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Review Article

Bioadhesive Properties of Natural Polymer in Drug Delivery: An Overview

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ABSTRACT

Natural polymers, gums, and mucilages have emerged as crucial bioadhesive components in various drug delivery routes, including oral, nasal, ocular, transdermal and vaginal applications. This study highlights the unique properties of these biopolymers, which enhance drug retention and absorption through mucoadhesion mechanisms. This comprehensive overview examines the advantages of these bioadhesives, focusing on their ability to enhance drug solubility, stability, and localized delivery. The mechanisms of adhesion, such as hydrogen bonding and van der Waals forces, are discussed in relation to different drug delivery systems. This overview explores the diverse functionalities of these biopolymers, focusing on their mucoadhesive properties that facilitate prolonged drug residence time and enhanced absorption. Case studies are presented, illustrating the various natural polymers in the pharmaceutical application like a suspending agent, emulsifying agent, mucoadhesive agent, binder, disintegrant, Drug release Biodegradable carrier for colon specific release, enteric resistant and sustained release substantial and many more. Additionally, the review addresses the physicochemical characteristics that contribute to bioadhesion and the implications for patient compliance and therapeutic efficacy. It concludes with insights into future research directions and the potential for these natural materials to improve drug delivery.

INTRODUCTION

Bioadhesion is stated as the ability of a natural or synthetic polymer to stick to a biological article. The term is referred to as mucoadhesion when the biological substrate is a mucosal layer [1].

The adherence of two materials where at least one of the components is biological is known as bioadhesion. The delivery of drugs with improved bioadhesion has drawn a lot of interest in the last few decades. Bioadhesive dosage forms can be made to stay at the application site for extended

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periods of time, allowing for regulated drug release and better therapeutic results. Dosage forms that are not soluble in acid or undergo severe first pass digestion can be applied to mucosal surfaces to potentially benefit medication molecules that are not suited for oral administration. A dosage form's capacity for bioadhesion is contingent upon several elements, such as the characteristics of the mucosal tissue and the physical and chemical properties of the polymeric composition. Bioadhesive materials and their synthesis, variables influencing bioadhesion, assessment techniques, and, lastly, several features of bioadhesion include various bioadhesive pharmaceutical delivery methods (buccal, nasal, ophthalmic, gastro, vaginal, and rectal) [2].

Adhesion is the bond created when a surface and pressure-sensitive adhesive (PSA) come into contact [3]. Bioadhesion is the long-term attachment of two materials—at least one of which is biological. due to interfacial forces. It can also refer to a substance's ability, whether synthetic or biological, to adhere to biological tissue for an extended period of time [4].

There are three primary categories of bioadhesion in biological systems:

Type 1: biological stages adhering to one another, as in the case of wound healing, platelet aggregation, cell fusion, and normal cells adhering to diseased or foreign materials

Type 2: refers to the attachment of a biological phase to an artificial substrate, such as the development of biofilms on prosthetic devices and inserts, microbial fouling and barnacle adherence to ships, adherence of platelets to biomaterials, and cell adhesion to culture plates.

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 [5,6]

A water-soluble polymer's ability to bioadhere, which turns adhesive upon hydration [7],makes it possible to target a drug to a specific area of the body for prolonged periods of time [8]

Theories Of Bioadhesion

1.1.1 The Wetting Theory:

The interaction between the thermodynamic work of adhesion, the bioadhesive, and its angle of contact are best described by the wetting theory when it comes to liquid bioadhesives. The Dupré equation describes how the work is connected to the surface tension of the adhesive and substrate [9]

$W_{AB} = \gamma_A + \gamma_B - \gamma_{AB}$.

interfacial energy, γ_{AB}.

interface between phase A and air (γ_A)

the interface between phase B and air (γ_B).

1.1.2 Electrostatic Theory of Bioadhesion:

When an electrical double layer arises between an adhesive and a substrate. electrostatic forces resulting from this formation must be overcome in order to separate two distinct substances. According to the electrostatic theory of repulsion, an electrical double layer is created when electrons are transferred across the adhesive interface, and a number of attractive forces keep the two layers in touch. The adhesive interface works similarly to a parallel-plate condenser, requiring labor against electrical charges to achieve separation. If no work is done to overcome van der Waal's forces, the work of adhesion can be associated to the energy of the condenser [10].

Mechanical Theory: According to this theory, bioadhesion occurs when a liquid or semi-solid bioadhesive polymer penetrates into the irregularities, pores, or crevices of a biological tissue (such as mucosa). After penetration, the polymer solidifies or swells, leading to mechanical anchoring that holds the dosage form in place.

Mechanism

1. The bioadhesive comes in close contact with the biological surface.
2. The polymer flows into surface irregularities of the tissue.
3. Upon hydration, swelling, or hardening, the polymer gets locked in place.
4. This results in adhesion due to mechanical interlocking, not chemical bonding.

Important Factors

- Surface roughness of the biological tissue
- Viscosity and flow properties of the polymer
- Degree of swelling or solidification
- Contact time and applied pressure

Significance

- Particularly important for rough or porous surfaces
- Commonly applies to mucoadhesive drug delivery systems
- Does not rely on
- chemical or molecular interactions

Limitation

- Less effective on smooth mucosal surfaces
- Adhesion strength is generally weaker compared to chemical or diffusion-based mechanisms

In summary, the mechanical theory states that bioadhesion occurs due to physical entrapment of the adhesive polymer within surface irregularities of the biological tissue.

Cohesive Theory of Bioadhesion

The cohesive theory of bioadhesion states that adhesion occurs due to the internal strength (cohesive forces) of the bioadhesive material rather than interactions with the biological surface. Once the bioadhesive polymer comes into contact with the tissue, it adheres and remains attached because of strong intermolecular forces within the polymer itself.

Mechanism

- The bioadhesive is placed in contact with the biological surface.
- Adhesion is maintained due to cohesive forces such as hydrogen bonding, van der Waals forces, and polymer chain entanglement within the adhesive.
- Failure of adhesion occurs when the cohesive bonds within the polymer break, not at the tissue–polymer interface.

Important Factors

- Molecular weight of the polymer
- Degree of cross-linking
- Polymer chain flexibility

- Presence of functional groups capable of intermolecular interactions

Significance

- Explains adhesion where polymer internal strength dominates
- Useful for understanding bioadhesive films, patches, and gels
- Emphasizes the role of polymer formulation and structure

Limitation

- Does not consider specific interactions with the biological surface
- Alone, it cannot fully explain mucoadhesion

In summary, the cohesive theory explains bioadhesion as a result of strong internal cohesive forces within the bioadhesive polymer that hold it in place on the biological tissue.

1.1.3 Theory of Diffusion:

Diffusion theory states that a semipermanent adhesive bond is formed when the polymer chains and mucus mix thoroughly enough. The diffusion coefficient and contact time determine the exact depth to which the polymer chains enter the mucus. As the cross-linking density rises, The diffusion coefficient, which is reliant on the molecular weight between cross-links, significantly decreases as shown in figure 1 [11].

