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Review on Mucoadhesive drug delivery system and natural polymers.

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ABSTRACT:
The main purpose of this review is to arrange the current literature with a main focus on role of natural polymer on mucoadhesive drug delivery system. Natural polymer basically are polysaccharides which are Biocompatible, non-toxic, stable and economical. When a biological substrate is in a mucosal layer then the phenomena known as muco-adhesion. Muco-adhesion refer to bond formed between a biological surface or a polymer surface. A polymer plays an major role as excipients designing dosage form that influenced drug release A natural polymers utilization of mucosal drug delivery innovative technique due to their ability to interact with mucosal layer of the body to improve effectiveness of the drug It's delivering a bioactive agent for a prolonged period of time at specific delivery site The polymer can exert and control over the rate and extent drug release which are selected in formulation of a mucoadhesive drug delivery system. In this review article there are several aspects discussed including mechanism of muco-adhesion, mucoadhesive polymer, application, advantage and disadvantages and further prospect in mucoadhesive drug delivery system has been discussed.

Keywords: natural polymer, excipients, dosage form, mucoadhesive polymer.

I. INTRODUCTION:

Muco-adhesion may be defined as a process by which the natural or synthetic polymers can adhere to a biological membrane for an extended period of time. The term polymer is derived from the Greek word, poly which means 'Many' and Meros means 'part or units of high molecular mass'. It is a large molecule mainly composed of repeating structural units. Which are typically connected by covalent chemical bonds. polymers prolong the residence time of the dosage form at the site of absorption and increases the therapeutic efficacy of the drug. the two basic types of polymers are Natural and synthetic. but the use of natural polymers in pharmaceutical formulation are superior because they are economic, safe, readily available, and non-toxic Characteristics of ideal Natural polymers, is that they are Non-irritant to mucosal membrane. And shows Good Spreadability, wetting, swelling, and biodegradable properties. Naturally occurring polymers produced by all living organisms such as plant and animals. Shows less adverse effects on the environment or human being. In opposite, synthetic polymers, being prepared by the help of chemicals have side effect on atmosphere as well as on the human being.

There are three basic types of polymers:

1. Natural Polymers: Originated from plant and animal source.
2. Synthetic Polymers: Synthesized in laboratory by simple polymerization or chemical reaction.
3. Semi synthetic: the polymers which are obtained from natural polymers by simple chemical reaction.

This review article helps us to understand the terminologies related to muco-adhesion, types of polymers used, importance and factors affecting natural polymers.

What is Mucoadhesion?

Understanding the term 'muco-adhesion':

Muco-adhesion specifically describes a phenomenon where natural and artificial substances can attach via their interfacial energetic some of the problems which the classic drug delivery systems face; like The first-pass metabolism and focus the active biomolecules such as Protein, peptide, and oligonucleotides, to only specific areas of the body. Using Mucoadhesion, many different drugs can be administered by different routes, such as:ocular, nasal, vaginal, and buccal, which will allow for extended regional or systemic therapeutic actions."

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Mechanism of Mucoadhesion :
The process of muco-adhesion is typically divided into two key sub-headings:

1.Contact stage
2.Consolidation stage
Contact Stage:

In the contact stage, the mucoadhesive material interacts with the mucoadhesive barrier. In this case, there is several advancements related to the spreading and swelling of the formulation, thus, enhancing the contact with the mucus layer.

In some cases, particularly ocular or vaginal formulations, the mucoadhesive system is applied onto the membrane. However, for deliveries like nasal delivery, the deposition is usually aided by the aerodynamics of the organ.

Consolidation stage:

This is also known as the second stage after the application of mucoadhesive. Here, moisture transfers are made to mucoadhesive materials, which cause them to be plasticized. With this,mucoadhesive molecules, once disengaged, are able to makeconnections, through weak bonds van der Waals bonds and hydrogen bonds. This stage is more accounted for based on two

Theories:
1.Diffusion Theory:

In this case, it is described that mucoadhesive molecules interpenetrates mucus glycoproteins and therefore, secondary bonds are created. Effective adhesion is describedto be otherwise based on the chemical and mechanical properties also of the mucoadhesive device in a case where promotion of chain interpenetration is not determined.

2.Dehydration Theory:

For polymeric materials which gell fast in aqueous environments, it is proposed that these polymeric materials can dehydrate the mucus due to osmotic pressure differences in cases where there are contact boundaries.

It is worth noting that these mechanisms in tandem enhance.The degree of mucoadhesion of any formulation to the mucosal surfaces.

ROUTES
Routes of administration for mucoadhesive drug delivery systems are multiple.
1.Oral drug delivery system.
2.Nasal drug delivery system.
3.Ocular drug delivery system.
4.Rectal drug delivery system.
5.Vaginal drug delivery system.

