wafer technology is already being used to treat migraines, and it is hoped that the fast dissolution of the wafers, the technology's self-administration, and the high blood supply of the oral mucosa will enable fast effective treatments for many more conditions in the future.

II. CONCLUSION

Mucoadhesion can be used as a model for controlled drug delivery approaches for a variety of drug candidates. The various advantages of oral mucoadhesive drug delivery systems, such as prolonged drug residence time, which increases drug absorption, are important factors in the oral bioavailability of many drugs. With the appropriate technologies, delivery techniques, and polymer selection for the oral mucosa, the oral mucosa could be used in the future for the treatment of many diseases, both mucosal and systemic, and the catalogue of drugs that can be delivered via the mucosa could be greatly expanded. Further advancements in muco-buccal adhesive technology and sustained local drug release have the potential to reduce systemic side effects from ingested or injected therapies that target an oral mucosal disease.

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