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"A COMPREHENSIVE REVIEW" OF MUCOADHESIVE POLYMERS IN DRUG DELIVERY

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ABSTRACT

This review article discusses mucoadhesive polymers, which are specialized compounds that adhere to mucosal surfaces, enhancing medication administration and retention. These polymers are crucial for drug formulations aimed at improving therapeutic efficacy by ensuring prolonged contact with mucosal tissues. This article explores emerging classes such as lectins, which enhance targeted drug delivery through specific carbohydrate binding, and thiolated polymers, which improve mucoadhesive properties through covalent interactions with mucus glycoproteins. By increasing adherence to mucosal tissues and enabling tailored therapeutic effects, new mucoadhesive polymers such as lectins, thiolated polymers, and poloxamers have shown great promise in improving drug delivery methods. Overall, mucoadhesive polymers represent a vital area in pharmaceutical development, offering significant benefits for localized drug delivery while posing challenges that require further research and innovation.

KEYWORDS: Mucoadhesive, Thiolated, lectins, Targeted delivery, Poloxamers.

INTRODUCTION

Mucoadhesive Polymers

Specialized compounds known as mucoadhesive polymers stick to mucosal surfaces to improve medication administration and retention at specific locations. They are essential to

many drug formulations that try to increase therapeutic efficacy by making extended contact with mucosal tissues.[1]

Ideal Characteristics: Characteristics of Mucoadhesive Polymers are.

- **Strong Adhesion:** Effective mucoadhesive polymers can form strong intermolecular hydrogen bonds with mucosal layers, facilitating adhesion through various interactions as van der Waals forces, electrostatic attractions, and hydrogen bonds.

- **High Molecular Weight:** Generally, The molecular weight of polymers 100 kDa or higher exhibit superior mucoadhesive properties. For instance, polyethylene glycol (PEG) shows increased mucoadhesion with rising molecular weight, where PEG 400 kDa demonstrates excellent adhesion compared to lower MW variants.

- **Hydrophilicity:** Hydrophilic functional groups, such as carboxyl and hydroxyl presence allows for swelling in aqueous environments, maximizing adhesive site exposure.[2]

ADVANTAGES

- Prolonged Residence Time at site of action for better interaction between drug and mucosal surface.
- Improved Bioavailability specially for drugs with poor surface solubility and drugs go extensive first pass metabolism.
- Targeted Drug Delivery for localized effect and minimum side effect.
- Enhanced Drug Stability by avoiding sensitive drug degradation in unfavorable environment.
- Versatile formulation options including gels, films, tablets etc.
- Reduced Dosing Frequency by prolonging drug release for better patient compliance.[3]

DISADVANTAGES

- Variability in mucoadhesion related to composition, molecular weight can lead to inconsistent drug delivery at site of action.
- Limited understanding of mechanisms of mucoadhesion are complicated and not fully understood. Predicting how changes in formulation will affect adhesive nature is hard.
- Swelling due to aquous environment can lead to excessive hydration creating a problem for mucoadhesion (i.e slippery) also dehydration reduce contact time with the mucosal surface.

- Manufacturing challenges includes manufacturing costs and complicated Quality Control process.[4]

Applications: Mucoadhesive polymers are utilized across various drug delivery systems including

- Oral/Buccal Formulations: Enhancing drug retention in the oral cavity.
- Nasal Delivery Systems: Improving absorption rates for intranasal medications.[5]
- Vaginal Applications: Providing sustained release of therapeutics in gynecological treatments.[6]

Classification of Mucoadhesive Polymers

1. Based on Origin

Natural Polymers: Derived from natural sources, these includes

- **Chitosan:** A biopolymer derived from chitin, known for its mucoadhesive properties due to its cationic nature.

Table I.

