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Mucoadhesive Drug Delivery Systems

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ABSTRACT

Mucoadhesion in drug delivery systems has recently gained interest among pharmaceutical scientists as a means of promoting dosage form residence time as well as improving intimacy of contact with various absorptive membranes of the biological system. Besides acting as platforms for sustained-release dosage forms, bioadhesive polymers can themselves exert some control over the rate and amount of drug release, and thus contribute to the therapeutic advantage of such systems. This paper describes some aspects of bioadhesion such as mucus layer, mucoadhesion, and theories of bioadhesion to explain the adhesion mechanism. The factors important to mucoadhesion, the methods used to study bioadhesion, and bioadhesive polymers are described. The methods that evaluate the mucoadhesive dosage forms and finally the bioadhesive drug delivery systems designed for several therapeutic purposes are presented.

Extensive efforts have recently been focused on targeting a drug or drug delivery system in a particular region of the body for extended period of time, not only for local targeting of drugs but also for the better control of systemic drug delivery. The concept of mucosal adhesives, or mucoadhesives, was introduced into the controlled drug delivery area in the early 1980s. Mucoadhesives are synthetic or natural polymers which interact with the mucus layer covering the mucosal epithelial surface and mucin molecules constituting a major part of mucus. The concept of mucoadhesives has alerted many investigators to be possibility that these polymers can be used to overcome physiological barriers in long-term drug delivery. They render the treatment more effective and safe, not only for topical disorders but also for systemic problems.

CONCEPTS

Adhesion can be defined as the bond produced by contact between a pressure-sensitive adhesive and a surface (1). The American Society of Testing and Materials (2) 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.

Good (3) defined *bioadhesion* as the state in which two materials, at least one biological in nature, are held

together for an extended period of time by interfacial forces. It is also defined as the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time (4,5). In biological systems, four types of bioadhesion can be distinguished (6):

1. Adhesion of a normal cell on another normal cell
2. Adhesion of a cell with a foreign substance
3. Adhesion of a normal cell to a pathological cell
4. Adhesion of an adhesive to a biological substrate

For drug delivery purposes, the term *bioadhesion* implies attachment of a drug carrier system to a specified biological location. The biological surface can be epithelial tissue or it can be the mucus coat on the surface of a tissue. If adhesive attachment is to a mucous coat, the phenomenon is referred to as *mucoadhesion*. Mucoadhesion can be modeled after the adherence of mucus on epithelial tissue (7). Leung and Robinson (8) described mucoadhesion as the interaction between a mucin surface and a synthetic or natural polymer.

A *bioadhesive* is defined as a substance that is capable of interacting with biological materials and being retained on them or holding them together for extended periods of time (9).

Bioadhesives are classified into three types based on phenomenological observation, rather than on the mechanisms of bioadhesion (9).

- *Type I*: Bioadhesion is characterized by adhesion occurring between biological objects without involvement of artificial materials. Cell fusion and cell aggregation (10) are good examples.
- *Type II*: Bioadhesion can be represented by cell adhesion onto culture dishes or adhesion to a variety of substances including metals, woods, and other synthetic materials.
- *Type III*: Bioadhesion can be described as adhesion of artificial substances to biological substrates such as adhesion of polymers to skin or other soft tissues.

The goal of the development of bioadhesive is to duplicate, mimic, or improve biological adhesives. They should be both durable where required and degradable where necessary, and not toxic at all.

Mucoadhesive drug delivery systems utilize the property of bioadhesion of certain water-soluble polymers which become adhesive on hydration (12) and hence can be used for targeting a drug to a particular region of the body for extended periods of time (13).

