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Recent progress in the development of localized drug delivery systems for oral mucosal disorders using mucoadhesive patches

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ABSTRACT: Oral diseases are becoming increasingly prevalent worldwide, posing a significant challenge in treating recurrent conditions due to the wet and movable environment of the oral cavity. This environment reduces the residence time of formulations, making it difficult to effectively treat oral diseases. To address this issue, the use of mucoadhesive systems could be a beneficial strategy to prevent accidental swallowing and wash-off. Various approaches have been suggested to provide mucoadhesion and mucosal penetration, including the use of naturally derived or synthetic polymers, bio-inspired materials, or thiomers. These biocompatible oral mucoadhesive systems with strong wet adhesion offer a promising opportunity for drug delivery applications. In this review, we have focused on current oral mucoadhesive systems that improve local treatment of oral diseases. We begin by providing a brief overview of the structural properties of the oral mucosa, permeability considerations, and the mechanism of mucoadhesion. We then provide examples of innovative materials commonly used in oral mucoadhesive drug delivery systems for local therapy.

KEYWORDS: Oral disease; mucoadhesion; mucoadhesive polymers; thiolated polymers; mussel inspired polymers

1. INTRODUCTION

Oral diseases such as oral mucositis, oropharyngeal cancers, fungal infections, aphthous ulcers, periodontitis, and maxillofacial bone defects are among the most common diseases globally. According to the World Health Organization (WHO), oral mucosal diseases affect approximately 3.5 billion people worldwide and this number is reported to be increasing globally [1]. Some oral mucosal diseases such as oral lichen planus, oral lichenoid lesions, discoid lupus erythematosus, oral submucosal fibrosis and oral leukoplakia may show malignant transformations if left untreated [2]. In particular, oral cancer is the 6th most common cancer [3]. Local drug delivery in oral diseases could offer multifunctional targeted delivery to diseased site compared to systemic delivery. Local drug delivery can achieve efficient therapy with lower amount of drug and less systemic side effects [4]. Conventional drug delivery approaches used in clinical practice to treat oral diseases includes powders, oinments, gels, sprays and mouthwashes. Nevertheless, the major drawback of these formulations is short residence time in disease site because of tongue movements, saliva secretion, the exogenous liquid flushing depending on food and drink, and highly dynamic nature of oral cavity due to masticating, speaking, swallowing [5-7].

To address drawbacks of current treatment approaches, several polymeric mucoadhesive drug delivery systems have been proposed to establish a stronger and longer contact with buccal mucosa. The mucoadhesive polymers used in buccal mucosa should be non-toxic and non-irritant and have

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high molecular weight, strong hydrogen bonding moieties, strong ionic potential (anionic or cationic), flexibility of chain, and suitable surface energy to allow better spreading on oral mucosa. The bioadhesion between polymer and mucin could arise through i) stickiness in the contact with mucin, ii) noncovalent interactions mainly due to electrostatic interactions, and iii) binding to defined receptors on the cell surface [8-10].

This review will focus on current oral mucoadhesive systems to accelerate the local treatment of oral disease. Understanding the structure and permeability properties of the oral mucosa is crucial for the development of effective delivery systems. Therefore, we first will focus on the basic aspects to develop well-established multifunctional oral delivery systems including the structure and permeability of oral mucosa, and the basis of mucoadhesion. Then, we will give a deep insight currently widely used mucoadhesive polymers, particularly emphasizing their local application in oral disease.

2. ORAL MUCOSA: STRUCTURE AND PERMEABILITY

2.1. Structure and characteristics of oral mucosa

The oral mucosa serves a number of functions, including chewing and swallowing food, as well as phonation and ventilation. The transition from the external sk(in surface to the oral mucosa takes place on the lips, which are supported by the orbicularis oris muscle. In standard anatomical circumstances, the lips cover the incisors entirely, with the tips of the upper incisors located below the upper lip's border and the lower lip's border. The lips are kept moist by saliva from inside the mouth or from the minor salivary glands located inside the lips [11].

The oral mucosa is composed of three fundamental layers: the epithelium, basement membrane, and connective tissue (Figure 1). The oral cavity, which is lined with epithelium, is supported by the basement membrane underneath. The connective tissue supported the basement membrane. The basement layer serves as a boundary between the connective tissues and epithelium, providing mechanical support to the epithelium and resistance to the transition of cells and macromolecules. There are basal keratinocytes that are positioned adjacent to the basement membrane and proliferate rapidly to repair and renew the epithelium [12, 13].

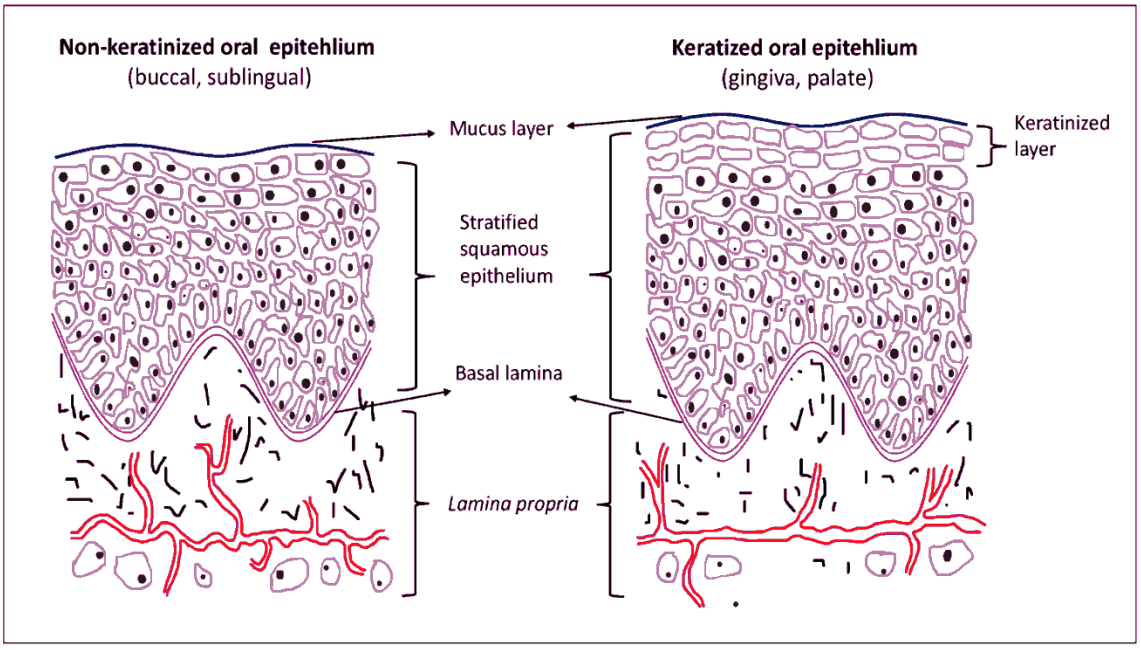

Figure 1. Structure of oral mucoza [13]. Reprinted from (Şenel 2021) with permission from Multidisciplinary Digital Publishing Institute.

