Review Article

Mucoadhesive microspheres: A novel approach to increase gastroretention

Abstract

The aim of this study is to review the advantages of mucoadhesive microspheres, mechanisms, and theories involved in mucoadhesion, factors that affect the mucoadhesion and polymers in mucoadhesive drug delivery systems. Gastroretentive drug delivery systems are those which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs. Mucoadhesion is a topic of current interest in the design of drug delivery systems. Mucoadhesion is currently explained by six theories: electronic, adsorption, wetting, mechanical, diffusion, and fracture. Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity, but coupling of bioadhesive properties to these microspheres has additional advantages such as prolong residence time of the dosage form at the site of absorption and intimate contact of the dosage form with the underline absorption surface contributed to improved therapeutic performance of the drug or improved bioavailability of drug, reduced dosing frequency, and improved patience compliance.

Key words:
Gastroretention, microspheres, mucoadhesion, mucoadhesive polymers

Introduction

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages. However, the problem frequently encountered with sustained release dosage forms is the inability to increase the residence time of the dosage form in the stomach and proximal portion of the small intestine. Therefore, it would be beneficial to develop sustained release formulations which remain at the absorption site for an extended period of time.[1] One of the feasible approaches for achieving prolonged and predictable drug delivery profile in gastrointestinal tract is to control gastric retention time of the formulation.[2] Dosage forms with prolonged gastric residence time, i.e., gastroretentive dosage forms, will offer new and important therapeutic options. Microspheres constitute an important part of this particulate drug delivery system by virtue of their small size and efficient carrier characteristics. However, the success of this novel drug delivery system is limited due to their short residence time at the site of absorption. It would therefore be advantageous to have means for providing an intimate contact of the drug delivery system with absorbing gastric mucosal membranes.[3,4] It can be achieved by coupling mucoadhesion characteristics to microspheres and developing novel delivery systems referred to as gastroretentive mucoadhesive microspheres.[5,6]

Gastro Retentive Drug Delivery System

The relatively short gastric emptying time in humans, which normally averages 2–3 hours through the major absorption zone (stomach or upper part of intestine), can result in incomplete drug release from the drug delivery system leading to diminished efficiency of the administered dose. Thus, localization of a drug delivery system in a specific region

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of the gastrointestinal tract offers numerous advantages, especially for drugs having narrow absorption window. The intimate contact of the dosage form with the absorbing membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption. These considerations have lead to the development of oral sustained release dosage forms possessing gastric retention potential. The primary concern in the development of once daily oral sustained release dosage form is not just to prolong the delivery of drugs for 24 hours but to prolong the presence of dosage forms in the stomach or somewhere in the upper small intestine. Gastroretentive dosage forms through local drug release will greatly enhance the pharmacotherapy of the stomach leading to high drug concentrations at the gastric mucosa, which are sustained over a long period of time. Gastroretentive dosage form can be used as potential delivery system for drugs with narrow absorption windows; these substances are taken up only from very specific sites of the gastrointestinal tract, often from the stomach and the proximal region of the intestine. Conventional sustained release dosage forms pass the absorption window although they still contain a large fraction of the drug which is consequently lost and not available for absorption.

Advantages of gastroretentive drug delivery systems

1. The bioavailability of therapeutic agents can be significantly enhanced
2. For drugs with relatively short half-life, sustained release may result in reduced frequency of dosing with improved patient compliance
3. They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time and the gastric emptying time
4. Gastroretentive drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence, they are useful in the treatment of disorders related to stomach and small intestine
5. The controlled, slow delivery of drug form gastroretentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces side effects
6. Gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects
7. Gastrointestinal side effects that are associated with high drug concentrations can be minimized by using gastroretentive dosage form[7]
8. The sustained mode of drug release from gastroretentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.

Disadvantages of gastroretentive drug delivery systems

1. Drugs such as aspirin breakdown into salicylic acid which also has the capability of damaging stomach lining and form ulceration, which can be dangerous
2. Drug such as ibuprofen can cause severe acidity and ulceration in case it sticks to gastric lining for longer time.

