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Review Article

Basics and Therapeutic Potential of Oral Mucoadhesive Microparticulate Drug Delivery Systems

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ABSTRACT
Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is biological are held together by means of interfacial forces, when the associated biological system is mucous, it is called mucoadhesion. This property of certain polymeric systems have got place in the drug delivery research in order to prolong contact time in the various mucosal route of drug administration as the ability to maintain a delivery system at a particular location for an extended period of time has a great appeal for both local disease treatment as well as systemic drug bioavailability. Considerable attention is focused on the development of controlled drug delivery systems, offering the advantages of better therapeutic efficacy and is easier to comply with than the conventional regimens requiring more frequent dosing. The objective of this paper is to establish the procedure to study polymer bioadhesion to understand structural requirement of bioadhesive in order to design improved bioadhesive polymer for oral use.

Key words: Mucoadhesion, drug delivery, bioadhesive systems

INTRODUCTION

The oral route of drug administration constitutes the most convenient and preferred means of drug delivery to systemic circulation body. However oral administration of most of the drugs in conventional dosage forms has short-term limitations due to their inability to restrain and localize the system at gastrointestinal tract. [1] In order to circumvent this problem, it has been proposed, successfully for several of them, to associate drugs to polymeric particulate systems because of their propensity to interact with the mucosal surface. [2] This is finally requires not only for the local targeting of drugs but also for a better control of systemic delivery. [3] Thus the real issue in the development of oral controlled release drug delivery systems is to provide drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time, through the predominantly controlled release profiles by special technological construction and design of the system itself. [4] The idea of using bioadhesive polymers to prolong the contact time in the mucosal route of drug delivery was introduced in early 1980s, and since then it has attracted considerable attention from pharmaceutical scientists. [5] The concept of mucoadhesive drug delivery is based on the bioadhesive property of certain polymers that becomes adhesive on hydration and hence can be used for localizing the drugs to a particular region of gastrointestinal tract and to extend the gastric residence time. Once the dosage form sticks to the mucosal surface of gastric tissue, it will reside there until removed by turnover of mucins. This is a simple and yet highly innovative concept. Soon after the idea of mucoadhesion was introduced, its utility to pharmaceutical systems was studied [6] and since then large number of investigators have been involved in exploring the fundamental aspects of mucoadhesion and potential application of mucoadhesive dosage forms.

Recent advances pertain to drug delivery systems incorporate different type of polymers within the matrix of drug delivery systems to protect the active ingredient and to induce slow release characteristics. [7] Mucoadhesives are the swellable or non-swellable, synthetic or natural polymers that interact with the mucosal layer covering the mucosal epithelial surface and mucin that prolong the residence time of dosage form at the site of absorption or application and facilitate the intimate contact of dosage form with the underlying absorption surface. [8-10] Mucoadhesive polymers are used in the design of oral sustained release tablets in order to prolong the residence time in the GI tract and their duration of drug action. [11-12]

Advantages of Mucoadhesive Systems

There has been considerable interest in the field of mucoadhesive drug delivery systems since the immobilization of drug carrying particles at mucosal surface would result in:

i. A prolonged residence time at the site of drug action or absorption. [13]

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ii. A localization of drug action of the delivery system at a given target site. [14-15]
iii. An increase in the drug concentration gradient due to the intense contact of particles with the mucosal. [14-15]
iv. A direct contact with intestinal cells that is the first step before particle absorption. [16]

Mechanism of Mucoadhesion

A complete understanding of how and why certain macromolecules attach to a mucus surface is not yet available, but a few steps involved in the process are generally accepted, at least for solid systems [17-18]:

i. Spreading, wetting and swelling of the dosage form at the mucus surface, initiates intimate contact between the polymer and mucus layer.
ii. Interdiffusion and interpenetration takes place between the chains of the mucoadhesive polymer and the mucus gel network, creating a greater area of contact (Fig. 1).
iii. Entanglements and secondary chemical bonds are formed between the polymer chain and mucin molecules (Fig. 2).