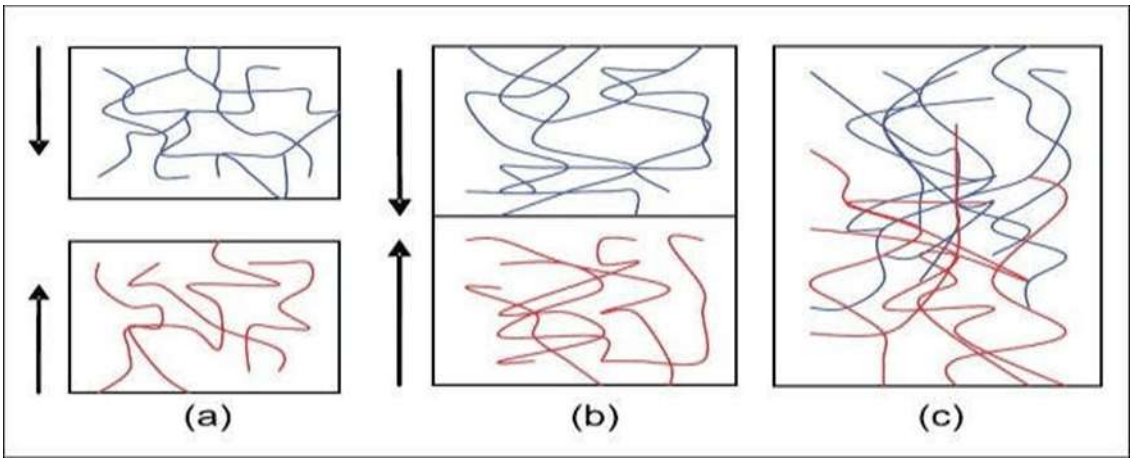

Fig.1: (a) Theory of diffusion -blue polymer layer and red mucus layer before interaction; (b) after interaction (c) The interface becomes diffuse after interaction for a period of time[11]

1.1.4 Adsorption Theory of Bioadhesion:

According to the adsorption theory, the adhesive interaction between the substrate surfaces is caused by intermolecular forces such as hydrogen bonding and VanderWaal's forces.

According to the theory, adherence to tissue is sustained by the combined effect of single or several secondary forces. The kinds of secondary forces are;

1) Van der Waal's forces

2) Hydrogen bonding

3) Hydrophobic interaction

In bioadhesion, it is not desirable for primary chemical bonds to form between tissue and adhesives used in dentist and surgery. This is due to the possibility of permanent adhesion caused by the strong ionic or covalent bonds [12].

1.1 Factors Important to Mucoadhesion

1.1.1 Factors Related to the Polymers:

- Weight of molecule
- Active Polymer concentration
- Polymer Chains flexibility
- Spatial Conformation

1.1.2 Factors Related to the Environment:

1. PH
2. Strength applied
3. Preliminary contact time
4. Assortment of the Model Substrate Surface
5. Swelling

1.2.3. Physiological Variables:

I] Mucin Turnover

II] Sickness States

Vaginal bioadhesive preparations have emerged as a novel controlled-release form of medication for the management of systemic and topical conditions in recent years. The biggest benefit of these dosage

forms is that they can be kept in the vagina for long stretches of time, both during the day and at night, which allows for fewer dosing intervals. [13-17].

1.2 VAGINAL MUCOSA

In recent years, there has been a growing investigation into the vagina as a potential site for drug delivery due to its anatomical position and physiological attributes. This approach, when combined with the bioadhesion phenomenon, has produced successful local and systemic drug delivery outcomes.

Treatment for vaginal disorders such as candidiasis, STDs, vaginal dryness, and others has been provided by bioadhesive vaginal drug delivery systems. Also, Studies have indicated that medications can be effectively absorbed into the bloodstream through the vaginal mucosa. Furthermore, this vaginal route has been employed for medication targeting in the uterus (18).

This is especially true for API that have low absorption rates following oral administration, which makes it necessary to take use of alternate drug delivery methods. Currently under investigation are the mucosal pathways of the nasal, ophthalmic, buccal, vaginal, and rectal regions. Among With these routes, vagina appears to be a viable site for medication delivery. The vagina is a tubular, fibromuscular organ that stretches from the uterine cervix to the vaginal vestibule and measures approximately 9 cm in length. [19].

The vagina is made up of four separate layers: stratified squamous epithelium, lamina propria, and muscle layer, and adventitia as shown in the below figure-2. The mucosal layer generates a series of transverse folds known as rugae, which drastically expand its surface. Even though considered a mucosal tissue, the normal vagina does not have glands, and vaginal discharge is a mixture of fluids from a variety of sources. This mucus covering has various critical physiological functions, including drug absorption or activity. It is also worth noting that vaginal characteristics alter with the menstrual cycle, particularly pH and vaginal fluid: the usual pH ranges from 4.5 to 5.5, while vaginal fluid changes greatly in volume, content, and rheological qualities. Lactobacilli are abundant in the healthy vagina and play a crucial function in maintaining vaginal pH and controlling infection by common pathogens [20,21].

Along with age as well as menstrual cycle Vaginal histology and physiology may differ. The thickness of the vaginal epithelium fluctuates with age because the levels of ovarian steroids change. From birth until adolescence, the vaginal epithelium is very thin, but after puberty, the usual thickness of the vaginal epithelium is roughly 200 pm [22].

The vaginal BDD (body dysmorphic disorder) system has been used for both local and systemic drug delivery, particularly in female-related disorders. Traditionally, the vaginal cavity has been utilized to administer locally acting medications such as antibacterial, antifungal, antiprotozoal, antiviral, labor- inducing, spermicidal, prostaglandin, and steroid. Formulations that can prevent the transmission of sexually transmitted diseases (STDs), including AIDS, have made significant progress during the last decade [21].

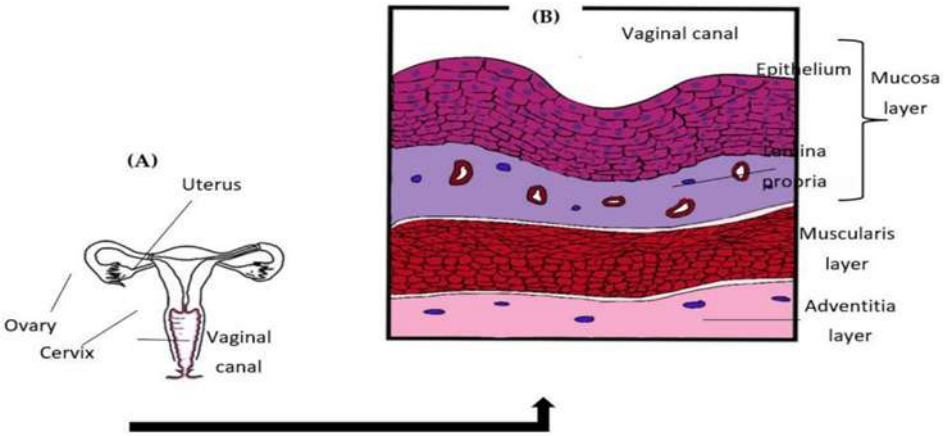

Fig. 2: Illustration of the vaginal wall structure [20]

1.3 ORAL MUCOSA

The oral mucosa is composed of an outermost layer of stratified squamous epithelium (about 40-50 layers thick), a lamina propria followed by the sub mucosa as the innermost layer. The composition of the epithelium varies depending on the site in the oral cavity. The mucosa of the gingival and hard palate are keratinized similar to the epidermis contain neutral lipids like ceramides and acylceramides which are relatively impermeable to water. The mucosa of the soft palate, the sublingual, and the buccal regions, however, are not keratinized contain only small amounts of ceramides.