Approaches to gastroretentive drug delivery system:[8,9] [Figure 1]

1. High-density (sinking) systems
2. Low-density (floating) systems
3. Expandable systems
4. Superporous hydrogel systems
5. Mucoadhesive (bioadhesive) systems
6. Magnetic systems

Mucoadhesive (Bioadhesive) System

Several approaches have been immerged to prolong the residence time of the dosage forms at the absorption site and one of them is the development of oral controlled release bioadhesive system. In the early 1980s, Professor Joseph R. Robinson, at the University of Wisconsin, pioneered the concept of bioadhesion as a new strategy to prolong the residence time of various drugs on the ocular surface. Various gastrointestinal mucoadhesive dosage forms such as discs, microspheres, and tablets have been prepared and reported by several research groups. Bioadhesive drug delivery systems are used to enhance drug absorption in a site-specific manner.[10]

Adhesion can be defined as the bond produced by contact between a pressure-sensitive adhesive and a surface.[11] 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.[12]

Bioadhesion has been defined as the attachment of synthetic or biological macromolecules to a biological tissue.[10] The biological surface can be epithelial tissue or the mucous coat on the surface of a tissue. If adhesive attachment is to a mucous coat, the phenomenon is referred to as

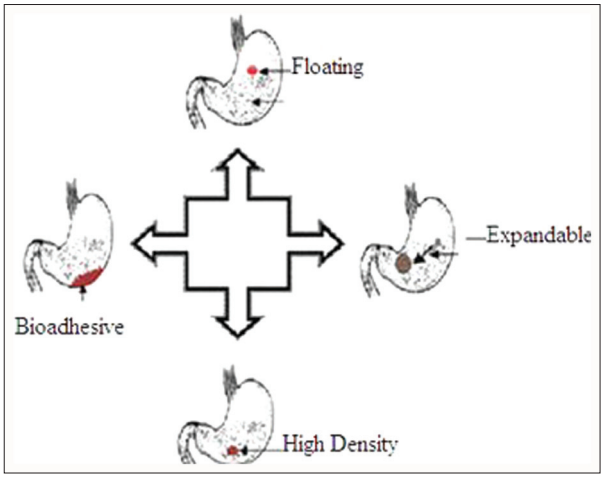

Figure 1: Approaches for gastroretention

mucoadhesion.[13] Mucus is a thin blanket covering all epithelia that are in contact with the external environment in the gastrointestinal, respiratory, and urogenital tracts. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach.[14] Adhesion of bioadhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration. This prolonged residence time can result in enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration.

Mechanisms of Mucoadhesion

The mechanism of adhesion of certain macromolecules to the surface of a mucous tissue is not well understood yet. The mucoadhesive must spread over the substrate to initiate close contact and increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a mucoadhesive to be successful, the attraction forces must dominate. Each step can be facilitated by the nature of the dosage form and how it is administered. For example, a partially hydrated polymer can be adsorbed by the substrate because of the attraction by the surface water.[15]

Thus, the mechanism of mucoadhesion is generally divided into two steps: the contact stage and the consolidation stage [Figure 2]. The first stage is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer.[16] In the consolidation step, the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak Vander Waals and hydrogen bonds.[17] There are two theories explaining the consolidation step: the diffusion theory and the dehydration theory.

Theories of Mucoadhesion

Several theories have been proposed to explain the fundamental mechanisms of adhesion.

Electronic theory

Electronic theory is based on the premise that both mucoadhesive and biological materials possess opposing electrical charges. Thus, when both materials come into contact, they transfer electrons leading to the building of a double electronic layer at the interface, where the attractive forces within this electronic double layer determine the mucoadhesive strength.[18]

Adsorption theory

According to the adsorption theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds resulting from these forces can be distinguished.

1. Primary chemical bonds of covalent nature, which are undesirable in bioadhesion because their high strength may result in permanent bonds
2. Secondary chemical bonds having many different forces of attraction, including electrostatic forces, Vander Waals forces, and hydrogen and hydrophobic bonds.

