RESEARCH PAPER

Mucoadhesive Agents From Natural And Synthetic Sources: A Review

Dhruba Sankar Goswami[1], Mrinmoy Basak*[2]

[1 & 2]Assam down town University, Sankar Madhab Path, Gandhi Nagar, Panikhaiti, Guwahati, Assam, India, 781026

*Corresponding Author: Dr. Mrinmoy Basak
*HOD and Dean of International Affairs Assam down town University Sankar Madhab Path, Gandhi Nagar, Panikhaiti, Guwahati, Assam, India, 781026 Email id- mrinmoybsk@gmail.com

ABSTRACT:
Substantial efforts have recently been focused on placing a drug or a delivery system in a particular region of the body for extended period of time. The need is not only for local targeting of drugs but also better control of systemic drug delivery. Hence bioadhesive polymers are used which attach to the various tissues or surface coating of the tissues. Mucoadhesive drug delivery systems utilize the property of certain hydrophilic polymer, which become adhesive on hydration and can be used for targeting a drug to a particular region of body for extended period of time. The mucosal layer lines a number of regions of the body including the G.I.tract, urogenital tract, in nose, eye, and ear. These represent potential sites for attachment of any bioadhesive system. The polymer systems maintain the release rate as well as the concentration in the biological system, characterize the adhesion through the appropriate biological membrane and any first-pass metabolic effects prior to entry of the drug into the systemic circulation Different studies have been carried out to find safe and suitable mucoadhesive agents. The present review describes synthetic mucoadhesive agents and natural mucoadhesive agents with their properties and mechanism of action, it will help in the selection of suitable mucoadhesive agents.

Keywords: Mucoadhesive drug delivery systems, Mucoadhesive agents, Natural, Synthetic

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INTRODUCTION:

The most important objective of the new drug delivery systems are it would be single dose, the duration of treatment, which releases the active ingredient over an extended period of time and, it should deliver the active entity directly to the site of action, thus minimizing or eliminating side effects [1]. Adhesion can be defined as the bond produced by contact between a pressure sensitive adhesive and a surface. The American Society of testing and materials has defined it as the state in which two surfaces are held together by interfacial forces, which may consist of valence forces, interlocking action or both [2].

Intimate contact between the interacting molecules that is the bioadhesive polymer and the membrane. Inter penetration of the polymer (bioadhesive) chains into the mucosa or inter digitations between the interacting species on a molecular level leads to formation of attractive repulsion interactions. Attractive interaction arises from vander wall's forces, electrostatic attraction, hydrogen bonding and hydrophobic interaction. Repulsive interactions occur because of electrostatic and steric repulsion. For mucoadhesion to occur the attractive interaction should be larger than the non-specific repulsion [3]. There are two broad classes of mucoadhesive polymers: hydrophilic polymer and hydrogels. In the large classes of hydrophilic polymers those containing carboxylic group exhibit the best mucoadhesive properties, poly vinyl pyrrolidone (PVP), Methyl cellulose (MC), Sodium carboxy methyl cellulose (SCMC) Hydroxy propyl cellulose (HPC) and other cellulose derivative. Hyrogels are the class of polymeric biomaterial that exhibit the basic characteristics of a hydrogels to swell by absorbing water interacting by means of adhesion with the mucus that covers epithelia [4]. With the disappointment in the merger of mucoadhesive systems into pharmaceuticals in the site specific drug delivery area, there has been an increasing interest from researchers in targeting regions of the GIT using more selective compounds capable of distinguishing between the types of cells found in different areas of the GIT. Loosely termed "cytoadhesion," this concept is specifically based on certain materials that can reversibly bind to cell surfaces in the GIT. These next generations of mucoadhesives function with greater specificity because they are based on receptor-ligand like interactions in which the molecules bind strongly and rapidly directly onto the mucosal cell surface rather than the mucus itself. One such class of compounds that has these unique requirements is called lectins. Lectins are proteins or glycoproteins and share the common ability to bind specifically and reversibly to carbohydrates. They exist in either soluble or cell associated forms and possess carbohydrate selective and recognizing parts. They are found mostly in plants, to a lesser extent in some vertebrates (referred to as endogenous lectins), and can also be produced from bacteria or invertebrates. Lectin based drug delivery systems have applicability in targeting epithelial cells, intestinal M cells, and enterocytes. The intestinal epithelial cells possess a cell surface composed of

*Author for Correspondence: mrinmoybsk@gmail.com

membrane-anchored glycoconjugates. It is these surfaces that could be targeted by lectins, thus enabling an intestinal delivery concept [5,6].