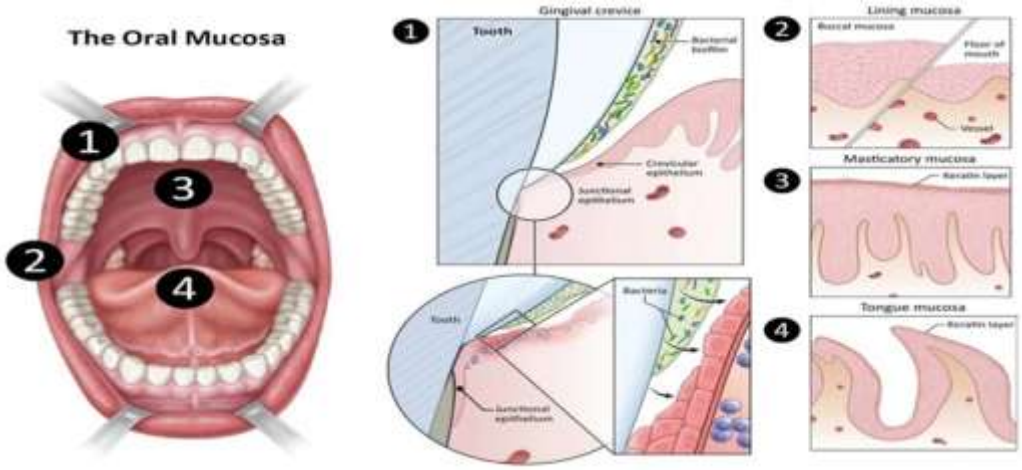

Fig 3: Illustration of the Oral Mucosa [23]

Novel buccal dosage forms: The novel type buccal dosage forms include buccal adhesive tablets, patches, films, semisolids (ointments and gels) and powders.

The oral cavity has a relatively small surface area (approximately 50 cm2). The oral mucosa is composed of stratified squamous epithelium, an outermost layer similar to that found in the rest of the body. It has a mitotically active basal cell layer, advancing through a number of differentiating. intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium The turnover time for the buccal epithelium has been estimated at 5–6 days, a time probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500–800 mm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200 mm [23-25] .

An ideal polymer for an oral bioadhesive drug delivery system should have the following characteristics

1. The polymer and its degradation products should be nontoxic and not absorbed through the mucous membrane.
2. It should not irritate the mucous membrane.
3. It should preferably form a strong noncovalent bond with the mucin-epithelial cell surfaces.
4. It should adhere quickly to moist tissue and should possess some site specificity.
5. It should allow easy incorporation of the drug and offer no hindrance to its release.
6. The polymer must not decompose during storage or during the shelf-life of the dosage form.
7. The cost of the polymer should not be high, so that the prepared dosage form remains competitive.
8. The polymer should allow flexibility and comfort of the dosage form [26-27].

1.4 OCULAR MUCOSA

Ocular mucosal drug delivery systems are designed to enhance the absorption and bioavailability of therapeutics applied to the eye. Traditional ocular formulations, such as eye drops, often suffer from rapid drainage and limited contact time with the mucosal surface. To address these challenges, various innovative approaches are being developed:

1.4.1 Mucoadhesive Formulations: Incorporating natural polymers, gums, and mucilages can improve retention time on the ocular surface. These materials enhance adhesion to the mucosal layer, allowing for sustained drug release.

1.4.2 Hydrogels and Nanoparticles: Hydrogels can provide a controlled release mechanism, while nanoparticles may enhance penetration through ocular barriers. Both strategies can improve the bioavailability of poorly soluble drugs.

1.4.3 In Situ Gelling Systems: These formulations transition from a liquid to a gel upon contact with ocular fluids, providing longer residence time and localized delivery.

1.4.4 Microneedle Arrays: This novel approach involves using tiny needles to penetrate the outer layer of the cornea, allowing for direct drug delivery to the deeper ocular tissues.

1.4.5 Sustained-Release Devices: Implants or inserts that release medication over an extended period can reduce the frequency of administration and improve patient compliance.

Overall, advancements in ocular mucosal drug delivery systems hold great promise for improving therapeutic outcomes in ophthalmic treatments. These innovative strategies aim to enhance drug absorption, reduce side effects, and increase the overall effectiveness of ocular therapies.

Anatomy of the Ocular Mucosa

Conjunctiva: A thin, transparent membrane covering the inner surface of the eyelids (palpebral conjunctiva) and the white part of the eyeball (bulbar conjunctiva). Contains goblet cells that produce mucus, contributing to tear film stability and ocular surface lubrication.

Cornea: The outermost layer of the eye, composed of five layers (epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium). The epithelium is rich in tight junctions, providing a barrier that regulates the permeability of substances.

Tear Film: A thin layer of fluid covering the ocular surface, composed of three layers like Lipid layer, Aqueous layer, Mucin layer

Sclera: The white, protective outer layer of the eye, providing structural support. Less permeable than the cornea but important in ocular drug delivery [28] .

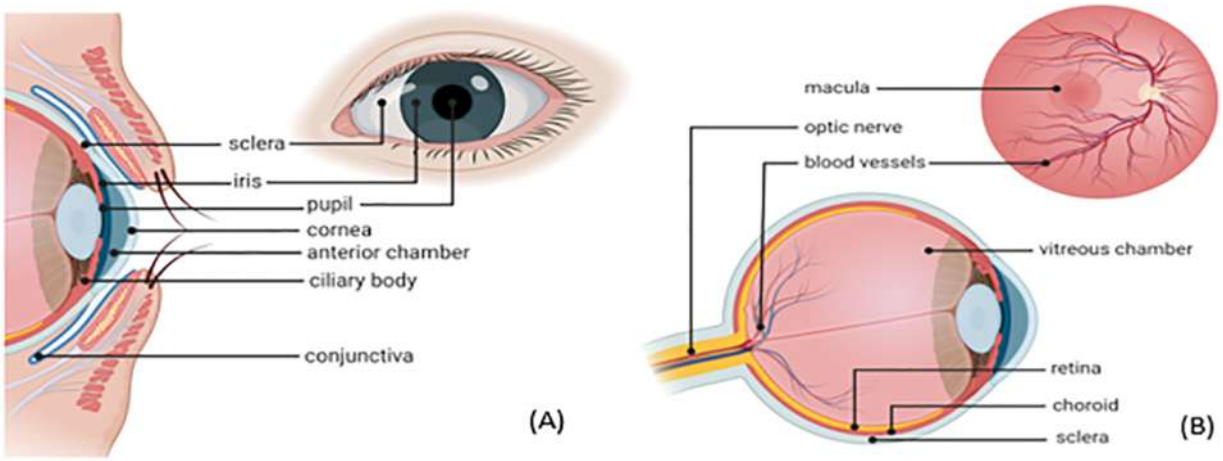

Fig 4: Schematic representation of the (A) anterior ocular anatomy (B) posterior ocular anatomy [28]

1.5 RECTAL SYSTEM

Rectal anatomy and scope of drug selection

Anatomically, the rectum forms the distal part of the large intestine. A normal adult human rectum is about 12–15 cm long and deviates in three lateral curves: upper, middle and lower.