It has been stated that at least one of the following polymer characteristics are required to obtain adhesion [18] (a) sufficient number of hydrogen bonding chemical groups (- OH and –COOH) (b) anionic surface chain (c) high molecular weight (d) high chain flexibility (e) surface tension that will induce spreading into the mucus layer. Each of these characteristics favours the formation of bonds that are either chemical or mechanical origin. [19-20]

Table 1: Different theories explaining the mechanism of bioadhesion

S. No.	Theory	Mechanism of bioadhesion	Comments
1.	Electronic Theory	Attractive electrostatic forces between glycoproteins mucin network and the bioadhesive material	Electron transfer occurs between the two forming a double layer of electrical charge at the interface
2.	Adsorption Theory	Surface forces resulting in the semi-permanent physical / chemical bonding	*Strong primary forces:* covalent bonds *Weak secondary forces:* ionic bonds, hydrogen bonds and van der Waals forces
3.	Wetting Theory	Ability of bioadhesive polymer to spread and develop intimate contact with the mucus membranes	Spreading coefficient of polymers must be positive & Contact angle between the polymer and cells must be near to zero
4.	Diffusion Theory	Physical entanglement of mucin strands at the flexible polymer chain & Interpenetration of mucin strands into the porous structure of the polymer substrate	For maximum diffusion and best bioadhesive strength: solubility parameters (δ) of the bioadhesive polymer and the mucus glycoproteins must be similar
5.	Fracture Theory	Analyses the maximum tensile strength developed during detachment of bioadhesive drug delivery systems from the mucosal surface	Does not require physical entanglement of bioadhesive polymer chains and mucin strands, hence appropriate to study the bioadhesion of hard polymers which lacks flexible chains

Mucus Layer

The potential sites for application of mucoadhesives include the Eye, nose, oral cavity, respiratory tract, gastrointestinal tract, and female reproductive tract, all of which are lined by the mucus layer. The Mucus is a translucent and viscid secretion, which forms a thin, continuous gel blanket adherent to the mucus epithelial surface. The major constituents of mucus are high molecular weight glycoproteins capable of forming slimy, viscoelastic gels containing more than 95 % water. [21-22] The molecular weight of glycoproteins varies from 2×10^6 daltons to 14×10^6 daltons. Typically, N-acetylgucosamine, N-acetylgalactosamine, Galactose, etc are found in mucin molecules. The mean thickness of this layer varies from above 50-450 μm in humans. Mucus contains some non-mucin fractions, which aid in its protective function: lipids, and covalently bound fatty acids are also frequently found in the mucus layer. The mucus layer, which covers the epithelial surface, has various roles like protective, barrier, adhesion and lubrication role. [20, 23]

Mucins can be classified broadly into two classes: (a) Membrane bound mucin (b) Secretory forms of mucin. Membrane bound mucins possess a hydrophobic membrane spanning domain and are attached to cell surfaces and plays important roles by modulating immune response, inflammation, tumourogenesis. The Secretory forms of mucins are secreted from both mucosal adsorptive epithelial cells and specialized goblet cells. Mucus acts as free radical scavenger partly because of its ability to bind lipids.

Theories of Mucoadhesion

A complete and comprehensive theory that can predict adhesion based on the chemical and/or physical nature of a polymer is not yet available. Five theories of adhesion that were originally developed to explain the performance of such diverse materials such as glues, adhesives, and paints, have been adopted to study the mucoadhesion. [17, 20, 24]

i. **Electronic Theory:** The electronic theory assumes that a double layer of electronic charge is formed at the interface as a result of different electronic characteristics of the mucoadhesive polymer and the mucus, and that attractive forces develop from the electron transfer across the electrical double layer. This system analogous to a capacitor: the system is charged when the adhesive and substrates are in contact and discharged when they are separated. [25]
ii. **Adsorption Theory:** Adsorption theory states that a mucoadhesive polymer adheres to mucus because of the van der Waals interactions, hydrogen bonds, electrostatic attraction, hydrophobic interactions, or other related forces. [7, 26]

iii. Wetting Theory: The wetting theory emphasize the intimate contact between the mucoadhesive polymer and the mucus, and, primarily in liquid systems, it uses interfacial tension to predict spreading and subsequent adhesion. The spreading coefficient should be positive in order to adhere to a biological membrane. It was found that interfacial tension was proportional to $X^{1/2}$, where 'X' is the Flory polymer-polymer interaction parameter. Low values of this parameter correspond to structural similarities between polymers and an increased miscibility. [7, 27]