Property	**Details**
Source	Produced by applying an alkaline solution to the chitin shells of shrimp and other crustaceans.
Molecular Formula	$C_6H_{11}NO_4X_2$
State	Powder
Color	White to off-white
Solubility	Dilute aqueous acid (pH < 6.5)
Storage Temp.	2°C to 8°C[7]

- **Structure**

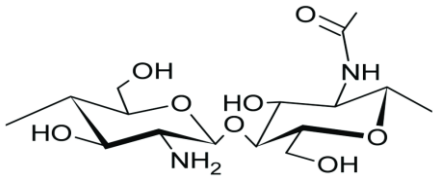

Fig. 1: Structure of Chitosan.[7]

- **Applications**

1) As a preservative and antimicrobial agent in food packaging.
2) As a nutraceuticals incorporated into dietary supplements for weight management and cholesterol reduction due to its ability to bind fats.

3) Chitosan employed in agriculture practices as a natural pesticides and soil conditioner, promoting plant growth and resistance to pathogens.[8]
4) Used in cosmetics for skin hydration and protection against environmental damage.
5) In water treatment processes for its flocculating properties, aiding in removal of contaminants from water.[9]

- **Alginate**: A polysaccharide that forms gels in the presence of calcium ions.

Table II.

Property	Details
Source	Alginates are polysaccharides derived primarily from brown seaweeds, a group of marine algae.
Molecular Formula	$C_6H_7O_6Na$
State	Powder
Color	White to yellowish brown
Solubility	Water-soluble; insoluble in ether, alcohol, and chloroform.
Storage Temp.	2°C to 8°C[10]

- **Structure**

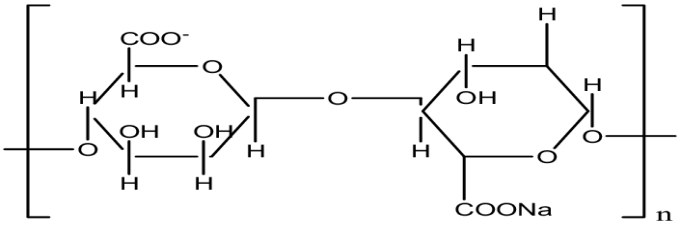

Fig. 2: Structure of Alginates.[11]

- **Applications**

1) In controlled release formulation because of their capacity to create drug-encapsulating hydrogels.
2) Calcium alginate dressing promote healing by maintaining a moist environment and can absorb exudate from wounds.
3) Alginates incorporated in various thickening agents.
4) Alginates are used in fertilizers.
5) Alginates used for encapsulating flavors, nutrients and probiotics, protecting them during processing and storage.[12]

- **Gellan Gum**: A polysaccharide that exhibits excellent gel-forming properties.

Table III.

Property	Details
Source	The bacteria *Sphingomonas elodea* is the main producer of gellan gum, identified in 1978 from lily plant tissue in Pennsylvania.
Molecular Formula	$C_{24}H_{38}O_{20}$
State	Powder
Color	White
Solubility	Soluble in water; insoluble in ether, alcohol, and chloroform.
Storage Temp.	15°C to 30°C[13]

- **Structure**

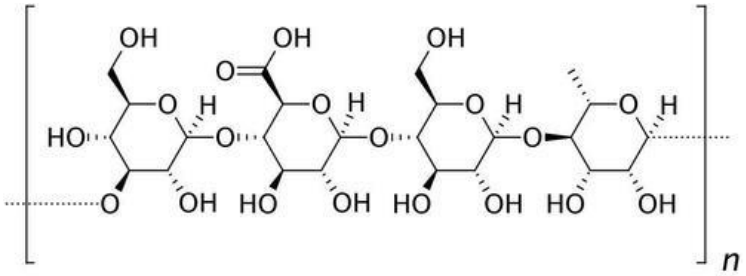

Fig. 3 Structure of Gellan Gum.[14]

- **Applications**

1) Gellan gum is a common gelling ingredient used in dairy dishes, sweets, and jellies, among other food products.
2) It is effective in stabilizing beverages with high sugar content, such as fruit juices and plant-based protein drinks.
3) Its potential in formulations for controlled drug release has been investigated. It can be used in oral, nasal, and ophthalmic applications due to its biocompatibility and non-toxic nature.
4) It is used in microencapsulation techniques for wastewater treatment and probiotic delivery systems, enhancing the viability of encapsulated microorganisms.[15]

- **Guar Gum** (synonyms: Jaguar gum, Guar Flour and Decorpa)

Table IV.