It is considered a cylindrical organ that does not contain villi or microvilli on the luminal surface and is mainly associated with water absorption and re-absorption from the gastro intestinal (GI) contents. Average rectal surface area is reported to be around 200–400 cm2 and the pH is 7.2–7.4,

The rectum is structured with columnar epithelial cells along with goblet cells that are responsible for mucous secretion. The mucous forms a layer approximately 100 mm that acts as a protectant to the rectal epithelia and is also a barrier for drug absorption [29-30].

Dosage forms for rectal route

Solid rectal dosage forms, Suppositories, Rectal capsules, tablets or powder for reconstitution, Liquid rectal dosage forms, Semi-solid rectal dosage forms.

1.6 NASAL ROUTE

The nasal cavity is one of the most easily accessible and well tolerated drug delivery region in the body. It has the advantages like high surface area (approximately 150 cm2) with very rich blood vessels and good nasal cavity volume (approximately 15-20 ml). The mucus layer is regularly renewed every 15-20 min.

The turbinate region is the middle and the most important region of the nasal cavity. This area is the main area for the delivery of different formulations. It is composed of Superior, Middle and Inferior turbinate. The entire turbinate region is richly supplied with blood vessels and lymph vessels. The epithelial cells present in these regions are mainly ciliated/non-ciliated, basal and mucus secreting goblet cells. The ciliated cells are responsible for secretion of mucus, the ciliated and nonciliated cells have microvilli which provide very high surface area required for improved drug absorption. [31-33].

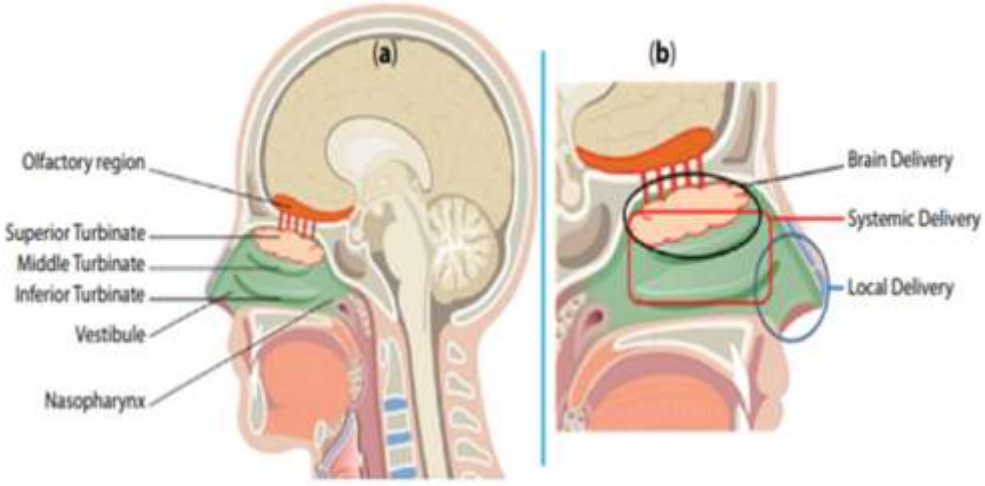

Fig 5: Illustration of the (a) Areas of Nasal Cavity (b) Possible drug delivery through nasal route [32]

Nasal Route for Brain Drug Delivery

Superior Turbinate region has a very rich supply of olfactory nerves and blood vessels. It is reported that the olfactory nerves reaching olfactory mucosa pass through cribriform plate of ethmoid bone. These nerves pass through the cribriform plate along with the arachnoid membrane which is filled with cerebrospinal fluid (CSF). The drugs to be delivered to the Central Nervous System (CNS), if delivered through nasal route, get adhered and lined to the olfactory mucosa of the Superior Turbinate region [34- 35].

Nasal Route for Local and Systemic Drug Delivery

The turbinate region of the nose is sectored as Superior, Middle and Inferior Turbinate. The whole turbinate area is richly supplied with blood and lymph vessels and thus is an important area for systemic drug and vaccine delivery. The cells present in turbinate region are mainly of four types: basal cells, ciliated cells, nonciliated cells, and goblet cells which are present on basement membrane and are richly supplied with blood vessels and thickly covered with mucus and pericillary fluid [36].

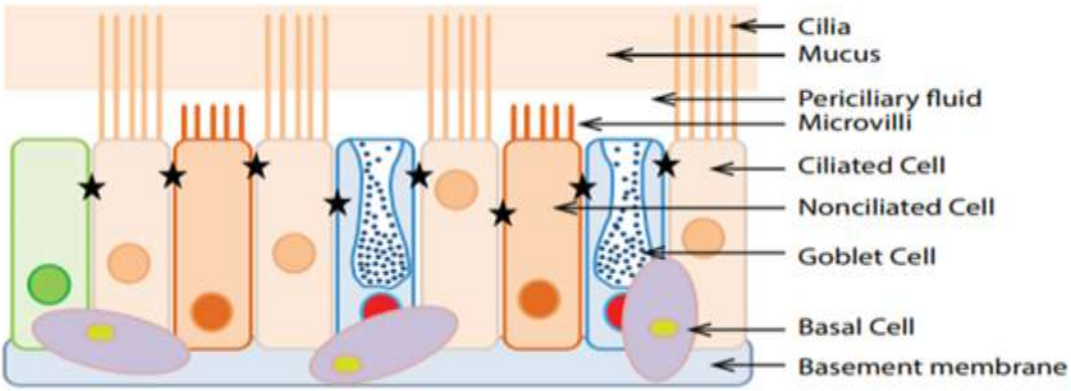

Fig 6: Cells in human nasal epithelium [32]

There are mainly four types of cells present in the nasal epithelium attached to basement membrane: Basal cells, goblet cells, ciliated cells, and nonciliated cells. Out of which goblet cells, ciliated cells and nonciliated cells are attached to each other through tight junction between cells (shown by blue star). The mucus layer is present over the periciliary fluid which acts as lubricating layer and provides sliding movement to mucus layer in ciliary clearance mechanism. These cells and tight junction also contribute to different drug absorption mechanisms [37].

TABLE 1: STUDIES ON NATURAL MUCILAGES AND GUMS [38-74]

Mucilage/ gums	Botanical name	Family	Pharmaceutical Application	Reference
Lipidium sativum	Lepidum sativum	Cruciferae	Suspending agent, emulsifying agent,	38-39
Cordia gum	Cordia dichotoma	Boraginaecae	Sustained release matrix	40
Mucuna gum	Mucuna flagillepes	Papillionaceae	Microspheres	41
Okra mucilage	Hibiscus esculentus	Malvaceae	Hydrophilic matrix for controlled	42
Acacia	Acacia Senegal	Leguminosae	Osmotic drug delivery	43,44
Bhara gum	Terminalia bellirica	Combretaceae	Sustained release	45,46
Cactus mucilage	Opuntia ficus-indica	Cactaceae	Gelling agent in sustained drug delivery	47
Guar gum	Cyamopsis tetraganoloba	Leguminosae	Colon targeted drug delivery,	48-51
Locust bean gum	Ceratania siliqua	Leguminosae	Controlled release agent	52
Okra gum	Abelmuschus esculentus	malvaceae	suitability as suspending and disintegrating agent	53
Almond gum	Prunus communis	Rosaceae	emulsifier, thickener, suspending pharmaceutical, adhesive, glazing agent and stabilizer. Gum obtained from Almond as a binder in tablet formulations	54
Neem gum	Azadirachta indica	Meliaceae	Binder	55-57
Gellan gum	Pseudomonas elodea		Disintegrating agent	58
Aloe mucilage	Aloe barbadensis Miller		A controlled delivery system	59