The epithelium is differentiated into two classes: non-keratinized and keratinized. The non-keratinized epithelium is found on the palate, the ventral side of the tongue, the floor of the mouth, the lips, and the cheeks, and protects underlying tissues. The keratinized epithelium is found on the

hard palate in the inflexible areas of the oral cavity. The thickness of the epithelium varies from 500 to 800 micrometers. Therefore, permeability considered as sublingual>buccal>palatal, based on keratinization and the thickness and of the tissues, and its permeability is greater in the sublingual region than in the buccal region, which is greater than in the palatal region [4, 12, 14, 15].

The buccal epithelium is comprised stratified squamous epithelial cells. These cells originate from basal cells, mature, change shape, and migrate towards the surface, where they differentiate, shed, and are replaced by overlying epithelial cells. The turnover time for the epithelium is generally considered to be 5-6 days [14, 16].

The oral mucosa has roughly 200 cm^2 total surface area. It has three types of mucosa. The first one, the masticatory mucosa, covers the gums and hard palate. The second one is the specialized mucosa, covers the dorsum of the tongue. The last one is the lining mucosa, covers the floor of the mouth and buccal tissue. The distribution of these mucous membranes in the oral cavity is approximately 25%, 15%, and 60% [17].

2.2. Permeability

The oral mucosa's permeability is a critical factor in determining the formulation design for drug absorption and delivery to deeper layers. The absorption of drugs through the mucosa depends on factors such as local variations in mucosal thickness, epithelium keratinization level, and lipid composition. These factors combine to form a permeability barrier in the oral mucosa [18].

The oral mucosal barrier serves to prevent endogenous and exogenous substances from entering the body and to prevent fluid loss in the underlying tissue. The barrier is typically composed of a lipid-dense epithelial layer, with supra-basal cells differentiating to create strong intercellular desmosomal junctions and membrane-coating granules on the apical surfaces. These granules provide for epithelial cohesion, and lipophilic substances secreted into the intercellular spaces make it difficult for hydrophilic substances to penetrate the epithelium. While tight junctions are hypothesized to play a role in the permeability barrier, they are rarely found in the epithelium of the oral mucosa. The epithelial tissue is the primary barrier for permeability, while connective tissue provides some resistance to lipophilic substances due to high hydration [4, 12].

The diffusion from the oral mucosa can occur via three mechanisms: i) passive diffusion, which includes trans-cellular crossing of cells and para-cellular crossing of lipid-rich domains between cells, ii) carrier-mediated transport, and iii) endocytosis/exocytosis, which involves cellular ingestion and excretion by the endocytic pathway [12, 19].

3. BUCCAL DRUG DELIVERY

Buccal administration refers to the delivery of a drug to the inside of the cheek in the mouth. This method of delivery can result in either local or systemic effects, depending on the specific drug being administered. Since, the buccal mucosa is not as permeable as the sublingual mucosa; it is not typically used for systemic treatment of chronic conditions. However, buccal delivery offers several advantages, such as ease of administration, increased patient compliance, rapid onset of action compared to oral systemic administration, and the removal of the drug carrier from the application site when treatment is no longer needed. Despite these advantages, there are some disadvantages to buccal delivery as well. For instance, saliva secretion can separate the carrier from the tissue due to the washing effect, the active substance may not be evenly distributed in the saliva, and the same concentration of active substance cannot be achieved in the entire oral mucosa. Additionally, there is a risk of decreased patient compliance due to unpleasant taste and irritation [18]. When a drug is administered through the buccal mucosa, it is absorbed through the reticular and jugular veins and enters the systemic circulation. The superficial layers of the mucosa act as the first barrier to substance entance and the absorption of active agent from the epithelium of the buccal mucosa can be through the transcellular and paracellular pathways. Permeation across the buccal mucosa primarily occurs through the paracellular pathway, which involves intercellular lipids produced by membrane-spanning granules. Generally, small lipophilic molecules with a logP value between 1.6 and 3.3 are absorbed most rapidly. Substances with a value above this range and low water solubility may have their absorption limited. In non-keratinized buccal and sublingual mucosa, the hydrophilic nature of lipids is the predominant route for absorption. Lipophilic substances can be absorbed via the transcellular pathway. The buccal mucosa is a potential site for the delivery of hydrophilic

macromolecules such as peptides, oligonucleotides, and polysaccharides through controlled-release formulations However, it generally has low permeability for high molecular weight drugs [20].

To be effective and patient-compliant, drug carriers used in oral mucosa must possess several essential properties. They should not impair eating and speech, and have an acceptable taste with no irritancy and toxicity. Generally, sustained drug delivery can be more advantageous for superior patient compliance, release profile must be tailored to each specific case being treated [12]. The surface charge of the material plays a critical role in its durability in biological fluids, as well as its affinity to biological membranes and cells. Additionally, the balance of lipophilic and hydrophilic components of the carrier can affect its interactions with biological fluids and its stability. The swelling behavior of the device is also essential to control drug release profile and bioadhesion. The mechanical durability of drug carrier ensures its stability in the oral cavity, where it is exposed to various stresses [21]. When applying a carrier into the oral mucosa, the rheological properties of the carrier are crucial. These properties determine the carrier's ability to remain in the application area for the desired duration after administration [22]. In particular, the use of mucoadhesive drug delivery systems can be a beneficial strategy for site-specific delivery. This approach allows for the application of the active agent to the target tissue, prolongs the residence time, and accelerates the local effect [23].

Liquid dosage forms applied to buccal mucosa can be prepared as solutions or suspensions. They are generally preferred in the pediatric population to reduce the risk of choking associated with swallowing solid dosage forms. The drawbacks of liquid dosage forms administered to the buccal mucosa include poor retention in the oral cavity and the potential to be swallowed before transmucosal absorption occurs. The dose and volume of liquid dosage forms are restricted by the solubility of the active ingredients, necessitating the use of co-solvents and surfactants [18]. In recent studies, crystalline compounds have been incorporated into liquid dosage forms applied to the buccal mucosa to increase viscosity when in contact with saliva. These systems can increase viscosity by changing their mesophase when in contact with saliva. Although the low-viscosity form is simple to administer, the high-viscosity form prolongs the medication's residence time in the tissue [24]. Semi-solid formulations (e.g. gels, creams and ointments) can distribute easily across the oral mucosa. However, the release of active substances from these formulations cannot be as consistent and effective as that from tablets, patches, or films. Increasing viscosity can provide a more uniform release of the active substance [25].