Property	Details
Source	Guar gum is a polysaccharide derived from the seeds of the guar plant (*Cyamopsis tetragonolobus*), which belongs to the Leguminosae family. It is primarily produced from the endosperm of guar seeds.
Molecular Formula	$C_{10}H_{14}N_5Na_2O_{12}P_3$
State	Free-flowing powder
Color	Yellow-white

Solubility	When dissolved in water, it produces a mucilage with varying viscosity; nearly insoluble in 96% ethanol. Guar gum is soluble in both hot and cold water, forming a thick paste.
Melting Point	>220°C
Storage Temp.	25°C to 30°C[16]

- **Structure**

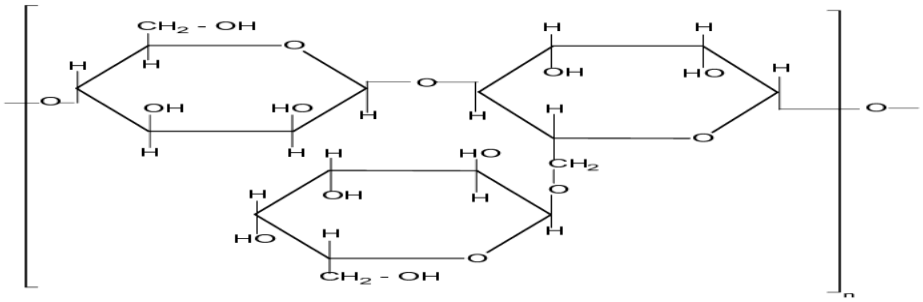

Fig. 4: Structure of Guar Gum.[17]

- **Applications**

1) Guar gum is employed as an emulsifying agent, bulk laxative, appetitite depressant, protective colloid, binding and dissolving agent, and in the treatment of peptic ulcers.
2) It is employed in the food and cosmetics industries as well as in the printing, polishing, paper, and textile industries.
3) Guar gum is widely utilized as a flocculant in water treatment and ore dressing.[18]

- **Agarose**

Table V.

Property	**Details**
Source	Agarose is a heteropolysaccharide primarily extracted from certain species of red algae, specifically from the genera *Gelidium* and *Gracilaria*.
Molecular Formula	$C_{10}H_{15}N_3O_3$
State	Suspension (75% in water)
Color	White to slightly cream
Solubility	Soluble in water
Melting Point	≤90°C (4% in water)
Boiling Point	100°C
Storage Temp.	2°C to 8°C[19]

- **Structure**

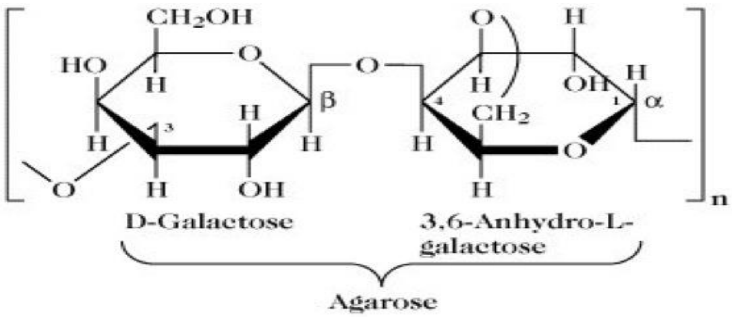

Fig. 5: Structure of Agarose.[20]

- **Applications**

1) Separation of DNA and RNA: Agarose gel electrophoresis is a common method for size-based nucleic acid separation. By generating an electric field that induces negatively charged DNA to flow across the gel matrix, it enables researchers to study DNA fragments, which generally range from 50 to 20,000 base pairs.
2) Protein Separation: Agarose is also used to separate proteins, particularly larger proteins, due to its relatively large pore size compared to other gels like polyacrylamide
3) Agarose plates can serve as a growth medium for various organisms, including autotrophic bacteria and cell lines. Its lower gelling temperature minimizes thermal shock during inoculation, making it suitable for sensitive cultures.
4) Agarose can function as a matrix in immunodiffusion assays, where it acts as an anchor for immunocomplexes, facilitating the study of antigen-antibody interaction.
5) Agarose beads are utilized in various chromatographic techniques such as affinity chromatography and gel filtration chromatography. These beads provide a stable medium for the purification of proteins and other biomolecules due to their high porosity and low non-specific binding properties.[21]

- **Xanthan Gum: (**Synonym: Xynthan gum).

