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Systematic Overview on Bio-adhesive Polymer for Buccal Delivery System

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Abstract

The adhesion between two materials, at least one of which is a mucosal surface, is known as mucoadhesion. Mucosal administration of drugs has drawn a lot of study in the last few decades. Mucoadhesive dosage forms offer a regulated rate of drug release for better therapeutic results by allowing for extended retention at the place of administration. Dosage forms applied to mucosal surfaces may help medications that are not soluble in acid or those require a lot of first-pass metabolism and are not suitable for oral administration. A dosage form's capacity to adhere to mucosal tissue depends on several parameters, such as the composition of the mucosal tissue and the physicochemical characteristics of the polymeric formulation. This review briefly describes the theories of Mucoadhesion, mucoadhesive polymers, factors affecting polymers and evaluation techniques.

Keywords: mucoadhesion, natural adhesive polymers, thiomers, evaluation study

Introduction

The buccal mode of administration offers a viable alternative to oral and intravenous medication delivery into the systemic circulation [1]. The buccal mucosa has high blood flow, low enzyme activity, and strong permeability, making it suitable for both systemic and local medication delivery [2]. Bio adhesion is the binding of a natural or synthetic polymer to a biological substrate.[3]. Drug administration has been thought to be possible through the oral mucosa. In addition to having a high patient compliance rate, the transmucosal route of drug delivery has various advantages over oral administration for systemic drug distribution. These advantages include avoiding potential gastric fluid degradation in the gastrointestinal tract and by passing the first pass effect [4]. The inner cheek is lined with buccal mucosa, and buccal dosage forms are placed in the mouth in between the upper gums and cheek to address both regional and systemic issues [5]. Developing mucoadhesive dosage forms that can maintain extended contact with the buccal mucosa can facilitate prolonged medication distribution through the mucosa. In the case of mucoadhesive polymers systems, the interpenetration of polymer chains over the mucous membrane contacts surface results in adhesion [6]. The buccal, sublingual, palatal, and gingival mucosa are the four potential drug-delivery zones of the oral mucosa. Of these, the sublingual area could prove of interest as an administration site because it possesses several advantageous to increase medication bioavailability when active components have no desired biological qualities [7]. Study on buccal drug delivery is highly promising for the systematic distribution of non-oral medications and as a feasible and desirable alternative for the delivery of potent peptide and protein therapeutic molecules [8].

Buccal Mucosal membrane

The mucosal layer, consisting of borders on the GI tract, eyes, mouths, nasal cavities, reproductive tract, and respiratory tract, functions as a lubricating and protecting barrier. It is around 95 percent water, with the remaining components including proteins, lipids, cholesterol, and other substances. The remaining portion of Glycoproteins and mucins primarily regulate the mucosal layer's viscoelastic characteristics, but water and ion content also play a role [12].

The fluid barriers that line the walls of several body cavities, including the gastrointestinal and respiratory tracts, are called mucous membranes [9]. After oral administration, non-keratinized epithelia, an efficient blood supply, and a low number of proteolytic enzymes boost the systemic bioavailability of medications [21]. Because of its steric barrier and adhesive qualities, mucus is a semi-permeable matrix that permits the interchange of nutrients, water, gasses, and hormones while preventing the entry of most pathogens [10].

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There are five areas in which the oral cavity's mucosal membranes are located:
1. The sublingual
2. The buccal mucosa (cheeks)
3. Gingival(gums)
4. Palatal mucosa
5. The lip lining.

Each of these locations has a unique anatomy, permeability to drugs, and capacity to hold onto a system for the intended duration of time. Both local and systemic medication therapy have been administered through the mouth cavity. Compared to buccal mucosa, sublingual mucosa is thinner, more porous, and has a richer blood supply.

The buccal mucosa contains a large, smooth, and mostly static surface that can be used to put a retentive system and provide regulated, prolonged drug delivery [11]. Mucus consists of mainly water (90–98%), glycoproteins (1-4%), electrolytes, cell components, lipids, proteins, enzymes, and immunological factors (1-4%). Mucus is sometimes seen as a single layer since it is a viscoelastic gel that exhibits shear-thinning action [10]. Although mucus is continuously secreted, each organ secretes it in different amounts and at different thicknesses, with the GI tract secreting the most. Mucins, glycoproteins, are responsible for mucus's mucoadhesive qualities. Goblets cells found in the epithelium it secretes mucins [12]. Because mucins can be conjugated to positively charged drug molecules and influence specific tissues, they play a crucial role in covering the mouth cavity with mucous secretions. This aids in the drug delivery mechanism. therefore, it employed in the modelling of mucoadhesive systems [13].