Albizia gum	Albizia zygia	Leguminosae	Binding agent, suspending agent	60
Karaya gum	Firmiana simplex	Malvaceae	gastric retentive dosage forms improve rate of dissolution of drug solid dispersions. Suspending agent Emulsifying agent. Dental adhesive Sustaining agent. Mucoadhesive	61
Tamarind gum	Tamarindus indica L.	Fabaceae	Drug release Biodegradable carrier for colon specific release	62
Grewia gum	Grewia mollis Juss	Malvaceae	Controlled release dose formulations. Suspending the agent increase. The release of cimetidine from tablets is controlled by the degree of packing and fluidity of the granules, which delay the release. Film making property	63-68
Cashew gum	Anacardium occidentale L.	Anacardiaceae	As suspending agent	69
Cordia mucilage	Cordia myxa	Boraginaceae	As enteric resistant and sustained release substantial	70
Fenugreek gum	Trigonella foenum graecum	Leguminosae	As an emulsifier and binding agent, suspending agent, mucoadhesive preparations.	71
Moi gum	Lannea coromandelica	Anacardiacea	As a microencapsulating agent, release rate control material.	72
Moringa gum	Moringa oleifera	Moringaceae	As a mucoadhesive agent, binder, disintegrant	73
Xanthan gum	Xanthomonas campestris	Xanthomonadacae	As a suspending agent, emulsifying agent,	74

1. Grafted Polymers

Definition: Grafted polymers are copolymers in which one or more types of polymer side chains (grafts) are chemically attached to a main polymer backbone, forming a branched structure with different polymers in the backbone and the branches.

TABLE 2: STUDIES ON GRAFTED POLYMERS

SR. NO.	Natural Gum / Mucilage	Source / Botanical Origin	Key Chemical Composition	Important Properties	Common Grafted Polymers (Graft Co-polymers)	Applications of Grafted Polymer
1	**Lepidium sativum (Garden cress mucilage)**	Seeds of *Lepidium sativum*	Polysaccharides (D-galactose, L-rhamnose, D-	High viscosity, gel-forming,	Polyacrylamide (PAM), Polyacrylic acid (PAA),	Hydrogels, drug delivery matrices, thickener

			xylose), uronic acids	biodegradable	Poly(N-vinyl-2-pyrrolidone) (PVP), Acrylic acid–Acrylamide copolymers	
2	**Cordia gum (Cordia dichotoma)**	Fruits of *Cordia dichotoma*	L-arabinose, D-galactose, uronic acids	High water absorption, film-forming	Polyacrylamide, Polyacrylic acid, Methyl methacrylate (MMA) grafts	Controlled drug release, bioadhesive films
3	**Mucuna gum (Mucuna pruriens)**	Seeds of *Mucuna pruriens*	Galactomannans	High viscosity, stable over pH, biodegradable	Polyacrylamide, Polyacrylic acid, GMA (glycidyl methacrylate) grafts	Hydrogels, tablets, biomedical coatings
4	**Okra mucilage (Abelmoschus esculentus)**	Okra pods	Rhamnose, galactose, galacturonic acid	Excellent thickening, mucoadhesive, non-toxic	Polyacrylic acid, Acrylamide, Acrylic acid–Acrylamide copolymers	Wound dressing, oral drug delivery, hydrogels
5	**Acacia gum (Gum Arabic)**	*Acacia senegal* tree exudate	Arabinogalactan protein, rhamnose, glucuronic acid	Emulsifying, soluble, film-forming	Acrylamide, Acrylic acid, N-vinyl pyrrolidone	Nanocomposites, controlled-release systems
6	**Bhara gum (Butea monosperma gum)**	Exudate of *Butea monosperma* tree	Galactose, arabinose, rhamnose	Swelling, gel-forming, biodegradable	Polyacrylamide, Polyacrylic acid, Methyl methacrylate	Drug release matrices, hydrogel films
7	**Cactus mucilage (Opuntia species)**	*Opuntia ficus-indica* and others	Arabinose, xylose, galactose, pectic substances	Water retention, flocculating, eco-friendly	Polyacrylic acid, Acrylamide, Acrylic acid–Acrylamide	Water treatment hydrogels, superabsorbents
8	**Guar gum**	Seeds of *Cyamopsis tetragonoloba*	Galactomannan	Excellent thickener, stable, high viscosity	Polyacrylamide, Polyacrylic acid, Polyvinyl alcohol (PVA), GMA	Superabsorbents, drilling fluids, drug carriers
9	**Locust bean gum (Carob gum)**	Seeds of *Ceratonia siliqua*	Galactomannan (mannose:galactose 4:1)	Synergy with other gums, gel-enhancing	Polyacrylamide, Polyacrylic acid, Acrylamide-	Hydrogels, packaging films, biomedical gels

					acrylate copolymers	
10	**Okra Gum (Okra Mucilage)**	Pods of *Abelmoschus esculentus*	Rhamnose, galactose, galacturonic acid	Thickener, mucoadhesive, biodegradable	Acrylic acid (AA), Acrylamide (AAm), Polyacrylic acid (PAA), N-vinyl pyrrolidone (NVP)	Hydrogels, wound dressing, controlled drug release
11	**Almond Gum**	Exudates of *Prunus amygdalus*	Arabinogalactans, glucose, uronic acids	Film-forming, emulsifying	Polyacrylamide, Polyacrylic acid, Methyl methacrylate (MMA)	Drug carriers, biodegradable films
12	**Neem Gum**	Exudate of *Azadirachta indica*	Arabinose, galactose, fucose	Swellable, stable	Polyacrylamide, Acrylic acid, AAm-AA copolymers	Hydrogel beads, heavy metal adsorption
13	**Gellan Gum**	Produced by *Sphingomonas elodea*	Glucose, rhamnose, glucuronic acid	Strong gel former, thermostable	Polyacrylamide, PEG-based grafts, Polyacrylic acid	Tissue engineering, drug release
14	**Aloe Mucilage (Aloe vera Gel)**	Leaves of *Aloe barbadensis*	Acetylated polysaccharides (acemannan)	Hydrating, bioactive	Polyacrylamide, Acrylic acid, Chitosan-graft polymers	Wound healing gels, moisturizing hydrogels
15	**Albizia Gum**	*Albizia zygia* exudate	Galactose, arabinose, rhamnose	Thickening, bioadhesive	Polyacrylic acid, Polyacrylamide	Tablets, sustained release systems
16	**Karaya Gum (Sterculia Gum)**	Exudate from *Sterculia urens*	Galactose, rhamnose, galacturonic acid	Highly swellable, bioadhesive	Polyacrylamide, Acrylic acid, GMA grafts	Superabsorbents, colon-targeted drug delivery
17	**Tamarind Gum (Tamarind Kernel Powder)**	Seeds of *Tamarindus indica*	Xyloglucan	Gel-forming, stable viscosity	Acrylic acid, Acrylamide, Polyacrylic acid, MMA	Hydrogels, sustained release tablets
18	**Grewia Gum (Grewia Polysaccharide)**	Bark of *Grewia mollis* or *Grewia gumifera*	Rhamnogalacturonan, arabinose, galactose	Thickener, mucoadhesive	Polyacrylamide, Acrylic acid, GMA	Drug release beads, hydrogels