1.Oral Drug delivery system.

So far, oral drug administration has been the most commonly used route. In this context,membrane type systems based on mucous membranes stand out; theyinclude:
I.Sublingual Delivery: Absorption of general medications through the mucosal surface of the oral cavity.
II.Buccal Delivery: Instillation of drugs through the buccal mucosa (the lining of the cheeks).
iii.Local Delivery: Delivery of the drug into the mouth to be absorbed by the throat and the mouth's tissues.

2.Nasal drug delivery system.

"Nasal Mucoadhesive Drug Delivery Systems: Exploiting the potential of the Nasal Cavity. The human nasal cavity measures about 150 cm^2 in area and has certain unique features:

Advantages:
1.Highly vascularized tissue.
2.Composed of a highly porous membrane.
3.Rapid uptake.
4.Bypassing first pass hepatic metabolism

Identified as Challenges:
1.Local toxicity and irritation
2.Rapid mucociliary clearance (within five minutes)
3.Zymogen
4.Influence of disease conditions i.e. cold, allergy

In overcoming these challenges, potential for some mucoadhesive application i.e. liquids or semi solids or solids which has proven to improve retention time significantly to an extent however, Nasal delivery system of Protein and Peptide therapeutics is still susceptible because of the short period of time the aerated therapeutic agent remains at the surface of the mucosa.

3.Ocular drug delivery system.
Ocular Mucoadhesive Drug Delivery systems:

Preparing for Obstacles in Eye Medication
An eye's natural defence mechanisms (tear production, flow and blinks) also makes effective drug delivery quite difficult.

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There are limitations with using conventional methods:

Solutions and suspensions are rapidly removed from the cornea.Ointments change the refractive index of tears leading to blurred vision so as a solution to these problems, mucoadhesive technology is useful in increasing effectiveness by prolonging residence time.

Innovative Options:

1.Muco adhesive polymers in ophthalmic gels.
2.NyoGel (timolol, Novartis). 3.Pilogel (pilocarpine hydrochloride, Alcon Laboratories).

4.Rectal drug delivery system.

Mucoadhesive Rectal Dosage Forms: A Different Approach to Facilitated Pharmacokinetics and Greater Targeted Delivery."Rectum of the colon measures about 10 cm and possesses 3oo cm square area and its main functions are water reabsorption. Although contributing partially to the total surface area of the colon owing to absence of villi, the rectum enjoys certain benefits such as:

-Passive diffusion mechanism for the absorption of drugs that require lipid membrance penetrance Pumped through their membranes.
-Since most of the drugs are targeted near the anus, such drugs are subject to lowered first pass metabolic inactivity.
-Drugs which are usually prone to extensive first pass elimination may also be delivered with greater bioavailability.
-The bio-adhesive polymers would further improve the rectal delivery of the drugs by reducing the distance to be covered for the rectal dosage forms.

5.Vaginal drug delivery System.

"Vaginal Mucoadhesives as Targeted Pharmacological Delivery Mechanisms: Facilitated Pharmacokinetics, Enhanced Efficacy, Higher Level of Comfort." The vaginal cavity or the fibroelastic conduits which extends from the uterus to the outer wall of the body cavity presents other advantages in delivering therapeutics,however, there are certain factors that seem to pose as hurdles:

Tissue composition as:
-Structured stratified squamous fold and lamina materials
-Taking medications in the form of suspension, solution gel, creams, tablets and suppository have short duration of action as they have a relatively low retention time or a low persistent time.

There are other advantages to these limitations which biopharmaceutical adherence provides:

1.Deliberate release of drugs
2.Longer presence in the body
3.Increased potency
4.It is even possible that the vaginal mucosa-adhesive dosage forms:
5.Implant the active chemical compounds
6.Assist in moisturizing tissues to combat dryness of the vagina.

Advantages and Disadvantages of mucoadhesive Drug delivery system.

Advantages:

1.Increase the amount of time that the topical treatment is in contact with the target area.
2.It requires less effort in instilling and retrieving the dosage form.
3.It circumvents the initial hepatic metabolism.
4.The effectiveness of the buccal drug delivery system is far superior to that from other types of non-oral routes.
5.Good vascularity leads to quick absorption.
6.Improving the bioavailability of drugs by avoiding first pass metabolism.
7.Preventing acid dissolution in GIT.
8.Improve compliance among patients.

Disadvantages:

1.While the buccal drug delivery system is placed in the mouth, its permeability is much less than that of the sublingual membrane.
2.Medications taken by mouth do not get into circulation immediately after mucosa absorption.
3.Within the gastro intestinal tract, a drug will not have immediate effects.
4.Food does pose a risk for mucoadhesive drug absorption.
5.Some of the orally unstable drugs cannot be given owing to oral pH range stripping.
6.Only a few dosages can be administered.