Theories of Mucoadhesion

a) Wetting theory

One of the oldest theories related to adhesion is the wetting theory. Here in, adhesion is expounded as an embedding process**.** Adhesives embed into substrates' surface imperfections, producing many locations adhesive anchors. Wetting theory uses calculations such as contact angle and thermodynamic work of adhesion. The process involves estimating the surface tension of the adhesive and substrate using Dupre's equation.

$$^{W}_{A} = yb + yt - ybt$$

where $^{W}_{A}$ is the specific thermodynamic work of adhesion and yb, yt and yb_t represent the surface tensions of the bio adhesive polymer, the substrate, and the interfacial tension, respectively. The adhesive work is calculated by adding the surface tensions of both adherent phases and subtracting the interfacial tensions between them [14].

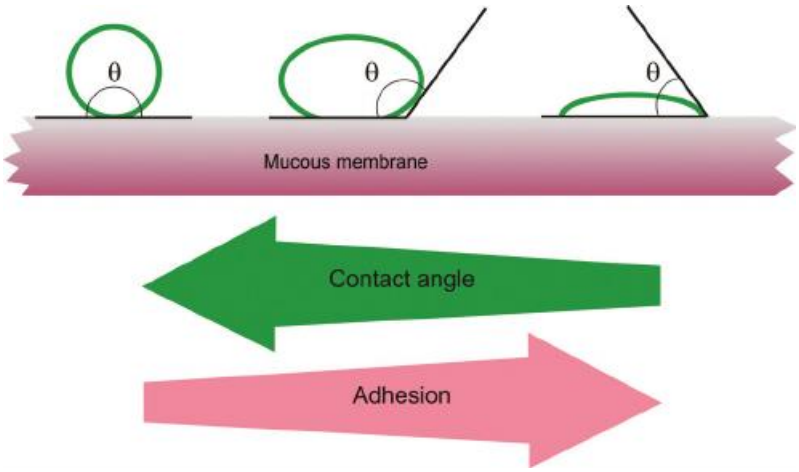

Figure 1; Displaying the effect of the contact angle between the device and the mucosal membrane on bio adhesion

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b) Adsorption theory

According to this theory, the mucoadhesive device adheres to the mucous following contact due to surface force between the atoms on both surfaces. This force generates secondary chemical interactions, including as van der Waals and hydrogen bonding, electrostatic fascination, and hydrophobic interactions [9].

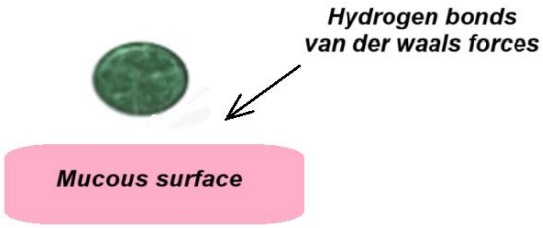
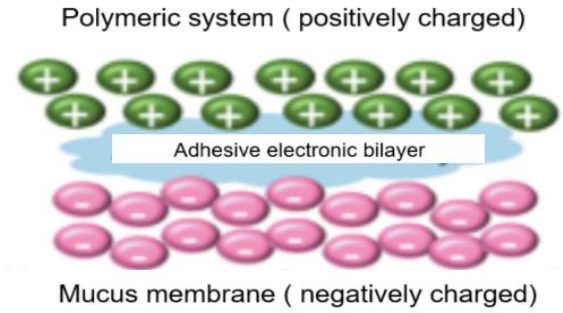


Figure 2; Adsorption theory

c) Electronic theory

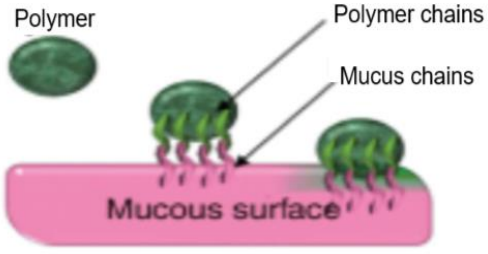
This theory explains how electrons flow between mucus and the mucoadhesive polymer due to their different electrical characteristics. Electron transfer creates a double layer of charges, which leads to electrostatic attraction. An interdiffusion layer forms between two surfaces with opposing charges. This idea is likely more important for adhesion between polymer metal substrates. Some argue that electrostatic forces are not a key element in the development of adhesive bonds, but rather a byproduct of high binding strength [15]



Figure; Diagrammatic view of electronic theory

d) **Diffusion theory**

e) This theory suggests that the adhesive and substrate chains interpenetrate deeply, forming a semi-permanent adhesive bond. The rate of penetration is determined by the diffusion coefficients of both polymers change with molecule weight and cross-linking density [16].