iv. Diffusion Theory: The diffusion theory states that the chains of mucoadhesive polymer and mucin interpenetrate to a sufficient depth (in the range of 0.2 to 0.5 μm) to create a semi-permanent bond through entanglement. The interpenetration is governed by diffusion coefficients and contact time, which are in turn dependent on the molecular weights, and flexibility of the chains. The probable penetration depth (L) can be estimated by the formula, $L = \sqrt{(tD_b)}$, where't' is the time of contact, and D_b is the diffusion coefficient of the bioadhesive material in mucus. [7]

v. Fracture Theory: The fracture theory analyzes the force that is required for the separation of two surfaces after adhesion. It is considered to be appropriate for the calculation of fracture strengths of the adhesive bonds involving rigid mucoadhesive materials [20], and has frequently been applied to the analysis of tensile strength measurements on, for example, microspheres [28] and powder specimens. [29] The maximum tensile strength produced during detachment can be determined by deviding the maximum force of detachment (F_m) by the total surface area (A_m) involved in the adhesion interactions. The equation can be written as:

$$S_m = F_m / A_m$$

These general theories are not particularly useful in establishing a mechanistic base to bioadhesives, but they do identify the variables that are important to the bioadhesion process. [30] Different theories explaining the mechanism of mucoadhesion are summarized in the Table. 1.

Factors Affecting Mucoadhesion

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

a. **Molecular Weight:** The optimum molecular weight for maximum mucoadhesion depends upon the type of mucoadhesive polymer and tissue. Numerous studies have identified that there is a certain molecular weight at which bioadhesive is at a maximum. The interpenetration of polymer molecules is favorable for low molecular weight polymers whereas entanglements are favors for high molecular weight polymers. The optimum molecular weight for the maximum bioadhesion depends on the type of polymer. [11, 23] According to Gurny *et al.,* (1984) it seems that the bioadhesive forces increases with the molecular weight of bioadhesive polymer up to 100,000 and that beyond this level there is not much effect.

b. **Flexibility of polymer chains:** Flexibility is important for interpenetration and entanglement. As water-soluble polymer becomes cross-linked, the mobility of the individual polymer chain decreases. As the cross linking density increases the effective length of the chain, which can penetrate into mucus layer, decreases even further and mucoadhesive strength is decreased. [23, 31]

c. **Spatial conformation:** Despite a high molecular weight of 19,500,000 for dextrans, spatial conformation of a molecule is also important. They have adhesive strength similar to that of polyethyleneglycol, which has a molecular weight of 200,000. The helical conformation of electrons may shield many adhesively active groups, primarily responsible for adhesion unlike PEG polymers that have a linear conformation. Also the effect of polymer concentration is dependable on the physical state (solid / liquid) of the bioadhesive drug delivery systems; more is the polymer concentration results the higher bioadhesive strength in Solid BDDS while an optimum concentration is required for best bioadhesion in liquids. [32]

Environment related Factors

a. **pH:** The hydrogen ion concentration can influence charge on the surface of mucus as well as certain ionizable mucoadhesive polymers. Mucus will have a different charge density depending on pH because of differences in dissociation of functional groups on the carbohydrate moiety and amino acids of polypeptide backbone. Some studies have shown that the pH of the medium is important for the degree of hydration of cross linked polyacrylic acid showing consistently increased hydration from pH 4 through pH 7, and then a decrease as alkalinity and ionic strength increases. For example polycarbophil shows maximum adhesive strength at pH 3 and gradually decreases as the pH increases up to 5. It does not show any mucoadhesive property above pH 5. [23, 31]

b. **Applied strength:** To place a solid bioadhesive system, it is necessary to apply a defined strength. The adhesive strength increases with the applied strength or with the density of its application up to an optimum. The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a satisfactory longer period of time polymers become mucoadhesive even though they do not have attractive interaction with mucins. [2, 31]

c. **Initial contact time:** The initial contact time between mucoadhesive and the mucus layer determines the extent of swelling and the interpenetration of polymer chains. Although with the initial pressure the initial contact time can dramatically affect the performance of a system the mucoadhesive strength increases as the initial contact time increases. [31]

d. **Secretion of the model substrate surface:** Since physical and biological changes may occur in the mucus gels on tissues under experimental conditions, the variability of biological substrate should be confirmed by examining properties like permeability, electro physiology, or histology etc. Such studies may be

necessary before and after preparing the in vitro tests using tissues for the better *in vitro / in vivo* correlation. [23, 32]

e. **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. [23, 31]