Classification of natural polymers:

Based on source:
Polysaccharides:
Plant origin-
Examples: cellulose, Agar, pectin, Inulin, gaur gum,gum acacia, karaya gum, gum tragacanth.
Animal origin:
Examples: Chitin, Alginate, Psyllium,Xanthun gum.
Proteins:
Plant origin:
Examples: Wheat gluten, Soy protein.

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Animal origin:
Examples: Collagen, Gelatin

Classification of Natural Polymers:
Plant origin
Agar:
Source: It consists of dried gelatinous substance obtained from Gelidiumamansii.It is obtained from several other species of red algae like Gracilaria (Graciliariaceae) and pterocladia (Golidaceae).

Application:
1.Agar is used a gelling agent in many foods including baked goods, jellies, ice-cream, etc.
2.Agar is also used in bacteriological agar for medical research band Biotechnology such as bacteria culture and testing.

Starches:
Source: Consist of polysaccharides granules obtained from grains of maize (zeamaysl) Rice(OryzaSavita) or wheat (Triticum aestivum).

Application:
Starches is used in food, paper, pharmaceuticals, oil exploration, cosmetics and health products.

Inulin:
Source: Consist of natural polysaccharides obtained from bulbs of Dehlia, Inula Helenium (Compositae), roots of Dandelion, Taraxacum officinale Burdock root, Chicory roots.

Application: Inulin is used in pharmaceutical industry as a stabilizer, drug carrier, and auxiliary therapeutic agent. Inulin is also used in food industry as thickener.

Gaur gum:
Source:Gaur gum is a galactomannan polysaccharide extracted from the endosperm of seed of gaur plant (Cyamopsis tetragonoloba) which belongs to family Fabaceae.

Application:
The guar gum is widely used in cosmetics, industrial applications as thickener, stabilizer and emulsifier, food, etc.

Animal origin
Chitin:
Source:Chitin is a natural polysaccharide primarily derived from exoskeleton of arthropods and insectsas well as cell wall of fungi.

Application:
1.Chitin and its derivatives can be used to create biopesticides, enhancing plant growth andresistance to pests.
2Chitosan can be used to remove pollutants from waste water, including heavy metals anddyes due to its high adsorption capacity.

Xanthun gum:
Source: Xanthun Gum is derived from the fermentation process including Xanthomonas Campestris.It is produced through fermentation of sugars, such as those wheat, Soy and corn.

Application:
1.Xanthun Gum is used in variety of industries including food, agriculture, oil paint, andcosmetics.
2.It is used addition to a healthy diet,specially for those who are gluten- free.

Alginate:
Source: Alginate are extracted from brown seaweeds such as, Laminaria hyperborea, Laminariadigitata, and Macrocystis Pyrifera.

Application:
1.Alginate is used as food additives in many products.
2.Alginate hydrogels are used in wound healing because they retain structural similarity toextracellular matrices in tissues.

Proteins from Animal source:
Collagen:
Source:
Collagen are found in animal products such as Bone, skin and ligaments.It is also found in aloe vera, which can help in skin condition like wound and scars.
Application:
1.Collagen dressing can be designed to control the moisture of wound bed.
2.It also provides several benefits for acute and chronic wound closure.

Gelatin:
Source:
gelatin is a protein derived from animal skin bones and connective tissues.The main source of gelatin are pork skin and bovine hides

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Application:
1.Gelatin is a versatile material with many application in food , pharmaceuticals, cosmetics andpackaging.
2.It is also used in food products Baker,Dairy, meat and Beverages.

Proteins from Vegetal source:
Soy protein: Soy protein is a protein that is isolated form soybeanSources of soy protein are Tofu, Tempeh, Soy milk, soy protein isolate, Soy nuts, soy flour.
Application: It is used in many food products Bakery, meat, dairy, frozen desserts, Bioprinting.Soy protein used to replace milk powder non- dairy beverages and various forms of milkproducts.

Application of natural polymers:
1.The natural polymer in mucoadhesive polymer can help to improvethe contact between the nasal mucosa and drug.
2. It can also improve the drug bioavailability.
3. It's target specific sites in the gastrointestinal tract.
4. Natural polymers can also be used to deliver proteins and peptides.
5. Natural polymers are used as binders in tablets, increase solubility of poorly solubledrug.
6. It also used as film coating on drug to disguise their taste and enhance their stability.
7. Natural polymer or polysaccharides have an extensive variety of dietary supplement pharmaceutical excipients.
8. The application of Mucoadhesive polymer can increase permeation and enhance theabsorption of drug.
9. The natural polymer find in oral drug delivery system as they stabilize and protects the delivery of the drug.
10. Natural polymers used in Mucoadhesive drug delivery system are chitosan, Alginate, pectin, poly (acrylic acid), carboxy methyl cellulose, Hydroxyl propyl methyl cellulose, and Hydroxyl ethyl cellulose.
11. The biocompatibility of natural polymer example, allows for cells infiltration into the matrix and transfection can occurs as these cells come in contact with imbedded DNA.
12. By promoting sustainability and environment: soil remediation natural polymers for soil stabilization and contaminant removal.
13. Natural polymers have diverse application across various industries implantable devicepolylactic acid polyglycolic acid for biodegradable implants.