Figure; Illustration of Diffusion Theory

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Mucoadhesive polymers

Polymers are becoming more and more significant as medication delivery vehicles. Normally, polymers intended for use as drug carriers should be immunogenicity-free, biocompatible, and biodegradable. High molecular weight increases electrostatic forces and entanglements to promote adherence [10]. In order both local disease therapy and systemic medication bioavailability, the capacity to keep a delivery system in place for a prolonged amount of time is highly desirable biodegradability [11]. Mucoadhesive polymers often have good swelling properties to allow for quick hydration upon contact and hydrogen bonding groups (amine, hydroxyl, or carboxyl) [17]. The creation of a viscous fluid upon wetting mucoadhesive polymers prolongs their adhesion to the mucosal surface. Consequently, this
increases the number of sticky contacts that occur, including covalent bonding, hydrogen bond formation, and electrostatic interactions [13].

Ideal characteristics of Mucoadhesive polymers[30]

- The polymer and its breakdown products should have properties that are harmless, non-irritating, and incapable of being absorbed in the gastrointestinal system.
- The polymer should have favourable characteristics such as swelling, solubility, biodegradability, and wetting.
- The polymer needs to adhere to the buccal mucosa immediately to demonstrate enough mechanical strength.
- The polymer should exhibit adequate shear and tensile strengths within the bio adhesive range.
- The polymer should have characteristics such as enhanced penetration and suppression of local enzymatic activity
- The polymer does not break down when the dosage form is being stored or during its shelf life.

Classification of Mucoadhesive polymer [22]

Based on source 1. Synthetic polymer	Cellulose derivatives, Poly (acrylic acid) polymers, Poly (hydroxyethyl methyl acrylate), Poly (ethylene oxide), Poly (vinyl alcohol), Poly (vinylpyrrolidone), Thiolated polymer, Polyurethanes.
2.Natural polymer	Tragacanth, Sodium alginate, Agarose, Guar gum, Xanthan gum, Karaya gum, carrageenan, Chitosan, Soluble starch, Pectin, Gelatin.
Based on solubility 1.Water-soluble polymer	Hydroxy Ethyl Cellulose, Hydroxy Propyl Cellulose, PAA, Sodium CMC, HPMC, Sodium alginate, Carbopol.
2.Water-insoluble polymer	Chitosan, Ethyl cellulose, Polycarbofil.
Based on charge 1.Cationic	Chitosan, dimethylamine ethyl-dextran, Amino dextran
2.Anionic	Chitosan-EDTA, CMC, CP, pectin, PC, PAA, xanthan gum, sodium CMC, alginate.
3.Non-ionic	Hydroxyethyl starch, PVA, PVP HPC, scleroglucan, poly (ethylene oxide)
Based on generation 1.First generation	Chitosan, dimethyl amino ethyl-dextran, Amino dextran Chitosan-EDTA, CMC, CP, pectin, PC, PAA, sodium, xanthan gum, sodium CMC alginate, Hydroxy ethyl starch, PVA, PVP HPC, scleroglucan, poly (ethylene oxide)
2. Second generation	Lectins, Thiolated polymers
Based on potential bio adhesive forces 1.Covalent bond	Cyanoacrylate
2.Hydrogen bond	CP, PVA, PC, Acrylates
3.Electrostatic bond	Chitosan

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Factors Affecting of Mucoadhesive Drug Delivery [31,32]

Environmental factors:

Applied strength:

Adhesion strength rises with applied strength and length of application. If high pressure is applied Polymers can become mucoadhesive with time, even if they don't interact well with mucin.

pH: Mucoadhesion can be altered by charges on the mucus surface as well as specific ionisable bio adhesive polymers. Mucus' charge density varies with pH due to differences in the dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. The degree of hydration depends on the medium's pH.

Swelling: The polymer content, ionic concentration, and presence of water all impact the outcome. Excessive hydration creates a slippery mucilage that does not adhere.

Initial contact time: Contact time between the bio adhesive and mucus layer affects swelling and interpenetration of the polymer chains. Bio adhesive strength improves with longer contact duration.

Polymer related factors

Molecular weight:

The molecular weight and polymeric linearity of a mucoadhesive polymer are the main factors influencing its mucoadhesion strength. One source of linear polymers is (e.g., Glycol (polyethylene glycol). Due to the strength of the mucoadhesive polymer in the case of a nonlinear polymer may or may not be influenced by its strength molecular weight. This is mainly because the structures of such polymer property may be shielded by the helical or coiled portion of the adhesive group, which is principally responsible for the adhesive.