The mucosal layer lines a number of regions of the body including the gastrointestinal tract, the urogenital tract, the airways, the ear, nose, and eye. These represent potential sites for attachment of any bioadhesive system and, hence, the mucoadhesive drug delivery system may include the following:

1. Buccal delivery system
2. Sublingual delivery system
3. Vaginal delivery system
4. Rectal delivery system
5. Nasal delivery system
6. Ocular delivery system
7. Gastrointestinal delivery system

USE OF MUCOSAL ADHESIVE PREPARATIONS

The idea of mucoadhesives was derived from the need to localize drugs at a certain site in the body. Often the extent of drug absorption is limited by the residence time of the drug at the absorption site. For example, in ocular drug delivery, less than 2 min are available for drug absorption after instillation of a drug solution into the eye, since it is removed rapidly by solution drainage; hence the ability to extend contact time of an ocular drug delivery system in front of the eye would undoubtedly improve drug bioavailability. In oral drug delivery, the drug absorption is limited by the gastrointestinal (GI) transit time of the dosage form. Since many drugs are absorbed only from the upper small intestine, localizing oral drug delivery systems in the stomach or in the duodenum would significantly improve the extent of drug absorption.

Since most of the routes of drug administration, such as ocular, nasal, buccal, respiratory, gastrointestinal, rectal, and vaginal routes, are coated with the mucus layer, mucoadhesives are expected to increase the residence time. In addition, they provide intimate contact between a dosage form and the absorbing tissue, which may result in high drug concentration in a local area and hence high drug flux through the absorbing tissue. Furthermore, the intimate contact may increase the total permeability of high molecular weight drugs such as peptides and proteins.

MUCUS LAYER

The tissue layer responsible for formation of the adhesive interface is mucus. Mucus is a translucent and

viscid secretion which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. The mean thickness of this layer varies from about 50 to 450 μm in humans (13).

The composition of mucus varies widely depending an animal species, anatomical location, and the normal or pathological state of the organism (14). It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells acini. The lubrication properties of mucus secretions are a result of their viscous and gel-forming properties, and general stickiness (1). Mucus has the following general composition (15).

Water	95%
Glycoproteins and lipids	0.5–5%
Mineral salts	1%
Free proteins	0.5–1%

Mucus glycoproteins are high molecular proteins possessing attached oligosaccharide units (see Fig. 1). These units contain an average of about 8–10 monosaccharide residues of five different types. They are (*a*) L-fucose, (*b*) D-galactose, (*c*) *N*-acetyl-D-glucosamine, (*d*) *N*-acetyl-D-galactosamine, and (*e*) sialic acid. In humans the only important sialic acid is *N*-acetylneuramic acid, although in animals a number of other sialic acids occur, including *N*-glycollyneuramic acid and various *O*-substituted derivatives. Amino acids are principally serine, threonine, and proline. The mucus layer which covers the epithelial surface has various roles (1).

Protective Role

The protective role results particularly from its hydrophobicity and protecting the mucosa from the lumen diffusion of hydrochloric acid from the lumen to the epithelial surface.

Barrier Role

The mucus constitutes a diffusion barrier for molecules, and especially against drug absorption. Diffusion through the mucus layer depends largely on physicochemical characteristics of the active ingredient such as molecule charge, hydration radius, ability to form hydrogen bonds, and molecular weight (16). However the mucus nature interferes also at the level of diffusion phenomena, especially by glycoprotein concentration and by the cross-linking ratio, or more accurately, the average molecular weight between two junctions in the mucus network, as shown by the following equation (16).