Advantages and disadvantages of natural polymer-

Advantages.	Disadvantage.
1.Inherently bioactive.	1. Difficult processing.
2.Less toxic.	2. Poor mechanical properties.
3.Biodegradable.	3. Rapid degradation.
4.Moisture retention.	4. Inflammatory response.
5.Low immune response.	5. Pathogen contamination.
6.Offers better cell attachment, growth, multiplication and differentiation.	6. Extraction process is complicated and required high cost.
7.Biocompatible.	7. More complex structurally.

Factors affecting natural polymer:
1. Physiological factors:
I) Mucin turns over.
II)Disease state.

2. Environment related factors:
I)PH of polymer - substrate interface
II)Applied strength
III)Initial contact time.

3.Natural polymer related factor:
I) Molecular weight

Physiological factors
Mucin turnover-
The natural process of mucin shedding, which is a key part of mucus, influences how long mucoadhesives can stay attached. Even if the adhesive is strong, it will eventually detach as new mucin is produced and old mucin is cleared away.

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While the presence of mucoadhesivesmight affect how this turnover happens, we don't yet know exactly how or if it changes the process. Extra mucin molecules floating around can sometimes attach to the adhesive before it even reaches the mucus layer, which makes it harder for the adhesive to stick properly. The rate at which mucin is replaced can be affected by things like eating. For example, in the stomach, mucin builds up when you're fasting and is released when acid is produced or when food is eaten. However, we still don't know exactly how fast this turnover process happens.

Disease state-

Natural polymers play a key role in medicine because they are biocompatible, biodegradable, and often mimic the body's own structures. This makes them very effective for treating and managing a variety of health conditions. These polymers come from natural sources like plants (such as cellulose and alginate), animals (like collagen and chitosan), and microorganisms. They are used in many medical applications, including tissue regeneration, drug delivery, and wound healing, by acting as scaffolds to support healing and help deliver treatments more effectively.

Environmental-related factors:
pH of polymer-substrate interface:

The pH of the environment can affect the charge on mucus and the charge on some polymers that bind to it. In fact, the amount of electrical charge carried by mucus depends on the pH since it modifies mucus and other interactions. Adapted from studies, for instance, we know that alters how polyacrylic acid polymers take in water. From acidic pH (around 4) to neutral pH (around 7). Becomes more hydrated, while the latter, at higher alkaline pH levels, becoming less hydrated. This occurs due to the pH influencing the swelling and water-binding capacity of the polymer.

Applied strength

Mucoadhesion is defined as the interaction between the adhesive polymer and the mucosal tissue, and the polymers type, applied pressure, and duration of applied pressure, are affecting factors. For polymers such as poly(acrylic acid/divinyl benzene) and Carbopol, the applied pressure enables deeper penetration into the mucosal layer, enhancing adhesion. The extent of this intermixing is entirely a function of the pressure applied and the time scale for which it is maintained. Applying enough pressure can also allow polymers that may not have native attractive interactions with mucin (the glycoprotein in mucus) to be adhesive via mechanical interlocking.

Initial contact time-

The amount of time a mucoadhesive stays in contact with the mucus layer plays a crucial role in its effectiveness. When the adhesive material remains in place longer, it has more time to absorb moisture and expand. This swelling allows it to penetrate deeper into the mucus layer, improving its grip. The longer the adhesive stays in contact, the stronger the bond becomes, making it stick more securely.

Natural polymer related factor
Molecular weight

The significance of the molecular weight of natural polymers is that it defines their strength, flexibility, and their interactions with the body. The molecular weight can be affected by various aspects, which include the source of the polymer or its extraction method. Additional aspects such as the average chain length of the polymer, the extent to which the chains are linked together (crosslinking), and the aging of the polymer can also change the properties of the polymer and its behavior in biological systems.

II. CONCLUSION:

The main purpose of this review is to understand the importance of mucoadhesive drug delivery system, theories related to it, different advantages and disadvantages. The polymers used in mucoadhesive drug delivery system and specially the role, classification, application and factors affecting the natural polymers. Based on the available literature, most studies point to mucoadhesive drug delivery systems as a promising alternative to traditional dosage forms. These systems help improve the bioavailability of poorly soluble drugs and can prevent the degradation in the gastrointestinal tract (GIT) as well as bypass the first-pass metabolism for certain medications.

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