Hydrogen bonding**:**

Another important component of a polymer's mucoadhesion is hydrogen bonding. Because functional groups in polymers must be able to create hydrogen bonds have the capacity to create hydrogen bonds since (COOH, OH etc.) is present. To increase the polymer's capacity for hydrogen bonding, it must be flexible. Good hydrogen bonding ability is possessed by polymers such polyvinyl alcohol, hydroxylated methacrylate, poly (methacrylic acid), and all their co-polymers.

Cross linking density:

The polymer's higher molecular weight is determined by the cross linking its density. The number of average molecular weight of the molecules is shown by the cross-linking density. The average pore size is determined by the cross-linked polymer. Water diffuses less into the polymer network when the cross-linking density of the polymer is higher because it decreases the pore size of the polymer chain.

Concentration of polymer:

Another significant aspect of a mucoadhesive polymer's mucoadhesive strength is its concentration. Beyond the optimal polymer concentration, the mucoadhesive ability of some highly concentrated polymeric systems begins to decline significantly. This is because the concentration of polymer molecules rises above the liquid medium's molecular concentration in a way that prevents additional chain formation between the polymer and liquid medium.

Polymers based on Generation

- First generation of mucoadhesive polymers.
- Second generation of mucoadhesive polymers.

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First generation of mucoadhesive polymers

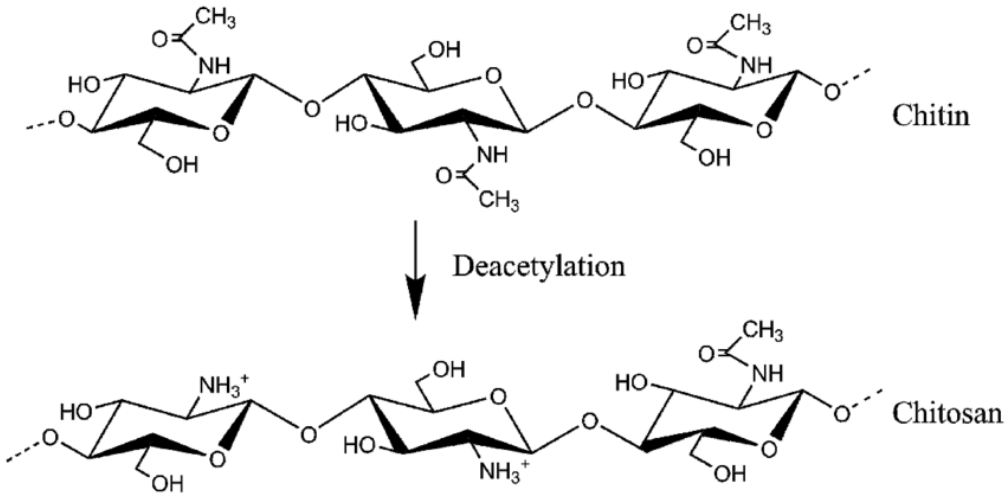
Lee classifies adhesive polymers as "first generation" into two categories. They bind to the mucus layer through non-covalent interactions (electrostatic, hydrogen, and hydrophobic bonds) and have short retention durations due to fast mucus turnover.
The first generation of polymers includes anionic, cationic, non-ionic, and amphoteric polymers. Anionic and cationic polymers exhibit the highest mucoadhesive strength. This group mostly includes poly (-acrylic acid) (PAA) and its weakly cross-linked derivatives, sodium carboxymethyl cellulose (NaCMC), and poly (methacrylic acid) sodium. Alginate and poly [(maleic acid)-co-(vinyl methyl ether)], Examples of polyacrylic acid-based polymers are Carbopol, polycarbophil, polyacrylate, poly (methylvinylether -co-methacrylic acid), poly(isobutylcyanoacrylate).

PAA polymers come in a variety of molecular weights, can form transparent, easily modifiable gel networks, and are regarded as safe. They are also non-toxic and irritating. The primary characteristics of polycarbophil are its high hydration or swelling at neutral pH values, which permits great levels of tangling within the mucus layer, and its insoluble nature in water. Moreover, the non-ionized carboxylic acid groups' presence enables the formation of hydrogen bonds, which are essential for binding mucosal surfaces [15].

Chitosan

Chitosan is a natural linear biopolyaminosacharide formed by alkaline deacetylation of chitin, the second most prevalent biopolymer after cellulose. Many living things, including insects (cuticles), crustaceans (skeletons), and fungus, produce chitin in their cell walls, whereas many fungi naturally produce chitosan. Chitosan has strong antibacterial properties against viruses, fungi, and bacteria. Its antibacterial activity has been linked to several possibilities. The generally acknowledged theory states that many bacteria negatively charged surface components interact with the polymer's positively charged protonated amino groups. Crustacean shell waste contains 15% to 30% chitin, 20% to 40% proteins, 30% to 50% calcium and magnesium ions, and 0% to 14% lipids [19]. Chitosan is a derivative of chitin generated through N-deacetylation, which removes the acetyl group from the amino group at the C-2 position. Chitin and chitosan, like cellulose, are naturally occurring polysaccharides with high nitrogen concentration that attract commercial attention.