Wetting theory

The wetting theory applies to liquid systems that present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that lower the contact angle greater will be the affinity. The contact angle should be equal or close to zero to provide adequate spreadability [Figure 3].

The spreadability coefficient, S_{AB}, can be calculated from the difference between the surface energies γ_B and γ_A and the interfacial energy γ_{AB}, as indicated in equation 1.[17]

$$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB} \quad (1)$$

The greater the individual surface energy of mucus and device in relation to the interfacial energy, the greater the

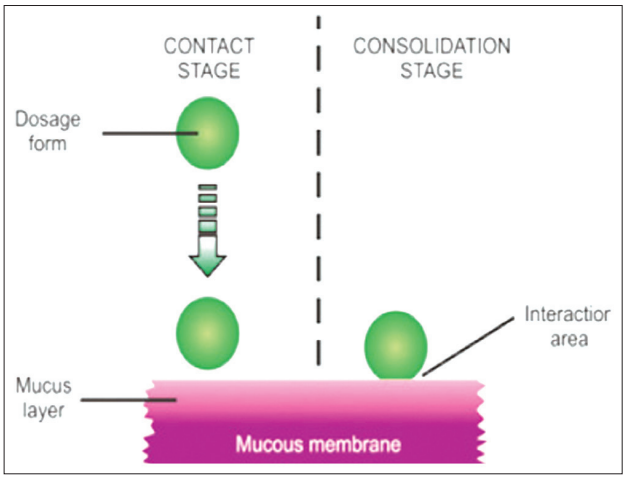

Figure 2: Mechanism of mucoadhesion

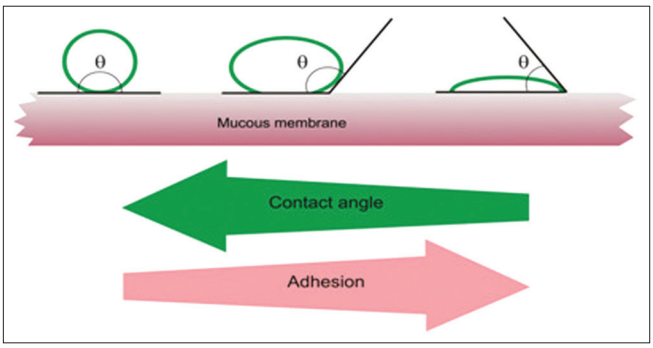

Figure 3: Schematic diagram showing influence of contact angle between device and mucous membrane on bioadhesion

adhesion work, W_A, i.e. the greater the energy needed to separate the two phases.

$$W_A = \gamma_B + \gamma_A - \gamma_{AB} \quad (2)$$

Mechanical theory

The mechanical theory assumes that adhesion arises from an interlocking of a liquid adhesive (on setting) into irregularities on a rough surface. However, rough surfaces also provide an increased surface area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are thought to be more important in the adhesion process than a mechanical effect.

Diffusion theory

According to diffusion theory, the polymer chains and the mucus mix to a sufficient depth to create a semi-permanent adhesive bond. The exact depth to which the polymer chains penetrate the mucus depends on the diffusion coefficient and the time of contact. This diffusion coefficient, in turn, depends on the value of molecular weight between cross-links and decreases significantly as the cross-linking density increases [Figure 4].

Fracture theory

Fracture theory attempts to relate the difficulty of separation of two surfaces after adhesion.[19] Fracture theory equivalent to adhesive strength is given by:

$$G = (E/L)\, l\, h$$

Where *E* is the Young's modulus of elasticity is the fracture energy and *L* is the critical crack length when two surfaces are separated [Figure 5].