Mucoadhesive tablets applied to the buccal mucosa are generally small, flat, or oval with a diameter of 5-8 mm. These tablets have the potential for controlled drug release and offer additional advantages, such as a high surface-to-volume ratio that ensures high bioavailability. These dosage forms are intended for transmucosal administration [25]. The mucoadhesive properties of these formulations must be released in contact with saliva and epithelium. The primary limitation of treatment with buccal mucosal tablets is the size of the tablet, which can cause discomfort for the patient and result in poor patient compliance [26].

Effervescent discs applied to the buccal mucosa are thicker and flatter than buccal tablets or conventional effervescent tablets, and they release the drug more rapidly. These discs are flat, thin, rigid, and inflexible, and they were designed to reduce the discomfort associated with the large volume of buccal tablets. According to a study conducted by Jaipal et al., carbon dioxide released from buccal effervescent discs enhances penetration [26, 27].

Films and patches applied to the buccal mucosa are retentive dosage forms that release the active ingredient directly into the buccal epithelium. They are patient-friendly and convenient products that have gained importance in the pharmaceutical industry due to their small size and thickness, which are within tolerable limits for patients, thereby increasing patient compliance. However, their small size limits the loading drug amount [26]. These dosage forms offer advantages over buccal mucosal tablets in terms of flexibility and comfort, and they also have an advantage over gels in that gels applied to the buccal mucosa are washed away with saliva, and the active ingredient is rapidly removed from the tissue. The ideal buccal film should have sufficient softness, flexibility and, elasticity, and it should also be strong enough to maintain its structural integrity against the stress caused by the mechanical movements of the mouth and mucoadhesives, which are not affected by saliva circulation [25].

4. MUCOADHESION

Mucoadhesion refers to the ability of adhesion between mucous membranes and a non-biological material surface for an extended period of time through interfacial forces. Mucoadhesive formulations are designed to adhere to the site of action, delivering the active substance to the absorption site [28]. The advantages of mucoadhesive formulations include a high concentration of the active agent in disease site, increased therapeutic efficacy due to increased tissue residence time, and higher patient compliance due to easy application [18]. Mucoadhesion of drug delivery system and mucus layer can be occurred by hydrogen-bonding, disulfide linkage, hydrophobic, van der Waals interactions, electrostatic, and macromolecule entanglement [29, 30].

4.1. Theories of mucoadhesion

Six different theories have been proposed to play a primary role in the mucoadhesion namely wetting theory, electronic theory, absorption theory, diffusion theory, mechanic theory and fracture theory (Figure 2) [20, 31]. Each theory explains a different aspect of mucoadhesion, and all of them can be analyzed in two phases: the contact phase and the hydration phase. The first phase of mucoadhesion includes intimate contact between mucoadhesive material and mucus layer and then wetting and spreading of material. In general, prolonged contact of material with mucus layer accelerates the drug dissolution and absorption. The mucoadhesive material interdiffuse or interpenetrate within mucus layer in the second hydration phase [29, 32].

The wetting theory of mucoadhesion is applicable to liquid or low viscosity systems and related to surface and interfacial energies. It indicates the ability of a liquid to spread on biological surfaces. Wetting rate is determined by analyzing of of contact angles and thermodynamic adhesion work. Based on the wetting theory, the higher the contact angle leads the lower affinity. Contact angle should be zero for desired spreadability and adhesiveness [29, 33].

The electronic theory states that the adhesion becomes due to differences in electronic structures of the mucus and the mucoadhesive system, which results in electron transfer between surfaces [34]. Then, an electrically charged double layer is generated at the interface of mucus and the mucoadhesive material as a result of electron transfer and followed by formation of attractive forces. This theory can only be applied when the polymer and mucosa have opposite electrical charges [28].

Diffusion theory considers interpenetration of mucoadhesive polymer chains into glycoprotein mucin chains of mucus layer. The penetration of polymer chains into the mucosa is affected by several variables, including the penetration depth, chain mobility or flexibility, diffusion coefficient, and contact time. Diffusion coefficient varies depending on molecular weight and decreases with increasing crosslink density. Sufficient penetration is required to form a semi-permanent mucoadhesive bond. Penetration depths in the range of about 0.2 to 0.5 micrometers are necessary for good mucoadhesive bonds [20, 35].

The absorption theory states adherence occurs through secondary forces including hydrogen bonding, van der Waals' forces and hydrophobic bonding. The presence of carboxyl and hydroxyl groups ensures the formation of hydrogen bonds between the mucosa and polymer. The increase in hydrophilic functional groups also increased the concentration of hydrogen bonds. Besides, chemisorption can become as a result of primary bonds such as ionic, covalent and metallic bonding which leads particularly strong adhesion [36-38].

The mechanical theory states that adhesion occurs because of roughness of the surface and during adhesion liquid fills the irregularities of a rough surface [39].

The fracture theory of mucoadhesion differs from the other five theories because it is related to the forces required to separate the two surfaces involved. According to this theory, the adhesive bond failure occurs at the interface, but the failure of the adhesive bond occurs at the weakest component [28].

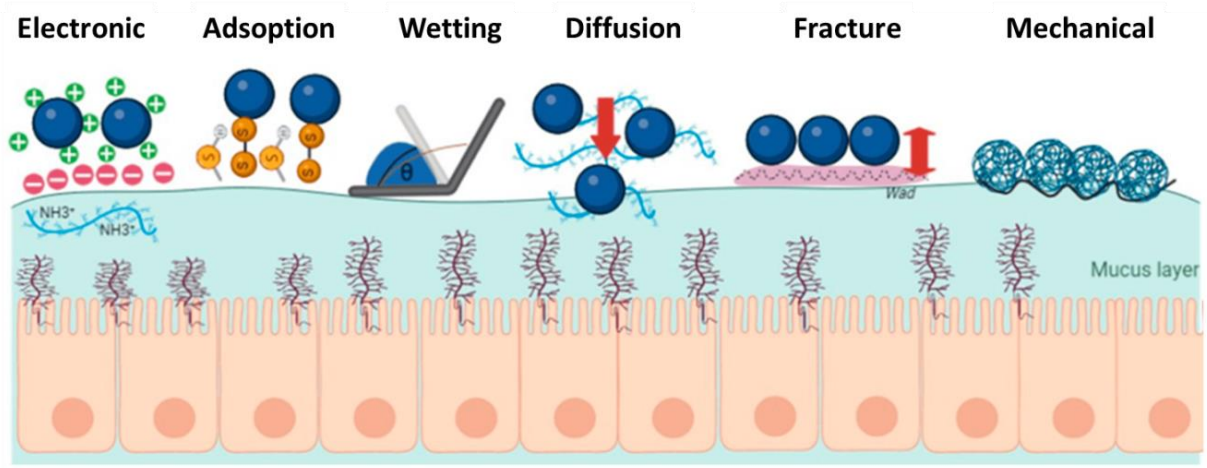

Figure 2. Mechanisms of mucoadhesion [40]. Reprinted from (Vasquez-Martínez et al. 2023) with permission from Multidisciplinary Digital Publishing Institute.