Table VI.

Property	**Details**
Source	Xanthan is a microbial polymer derived from *Xanthomonas campestris*.
Molecular Formula	$C_8H_{14}C_{12}N_2O_2$
State	Solid
Color	Off white to pale yellow
Solubility	Water-soluble but nearly insoluble in organic solvents.

Melting Point	64.43°C
Storage Temp.	-20°C , under inert atmosphere[22]

- **Structure**

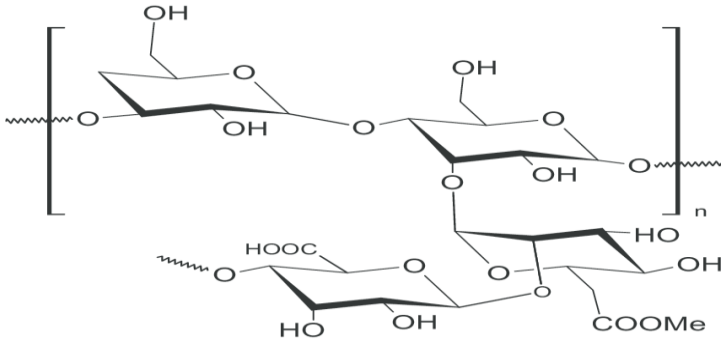

Fig. VI: Structure of Xanthan Gum.[23]

- **Applications**

1) It is frequently used in paints, emulsions, and herbicidal and agricultural sprays as a stabilizer and suspending agent.
2) The food and pharmaceutical sectors, among others, use them. The rheological behavior of xanthan in solution determines its specific usage.
3) When galactomannans like locust bean gum or guar gum are combined with xanthan, synergistic effects are seen in the meal.[24]

Synthetic Polymers: Chemically synthesized polymers such as.

- **Polyacrylic Acid (PAA)**: Known for its high swelling capacity and bioadhesive properties.

TABLE VII.

Property	**Details**
Source	Acrylic acid is the source of the synthetic polymer known as polyacrylic acid (PAA).
Molecular Formula	$C_5H_{10}O_2$
Color	White
Solubility	Soluble in water, ethanol, methanol, and dioxane.
Melting Point	95°C - 106^{0}C
Boiling Point	110^{0}C - 116°C
Storage Temp.	2°C to 80°C[25]

- **Structure**

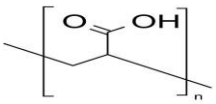

Fig. 7: Polyacrylic Acid (PAA).[26]

- **Application**

1) PAA is a primary component in superabsorbent polymers (SAPs), capable of absorbing and retaining large quantities of liquid, making it essential for disposable diapers and feminine hygiene products.
2) It is used in detergents as a dispersant to enhance cleaning efficiency by preventing dirt from redepositing onto surfaces.
3) It helps in softening water by binding calcium and magnesium ions, improving the effectiveness of cleaning products.
4) PAA's swelling behavior in response to pH changes makes it suitable for controlled drug release applications. It is used in hydrogels for oral, transdermal, and topical drug delivery.[27]

- **Polyethylene Glycol (PEG)**: Used in various formulations, with mucoadhesiveness increasing with molecular weight.

Table VIII.

Source	Petroleum is the main source of polyethylene glycol (PEG), made by polymerizing ethylene oxide and ethylene glycol.
Molecular Formula	$HO(C_2H_4O)$
Color	Clear colorless
Solubility	Soluble in water, acetonitrile, ethanol, toluene, dichloromethane, hexane, chloroform.
Melting Point	17-220°C
Boiling Point	>300°C
Storage Temp.	≤ -150°C[28]

- **Structure**

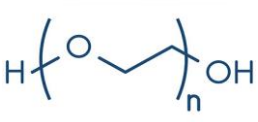

Fig. 8: Polyethylene Glycol.[29]