Factors Affecting Mucoadhesion

Polymer-related factors

The adhesive bond between a bioadhesive system and mucin gel can be investigated in terms of contribution of the following factors:

1. Molecular weight: The optimum molecular weight for maximum mucoadhesion depends on the type of mucoadhesive polymer and tissue. The interpenetration of polymer molecules into the mucus layer is variable, for low-molecular weight polymers penetration is more than high-molecular weight polymers because entanglements are favored in high-molecular weight polymers.
2. Concentration of active polymer: For solid dosage forms such as tablets, the higher the concentration of polymer, the stronger the bioadhesion force while an optimum concentration is required for best bioadhesion in liquids.[6]
3. Spatial conformation: Bioadhesive force is also dependent on the conformation of polymers, i.e., helical or linear. The helical conformation of polymers may shield many active groups, primarily responsible for adhesion, thus reducing the mucoadhesive strength of the polymer.
4. Chain flexibility of polymer: Chain flexibility is important for interpenetration and enlargement. As water-soluble polymers become more and more cross-linked, the mobility of the individual polymer chain decreases, also as the cross-linking density increases, the effective length of the chain which can penetrate into mucus decrease even further and mucoadhesive strength is reduced.[20]
5. Degree of hydration: In this respect, many polymers will exhibit adhesive properties under conditions where the amount of water is limited. However, in such a situation, adhesion is thought to be a result of a combination of capillary attraction and osmotic forces between the dry polymer and the wet mucosal surface which act to dehydrate and strengthen the mucus layer. Although this kind of "sticking" has been referred to as mucoadhesion, it is important to clearly distinguish such processes from "wet-on-wet" adhesion in which swollen mucoadhesive polymers attach to mucosal surfaces. While hydration is essential for the relaxation and interpenetration of polymer chains, excess

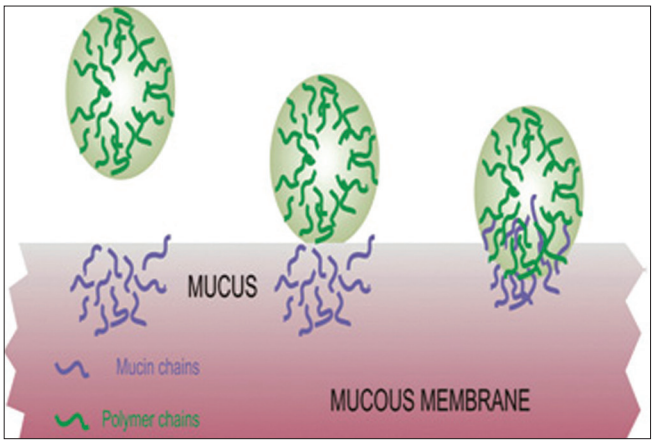

Figure 4: Secondary interactions resulting from interdiffusion of polymer chains of bioadhesive device and of mucus

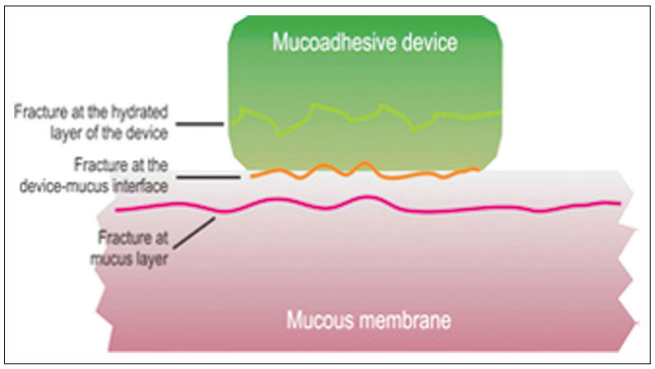

Figure 5: Regions where the mucoadhesive bond rupture can occur

hydration could lead to decreased mucoadhesion and/or retention due to the formation of slippery mucilage. In this situation, cross-linked polymers that only permit a certain degree of hydration may be advantageous for providing a prolonged mucoadhesive effect.

6. Functional group contribution: The attachment and bonding of bioadhesive polymers to biological substrates occur mainly through interpenetration followed by secondary noncovalent bonding between substrates. Given that secondary bonding mainly arises due to hydrogen bond formation, it is well accepted that mucoadhesive polymers possessing hydrophilic functional such as carboxyl (COOH), hydroxyl (OH), amide (NH_2), and sulfate groups (SO_4H) may be more favorable in formulating targeted drug delivery platforms. Typically, physical entanglements and secondary interactions (hydrogen bonds) contribute to the formation of a strengthened network; therefore polymers that exhibit a high density of available hydrogen bonding groups would be able to interact more strongly with mucin glycoproteins.