19	**Cashew Gum**	Exudate of *Anacardium occidentale*	Arabinogalactan, glucose, glucuronic acid	Soluble, emulsifying	Polyacrylamide, Polyacrylic acid, MMA	Nanoparticles, drug delivery, coatings
20	**Cordia Mucilage (Cordia gum)**	Fruits of *Cordia myxa / Cordia dichotoma*	L-arabinose, D-galactose, uronic acids	Water absorption, film-forming	Polyacrylamide, Polyacrylic acid, MMA	Bioadhesive films, hydrogels
21	**Fenugreek Gum (Fenugreek Galactomannan)**	Seeds of *Trigonella foenum-graecum*	Galactomannan (mannose:galactose 1:1)	Thickener, stabilizer	Acrylic acid, Acrylamide, NVP, GMA	Superabsorbents, drug delivery
22	**Moi Gum (Moi seed gum)**	Seeds of *Bassia latifolia* (also known as Mahua tree)	Galactomannans (mannose + galactose), uronic acids, minor proteins	High viscosity, strong gel-former, biodegradable	Acrylic acid (AA), Acrylamide (AAm), Polyacrylamide (PAM), Methyl methacrylate (MMA)	Superabsorbent hydrogels, drug controlled-release matrices, water retention polymers
23	**Moringa Gum**	Exudate from bark of *Moringa oleifera*	Arabinose, galactose, xylose, rhamnose, uronic acids	Thickener, emulsifier, bioadhesive, stable	Polyacrylamide (PAM), Polyacrylic acid (PAA), N-vinyl pyrrolidone (NVP), Acrylamide-acrylate copolymers	Bioadhesive tablets, hydrogels, flocculants, biomedical films
24	**Xanthan Gum**	Fermentation gum produced by *Xanthomonas campestris*	Glucose, mannose, glucuronic acid; cellulose-like backbone	High viscosity at low concentrations, shear thinning, stable across pH & temperature	Polyacrylamide, Polyacrylic acid, GMA (glycidyl methacrylate), MMA, NVP	Drug delivery hydrogels, sustained-release matrices, tissue engineering scaffolds, viscosity modifiers

1.7 APPLICATION OF POLYMERS

1) Formulations for spermicidal action and combating STD: Condom use has surged as a result of STDs, particularly infections with HIV. By combining a condom with a spermicidal composition has been shown to work synergistically to prevent these illnesses more effectively than just provide contraception [75].

2) Using gums, hydrogel and polymeric film formulations have been created for topical use [76]

3) Mucilages are often used in a variety of pharmaceutical preparations as adjuvants, thickening, binding, suspending, dissolving, emulsifying, gelling, stabilizing agents, etc. [77]

4) Because of their bioactivity, biodegradability, hydrophilicity, and superabsorbent qualities, natural gums have the potential to replace synthetic polymers used in pharmaceutical and biomedical technologies. These gums can also yield hydrogels [78].

5) Cell proliferation scaffolds are another use for mucilage. Hilary Urena-Saborio [79] reported on recent study that created electro spun nanofibers (ESNFs) using mucilage extracted from chan and linaza beans and mozote stem that is commercially accessible in Costa Rica.

6) The application of gum in wound healing has significantly increased in recent years. Quince seed mucilage (QSM) has been used to heal burns and wounds in traditional Iranian medicine [80].

1.8 ADVANTAGES

1) Local availability: Since guar gum and tragacanth are grown in the majority of poor nations, they will be readily available.

2) Non-toxic and biocompatible: Almost majority of these plant components are carbohydrates in chemical form, made up of units of sugar that repeat. Hence, they are non-poisonous.

3) Little cost: Using natural sources is constantly less expensive. In addition, manufacturing cost is suggestively less than that of synthetic materials. India and many other emerging nations rely heavily on agriculture.

4) Biodegradable: Ev ery living thing produces naturally occurring biodegradable polymers. They are a really renewable resource and don't harm people or the environment in any way (e.g., causing skin and eye discomfort).

5) Processing that is environmentally friendly – Because the manufacturing procedures are straightforward, it is possible to gather gums and mucilage's from numerous springs in diverse seasons in big numbers [81].

1.9 DISADVANTAGES

1) Due to their carbohydrate composition and usually 10% greater moisture content, gum and mucilage may contain microbial contamination [82-84].

2) Decreased viscosity during storage – Typically, formulations become more viscous when water comes into contact with gums and mucilages. It has been discovered that there is a decrease in viscosity after storage because gums and mucilages are complex substances.

3) Batch-to-batch variation: While the production of gums and mucilages is dependent on periodic and environmental conditions, artificial manufacture follows a controlled process with fixed amounts of components.

4) Unrestrained rate of hydration: The percentage of chemical elements present in a particular substance might change owing to variations in the gathering of natural materials at diverse periods, and variations in area, classes, and weather conditions. Appropriate monographs on the various gums and mucilage on the market must be created [81].

1.10 MECHANISM OF ACTION

The mechanism of action of gums and mucilage on the vaginal route primarily involves their ability to provide lubrication, hydration, mucoadhesion, and

potentially act as carriers for drug delivery systems.

Hydration and Lubrication: Gums and mucilage possess hydrophilic properties, enabling them to absorb water and form a gel-like consistency. When applied vaginally, they help hydrate the vaginal mucosa and provide lubrication, reducing friction and discomfort. This is particularly beneficial in cases of vaginal dryness [85].

Mucoadhesion: Gums and mucilage can adhere to the mucosal surfaces of the vagina dueto their adhesive properties. This mucoadhesive effect prolongs the residence time of drugs or formulations on the vaginal mucosa, enhancing their therapeutic efficacy [86].

Protective Barrier: Gums and mucilage may form a protective barrier on the vaginal mucosa, protecting it from irritants, pathogens, and other external agents. This function helps maintain the integrity of the vaginal epithelium and reduces the risk of infections or inflammation [87,88].

1.11 MECHANISM OF BIOADHESION

The mucus is secreted by the goblet cells. It is a highly viscous liquid covering the internal tract of the body. Its role is to protect the mucosa against various aggressions. Its exact composition varies, depending on its source and location. However, its major components are mucin, electrolytes, lipids, enzymes, sloughed epithelial cells, bacterial products and water (95%) [89].

Mucin is a glycoprotein in which 160-200 oligo-saccharides side-chains of the glycosylated regions

represent 50-60% of its weight. The mucus gel structure results from the intermolecular association of glycoproteins (mucin) in a polymeric network. The polymer is probably a terminally linked chain with numerous cross-linkings. A large proportion of the glycop~tein is not incorporated in the network, but present as a soluble fraction, enhancing the viscosity of the interstitial fluid.

Besides its protective role against chemical (pH) or enzymatic aggression, the mucus constitutes a diffusion barrier for molecules, not only against drug absorption but also against bioadhesive polymer molecular chain interdiffusion. Diffusion through the mucus layer depends largely on the physico- chemical characteristics of the diffusive molecule: molecule charge, hydration radius, ability to form hydrogen bonds and molecular weight [90].

1. Topical Bioadhesive Drug Delivery Systems (DDS)

Topical DDS aim to enhance drug residence time on the skin or mucosal surfaces (buccal, nasal, ocular, vaginal). Natural polymers provide adhesion, controlled release, and biocompatibility.