Mucoadhesive agents:
There is great interest among pharmaceutical scientist to develop chemical permeation enhancers, natural permeation enhancers and physical method that can increase percutaneous absorption of therapeutic agents [6].

Synthetic Mucoadhesive agents:
Cellulose derivatives, Poly (acrylic acid) polymers, Poly (hydroxyl ethyl methyl acrylate), Poly (ethylene oxide), Poly (vinyl pyrrolidone), Poly (vinyl alcohol) [7].

HPMC:
There are various types of natural polymer were used in preparation of mucoadhesive formulation. HPMC is one of the most popular biologically degradable, non-toxic & hydrophilic in nature. It is a controlled delivery component in oral formulations that serves as a drug-dispersing and viscosity-modifying agent. It is used a thickener, binder, film forming, and hydrophilic matrix material. The mucoadhesive property of HPMC were also performed in a ratio with sodium alginate and it was confirmed that formulations containing higher amount of HPMC had a good muco-adhesion property. The strong hydrogen bonding with mucin in mucus layer enhance to exhibit the muco-adhesion property of HPMC [8].

SCMC:
It is a carboxy methyl ether cellulose sodium salt, comprising 6.5–9.5% sodium. It is offered in three viscosity grades: low, medium, and high. It is also classified as a hydrogel and is commonly utilized in the manufacturing of oral sustained release tablets in conjunction with other non-ionic hydrogels. Formulation of mucoadhesive gel using various combination of mucoadhesive gel for the treatment of periodontitis and a concentration of 3% w/v of sodium carboxy methyl cellulose shows the highest amount of muco-adhesion strength [9].

SODIUM ALGINATE:
Brown algae (pheophyta) of the genera "Macrocystis, Laminaria, Ascophyllum, Alario, Ecklonia, Eisenia, Nercocystis, Sargassum, Cystoseira, and Fucus" are plentiful in alginic acid and its salts [Ca, Mg, Na, and K]. The most significant are Laminaria species known as kelps or sea tangles and Fucus specimens known as Wracks. However, two species, Macrocystis porifera and Ascophyllum nodosum, provide the majority of the world's alginates. It is biocompatible and bio adhesive in nature, makes it suitable candidate for Mucoadhesive drug delivery system. Alginate is an anionic mucoadhesive polymer with carboxyl end groups, and studies have shown that alginate has the highest mucoadhesive strength compared to polymers such as polystyrene, chitosan, and poly (lactic acid), because polyanion polymers are more effective bio adhesive than polycation polymers or non-ionic polymers. It has several uses in the food and pharmaceutical industries & has a wide range of pharmacological applications, from thickening agents to polymeric backbones in sustained release dosage forms [10].

EC:
For decades, EC has been widely employed in the pharmaceutical sector, where it is found in oral and topical medicinal formulations for a variety of reasons. Because of its hydrophobic nature and swelling capability, it has the potential to modify and improve the physiological performance of therapeutic dosage forms. The primary goal of EC utilisation is the development of drug dosage forms with modified release (MR), because EC ensures drug dissolution throughout the gastrointestinal tract, providing constant drug concentration and eliminating the need for multiple doses per day, thereby improving pharmacotherapeutic effectiveness. It is useful for constructing sustained-release preparations since it is an inert hydrophobic polymer with qualities such as lack of toxicity, stability during storage, and high compressibility. Bio adhesive polymers that do not disintegrate before releasing the integrated medicine are highly valued for long-term drug release. Because of its film-forming capability, low water permeability, drug impermeability, and moderate flexibility as a water-insoluble polymer, EC is frequently utilised as a backing membrane. It has bioadhesive characteristics, although not as strong as carbopol and chitosan [11,12].