When deacetylation reaches 50%, chitosan becomes water-soluble at acidic pH levels due to protonation of the polymer's −NH2 groups. After protonation, chitosan's d-glucosamine repeat unit gains positive surface charges, making it the only pseudo-natural cationic biopolymer [20]. Chitosan's solubility is determined by its biological origin, molecular weight, and degree of deacetylation. Chitosan is insoluble in water and very viscous in diluted acidic solutions. It dissolves in aqueous acids due to the presence of free amino groups.



Figure; Deacetylation of Chitin into Chitosan

Chitosan's mucoadhesive characteristics depend on its structure, which forms ionic connections with sialic acid residues on the mucosal epithelium. The polymer shields the medication against acidic denaturation and enzymatic breakdown, extending its intestinal residence duration [19].

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Second generation of mucoadhesive polymers

The development of second-generation polymers has solved this issue by demonstrating more precise (site-specific) binding. Additionally, these polymers offer an advantage in the development of mucoadhesive drug delivery systems since they are less vulnerable to mucus turnover rates. Using bacterial adhesions, amino acid sequences, and surface modification of already-existing polymers—such as lectin-modified or functionalized polymers—one can create second-generation polymers. Enhancing the mucoadhesive property of polymers through chemical modification, such as adding a thiol group or thiolation, is another technique that is actively being researched. First-generation polymers non-specific attachment to the mucosal substrate is their main drawback [18].

Lectins

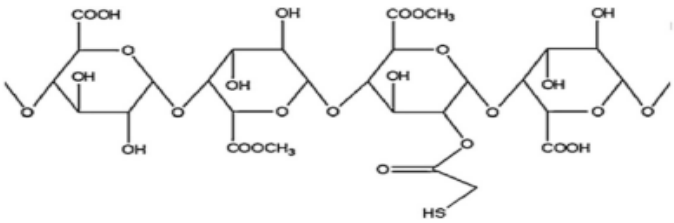
Glycoproteins or non-immunological proteins are known as lectins, and they are specifically identify sugar molecules and can attach to parts of glycosylated membranes.

Sugars can be found in mucous layers, on the surface of epithelial cells, and in the glycolipids and glycoproteins of the mammalian mucosa. Following their attachment to the cell, lectins have two possible fates: they can either stay on the cell surface or enter the cell by endocytosis. It has been discovered that certain lectins, such as those taken from Lensculinarius, Soybean, Peanut, and Ulex europaeus, bind exclusively to mucosal cells of all the lectins, wheat germ agglutinin has the fewest immunogenic reactions. Lectins offer good protection against acids and enzymes, making them an appropriate choice for oral administration [13]

Thiomers [21]

Thiolated polymers represent a potential novel phase in mucoadhesion polymers. Alleged thiomers, which have a thiol side chain have shown to be a potential new class of polymeric excipients. Rather than permanently bonded polymers, thiomers can form persistent bonds with cysteine-rich mucus subdomains through thiol/di sulfide exchange reactions. Strong cohesive properties are produced by thiomers' ability in creating intra- and inter-chain disulfide bonds. The degree to which inter, and intramolecular disulphide linkages are formed correlates with the thiomers crosslinking property. Thiomers increase permeability, prevent the efflux pump, and provide a protective barrier against enzymatic attack especially for proteins and peptides. E.g., Thiolated Pectin.

Pectin is an economical nontoxic, acidic, water-soluble heterogenous polymer that is isolated from apple pomace or citrus peel. It is made up of linear chains of (1–4) connected a–d-galactouronic acid residues broken up by l-rhamnopyranose through a–1-2 linkage and some rhamnogalacto uronic acid residue. Its ability to stick to gastrointestinal tissues makes it a useful tool for target release and effective medication delivery. Pectin was thiolated by esterification using TGA. The creation of a disulfide bond between mucus and thiolated pectin (TP) can be supported by the TP's enhanced mucoadhesive properties over pectin.



Figure; Structure of Thiolated Pectin

Polymers based on Source

- Synthetic polymers
- Natural polymers

Synthetic polymers

The synthetic product known as synthetic polymers are created by chemically modifying other polymers, including natural polymers. These consist of synthetic fibres, elastomers, thermosets, and thermoplastics. The artificial polymers that are frequently used in the pharmaceutical and vinyl polymers (such as Eudragit®), polyvinylpyrrolidone (PVP) (Povidone), carbomers, cellulose ethers,

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methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, sodium carboxymethyl cellulose (SCMC), polyether's, and silicones are among the industries that are involved in the food industry [23].