- **Applications**

1) They are non-toxic, PEGs are frequently utilized in tissue engineering, drug transport, biomedical research, bioconjugation and surface functionalization applications, as well as the food and cosmetics sectors.
2) PEGylation is the term used to describe the conjugation or non-covalent attachment of PEG polymer chains to molecules.
3) To increase the safety and effectiveness of treatments in targeted diagnostics and drug delivery, the PEGylation process can improve their water biocompatibility, solubility, stability, and pharmacokinetic characteristics.
4) PEG hydrogels are frequently utilized in tissue engineering, wound healing, regenerative medicine, cell culture scaffolds, and the controlled release of medications.[30]

- **Semi-synthetic Polymers**: Modified natural polymers that retain some natural characteristics while enhancing performance, such as
- **Hydroxypropyl Methylcellulose (HPMC)**: A cellulose derivative used for its thickening and mucoadhesive properties.

Table IX.

Property	**Details**
Sources	Cotton linters, wood pulp
Molecular Formula	C_3H_7O
State	Solid
Color	White to off-white powder
Solubility	Swells in water; insoluble in ethanol
Melting Point	225-230 °C
Storage Temperature	Room temperature[31]

- **Structure**

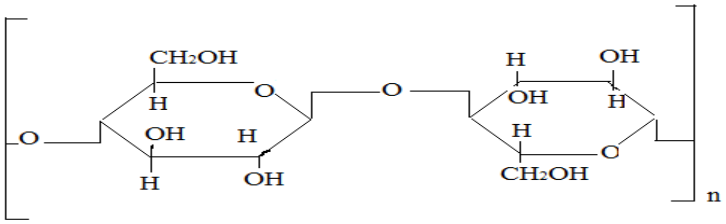

Fig. 9: Structure of Hydroxypropyl Methylcellulose (HPMC).[32]

- **Applications**

1) They are commonly employed as water retention agents, film formers, thickeners, and binders. They also serve as protective colloids, lubricants, emulsifiers, surfactants, and suspension aids. Additionally, these polymer solutions gel thermally.
2) Food industry: binder, non-caloric bulking agent in foods, emulsion and foam stabilizers, fat substitutes, and more.
3) Pharmaceutical industry: as a thickening and dispersion agent, for tablet film coating, for medication formulations, and more.

Hair shampoo, eye makeup, and skin care products are all part of the cosmetics sector.[33]

Novel Mucoadhesive Polymers

Lectins

Natural proteins called lectins are found in a wide variety of animals and are essential for biological recognition processes that include both cells and proteins. These proteins bind reversibly to particular carbohydrate residues and can have a variety of structural variations. Lectins can either remain on the cell surface or undergo endocytosis after attaching to mucosal cells. Through active cellular absorption, they can distribute macromolecular medicines in a controlled manner and enhance targeted attachment.[34] Three primary types of lectins can be distinguished based on their molecular structure:

Table X.

Type of Lectin	Description
Merolectins	Lectins that possess a single carbohydrate-recognizing domain.
Hololectins	Lectins that contain two or more carbohydrate-recognizing domains.
Chimerolectins	Lectins that have one or more carbohydrate-recognizing domains along with other, unrelated domains.(35)

This classification highlights the functional diversity of lectins in biological systems and their potential applications in drug delivery and other therapeutic contexts.

Thiolated Polymers

Hydrophilic macromolecules having free thiol functions integrated in their polymeric structure are known as thiomers, a specific class of multifunctional polymers that have been altered to incorporate thiol groups. These polymers have the potential to create disulfide

connections both within and between chains, which greatly improves the cohesiveness and stability of drug delivery systems, especially in matrix formulations. Thiomers have remarkable mucoadhesive qualities because they establish strong covalent interactions with mucus glycoproteins.[36]

Examples of Thiolated Polymers

- **Chitosan derivatives**
- Chitosan–iminothiolane
- Chitosan–thioglycolic acid.