Natural Mucoadhesive agents:
The polymers within this category are soluble in water. Matrices developed with these polymers swell when they come in contact an aqueous media with subsequent dissolution of the matrix. The polyelectrolytes widen greater mucoadhesive property such as. poloxamer, hydroxypropyl methyl cellulose, methyl cellulose, poly (vinyl alcohol) and poly (vinyl pyrrolidone), have been used for mucoadhesive properties. The natural polysaccharides and its derivatives like chitosan, methyl cellulose, hyaluronic acid, hydroxy propyl methylcellulose, hydroxy propyl cellulose, Xanthan gum, gellan gum, guar gum, and Carrageenan have been utilized in development of ocular drug delivery systems [13].

Locust Bean Gum-
Locust bean gum (LBG) (also known as carob gum) is obtained from the refined endosperm of seeds from the carob tree *Ceratonia siliqua* (family: Leguminosae). The polymer is neutral, slightly soluble in cold water

and requires heat to achieve full hydration, solubilisation, and maximum viscosity [14]. The gum contains D-galacto- Dmannoglycan, pentane, proteins, and cellulose. Super disintegrant property of this gum was studied by oral dispersible tablets containing locust bean gum and evaluating it against standard super disintegrant that is croscarmellose sodium [15]. This gum has also been investigated for its controlled delivery property [16] and also as a compression coat which when applied over core tablets acts as a suitable carrier for colonic drug delivery, as it proves capable of protecting the core tablet and thus is a potential carrier for drug targeting to the colon [17,18].

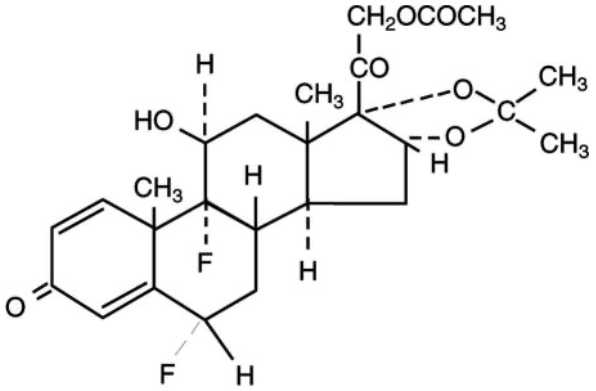
Gallan gum-

Gellan gum (GG) is an exopolysaccharide produced by the bacterium *Pseudomonas elodea*. [19] The backbone of GG is composed of a repeating unit of glucose, glucuronic acid, rhamnose in a ratio of 2:1:1. With abundant glucuronic acid units (20%), the native GG carries negative charges when dissolved in water. Due to biocompatibility and low toxicity, GG has been widely investigated in the fields of food and tissue engineering. The gelation of GG is temperature-dependent, showing that upon the increase of temperature a thermally-reversible coil to double helix transition process occurs and then during the cooling process the junction zones of GG are formed by aggregation of double helical molecules. The transition temperature has also been reported to increase at higher concentration of GG and affected by cations [20]. It is an exocellular polysaccharide secreted by *Pseudomonas elodea*. This gum had been investigated for pharmaceutical applications such as tablet disintegrant, binder, gelling agent and controlled release polymer [21]. Preparation of enteric coated dosage form by utilizing gellan gum, sodium alginate and hypromellose. The dosage form remined intact for about two hours in HCl (pH 1.2) but when placed in buffer (pH 6.8) it was ruptured. Thus, it was concluded that these natural polymers can be used in the formulation of delayed release dosage forms [22]. Preparation of matrix tablets of metronidazole using gellan gum in different concentrations and studied its release profile. It was concluded from the study that optimum concentration of gum (0.2%w/w) showed most effective as a disintegrant [23]. The use of gellan gum as a controlled release carrier in the formulation of gastro-floating matrix tablets was done [24]. In a study, an attempt to design bi-layer tablet of metoclopramide HCl and ibuprofen, the use of gellan gum as disintegrant was done [25]. Used of gellan gum in preparation of stomach-specific controlled release mucoadhesive drug delivery system. They employed amoxicillin trihydrate as model drug. The *in vitro* dissolution study showed that drug release upto 7 hrs in a controlled manner and following the Peppas model. From the results of both *in vitro* and *in vivo* mucoadhesivity study, it was revealed that gellan gum beads possess good mucoadhesivity even after 7 hrs [26]. Investigation of the suitability of gellan beads for the development of colon specific controlled drug delivery system. Gellan beads to deliver azathioprine were prepared as a potential colonic delivery system by ionotropic gelation and were coated with Eudragit S-100. Gum releases drug in controlled manner. Thus, it was suggested the use of gellan gum as a carrier for controlled colonic specific drug delivery systems [27].