Polyacrylates

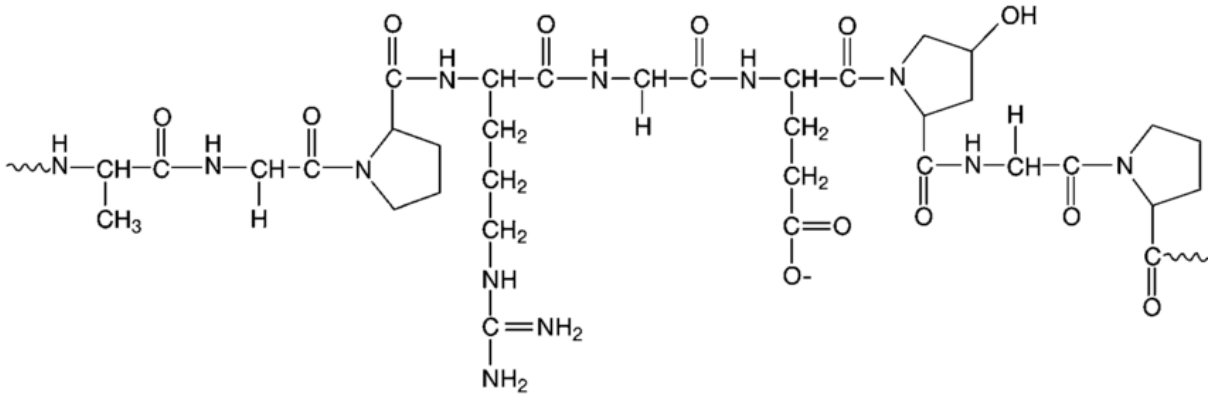
These polymers are found in a wide range of molecular weights, clearly modified gel systems, and safe in addition to non-toxic for usage in oral applications. The best polymers to employ as mucoadhesive polymers are polycarbophil and carbomers (derived from PAA). Tablets, oral preparations, and suspensions all use Carbopol as a polymer. Water-insoluble polymer Polycarbophil has a high swelling characteristic that permits significant mucus layer growth. The coupling of PAA with cysteine improved its mucoadhesive characteristics [24].

Natural polymers

Natural materials are more effective because they are more easily accessible, biocompatible, and modifiable. In addition, the native natural materials have reactive groups, it is possible to incorporate other functional groups into them to give the newly created materials amazing functionalities or change their chemical and physical properties to create hybrid materials, native materials may also be combined with other synthetic or native materials[25].
Natural sources of polysaccharides, nucleic acids, and proteins are the sources of the polymers found in plants and animals. In the food and pharmaceutical industries, some commonly used polysaccharides are xanthan gum, acacia, tragacanth, alginates, and chitosan [23].

Gelatin

Natural polymers that are frequently found in nature include gelatin. Gelatin is a water-soluble polymer that is primarily made by the denaturation process. Gelatin was created through the denaturation of the collagen polymer [26]. Moreover, this polymer finds extensive application in tissue, pharmaceutical, and medical fields. Outstanding chemical and physical qualities characterize gelatin polymer. It has minimal antigenicity, is biocompatible, and biodegrades. Additionally, gelatin is a supportive substance that can be applied to tissue



Figure; Structure of Gelatin

engineering, gene delivery, and cell culture. Gelatin-containing formulations possess the capability to both integrate and release bioactive substances such as dual growth factors, proteins and peptides, active medicines [27].

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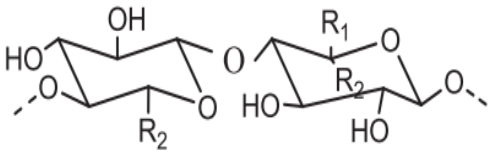
Alginate

Alginate is a polysaccharide extracted from brown algae, such as Laminaria hyperborea and lessonia. Alginate is not biodegradable in the body due to the absence of enzymes that can break down its polymer chains. Ionically cross-linked alginate, Polymers with molecular weights over the renal clearance threshold may not be fully eliminated from the body due to divalent ion loss alginate is therefore frequently oxidized before being used by the body. Sodium periodate is usually used to perform oxidation. This breaks the cis-diol group's carbon-carbon link in the uronate yields hydrolytically labile bonds by changing the conformation to an open chain and removing residue.