Physiological Variables:

a. **Mucins Turnover:** The natural turnover of mucins molecules from the mucus layer is important for at least two reasons. First, the mucins 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. [33-35] Mucins turnover may depend on the other factors such as presence of blood. Lehr *et al.* (1991) calculated mucins turnover time of 47-270 minutes. [33] The ciliated cells in the nasal cavity are known to transport the mucus to the throat at a rate of 5mm/min. the mucociliary clearance in the tracheal region has been found to be in the range of 4-10mm/min. [23, 31, 34-35]

b. **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. [23, 31]

Table 2: Comparison of the various processes used for the preparation of bioadhesive microcarriers

S. No.	*Process used*	*Polymers*	*Comment*
1.	Solvent evaporation:	Relatively stable polymers, for examples, polyesters, polystyrene etc.	Liable polymers may degrade during the fabrication process due to the presence of water, heat and other solvent system for prolonged time.
2.	Hot melt microencapsulation:	Water liable polymers, e.g. polyanhydrides and polyesters etc. with a molecular weight 1000 to 5000.	Smooth and dense external surface of microspheres. Heat liable drugs may not be entrapped.
3.	Solvent removal:	High melting point polymers especially polyanhydrides.	Avoids use of water, usually organic solvents are used. Exclusively small spheres are producible.
4.	Spray drying:	---	Primarily for the microspheres used for the intestinal imaging.
5.	Ionic gelation and size extrusion:	Chitosan, CMC, alginates, starches, and other polymeric blends.	Involves the all-aqueous system, used for the encapsulation of live cells, and other bioactive biological materials. Involves low polymer loss and low drug loss during fabrication process.
6.	Phase inversion:	Mostly polyanhydrides.	---

General Properties of Mucoadhesive Microcarriers

Mucoadhesive microcarriers (microspheres, microbeads, microcapsules etc) can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary and gastrointestinal tract, thus offering the possibility of localized as well as systemic control release of drug application of mucoadhesive microsphere to the mucosal tissues of ocular cavity, gastric and colonic epithelium is used for administration of drug for localized action. Prolonged release of drug and a reduction in frequency of drug administration to the ocular cavity can highly improve the patient compliance. [30] The latter advantage can also be obtained for drugs administered intranasally due to reduction in mucociliary clearance of drug adhering to nasal mucosa. [36-37] Microsphere prepared with mucoadhesive and bioerodable polymers undergo selective uptake by the M cells of peyer's patches in gastrointestinal mucosa. This uptake mechanism has been used for the delivery of protein and peptide drug, antigens for vaccination and plasmid DNA for gene therapy. Moreover the carrier helps in keeping the drug in close proximity to their absorption window in the GI mucosa. [9, 32, 38]

Choice of polymer used for preparation of mucoadhesive microcarriers

The properties of mucoadhesive microcarriers (microspheres, microbeads, microcapsules etc.), e.g. their surface characteristics, force of mucoadhesion, release pattern of drug and clearance, are influenced by the type of polymer used to prepare them. Suitably polymers that can be used to form mucoadhesive microsphere include soluble or insoluble, non-biodegradable and biodegradable polymers. These can be hydrogels or thermoplastics, homopolymers, copolymers or blend, natural or synthetic polymers. [9, 32]

General Preparation Methods of Mucoadhesive Microsphers

Mucoadhesive microsphere can be prepared using different techniques like solvent evaporation method, hot melt microencapsulation, solvent removal technique, hydrogel microsphere technique, spray drying technique, phase inversion technique etc. [9, 32, 38] A comparison of various processes used for the preparation of bioadhesive microspheres is presented in Table 2.

CONCLUSION

In conclusion, the concept of mucoadhesive drug delivery is to scope the property of mucoadhesion of certain polymers with the sustained release delivery systems in order to circumvent the problem of inability of oral formulations to restrain and localize at the site of absorption in gastrointestinal tract. They offer advantage of enhanced bioavailability of drugs entrapped in, and to localize them at absorption window for longer period of time.

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