Tragacanth-

Tragacanth is the air-hardened gummy exudate, flowing naturally or obtained by incision, from the trunk and branches of *Astragalus gummifer* labill. and certain other species of Astragalus. It is pale yellow, thin, flattened ribbons or brittle pieces; odourless and almost tasteless. On the addition of about 10 times its weight of water, it forms a mucilaginous gel. It should be stored in well-closed containers. [28] Based on solubility in water gums are classified as soluble, insoluble and partially soluble gums. Certain gums dissolve in water to form a transparent colloidal solution (e.g. Gum Arabic). Gums such as gum tragacanth, gum karaya do not dissolve in water but swell up into a jelly-like mass. However, if sufficient amount of water is added they yield a thick transparent solution. Partially soluble gums first form a swollen jelly by dispersing in water and become solution on addition of more water. [29] Tragacanth gum evaluated combination of polyvinyl lpyrrolidone K90 with gum tragacanth for sustained release by using diclofenac sodium as model drug. They carried out *in vitro* and *in vivo* release study. Both these studies showed that gum tragacanth could be used for sustain release of drug [30].

Acacia-



It is obtained from stems of tree *Acacia arabica*. It is water soluble and form viscous gel in water. In studies it was showed that gum acacia could be used as binder in tablets [31-32]. In combination with gelatin, gum acacia can be used as encapsulating agent in preparation of microspheres. Preparation of microspheres and microcapsules of tolnaftate by using gelatin-acacia coacervation method. Stability study of formulation was performed and found that the drug was stable in microspheres and microcapsules

formulation for about 6 months [33]. suggested the use of gum Arabic in preparation of oral controlled drug delivery. They prepared naproxen osmotic tablets. In their tablets they use gum arabic as osmotic agent. The effect of gum arabic on drug release was studied. The optimal formulation deliver drug by following zero order for 12 hrs [34].

Neem gum-

Neem tree (*Azadirachta indica*) is a tropical evergreen tree native to India and is also found in other southeast countries. In India, neem is known as "the village pharmacy" because of its healing versatility, and it has been used in Ayurvedic medicine for more than 4,000 years due to its medicinal properties. Neem is also called '*arista*' in Sanskrit- a word that means 'perfect, complete and imperishable'. The seeds bark and leaves contain compounds with proven anti-septic, anti-viral, anti-pyretic, anti-inflammatory, anti-ulcer and anti-fungal uses. The Sanskrit name '*nimba*' comes from the term '*nimbati syasthyamdadati*' which means 'to give good health'. It contains different components which have insect repellant, insecticide, anti-feedant, nematicide, spermicidal, anti-viral, anti-fungal and anti-microbial properties. It is also used in soaps, tooth paste and tooth powders. [35]. According to the study of *Azadirachta indica* fruit mucilage increases, the overall time of release of the drug from the matrix tablet also increases [36].