Figure; Structure of Alginate

The formation of aldehyde functional groups on the backbone is an additional advantage of oxidation. Owing to aldehydes' amine-reactivity, oxidized alginate is frequently combined with amine-presenting cross-linkers, such as gelatin, chitosan or a multiarm PEG-cross-linker, to create a tissue adhesive. Two crosslinking mechanisms worked together to generate the adhesive: photo crosslinking of the methacrylate groups followed by imine bonding between the amines of the PEG cross-linker and the aldehydes of the alginate. The Cross-linking happened in five minutes. Although tissue adherence was increased by imine bonding alone compared to fibrin glue, adhesion was further improved by photo-cross-linking [28].

Water soluble polymer: Hydroxypropyl methylcellulose

The cellulose derivative known as hydroxypropyl methylcellulose (HPMC), or Hypromellose, is electro-neutral and soluble in water, after the cellulose substrate has been modified by the addition of methyl and hydroxypropyl groups. Methoxy groups make up no less than 16.5% and no more than 30% of HPMC, while hydroxypropyl residues range from 4% to 32%, to extend the duration of drug release, HPMC modifies drug release in a regulated manner its therapeutic effect, and it can be utilized either by itself or in conjunction with non-ionic or ionic polymers that are hydrophilic or hydrophobic. In addition to their utility in conventional oral medication formulations, the derivatives of HPMC are heavily used in contemporary drug technologies (such as hot-melt extrusion, spray drying, and 3D

electrospinning, nanoprecipitation, and printing), which make nanoparticles possible, microparticles and distribution via nanofiber systems for use in the mouth and on the mucosa HPMC has many hydroxyl groups that interact with mucin glycoproteins found in the mucus layer. It has a significant potential for application in various mucoadhesive drug delivery formulations because of this. HPMC is typically used in conjunction with other polymers in mucoadhesive Buccal drug delivery system [29].

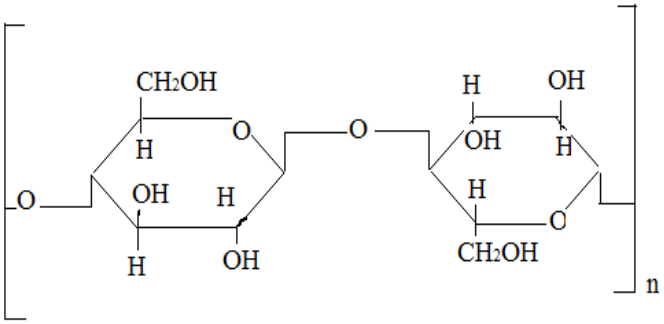


Figure: Structure of Hydroxypropyl methyl cellulose

Techniques for the evaluation of Mucoadhesive Polymer

The study of bio adhesive characteristics is critical in the development of new bio adhesive delivery systems. These assays are also useful for screening a large variety of compounds and their mechanisms. Several approaches have been devised to study

mucoadhesion. Because no standard apparatus for assessing bio adhesive strength exists, there is an unavoidable lack of consistency among test procedures. The most common technique for determining force of separation in bio adhesive testing is the application of force perpendicularly to the tissue/adhesive contact, during which a condition of tensile stress is established [33].

A) **In vitro studies** [30,34]

1) Tensile stress measurement by using Wilhelmy plate technique.

This technique is used to assess mucoadhesive strength. This approach involves dipping a glass plate into a mucoadhesive polymer solution. The mucus gel is extracted from animal skin, often goat intestine, and stored in a container at 37ºC. The glass plate is fastened to one side with nylon thread, while the weight is increased on the other. At precise intervals, water is needed to remove the glass plate from the mucus. The force needed to break the contact between mucus and polymer and prevent adhesion. The test uses six plates and calculates the average value.

2) Shear stress measurement.

Metia and Bandyopadhyay used specialized equipment to test the adhesive cups' shear strength and the force required for parallel detachment from freshly excised bovine buccal mucosa. The mucoadhesive cup was attached to a moveable plastic strip using synthetic polymers. The cup was pushed over the excised bovine buccal mucosa for 30 seconds, maintaining steady pressure. After 5 minutes, the weight required to dislodge the adhesive cup from the mucosa was measured using the following formula.

$$\text{Force of adhesion (N)} = \text{Weight(g)}/1000\times 9.81$$

$$\text{Bond strength (N/m}^2\text{)} = \text{Force of adhesion (N)/Surface area of cup (m}^2\text{)}.$$

3) Peel strength test.

Peel strength refers to the force required to separate mucoadhesive cups from freshly excised bovine buccal mucosa. The test has limited applicability for mucoadhesive compounds. However, patches hold significant utility. The stress in this test primarily focuses on the adhesive system's edge. The mechanical properties of the created mucoadhesive formulations have been determined by tensile and shear strength tests, whereas resistance to the peeling force is determined by the peel strength test. The literature makes it evident that the tensile strength test is the most widely used technique for evaluating mucoadhesive.