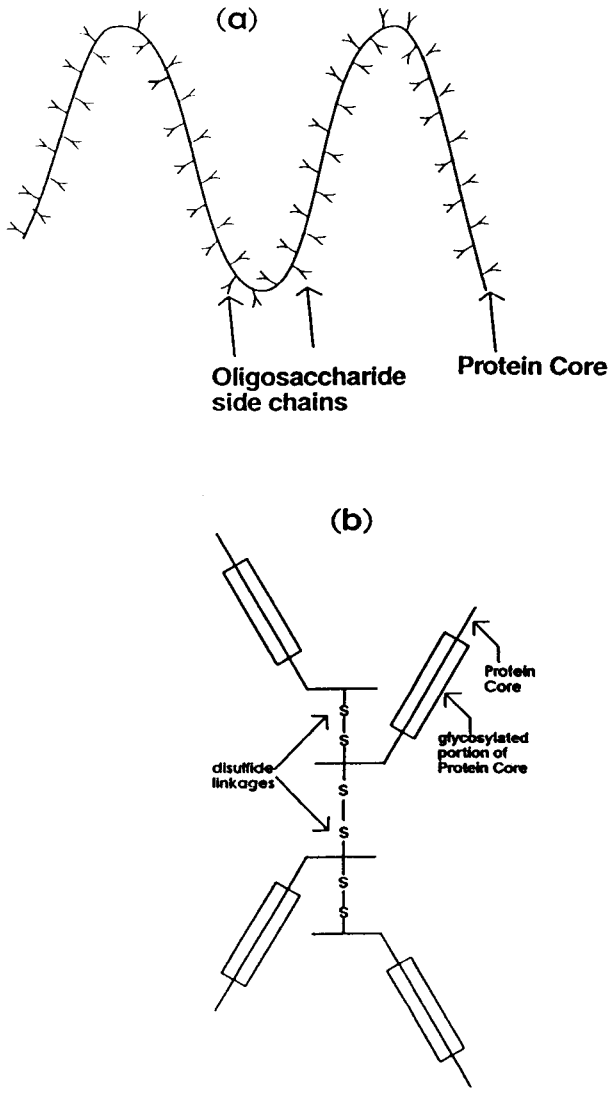


Figure 1. Schematic representations of mucus: (a) glycoprotein chain; (b) glycoprotein tetramer.

$$\frac{D_{in}}{D_{iw}} KC_m^{-1/3} M_j \exp - \left[\frac{K^1 r_i^2}{\frac{1}{C_m} - V} \right]$$

where D_{in} is the diffusion coefficient of the active ingredient through the mucus network; D_{iw} is the diffusion coefficient in water; K and K' are constants; C_m is the glycoprotein concentration in the mucus; M_j is the average molecular weight between two junctions in the mucus; r_i is the molecular radius of the diffusing active ingredient; and V is the glycoprotein specific volume.

A large number of active ingredients may interact with the mucus, particularly antibiotics. It seems that the formation of insoluble complexes would occur, impeding resorption by the gastrointestinal tract as well as by the submaxillary route. Gastric mucus may act as an unstirred water layer, in which hydrogen ions diffusing from the lumen are neutralized by the bicarbonate of the surface epithelium secretion. A dynamic equilibrium exists at the mucosal surface between a continuous erosion by proteolyse and mechanical abrasion and the equally continuous new mucus secretion.

Adhesion Role

Mucus has strong cohesional properties and firmly binds to the epithelial cell surface as a continuous gel layer.

Lubrication Role

The mucus layer keeps the mucosal membrane moist.

Continuous secretion of mucus from the goblet cells is necessary to compensate for the removal of the mucus layer due to digestion, bacterial degradation, and solubilization of mucin molecules. At physiological pH, the mucus network may carry a significant negative charge because of the presence of sialic acid and sulfate residues, and this high charge density due to negative charge contributes significantly to bioadhesion.

MUCOADHESION

For bioadhesion to occur, a succession of phenomena is required. The first stage involves an intimate contact between a bioadhesive and a membrane, either from a good wetting of the bioadhesive surface or from the swelling of the bioadhesive. In the second stage, after contact is established, penetration of the bioadhesive into the crevice of the tissue surface or interpenetration of the chains of the bioadhesive with those of the mucus takes place. Low chemical bonds can then settle (16).