4.2. Factors effecting mucoadhesion in the oral cavity

The molecular weight of the polymer used in formulation plays a crucial role in determining the efficacy of mucoadhesion. For optimal mucoadhesion, the minimum molecular weight threshold for the polymer is 100 kDa, and it must be optimized for the specific application. In linear polymers, the molecular weight directly influences the adhesive property, but in nonlinear polymers, the relationship between molecular weight and adhesion is not always straightforward [41]. Additionally, the concentration of the polymer must be optimal for successful mucoadhesion. Above the optimal level, the adhesive force may decrease due to the separation of the helical polymeric structure. It is essential to note that the optimum concentration varies between different polymers [34, 42].

The flexibility of the polymer chains has a significant impact on the viscosity and diffusion coefficient. Polymers with greater flexibility exhibit increased diffusion on the mucosal surface, resulting in enhanced mucoadhesion force [34]. For successful mucoadhesion, the polymer must be properly hydrated and form a macromolecular network. The swelling behavior of the polymer is influenced by factors such as the concentration of the polymer in the formulation, the presence of water, and the ionic strength [34]. When the polymer fuses with the mucosa, the free surface energy decreases due to the disappearance of the free surfaces of the polymer and mucus layer, and the formation of a new interface. The next step involves the activation of mucoadhesive substances in the presence of moisture, which provides a plasticizing effect and releases mucoadhesive particles. These particles then bind with mucin by forming van der Waals or hydrogen bonds [43]. Microscale topography of biomaterial is crucial to determine cellular adhesion and growth [44].

The pH of the environment can significantly impact the electrostatic charge on the mucosal surface. Both the mucosa and the polymers have surface charges that are influenced by the pH level. The charge density of the mucosal membrane is dependent on the pH level, which is influenced by the dissociation of functional groups on amino acids and carbohydrates. Besides, electron-rich hydroxyl and carboxylic acid functional groups are found in many bioadhesive polymers. These functional groups cause electronic clouding of the functional groups, which may be providing adhesion. The interaction between the substrate and polymer can be determined by the molecular configuration [34].

Some physiological factors influence the mucoadhesion process. For example, fibrin utilized as tissue adhesive in surgical operations provides mucoadhesion using the process of the physiology of the blood coagulation. As a result of polymerization of fibrin, clot formation and mucoadhesion occurs. A high rate of mucosal turnover shortens the residence time of the polymer in the tissue. Although the polymer provides good adhesive strength, it tends to detach from tissue when the mucosa regenerates [34]. It is known that disease states, such as ulcers, colitis, cystic fibrosis and bacterial and fungal infection affects the physicochemical properties of the mucosa as well as mucoadhesion [45].

5. MUCOADHESIVE POLYMERS

The interactions (e.g. hydrogen bonds, van der Waals interactions) between the mucosa and bioadhesive polymers used in the formulation are directly dependent to the chemical structure of the bioadhesive polymers. The molecular weight and length of the polymers used in these formulations are key parameters to allow for inter-chain interactions. Anionic polymers are generally preferred because the mucus layer is negatively charged at physiological pH values. The hydration rate and rheological properties of polymers also affect the bioadhesion forces. Excessive hydration of the polymer causes lubrication and decreases bioadhesion force [46].

Mucoadhesive polymers can be categorized based on source, solubility, charge and bioadhesive force (Figure 3) [29, 47, 48]. In particular, water soluble polymers can generate swelling structure through wetting, and interpenetrating with mucin. Although, polycarbophil is not water soluble, it can swell based on the pH and ionic strength [45, 49]. Charged polymers can allow stronger interaction with mucin compared to neutral polymers. Cationic polymers possess a net positive charge and exhibit superior interaction with mucin than anionic polymers. Chitosan is the most common example of cationic polymers used in oral mucosa [48, 50]. Some polymers such as polyvinyl alcohol (PVA) and poly(acrylic acid) (PAA) demonstrate hydrogen bonding because of functional groups such as carboxyl, hydroxyl, sulfate, and amine [51]. To provide sufficient mucoadhesion force, mucoadhesive polymer can be utilized alone or in hybridization with other polymers [29].

One of the major shortcomings of the oral mucosal route of drug administration is its low bioavailability. Therefore, various substances are used as penetration enhancers to increase the passage through the mucosa. In the selection of penetration enhancers, it is very important to select substances with increased efficacy and reduced toxicity profiles and to understand the mechanism of action induced in the membrane [47]. Some of the known penetration enhancers may cause irritation and bad taste sensation. These issues should be considered when selecting a penetration enhancer in terms of patient compliance.

While the buccal mucosa has a relatively low enzymatic activity than other transmucosal drug administration routes, the presence of enzyme inhibitors in buccal formulations can enhance absorption from the buccal mucosa [46]. Aprotinin, bestatin, puromycin and bile salts can be used to reduce enzymatic degradation by altering enzyme activity [47].

In oral mucosal administration, poor solubilization of the drug in saliva can reduce therapeutic efficacy. To overcome this issue, solubility modifiers can be used. For instance, complexation with cyclodextrins can enhance the absorption and bioavailability of drugs in the oral mucosa [47]. For instance, imidazole-derived antimycotics (e.g. econazole, miconazole, clotrimazole), which are commonly used for the local treatment of oral fungal infections, result in slow release from lipophilic chewing preparations because of their low hydrophilicity. Nonetheless, after complexation with hydroxypropyl-β-cyclodextrin, an increased release from the preparations was observed [46].