B) Ex vivo studies

Mucoadhesive strength will be determined by means of a modified balance scale which has two platforms located in a vertical axis, with an adjustable distance from each other. Freshly obtained sheep buccal mucosal membrane (the papillae are all removed) were stored frozen in phosphate buffer pH 6.8 for 1 day. After this period, the mucosal tissue of sheep is thawed to room temperature before use. At the time of testing, the mucoadhesive tablet is fastened to the upper platform by cyanoacrylate glue. Also, a section of the buccal mucosal tissue is fastened to the lower platform. Then, the lower platform that the buccal mucosal tissue bonded on it, placed into the cell containing phosphate buffer. Next step, the mucosal surface is exposed to the mucoadhesive tablet to adhere to it. Thereafter, the lower platform is slowly moved down at a rate of 1 mm/min, until the mucoadhesive tablet completely separated from mucosal tissue. The maximum force needed for the separation of the two platforms from each other will measured and reported as the mucoadhesive strength of tablet.

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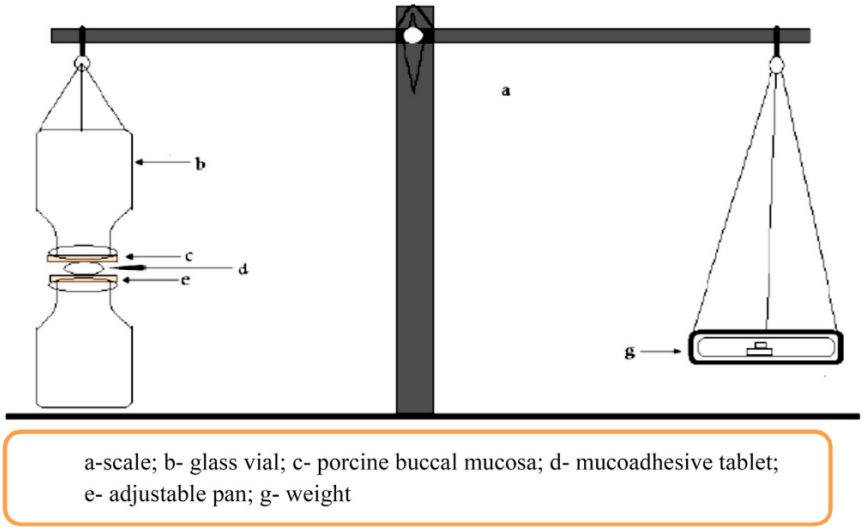

Figure: Determination of Mucoadhesive strength by using modified scale balance

Current and future development

Mucosal sites provide an appealing non-invasive alternative for quick, controlled drug administration for both local and systemic applications because of their easy accessibility and minimal enzymatic activity, which makes it simple to remove the carriers. To deal with pressures that contribute to the loss of mucosal cohesiveness, such as mastication, saliva secretion, swallowing and menstrual cycle-related interventions, strong mucoadhesiveness is extremely desirable. Therefore, the retention period of drug delivery systems at the site of application is largely determined by factors such as chemical structure, surface charge, surface tension, molecular weight, rate of hydration, and polymer concentration. Lately, there has been a lot of research on the use of cationic, thiolated, and pre-activated thiomers in mucosal drug delivery. To get around the problems with accepted manuscript conventional mucoadhesive drug delivery systems, it is highly desirable to have a carrier system that is effective, has a high pay load, controllable physicochemical properties, proper drug localization, minimal premature release, and controlled release behaviour in addition to the right polymer. According to recent developments in the use of carriers for mucosal delivery, nanocarriers provide improved permeability more retention at the mucosal site, and tunable drug release behaviour, all of which contribute to better therapeutic effects [35].

Conclusion

Drug distribution through buccal administration has several benefits. Due to the buccal mucosa's abundance in vascular and lymphatic systems, medications are directly drained from the bloodstream, bypassed by the liver's first-pass metabolism, and avoided by the gastrointestinal tract's pre systemic clearance. Buccal drug delivery is safe and simple, with the added benefit of being able to stop in the event of toxicity. Research on buccal drug administration is promising in terms of systemic transport and attractive substitute for the delivery of powerful peptide and protein therapeutic molecules. There are two methods developed evaluating the buccal drugs: in vitro and in vivo. The expanded versions of the basic oral medication delivery system are called mucoadhesive dosage forms and they have several benefits compared to it. This number could rise in the future, though, given the recent discoveries of novel formulation types such mucoadhesive preparations and the usage of peptides as medications.

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