Environmental-related factors[21]

1. pH: pH influences the charge on the surface of both mucus and polymers. Mucus will have a different charge density depending on pH, because of difference in dissociation of functional groups on carbohydrate moiety and amino acids of the polypeptide backbone, which may affect adhesion[22]
2. Applied strength: To place a solid bioadhesive system, it is necessary to apply a defined strength. Whichever the polymer, may be the adhesion strength of those polymers increases with the increase in the applied strength
3. Initial contact time: The initial contact time between mucoadhesive and the mucus layer determines the extent of swelling and the interpenetration of polymer chains. The mucoadhesive strength increases as the initial contact time increases
4. Selection of the model substrate surface: The handling and treatment of biological substrates during the testing of mucoadhesive is an important factor, as physical and biological changes may occur in the mucus gels or tissues under the experimental conditions
5. Swelling: Swelling depends both on polymer concentration and on water presence. When swelling is too great, decrease in bioadhesion occurs; such phenomena must not occur too early, in order to exhibit to a sufficient action of the bioadhesive system.

Physiological variables

1. Mucins turnover: The natural turnover of mucins molecules from the mucus layer is important for at least two reasons. First, the mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layer. No matter how high the mucoadhesive strength is, mucoadhesives are detached from the surface due to mucin turnover. The turnover rate may be different in the presence of mucoadhesive. Second, mucin turnover results in substantial amount of soluble mucin molecules. These molecules interact with mucoadhesives before they have a chance to interact with mucus layer.[23]
2. Disease state: The physicochemical properties of the mucus are known to change during disease conditions such as common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial, and fungal infections of the female reproductive tract and inflammatory conditions of the eye. The exact structural changes taking place in mucus under these conditions are not clearly understood. If mucoadhesives are to be used in the diseased state, the mucoadhesive property needs to be evaluated under it.

Mucoadhesive microspheres

Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity, and coupling of bioadhesive properties to microspheres has additional advantages. These are characteristically free flowing powders consisting of proteins or natural and synthetic polymers, which are biodegradable in nature. Mucoadhesive microspheres include microparticles and microcapsules (having a core of the drug) and consisting either entirely of a bioadhesive polymer or having an outer coating of it. Microspheres are one of the particulate delivery systems used to achieve sustained or controlled drug release, improve bioavailability, stability, and target drug to specific sites. However, the success of these microspheres is limited owing to their short residence time at the site of absorption. It would therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes.[3,4] This can be achieved by coupling mucoadhesion characteristics to microspheres and developing mucoadhesive microspheres. Microspheres adhere to the gastrointestinal mucosa and release the drug for a prolonged period of time [Figure 6]. The slow but complete drug release in the stomach is expected to increase bioavailability of the drug as well as its complete utilization which may result in lower dose and gastrointestinal side effects. Thus, not only the dosing interval is prolonged but also the patience compliance is increased.

Advantages of mucoadhesive microspheres

- Readily localized in the region applied to improve and enhance the bioavailability of drugs
- Facilitate intimate contact of the formulation with the underlying absorption surface
- Prolong residence time of the dosage form at the site of application
- Sustained drug delivery
- Reduced frequency of dosing
- Reduced fluctuations of drug concentration.