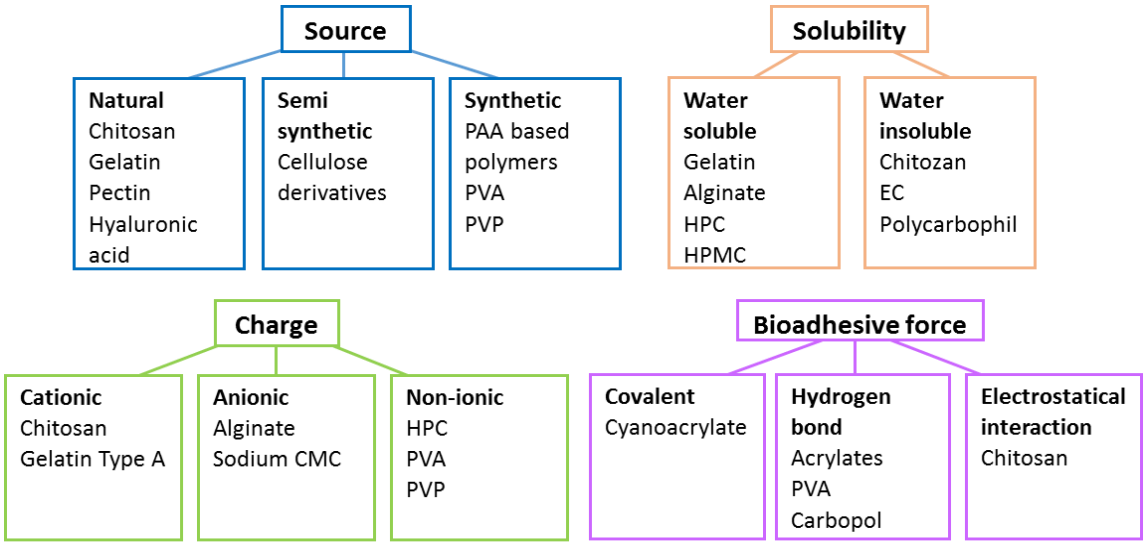

Figure 3. Mucoadhesive polymers used in oral mucosal drug delivery systems

5.1. Chitosan

Chitosan (CS) is a natural polysaccharide composed of β-1,4-linked D-glucosamine and N-acetyl-D-glucosamine units, which can be derived from full or partial deacetylation of chitin [52]. Due to its mucoadhesive properties resulting from the electrostatic attraction between positively charged amino groups in chitosan and negatively charged sialic acid residues on mucosal surfaces, CS is an ideal candidate for oral mucosal drug delivery [53]. Ryu and colleagues developed an adhesive chitosan-catechol (ChiC) patch (Chitoral) through freeze drying to generate a porous hydrogel with greater mucoadhesion in the oral cavity. They reported that when Chitoral comes into contact with saliva, it dissolves instantly to generate insoluble inter-molecular complexes with oral mucins, and then constitutes an adhesive hydrogel through covalent crosslinking and physical entanglement. Triamcinolone acetonide (TA) was loaded into Chitoral to treat oral ulcers. Chitoral exhibited slower TA release in mucin solution due to the inter-molecular interaction between Chitoral and mucin in saliva, which achieved a dense structure to improve the durability of Chitoral [54]. Onnainty et al. developed a nanocomposite CS and montmorillonite hydrogel for the buccal delivery of chlorhexidine (CLX) by ion-exchange. Long-term CLX release was obtained with no initial burst release. This nanocomposite hydrogel showed desired mucoadhesion properties with antimicrobial efficacy [55]. Aksungur and coworkers designed nystatin loaded occlusive bioadhesive gels and films based on CS for prophylaxis and/or treatment of oral mucositis. As the molecular weight of chitosan increased, nystatin release decreased. In an in vivo chemotherapy-induced mucositis model in hamsters, nystatin-loaded gels and suspensions showed significantly lower mucositis scores compared to the chitosan gel alone. Additionally, gels demonstrated longer retention time and slower distribution of nystatin in the oral cavity of healthy volunteers compared to suspensions [56].

Pornpitchanarong and coworkers prepared catechol-modified chitosan and hyaluronic acid (HA) nanoparticles (NPs) for the delivery of doxorubicin to the tumor site in the oral cavity to avoid systemic side effects. The Cat-NPs exhibited higher mucoadhesive properties on ex vivo porcine oral mucosal tissues than unmodified NPs, and over 60% of the NPs maintained on the tissue after washing with artificial saliva. The release of doxorubicin resulted in a decrease in the growth of HN22 oral squamous cell carcinoma cell line [57].

5.2. Hyaluronic acid

Hyaluronic acid (HA), a natural polysaccharide, is synthesized by cells during certain points in the cell cycle in various tissues. HA is highly biocompatible, biodegradable, water-soluble, and viscoelastic. When combined with natural or synthetic polymers, HA's physicochemical properties can be enhanced. HA can accelerate cell adhesion, growth, and migration, promote re-epithelization, reduce collagen disposition and scarring [21, 58]. The topical HA 0.2% application is reorted as effective for the treatment of aphthous ulcers [59].

Alkhalidi et al. developed HA acid-based hydrogel with fluconazole-loaded sesame oil nanotransfersomes (HA-FS-NTF) for the treatment of oral ulcers. The hydrogels exhibited thixotropic behavior, which is beneficial for oral application. According to ex vivo permeation studies in sheep buccal mucosa, the permeation of HA-FS-NTF (400 µg/cm^2) was higher compared to fluconazole suspension (122 µg/cm^2) and HA hydrogel (294 µg/cm^2). In vivo ulcer index was found to be 0.67, 1.33, 2.17, 2.83, and 4.67 for HA-FS-NTF, HA hydrogel with fluconazole-loaded nanotransfersomes (without sesame oil), HA hydrogel with fluconazole, fluconazole aqueous dispersion, and blank HA hydrogel applied in animals, respectively. Thus, HA-FS-NTF achieved effective fluconazole delivery in the treatment of oral candidiasis [60].

Paris and coworkers used chitosan and hyaluronic acid to develop a mucoadhesive membrane by Layer-by-Layer technology. The membrane dissolved in saliva due to hyaluronidases and other enzymes that degrade these polysaccharides. They achieved better contact time between the protein and the oral mucosa than the liquid formulation in the mouse model. The model protein penetrated in the epithelium after 10 min from the patch administration to the mouse sublingual mucosa [61].

Pornpitchanarong and co-workers proposed the use of mucoadhesive films containing catechol-functionalized HA (HA-cat) and PVA loaded with clotrimazole (CZ) nanosuspension for treatment of oral candidiasis. The mucoadhesion of HA-cat/PVA films was higher than unmodified HA/PVA films. These films exhibited gradual CZ release for 6 hours and were non-toxic to human

gingival fibroblast cells. Moreover, CZ nanosuspension-loaded films had significantly higher antifungal activity than CZ suspension [62].

The utilization of microneedles could serve as a beneficial strategy for enhancing local or systemic drug delivery, thus accelerating drug penetration. For instance Zhu et al. designed a microneedle patch using HA (HAMNs) including fast-dissolving lidocaine hydrochloride (LDC) encapsulated tips and an adhesive backing layer from PVA/carboxymethylcellulose sodium (CMC-Na). The microneedle applied to the stratum corneum of isolated porcine oral mucosal with an approximate insertion depth of 279 micrometers. Compared to clinically used lidocaine cream (EMLA cream, LDC, 1.2 mg), the microneedle patch (LDC, 0.5 mg) demonstrated more efficient anesthesia, despite a relatively lower LDC dose [63].