One of the most important factors for bioadhesion is tissue surface roughness. Castellanos et al. (1) showed that adhesive joints may fail at relatively low applied stresses if cracks, air bubbles, voids, inclusions, or other surface defects are present. Viscosity and wetting power are the most important factors for satisfactory bioadhesion. Wachem et al. (17) studied in vitro interaction of human endothelial cells with polymeric substances processing different metabolites in a culture medium containing serum.

On a molecular level, mucoadhesion can be explained on the basis of molecular interactions. The interaction between two molecules is composed of attraction and repulsion. Attractive interactions arise from van der Waals 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 nonspecific repulsion (13).

Theories of Bioadhesion

Several theories have been proposed to explain the fundamental mechanisms of adhesion (1,5,14,16,18). In a particular system, one or more theories can equally well explain or contribute to the formation of bioadhesive bonds.

Electronic Theory

According to the electronic theory, electron transfer occurs upon contact of an adhesive polymer with a mucus glycoprotein network because of differences in their electronic structures. This results in the formation of an electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer.

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, van der Waals forces, and hydrogen and hydrophobic bonds.

Wetting Theory

Wetting theory is predominantly applicable to liquid bioadhesive systems. It analyzes adhesive and contact behavior in terms of the ability of a liquid or paste to spread over a biological system.

The work of adhesion (expressed in terms of surface and interfacial tension, Y) is defined as the energy per square centimeter released when an interface is formed. The work of adhesion is given by:

$$W_a = Y_A + Y_B - Y_{AB}$$

where A and B refer to the biological membrane and the bioadhesive formulation respectively. The work of cohesion is given by:

$$W_c = 2Y_A \quad \text{or} \quad Y_B$$

For a bioadhesive material B spreading on a biological substrate A, the spreading coefficient is given by:

$$S_{B/A} = Y_A - (Y_B + Y_{AB})$$

$S_{B/A}$ should be positive for a bioadhesive material to adhere to a biological membrane.

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.

Fracture Theory

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

$$G = (E\acute{\varepsilon}/L)^{1/2}$$

where E is the Young's modulus of elasticity, $\acute{\varepsilon}$ is the fracture energy, and L is the critical crack length when two surfaces are separated.

Factors Important to Mucoadhesion

The bioadhesive power of a polymer or of a series of polymers is affected by the nature of the polymer and also by the nature of the surrounding media (1,13, 14,16).

Polymer-Related Factors

Molecular Weight

Numerous studies have indicated that there is a certain molecular weight at which bioadhesion is at a maximum. The interpenetration of polymer molecules is favorable for low molecular weight polymers, whereas entanglements are favored for high molecular weight polymers. The optimum molecular weight for the maximum bioadhesion depends on the type of polymer. Their nature dictates the degree of swelling in water, which in turn determines interpenetration of polymer molecules within the mucus. According to Gurny et al. (52), it seems that the bioadhesive force increases with the molecular weight of the bioadhesive polymer up to 100,000, and that beyond this level there is not much effect. To allow chain interpenetration, the polymer molecule must have an adequate length. Size and configuration of the polymers molecule are also important factors. For example, with polyethylene oxide adhesive strength increases even up to molecular weights of 4,000,000; these polymers are well known to contain molecules of highly linear configuration, which contribute to interpenetration with dextran. Molecules with molecular weights as high as 19,500,000 do not exhibit better bioadhesion than molecules with a molecular weight of 200,000 (16).

Concentration of Active Polymer

Bremecker (141) relates that there is an optimum concentration of polymer corresponding to the best bioadhesion. In highly concentrated systems, the adhesive strength drops significantly. In fact, in concentrated solutions, the coiled molecules become solvent poor and the chains available for interpenetration are not numerous. This result seems to be of interest only for more or less liquid bioadhesive forms. Duchene et al. (16), for solid dosage forms such as tablets, showed that the higher the polymer concentration, the stronger the bioadhesion.

Flexibility of Polymer Chains

Flexiblity is important for interpenetration and entanglement. As water-soluble polymers become 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 the mucus layer decreases even further and mucoadhesive strength is reduced.