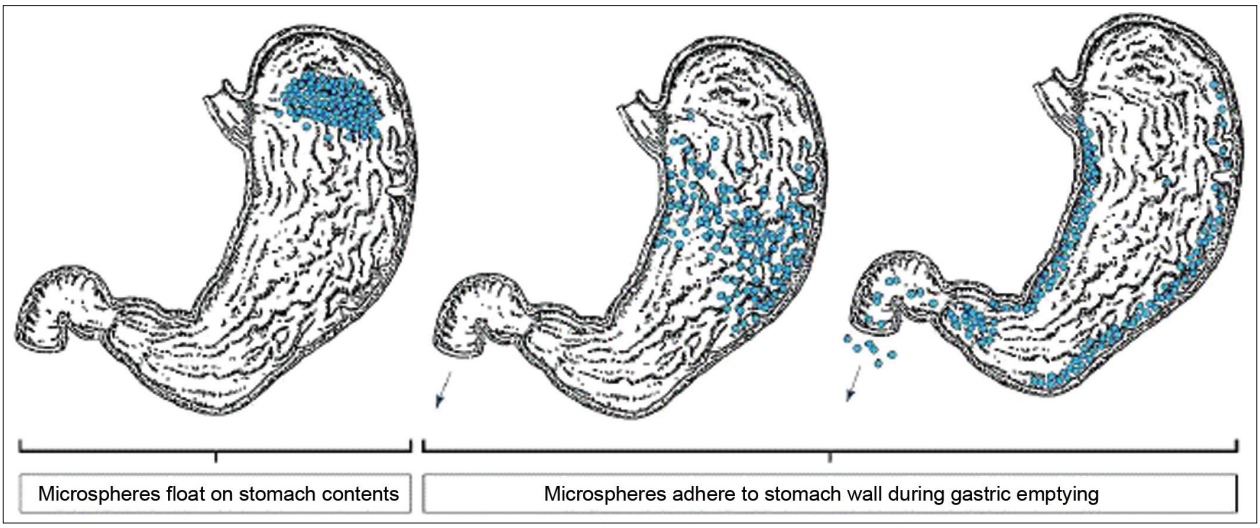

Figure 6: Proposed mechanism for retention of microspheres in the human stomach

Mucoadhesive polymers

The properties of the mucoadhesive microspheres, e.g., their surface characteristics, force of mucoadhesion, release pattern of the drug, and clearance, are influenced by the type of polymers used to prepare them. Suitable polymers that can be used to form mucoadhesive microspheres include soluble, insoluble, nonbiodegradable, and biodegradable polymers. Mucoadhesive polymers are water-soluble or water-insoluble polymers with swellable networks. The polymer should possess optimal polarity to make sure it is sufficiently wetted by the mucus and should have optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place.

Mucoadhesive polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad classes:

1. Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness
2. Polymers that adhere through nonspecific, noncovalent interactions those are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant)
3. Polymers that bind to specific receptor site on tile self-surface.

All three polymer types can be used for drug delivery. Different types of mucoadhesive polymers and mucoadhesive property of some mucoadhesive polymers are shown in Tables 1 and 2.

Characteristics of an ideal mucoadhesive polymer[24]

1. The polymer and its degradation products should be nontoxic and should be nonabsorbable from the gastrointestinal tract
2. It should be nonirritant to the mucus membrane
3. It should preferably form a strong noncovalent bond with the mucin epithelial cell surfaces

Table 1: Mucoadhesive polymers

Natural	Synthetic	Biocompatible	Biodegradable
Sod alginate Pectin Tragacanth Gelatin Carrageenan	Polyvinyl alcohol Polyamides polycarbonates, Polyalkylene glycols Polyvinyl ethers, Polymethacrylic acid, Polymethyl methacrylic acid Methylcellulose Ethylcellulose Hydroxypropyl cellulose Hydroxypropyl Methylcellulose Sodium carboxymethyl cellulose	Esters of haluronic acid, Polyvinyl acetate Ethylene glycol	Poly (lactides) Poly (glycolides) Poly (lactide-co-glycolides) Polycaprolactones Polyalkyl cyanoacrylates. Polyorthoesters Polyphosphoesters Polyanhydrides Polyphosphazenes Chitosan Polyethylene oxide

Table 2: Mucoadhesive properties of some polymers

Polymers	Mucoadhesive property
Carboxy methyl cellulose	+++
Carbopol	+++
Tragacanth	+++
Polyacrylic acid	+++
Sodium alginate	+++
Hydroxy ethyl cellulose	+++
Hydroxy propyl methyl cellulose	+++
Gelatin	++
Guar gum	++
Hydroxyl propyl cellulose	+
Thermally modified starch	+
Chitosan	+
Acacia	+
Polyethylene glycol	+

4. It should adhere quickly to most tissue and should possess some site specificity
5. It should allow easy incorporation of the drug and should offer no hindrance to its release
6. The polymers must not decompose on storage or during shelf life of the dosage form
7. The cost of polymer should not be high so that the prepared dosage form remains competitive.