Common Natural Bioadhesive Polymers Used

- Chitosan
- Pectin
- Sodium alginate
- Hyaluronic acid
- Gelatin
- Guar gum
- Xanthan gum

Topical DDS Types & Their Features

a) Bioadhesive Gels

- Polymers: chitosan, carbopol + natural gums
- Advantages: easy application, good spreading, sustained drug release

- Applications: anti-inflammatory drugs, antifungals, wound healing

b) Bioadhesive Creams and Ointments

- Enhanced retention on skin/mucosa
- Used for: corticosteroids, antimicrobials, analgesics

c) Bioadhesive Patches/Films

- Thin films for buccal, nasal, or transdermal delivery
- Benefits: precise dosing, prolonged adhesion
- Example: chitosan or alginate-based buccal films for systemic delivery (e.g., nicotine, analgesics)

d) Bioadhesive Nanoparticles

- Chitosan nanoparticles enhance mucosal uptake
- Used in: intranasal vaccines, ocular drug delivery

e) Wound Dressings/Hydrogels

- Polymers: alginate, hyaluronic acid, chitosan
- Provide moisture, adhesion, antimicrobial properties
- Applications: chronic wounds, burns

2. Gastrointestinal (GI) Bioadhesive Drug Delivery Systems (DDS)

GI DDS use mucoadhesive materials to prolong drug residence time in stomach or intestines, enhance absorption, and target specific regions.

Natural Bioadhesive Polymers Used

- Chitosan
- Pectin
- Guar gum
- Alginate
- Locust bean gum
- Gum karaya
- Tragacanth gum

GI DDS Types & Characteristics

a) Mucoadhesive Tablets

- Polymers form strong adhesion to GI mucosa
- Prolonged gastric retention
- Used for: antihypertensives, antidiabetics, antibiotics

b) Mucoadhesive Microspheres/Nanospheres

- Made from chitosan, alginate
- Advantages:
  - Large surface area
  - Improved absorption
  - Controlled release
- Applications: insulin, peptides, antiulcer drugs

c) Floating Bioadhesive Systems

- Combine buoyancy + mucoadhesion for gastric retention
- Polymers: chitosan, alginate
- Used for: drugs absorbed in stomach (e.g., amoxicillin for H. pylori)

d) Colon-Targeted Mucoadhesive Systems

- Natural polymers degraded by colonic bacteria:
  - pectin
  - guar gum
  - xanthan gum
- Applications: inflammatory bowel disease (IBD), colon cancer drugs

e) In-situ Gelling Systems

- Liquid dosage forms that gel upon contact with gastric pH or ions
- Example: alginate gels in presence of Ca^{2+}
- Used for: antacids, local antibiotics

f) Bioadhesive Films for GI Delivery

- Swell and adhere to mucosa
- Good for peptides and proteins
- Polymers: chitosan, gelatin

Five Drug Properties Important for Bioadhesive DDS

1. Drug Solubility

- Drugs should have adequate solubility at the site of application (skin or mucosa).
- Poorly soluble drugs benefit from sustained release, but extremely insoluble drugs may not diffuse from the bioadhesive matrix.

2. Molecular Weight

- Low to moderate molecular weight drugs penetrate mucosa more easily.
- High molecular weight drugs (like peptides) may require permeation enhancers.

3. Partition Coefficient (Lipophilicity)

- A balanced hydrophilic–lipophilic nature is required.
- Too hydrophilic → poor permeability.
- Too lipophilic → slow release from polymer.

4. Stability at the Application Site

- Drug must remain stable at local physiological conditions:
  - pH of buccal, nasal, vaginal, or GI mucosa
  - Presence of enzymes
- Unstable drugs degrade before absorption.

5. Dose Requirement

- Drugs with low dose (milligrams or micrograms) are ideal.
- High-dose drugs make films/gels too large or uncomfortable for topical/mucosal application.

Effect of Polymer Properties on Mucoadhesive Drug Delivery Systems

The performance of any mucoadhesive drug delivery system depends strongly on the physicochemical properties of the polymer used. These properties influence adhesion strength, swelling, drug release, residence time, and overall therapeutic effect.

1. Molecular Weight of Polymer

- Higher molecular weight polymers (e.g., chitosan, carbopol) exhibit stronger

mucoadhesion because longer polymer chains interpenetrate better with mucin.

- Very high molecular weight may reduce solubility and spreadability.

Effect:
✓ Strong adhesion, ✓ sustained release, ✗ slower hydration.

2. Degree of Crosslinking

- Lightly crosslinked polymers swell more and form stronger adhesive bonds.
- Highly crosslinked polymers have limited swelling → lower mucoadhesion.

Effect:
✓ Controls drug release rate, ✓ affects adhesive strength, ✗ excessive crosslinking reduces mucoadhesion.

3. Polymer Charge (Ionic Character)

- **Cationic polymers** (e.g., chitosan) interact strongly with negatively charged mucin → excellent mucoadhesion.
- **Anionic polymers** (pectin, alginate) adhere in acidic pH but lose adhesion at higher pH.
- **Non-ionic polymers** (HPMC) rely on hydrogen bonding.

Effect:
✓ Strong bonds with mucin, ✓ pH-dependent adhesion.

4. Functional Groups

Presence of –COOH, –OH, –NH2 enhances adhesion.

- Carboxyl groups (in pectin, alginate) form hydrogen bonds.
- Amino groups (chitosan) form electrostatic bonds.

Effect:
✓ Increases chemical bonding with mucosal surface.

5. Swelling Ability

- Swelling allows polymer chains to relax, spread, and interpenetrate mucin.
- Too much swelling → gel erodes quickly.
- Too little swelling → weak adhesion.

Effect:
✓ Improves adhesion and drug release, ✗ excessive swelling reduces retention.

6. Polymer Concentration

- Higher concentration increases viscosity → improves adhesion.
- Very high concentration makes the formulation too thick, reducing spreadability.

Effect:
✓ Optimal concentration needed for balance between viscosity and adhesion.

7. Polymer Flexibility

- Flexible polymer chains penetrate mucin more easily.
- Rigid polymers show poor mucoadhesion.

Effect:
✓ Improved chain interpenetration → stronger adhesion.

8. Hydrophilicity

- Hydrophilic polymers absorb water → swell → promote adhesion.
- Excessive hydrophilicity causes fast dissolution.

Effect:
✓ Facilitates hydration, swelling, and adhesion.

9. pH Sensitivity

- Some natural polymers show pH-dependent charge and swelling.
  - Example: Pectin swells more at higher pH (intestinal).
  - Chitosan adheres at acidic pH (stomach).

Effect:
✓ Determines site-specific adhesion in GI tract.

1. Adsorption Theory

Adsorption theory states that bioadhesion occurs due to the formation of weak chemical bonds between the polymer and the biological surface after initial contact. These include:

- Hydrogen bonds
- Van der Waals forces
- Electrostatic interactions

Key point: Adhesion results from *secondary chemical interactions* between polymer chains and mucin.

2. Mechanical Theory

Mechanical theory explains that bioadhesion occurs when the polymer penetrates into surface irregularities or pores of the mucosal membrane. After penetration, the polymer locks into the surface, creating mechanical interlocking.

Key point: Adhesion results from *physical interlocking* between polymer and mucosa.

3. Cohesive Theory

Cohesive theory states that the internal strength of the polymer itself plays a major role in adhesion. If the polymer has strong cohesive forces (good viscoelasticity and chain entanglement), it maintains integrity and adheres better.

Key point: Adhesion depends on *internal strength and chain entanglement* of the polymer.