Li et al. fabricated a microneedle patch comprised of an array of 100 dissolvable microneedles, with HA tip part and the polyvinylpyrrolidone (PVP) base part and a bilayer backing layer consists of an adhesive layer (PVA) and waterproof layer (ethyl cellulose) for avoiding saliva flow in oral site. The detachment forces exerted on oral mucosa were measured as 0.525 N, 0.987 N, and 1.086 N for the backing layer, HA-PVP microneedles, and microneedle patch, respectively.

The in vitro mucoadhesion time for the artificial saliva was approximately three hours, which was longer than that of the backing layer, as demonstrated by the small cup slurry test. Following the local application of the FITC- betamethasone sodium phosphate-loaded microneedle patch, histological analysis revealed the presence of fluorescence signal in the epithelium and surrounding tissue after five minutes, with an increased signal near the basal layer after sixty minutes. In contrast, the application of FITC- betamethasone sodium phosphate solution resulted in the appearance of fluorescence on the epithelial surface without any distribution in the oral mucosa, with a slight enhancement of the signal in the basal layer [64].

5.3. Alginate

Alginates are natural polysaccharides composed of β-1,4-linked d-mannuronic acid (M) and l-guluronic acid (G) derived from the Phaeophyceae family. Alginate is biocompatible, biodegradable, and non-irritant [65, 66]. The mucoadhesive properties of alginate can be attributed to hydrogen bonds between alginate and mucosal glycoproteins through carboxyl–hydroxyl interactions. Alginate can undergo mild gelation in the presence of divalent cations, such as Ca^{2+} [67].

Shtenberg et al. developed a hybrid alginate/liposomes system for the local treatment of oral cancers caused by the human papillomavirus. They first created a hybrid paste with excellent mucoadhesive properties, but it demonstrated a burst release of 90% within two hours. Next, they formulated a hybrid hydrogel with controllable doxorubicin release for two hours, although it exhibited poor adhesive capabilities. Ultimately, they designed cross-linked hybrid alginate pastes, which combined the benefits of both systems. To test their application, the researchers applied the paste onto porcine tongue tissue and then added a Ca+2/Ba+2 solution to the top layer to induce crosslinking. The crosslinked paste adhered to the tissue for 80%, while only 50% of the non-crosslinked paste remained. The crosslinked paste also released 20% of the doxorubicin after two hours, suggesting its potential for treating oral cancers due to its sustained release capability and superior mucoadhesion behavior [66]. In another study, Özbaş et al. developed an alginate/pectin (thiolated or unmodified) buccal patch for the delivery of triamcinolone acetonide using solvent casting. The alginate/thiolated pectin patches demonstrated approximately 2.6 times higher mucoadhesion than the alginate/unmodified pectin patches in ex-vivo mucoadhesion studies. The drug release from Alginate/thiolated pectin and unmodified pectin patches were 32.6 and 28.5 mg/g, respectively. All patches with or without drug were reported as non-toxic on L929 cell line [68].

5.4. Pectin

Pectin is a natural biocompatible, biodegradable, hydrophilic and mucoadhesive polysaccharide. It includes linear chains of (1–4)-linked α-D-galacturonic acid residues and is extracted from the cell walls of most plants. The mucoadhesion property of pectin can be attributed to hydrogen bonding between carboxylic acid group in pectin and mucin-type glycoproteins and physical entanglement [69-71]

Prezotti and colleagues formulated mucoadhesive films consisting of gellan gum:pectin (weight ratios of 4:1; 1:1; 1:4) using solvent casting at various concentrations (3% or 4%). The films

exhibited elevated levels of mucoadhesion force. As the ratio of gellan gum increased, both the mechanical durability and mucoadhesion force improved. Additionally, the films were found to release curcumin in a sustained manner for up to twelve hours [23]. Özkahraman and colleagues prepared Vitamin C-loaded mucoadhesive buccal patches using pectin and thiolated alginate. The presence of Vitamin C did not affect the mucoadhesion force or work of adhesion of the patches. The release amount was found to be 2.10 mg/g polymer in simulated salivary pH 6.8, and the Vitamin C-loaded patches promoted wound healing in an in vitro scratch assay test on NIH/3T3 cells [72].

5.5. Gelatin

Gelatin is a single-strain protein derived from irreversible hydrolysis of collagen. Gelatin is extensively studied in biomedical and pharmaceutical applications due to its biodegradability, biocompatibility, non-immunogenicity, cost-effectiveness. It is also considered as safe (Generally Regarded as Safe) by the United States Food and Drug Administration (FDA). Two type of gelatin is available: Type A gelatin (GA), obtained through acid-treated processes; and type B gelatin (GB), obtained through alkali-treated processes [73, 74]. Gelatin is often used in combination with different synthetic and natural polymers. For instance, Davoudi and coworkers designed a hydrocortisone sodium succinate loaded chitosan/gelatin/keratin buccal patch, using an environmental friendly process, for the treatment of desquamative gingivitis. The increased keratin amount in mucoadhesive patches exhibited superior mechanical, mucoadhesive properties and stability, and lower swelling capacity [75]. Dekina et al. developed gelatin/carboxymethyl cellulose mucoadhesive films for the delivery of lysozyme. The lysozyme in buccal films maintained more than 95% of its initial activity after 3 years of storage. Lysozyme loaded films demostrated 100% bactericidal effect on Staphylococcus aureus ATCC 25923 F-9 [76].

5.6. Cellulose derivatives

Hydroxypropylcelluloses (HPC), hydroxyethylcelluloses (HEC), hydroxypropylmethylcelluloses (HPMC), and carboxymethylcelluloses (CMC) are widely used cellulose derivatives as mucoadhesive systems. The mucoadhesion property of cellulose can be attributed to hydrogen bonding between its carboxylic acid groups and glycoprotein of mucin. Among cellulose derivatives, anionic CMC presents the highest mucoadhesion taking advantage of stronger hydrogen bonding. However, other non-ionic neutral cellulose derivatives (e.g. HPMC) possess lower adhesion due to lack of carboxyl groups [36, 77].

Fini et al. developed mucoadhesive systems using ionic CMC and/or nonionic HPC and HPMC. The blend of HPMC or HPC with CMC demonstrated slower chlorhexidine release compared to each of the individual polymers. All gels revelaed prolonged chlorhexidine release. In particular, the combination of CMC and HPC with the ratio of 2/3 resulted in higher penetration (0.8 µg/cm^2.h) and more controlled release over other formulations [78].