Molecular characteristics[25]

Investigations into polymers with various molecular characteristics conducted by many authors have led to a number of conclusions regarding the molecular characteristics required for mucoadhesion.[26-29] The properties exhibited by a good mucoadhesive may be summarized as follows:[30,31]

1. Strong hydrogen bonding groups (-OH, -COOH)
2. Strong anionic charges
3. Sufficient flexibility to penetrate the mucus network or tissue crevices
4. Surface tension characteristics suitable for wetting mucosal tissue surface
5. High molecular weight.

Although an anionic nature is preferable for a good mucoadhesive, a range of nonionic molecules (e.g., cellulose derivatives) and some cationic (e.g., Chitosan) can be successfully used.

Classification of Polymers[32-36]

Hydrophilic polymers

These are the water-soluble polymers that swell indefinitely in contact with water and eventually undergo complete dissolution, e.g., methylcellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, sodium carboxy methyl cellulose, carbomers, chitosan, and plant gums.

Hydrogels

These are water-swellable materials, usually a cross-link polymer with limited swelling capacity, e.g., poly (acrylic acid co acrylamide) copolymers, carrageenan, sodium alginate, guar gum, and modified guar gum.

Thermoplastic polymers

These polymers include the nonerodible neutral polystyrene and semi-crystalline bioerodible polymers, which generate the carboxylic acid groups as they degrade, e.g., polyanhydrides and polylactic acid.

Various synthetic polymers used in mucoadhesive formulations include polyvinyl alcohol, polyamides, polycarponates, polyalkylene glycols, polyvinyl ethers, esters and halides, polymethacrylic acid, polymethylmethacrylic acid, methylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, and sodium carboxymethylcellulose.[37]

Various biocompatible polymers used in mucoadhesive formulations include cellulose-based polymers, ethylene glycol polymers and its copolymers, oxyethylene polymers, polyvinyl alcohol, polyvinyl acetate, and esters of haluronic acid.

Various biodegradable polymers used in mucoadhesive formulations are polylactides, polyglycolides, and polyalkyl cyanoacrylates.

Polyorthoesters, polyphosphoesters, polyanhydrides, and polyphosphazenes are the recent additions to the polymers.

Conclusion

To derive maximum therapeutic benefits from certain drug substances, it is desirable to prolong their gastric residence time. In addition, the delivery system should exhibit a burst followed by a sustained release of the active agent.[38] Various techniques and approaches have been used to develop gastroretentive drug delivery system.[39] Mucoadhesive drug delivery systems are gaining popularity day by day in the global pharma industry and a burning area of further research and development. Extensive research efforts throughout the world have resulted in significant advances in understanding the various aspects of mucoadhesion. There is no doubt that mucoadhesion has moved into a new area with these new specific targeting compounds (lectins, thiomers, etc.) with researchers and drug companies looking further into potential involvement of more smaller complex molecules, proteins and peptides, and DNA for future technological advancement in the ever-evolving drug delivery arena.

Mucoadhesive microspheres offer unique carrier system for many pharmaceuticals and can be tailored to adhere to any mucosal tissue, including those found in eyes, oral cavity, and throughout the respiratory, urinary, and gastrointestinal tract. The mucoadhesive microspheres can be used not only for controlled release but also for enhancing bioavailability, for targeted delivery of the drugs to specific sites in the body. Drug delivery through mucoadhesive microspheres is a promising area for continued research with the aim of achieving controlled release with enhanced bioavailability over longer periods of time and for drug targeting to various sites in the body.

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