Spatial Conformation

Besides molecular weight or chain length, spatial conformation of a molecule is also important. Despite a high molecular weight of 19,500,000 for dextrans,

they have adhesive strength similar to that of polyethylene glycol, with a molecular weight of 200,000. The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, unlike PEG polymers, which have a linear conformation.

Environment-Related Factors

pH

pH was found to have a significant effect on mucoadhesion as observed in studies of polyacrylic polymers cross-linked with COOH groups. pH influences the charge on the surface of both mucus and the 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 the polypeptide backbone.

Robinson and his group (19) observed that the pH of the medium was critical for the degree of hydration of highly cross-linked polyacrylic acid polymers, increasing between pH 4 and pH 5, continuing to increase slightly at pH 6 and pH 7, and decreasing at more alkaline pH levels. This behavior was attributed to differences in charge density at the different pH levels.

Polycarbophil shows maximum adhesive strength at pH 3; the adhesive strength decreases gradually as the pH increases up to 5. Polycarbophil does not show any mucoadhesive property above pH 5. This study (22), the first systematic investigation of the mechanism of mucoadhesion, clearly shows that the protonated carboxyl groups rather than ionized carboxyl groups react with mucin molecules, presumably by numerous simultaneous hydrogen bonding reactions. At pH above 5, polycarbophil swells to a larger extent than at pH 3 or below. At high pH, however, the chains are fully extended because of the electrostatic repulsion of carboxylate anions. The polymer chains are also repelled by the negatively charged mucin molecules. It has been also observed that, due to hydrogen bonding between hydroxypropyl cellulose and carbopol 934, interpolymer complexes form at pH values below 4.5.

Applied Strength

To place a solid bioadhesive system, it is necessary to apply a defined strength. Whatever the polymer, poly[acrylic acid/divinyl benzene poly(HEMA)] or carbopol 934, the adhesion strength increases with the applied strength or with the duration of its application, up to an optimum (16). The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interactions with mucin.

Initial Contact Time

The intial contact time between mucoadhesives and the mucus layer determines the extent of swelling and the interpenetration of polymer chains. Along with the initial pressure, the initial contact time can dramatically effect the performance of a system. The mucoadhesive strength increases as the initial contact time increases. However, longer initial contact time should be based on tissue viability. In case of mucoadhesives that need to be polymerized at the application sites, the initial contact time is critical. It is easily controlled when mucoadhesives are applied to exposed areas such as eye, nose, or mouth. For the application of mucoadhesives to the GI tract, however, the initial contact time cannot be controlled, which is one of the difficulties in applying mucoadhesives to the GI tract (13).

Selection of the Model Substrate Surface

The handling and treatment of biological substrates during the testing of mucoadhesives is an important factor, since physical and biological changes may occur in the mucus gels or tissues under the experimental conditions. The viability of the biological substrate should be confirmed by examining properties such as permeability, electrophysiology, or histology. Such studies may be necessary before and after performing the in vitro tests using tissues (13).

Swelling

The swelling characteristic is related to the polymer itself, and also to its environment. Interpenetration of chains is easier as polymer chains are disentangled and free of interactions. Swelling depends both on polymer concentration and on water presence. When swelling is too great, a decrease in bioadhesion occurs; such a phenomenon must not occur too early, in order to lead to a sufficient action of the bioadhesive system. Its appearance allows easy detachment of the bioadhesive system after the discharge of the active ingredient.

Physiological Variables

Mucin Turnover

The natural turnover of mucin molecules from the mucus layer is important for at least two reasons (13).