Timur and coworkers developed chitosan and hydroxypropyl methylcellulose (HPMC) monolayer and bilayered mucoadhesive film and wafers for the local delivery cefuroxime axetil in oral infections. HPMC based formulations disintegrated around 30 min, while chitosan based formulations were intact to 6 h. Drug loaded monolayer chitosan films exhibited significantly lower adhesive force, whereas in wafer formulations this difference was not significant. Moreover, wafer formulations exhibited remarkably higher drug release and accordingly antimicrobial activity of chitosan and HPMC containing formulations was also increased. As result, bilayered wafer formulations, including adhesive chitosan backing layer and HPMC based drug loaded layer, reported as advantageous systems to allow deeper penetration of drug for treatment of the infections in the oral cavity [79].

Ho et al. developed HEC gels incorporated metronidazole loaded in solid lipid nanoparticles (SLNs) to treat periodontitis. To obtain suitable viscosity and adhesiveness, they blended HEC with NaCMC, HPMC, and Carbopol. For a single gel-forming agent, the maximum hardness and adhesiveness were determined 0.5% (w/w) Carbopol (10.40 ± 0.40 g of hardness and 0.34 ± 0.04 mJ of adhesiveness) and 3% (w/w) HEC (7.06 ± 0.21 g of hardness and 0.77 ± 0.01 mJ of adhesiveness). The gels including 3% (w/w) HEC, 3% (w/w) NaCMC, and 3% (w/w) HPMC reported as optimum formulation with appropriate hardness and adhesiveness. All gels had shear-thinning behavior and

the gel with 3% (w/w) HEC formulation including metronidazole SLNs revelaed the best recovery [80].

5.7. Poly (acrylic acid)-based polymers

Poly (acrylic acid) (PAA) is cross linked polymer of acrylic acid with divinyl glycol or polyalkenyl ethers. PAA has great mucoadhesive properties because of its carboxylic groups which can make strong hydrogen bonds with mucin. Also, the physical entanglement of the PAA and mucus layers can enhance mucoadhesion. It has no toxicity and is known as safe for oral use by the FDA. It possesses different molecular weights, and generates transparent and easily modified gel networks. Carbomer (Carbopol®) and polycarbophil (Noveon®) are extensively used PAA derivatives in mucoadhesive systems [36, 77].

Carbomers, high molecular weight polymers, can be crosslinked by allyl sucrose or allyl ethers of pentaerythritol. Carbomers have 56% and 68% of carboxylic acid groups in dry condition. Carbomer shows superior mucoadhesive properties compared to number of polymers such as cellulose derivatives and PVA [39, 81]. Syed et al. blended agarose and Carbopol® to obtain mucoadhesive gel for local delivery of benzocaine and tibezonium iodide. The mucoadhesive strength of gels 0.4 (%wt) Carbopol® was 13.60 g, whereas it was 27.03 g for the gels including 0.4 (%wt) agarose and 0.4 (%wt) Carbopol®. Moreover, the gels with 0.4 (%wt) agarose and 0.4 (%wt) Carbopol® exhibited higher mucoadhesive flow time as 192.2 min and mucoadhesive time in volunteers as 203.2 min. This formulation released active agents in sustained manner for 3 h. Also, formulations reported as stable for 6 months [82].

Polycarbophil (Noveon®) is crosslinked by divinylglycol. Although it is not soluble in water, it can swell in medium starting from pH 4, which allows entanglement with oral mucosa. Furthermore, its carboxylic groups can bind mucin by hydrogen binding [77, 83]. Li et al. developed Bupivacaine γ-linoleate (Bup-γL) loaded in situ forming gel, for oral mucositis pain control, composed of Pluronic® F127 and F68 and also Carbopol® or Noveon® was added for enhancing mucoadhesion. Carbopol® and Noveon® significantly improved mucoadhesion without changing key properties [84]. Tamburic and coworkers evaluated the mucoadhesive characteristics of various polyacrylic acid gel systems. Carbopols 934P and 974P exhibited remarkably higher mucoadhesive strength compared to EX-214 and Noveon AA-1. In particular, mucoadhesive strength showed a correlation with rheological tan δ (phase lag) values [85].

6. NEW GENERATION OF MUCOADHESIVE POLYMERS

New mucoadhesive carrier systems are being developed to provide better penetration of active substances by mucoadhesion and subsequently increase the efficacy of treatment. Thiolated polymers are called second- or new-generation mucoadhesive polymers [45].

6.1. Thiolated mucoadhesive polymers

Thiolated polymers, also known as thiomers, are a class of mucoadhesive materials that are derived from both natural carbohydrates, such as chitosan, HA, alginate, pectin, and synthetic polymers, such as PVA and acrylic acid. The incorporation of thiol groups into these polymers enables the formation of covalent bonds with cysteine-rich subdomains of the mucus gel layer, leading to increased tissue residence time and enhanced bioavailability. This mechanism of action differs from first-generation mucoadhesive polymers, which rely on non-covalent interactions. The covalent binding mechanisms of second-generation systems are less sensitive to changes in ionic strength and pH, which makes them more stable and reliable. Moreover, the presence of disulfide bonds in thiomers can increase the release of active amides due to increased rigidity and cross-linking [47, 86]. To date, several natural carbohydrates have been successfully thiolated, including chitosan [87], alginate [88], carboxymethylcellulose [89], gelatin [90] and xanthan gum [91].

Laffleur et al. utilized cysteine to develop thio-poly acrylic acid, which demonstrated superior mucoadhesion performance compared to non-thiolated poly acrylic acid with a 7.61-fold enhancement. Additionally, thio-poly acrylic acid exhibited controlled release capabilities, with 1.98-fold more release after 3 hours compared to unmodified poly acrylic acid [92]. Özbaş and colleagues synthesized pectin-grafted acrylic acid (PA) and thiolated PA (PA-S) using L-cystein, and developed buccal patches by blending PA-S/alginate or PA/alginate. The mucoadhesion force was measured as

0.043 ± 0.0048 N and 0.11 ± 0.033 N for PA/alginate and PA-S/alginate patches, respectively. The work of mucoadhesion values were found to be 0.034 ± 0.0048 N•mm and 0.184 ± 0.080 N•mm for the PA/alginate and PA-S/alginate patches, respectively. The PA-S/alginate buccal patch demonstrated superior mucoadhesion with no negative impact on swelling and degradation behavior. The amount of triamcinolone acetonide released after 50 hours for P/alginate and PA-S/alginate was reported as 28.5 and 32.6 mg/g, respectively. Both drug-free and triamcinolone acetonide-loaded patches exhibited no cytotoxicity against the L929 cell line [68].