What kinds of bioadhesive formulations exist (or have existed) on the market or in clinical/research use

• Buccal Films / Tablets / Patches

- There have been commercial buccal mucoadhesive products — such as buccal tablets/films delivering systemic or local drugs.
- For example, older mucoadhesive oral pastes/patches like Orabase used natural polymers (blends including pectin, gelatin) as the mucoadhesive component.
- Other types: combination of natural polymers (e.g., gums, gelatin) with synthetic/semi-synthetic for mucoadhesive buccal films, often in research — e.g. films combining natural protein (gelatin, albumin, casein) with synthetic polymer to deliver drugs such as Glipizide through the buccal mucosa.
- Bioadesive Gels / Hydrogels (Oral, Mucosal, Topical)

- Gel or hydrogel formulations using natural polymers (e.g. chitosan, alginate, gums) have been studied for mucoadhesive delivery (oral cavity, nasal, etc.).
- For example, natural-gum or chitosan-based mucoadhesive gels containing antimicrobial or other drugs have been formulated for local or systemic mucosal delivery.

• Microspheres / Nanoparticles / Particulate Systems with Mucoadhesive Polymers

- Research formulations have used natural polymer-based microspheres or nanoparticles for mucoadhesion — though as of now these are mostly at lab/preclinical stage rather than wide commercial use.

TABLE 2: APPLICATIONS OF NATURAL POLYMERS IN DRUG DELIVERY [91,92]

Mucilage/ Gum	Dosage form	Disease/ Disorder	Application
Xanthine	Pellets	Kidney stone	Controlled drug delivery
Tamarind	Hydrogel	Dry eye, glaucoma	Ocular mucoadhesive drug delivery
Pectin	Beads, floating beads	Colon cancer, chron's disease	Collon drug delivery
Luciana seed gum	Tablet	Constipation and diarrhea	Emulsifying agent, suspending agent
Agar	Gelletin agent in suppository	Diarrhea, Laxative, purgative	Suspending agent, emulsifying agent
Gum ghatti	Tablets, Emulsion and suspension	Constipation and diarrhea	Binder, emulsifying and suspending agent
Acacia	Tablet	Throat and stomach inflammation	Binder
Albizia	Tablet	Arthritis and Burn	Binder
Galan	Hydrogel, beads	Correct vision	Opthalmic drug delivery system
Isapgol	Powder, tablet	Diarrhea	Colon drug delivery and gastroretentive drug delivery

Evaluation Parameters for Mucoadhesive Dosage Forms

In-Vitro Evaluation Parameters

1. **Mucoadhesive Strength / Force of Adhesion –** Measured using texture analyzer, modified balance, or tensile strength apparatus.
2. **Residence Time –** Determined using USP disintegration apparatus or modified flow-through methods.
3. **Swelling Index –** Percentage weight/volume increase after hydration in simulated biological fluids.
4. **In-Vitro Drug Release Studies –** Performed using USP dissolution apparatus (Type I, II, or modified).
5. **Surface pH –** Ensures compatibility with mucosal tissue**.**
6. **Viscosity / Rheological Studies –** Important for gels and liquid formulations.
7. **Bioadhesion Time –** Time for which dosage form remains adhered to mucosal tissue.
8. **Ex-Vivo Mucoadhesion Study** – Using excised animal mucosa (goat, sheep, porcine).
9. **Mechanical Properties –** Tensile strength, folding endurance (films/patches).

10. **Drug Content Uniformity** – Ensures dose accuracy**.**

In-Vivo Evaluation Parameters

1. **Residence Time in Biological Site –** Evaluated in animals or human volunteers.
2. **Pharmacokinetic Studies –** Cmax, Tmax, AUC for bioavailability assessment.
3. **Pharmacodynamic Studies** – Therapeutic efficacy.
4. **Irritation / Histopathological Studies** – Safety assessment on mucosal tissues.
5. **In-Vivo Imaging Techniques** – Gamma scintigraphy, fluorescence imaging.
6. **Clinical Performance** – Patient acceptability and compliance.

Different Dosage Forms for Bioadhesive Drug Delivery Systems

Sr. No.	Polymer Used	Model Drug	Dosage Form	Result	Reference
1	Carbopol 934	Metronidazole	Buccal Gel	Prolonged mucosal residence time	Lachman et al., *Theory & Practice of Industrial Pharmacy*
2	Chitosan	Insulin	Nasal Microspheres	Enhanced bioavailability	Ahuja et al., *Int. J. Pharm.*
3	HPMC	Propranolol HCl	Buccal Tablet	Sustained drug release	Banker & Rhodes
4	Sodium Alginate	Diclofenac Sodium	Mucoadhesive Gel	Improved retention at site	Remington
5	Polycarbophil	Lidocaine	Buccal Patch	Increased contact time	Smart JD, *J. Pharm. Pharmacol.*
6	Xanthan Gum	Theophylline	Mucoadhesive Tablet	Controlled drug release	USP Monograph
7	Pectin	Clotrimazole	Vaginal Gel	Improved therapeutic efficacy	Martin's Physical Pharmacy
8	Guar Gum	Atenolol	Oral Bioadhesive Tablet	Enhanced absorption	*Indian Journal of Pharmaceutical Sciences*
9	Gelatin	Amoxicillin	Microspheres	Sustained drug delivery	*International Journal of Pharmaceutics*
10	Carbopol 971P	Fluconazole	Buccal Film	Increased residence time	*European Journal of Pharmaceutical Sciences*
11	Chitosan–Alginate	Insulin	Nanoparticles	Improved permeation	*Journal of Controlled Release*
12	HPMC–PVA	Nicotine	Buccal Patch	Reduced dosing frequency	*Drug Development and Industrial Pharmacy*
13	Tragacanth Gum	Metformin	Mucoadhesive Tablet	Prolonged drug release	*Asian Journal of Pharmaceutics*
14	Sodium CMC	Ibuprofen	Oral Gel	Improved patient compliance	*Pharmaceutical Development and Technology*
15	Aloe Vera Gel	Acyclovir	Mucoadhesive Gel	Enhanced healing and retention	*Herbal Drug Research Review*

CONCLUSION

Natural polymers, gums, and mucilages represent a versatile and promising class of bioadhesive components in drug delivery systems across various routes, including oral, nasal, transdermal, and ocular and vaginal applications. Their biocompatibility, biodegradability, and inherent adhesive properties make them ideal candidates for enhancing drug retention and absorption, ultimately improving therapeutic efficacy and patient compliance. As research continues to elucidate the mechanisms behind their bioadhesive behavior and optimize their formulation strategies, these natural materials are poised to play an increasingly vital role in pharmaceutical innovations.

Moreover, the shift towards sustainable and eco-friendly materials in drug delivery highlights the importance of leveraging these natural resources. The utilization of gums and mucilage as bioadhesive agents in the various route holds significant promise for enhancing drug delivery systems and improving patient healthcare, it is important to acknowledge the challenges associated with formulation development, including stability, consistency and scalability. These challenges necessitate ongoing research and optimization efforts to ensure the reliability and efficacy of different drug delivery systems containing gums and mucilage. Looking ahead continued research endeavours are expected to further refine the use of gums and mucilage in drug delivery. This includes exploring novel natural polymers, improving bioadhesive properties and advancing formulation technologies. ultimately, these efforts have the potential to enhance patient healthcare.

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