Moringa Gum-

Gum is obtained from exudes of stem of *Moringa oleifera* (family: *Moringaceae*). The gum is a polyuronide constituting of arabinose, galactose, and glucuronic acid in the preparation of 10 : 7 : 2, rhamnose present in traces [37, 38]. Studies were performed on this gum for its gelling property. The gelling concentration of the gum was found to lie between 7 and 8.5% w/v. The gels exhibited pseudoplastic flow and viscosity were found to be ideal for topical application [37], binding property [39], and release retardant property. Different batches of tablet were prepared and evaluated for drug release. It was observed that drug release increased with increasing proportions of the excipient and decreased proportion of the gum. Release mechanism was found to be Fickian [40]. Gum was also studied for its disintegrating property. Different batches of tablets were formulated varying them by quantity of the gum. It was observed that wetting time decreased with the increase in concentration of gum in formulation; thus disintegration time of tablet formulation prepared from gum was found lesser as compared to tablet formulation prepared from synthetic disintegrant like starch, sodium glycolate (SSG), and croscarmellose sodium (CCS) [41].

Fenugreek Mucilage

Mucilageis obtained from seeds of *Trigonella foenum-graceum* (family: *Leguminosae*).Its seeds contain a high percentage of mucilage and do not dissolve in water but form viscous tacky mass and swell up when exposed to fluids. Gum contains mannose, galactose, and xylose. The mucilage obtained from fenugreek was found to be better release retardant compared to hypromellose at equivalent content [42].

TABLE-1 List of Mucoahesive agents:

S. NO.	SYNTHETIC MUCOAHESIVE AGENTS	NATURAL MUCOAHESIVE AGENTS
1	HPMC[43,45,49,51,54,56,58,59,63,64,73,75,76,78,79,80,81,87]	GELATIN[47,82]
2	SCMC[43,46,52,54,55,56,57,72]	TRAGACANTH[71]
3	EC[43,50,58,60,89,91]	STARCH[71,78]
4	CARBOPOL[45,46,48,50,54,55,56,58,59,61,62,63,64,65 ,67,69,76,79,81,86,89,90,91]	CARRAGEENAN[71,92]
5	EUDRAGIT RS[45,87]	JUJUBE[73,74]
6	AC-DI-SOL[46]	BAEL[73,74]
7	SSG[46]	PEACOCK FLOWER[75]
8	PVP[44,47,52,76,88]	BABOOL[75]
9	HEC[47,54]	XANTHAN GUM[76,78,93]
10	SODIUM ALGINATE[49,50,51,67,75,80]	MORINGA GUM[77,78,92,93,94]
11	CAP[49]	MAIZE STARCH[84]
12	PVA[47,52]	HAKEA GUM[85,92,93,94]
13	PEG[44,60]	OKRA GUM[92,93,94]
14	CMC[62,65]	ALBIZIA GUM[92,93,94]
15	CYCLODEXTRIN[62]	TAMARIND GUM[92,93,94]
16	HPC[75,79,80,83]	LOCUST BEAN GUM[92,93,94]
17		FENUGREEK MUCILAGE[92,94]
18		HIBISCUS MUCILAGE[94]
19		HONEY LOCUST GUM[92,93,94]

20		TARA GUM[92,93,94]
21		ALMOND GUM[92,94]
22		NEEM GUM[92,93,94]
23		MANGO GUM[92,94]
24		GUM ACACIA[93]
25		GUM TRAGACANTH[93]
26		KARAYA GUM[93]
27		KHAYA GUM[92,93]
28		GUAR GUM[93]
29		GELLAN GUM[92,93]
30		CHITOSAN[53,60,66,68,70,71,78,80,81,86]

CONCLUSION:

Because natural gums are affordable, easily accessible, nontoxic, chemically modifiable, perhaps biodegradable, and, with rare exceptions, biocompatible, their use in medicinal applications is appealing.

Polysaccharides are the focus of the majority of research on natural polymers in drug delivery systems. Natural gums can also be altered to provide customized goods for medication administration systems, which enables them to rival the market's synthetic excipients. Newer gums, some of which have remarkable properties, have been employed even though traditional gums have remained popular. Newer gums and mucilages derived from plants offer a wealth of research opportunities and may one day be used as a novel natural polymer to develop various drug delivery systems for the pharmaceutical industry.

Natural polymers are crucial for the delivery of drugs. When choosing polymers, consideration must be given to their compatibility and toxicity. The purpose of this review was to investigate natural polymers that might work well as a replacement for synthetic ones.

Conflict of Interests

The authors declare that there is no conflict of interests
regarding the publication of this paper.

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