- **Poly (acrylic acid) derivatives**
- Poly(acrylic acid)–cysteine
- Poly(acrylic acid)–homocysteine.[37]

Poloxomer

A hydrophobic length of polyoxypropylene (poly(propylene oxide)) in the middle is surrounded by two hydrophilic segments of polyoxyethylene (poly(ethylene oxide)) to form poloxymers, a family of nonionic triblock copolymers. Because of these special features, poloxamers can change phases at physiological temperatures from liquid to mucoadhesive gel states, which makes it easier for them to gel in-situ at specific body locations. Temperature, concentration, and the presence of different additives all affect poloxamers' capacity to form gels. They can improve the solubility and stability of medicinal substances, which makes them especially helpful in drug delivery systems. Poloxamers' low toxicity and biocompatibility make them widely used in a variety of applications, including as medicinal excipients.[38]

Table XI.

Poloxamer Type	Common Name	Molecular Weight	Physical Form	Applications
P188	F-68	~13,000	Liquid	Drug delivery, solubilizing agent
P237	F-87	~9,000	Liquid	Solubilizer for pharmaceuticals
P338	F-108	~14,600	Liquid	Used in hydrogels for drug delivery
P407	F-127	~12,600	Liquid	Commonly used in topical formulations[39]

Recent Developments

In comparison to conventional polymers, the production of novel mucoadhesive polymers, such as maleimide-functionalized carboxymethyl cellulose (CMC-MAL), has demonstrated encouraging outcomes in improving mucoadhesive qualities. Because of its strong adhesive properties, CMC-MAL can be used in transmucosal drug delivery systems3. These developments are especially important for nasal medication delivery since they can boost systemic absorption by avoiding first-pass metabolism.[40]

Evaluation of Mucoadhesive Polymers

Evaluation can be done by both In vivo and In Vitro tests.

Method	Type	Description
Tensile Strength	In Vitro	Measures the resistance of materials to being pulled apart, important for assessing the mechanical integrity of drug delivery systems.
Drug Release In Vitro	In Vitro	Evaluates how drugs are released from formulations using methods like dialysis bag and direct addition, crucial for understanding pharmacokinetics.
Viscometer	In Vitro	Used to measure the viscosity of solutions, influencing drug release rates and formulation stability.
Conductance of Electricity	In Vitro	Measures ionic strength and solubility of formulations, impacting stability and release profiles.
The Process of Falling Liquid Film	In Vitro	Analyzes the behavior of liquid films under gravity, relevant for understanding drug release mechanisms.
The Method of Colloidal Gold Coloring	In Vitro	Visualizes drug distribution within formulations, aiding in assessing localization and bioavailability.
The Thumb Method	In Vitro	A manual test for evaluating adhesion properties by applying thumb pressure to assess cohesiveness and integrity.
Adhesion Quantity and Swelling Characteristics	In Vitro	Assesses mucoadhesive properties and swelling ability of formulations, affecting drug release rates.
Studies on Stability	In Vitro	Evaluates how formulations maintain integrity over time under various conditions, assessing physical appearance and potency.
Use of Radio-Opaque Markers	In Vivo	Employed in imaging studies to track the movement and localization of drug formulations within biological systems.
Use of Gamma Scintigraphy	In Vivo	Visualizes distribution and kinetics of radiolabeled drugs in living organisms, providing insights into absorption and bioavailability.
X-Ray Studies	In Vivo	Investigates physical state and location of drug formulations post-administration, facilitating

		performance assessments.
Isolated Loop Technique	In Vivo	Uses segments of intestines in animal models to study localized drug absorption characteristics without systemic interference.
Use of Electron Paramagnetic Resonance (EPR)	In Vivo	Studies free radicals and paramagnetic species in vivo, providing insights into oxidative stress and molecular interactions involving drugs within biological systems.[41,42]

CONCLUSION

Mucoadhesive polymers are essential for extending the duration of effect by extending the drug's residence time on the mucosal membrane. Mucoadhesive polymers are also essential for improving the solubility and dissolving properties of medications that are not very soluble. The development of novel mucoadhesive polymers represents a significant advancement in drug delivery systems. By improving adhesion properties and biocompatibility, these polymers can enhance drug efficacy through prolonged residence time at target sites. Future research should continue to explore innovative formulations and the underlying mechanisms of mucoadhesion to optimize therapeutic outcomes across various routes of administration.

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