Bal-Öztürk et al. have utilized chitosan in combination with bovine serum albumin (BSA) or thiolated BSA (BSA-SH) to develop mucoadhesive patches to evaluate the effect of thiol functional groups on adhesion (Figure 4). The tensile strength of BSA-SH/Chi and BSA/Chi were reported as 31.36 ± 5.74 MPa and 16.15 ± 3.49 MPa, respectively. Ex vivo mucoadhesion studies revealed that BSA-SH/Chi (1.36 ± 0.83 N mm) had a higher work of adhesion compared to BSA/Chi (0.92 ± 0.37 N mm). Permeation studies showed that 62.32 ± 9.87 µg/cm2 and 76.43 ± 10.45 µg/cm2 of triamcinolone acetonide permeated from BSA/Chi and BSA-SH/Chi buccal patches, respectively, after 12 hours. All patches, with or without drug, showed no toxic effect on NIH/3T3 cells [87].

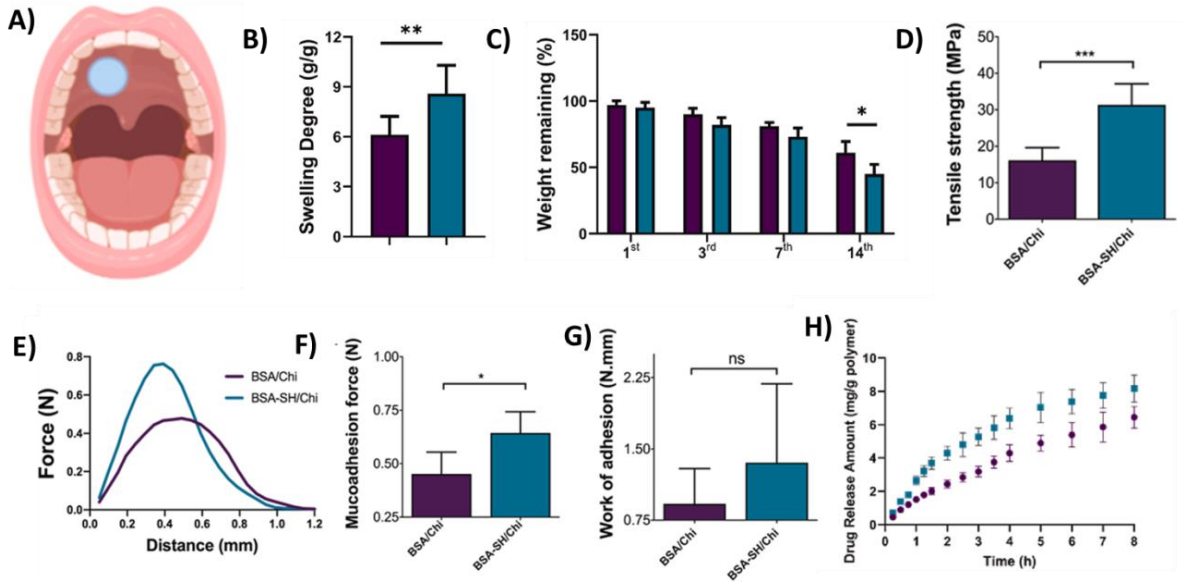

Figure 4. In vitro characterization of thioloted BSA/chitosan based mucoadhesive buccal patches A) Shematic of local application of buccal patch, Graphs showing B) swelling degree of mucoadhesive patches C) weight remaining D)tensile strength, E) mucoadhesion curves, F) mucoadhesion force and G)work of adhesion of mucoadhesive patches, H) *In-vitro* cumulative drug release profile from mucoadhesive patches. Represented data are means ± standard deviation of at least three experiments (***: $p < 0.001$, *: $p < 0.05$, ns: $p > 0.05$) [87]. Reprinted from (Bal-Öztürk et al. 2022) with permission from Elsevier.

6.2. Mussel inspired mucoadhesive polymers

Currently, researchers have been inspired by the strong adhesive properties of sea mussels even under flowing water. They can adhere strongly to the surface through a combination of covalent and non-covalent chemical bonds. Sea mussels (Mytilus edulis) exhibit strong adhesive properties to a range of materials, such as concrete, rocks, boat hulls, and propellers, regardless of whether these surfaces are organic or inorganic, rough or smooth. It is also well known that mussels can adhere to inert surfaces like teflon. The mytilus edulis foot protein (Mefp) provides all of the adhesive properties of mussels. Mefp solidifies in aqueous media and forms structures known as bysas, which then form distal byssal plates in areas where they come into contact with the surface [93-95].

To date, 20 types of Mefp have been identified, which have distinct functions. Mefp-1 is responsible for the byssus and plaque coating, while Mefp-3 and Mefp-5 are crucial for adhesion. Their molecular weight is between 5 and 10 kDa and they are found in the boundary layer near surface. The common feature of all these proteins is the presence of 3,4-dihydroxy-*L*-phenylalanine (dopa) amino acid, which is rich in catechols, imparting wet adhesion. The DOPA content of Mefp-1,

Mefp-3 and Mefp-5 are around 10–15 mol%, 21 mol% and 27 mol%. DOPA is the crucial amino acid for adhesion and cohesion because of the possibility of many chemical reactions. Indeed, DOPA or other substances with catechol moieties exhibited number of physical and chemical interactions. Its derivatives including dopamine (DA) and 3,4-dihydroxyphenylpropionic acid has been widely used to modify the biopolymers for accelerating adhesive strength [96-99].

More recently, Hu et al. designed a mussel-inspired film comprised of PVA and the mussel adhesive protein DOPA (PVA-DOPA film) for adhesion to wet buccal tissue. The DOPA-modified mucoadhesive films demonstrated strong adhesion to wet buccal tissues (up to 38.72 ± 10.94 kPa) in ex vivo experiments. The mucoadhesion strength varied with DOPA content, and the adhesion mechanism involved physical association as well as the covalent bonding between the film and mucus. Then, the researchers incorporated the DOPA-modified film with polydopamine nanoparticles, resulting in superior transport across the mucosal barrier, enhanced drug bioavailability, and effective treatment in oral mucositis models [100].

7. CONCLUSION

Oral mucosal diseases are one of the most prevalent disease group in the world. They could give rise to pain, difficulty speaking and eating, resulting lower quality of life. Nevertheless, the efficacy of traditional therapy including sprays, ointments, gels, and mouthwashes is limited because of wet environment and continuous movement of oral region. Recently, the development of novel mucoadhesive polymers and design of new generation polymers such as thiomers and bioinspired materials as local drug delivery systems for oral disease could be promising to enhance therapeutic efficacy and decrease systemic side effects. However, there is an urgent need for clinical studies to validate usage of these systems. We envision that these mucoadhesive polymer based systems fabricated with sufficient delivery techniques will continue to play an important role in clinical treatment of oral diseases.

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