First, the mucin turnover is expected to limit the residence time of the mucoadhesives on the mucus layer. No matter how high the mucoadhesive strength, mucoadhesives are detached from the surface due to mucin turnover. The turnover rate may be different in the presence of mucoadhesives, but no information is available on this aspect. Second, mucin turnover results in substantial amounts of soluble mucin molecules. These molecules interact with mucoadhesives before they have a chance to interact with the mucus layer. Surface fouling is unfavorable for mucoadhesion to the tissue surface. Mucin turnover may depend on other factors such as the presence of food. The gastic mucosa accumulates secreted mucin on the luminal surface of the tissue during the early stages of fasting. The accumulated mucin is subsequently released by freshly secreted acid or simply by the passage of ingested food; the exact turnover rate of the mucus layer remains to be determined. Lehr et al. (20) calculated a mucin turnover time of 47–270 min. The ciliated cells in the nasal cavity are known to transport the mucus to the throat at a rate of 5 mm/min. The mucociliary clearance in the tracheal region has been found to be in the range of 4–10 mm/min (21).

Disease States

The physicochemical properties of the mucus are known to change during disease conditions such as the 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 disease states, the mucoadhesive property needs to be evaluated under the same conditions (13).

METHODS USED TO STUDY BIOADHESION

Several test methods have been reported in the literature for studying bioadhesion. These tests are necessary not only to screen a large number of candidate mucoadhesives, but also to study their mechanisms (9). These tests are also important during the design and development of a bioadhesive controlled-release system as they ensure compatibility, physical and mechanical stability, surface analysis, and bioadhesive bond strength (4). The test methods can broadly be classified into two major categories:

1. In vitro/ex vivo methods
2. In vivo methods

In Vitro/Ex Vivo Methods

Most in vitro methods are based on the measurement of either tensile or shear stress. Bioadhesiveness determined by measurement of stress tends to be subjective since there is no standard test method established for bioadhesion (13).

Methods Based on Measurement of Tensile Strength

Methods using tensile strength usually measure the force required to break the adhesive bond between a model membrane and the test polymers. The instruments usually employed are modified balances or tensile testers. A typical example is the method employed by Robinson and his group (22). In this method, the force required to separate the bioadhesive sample from freshly excised rabbit stomach tissue was determined using a modified tensiometer. A section of the tissue, having the mucus side exposed, was secured on a weighed glass vial placed in a beaker containing USP simulated gastric fluid. Another section of the same tissue was placed over a rubber stopper, again with the mucus side exposed, and secured with a vial cap. Then a small quantity of polymer was placed between the two mucosal tissues. The force used to detach the polymer from the tissue was then recorded. The results of the study provided important information regarding the effects of charge density, hydrophobicity, and experimental conditions such as pH, ionic strength, mucolytic agents, and applied pressure on bioadhesion. Examples of tensile strength measurements are given in Table 1.

Methods Based on Measurement of Shear Strength

Shear stress measures the force that causes the bioadhesive to slide with respect to the mucus layer in a direction parallel to their plane of contact. An example is the wilhelmy plate method reported by Smart et al. (49). The method uses a glass plate suspended from a microbalance which is dipped in a temperature-controlled mucus sample. The force required to pull the plate out of the solution is determined under constant experimental conditions.

A summary of the methods involving shear strength measurement are given in Table 2.

Other In Vitro Methods

Adhesion Weight Method

Smart and Kellaway (50) developed a test system where suspensions of ion-exchange resin particles

Table 1

Bioadhesion Measurements by Tensile Strength

Bioadhesive[a]	Substrate	Instrument	Ref.
CP 934, HPC	Mouse peritoneal membrane	Spring balance	23
Gelatin capsule	Porcine esophagus	Modified prescription balance	24, 25
Cross-linked PAA, PMA, PHEMA	Rabbit stomach tissue	Modified surface tensiometer	19, 22, 26
PAA, HPMC	Bovine sublingual mucosa	Tensile apparatus (Instron, U.K.)	27, 28
CP 934, CP Ex 55, HPMC, HPC	Fresh intestine from male Wistar rats	Modified pan balance	29
CP, HPC	Mouse peritoneal membrane	Modified spring balance	30
Modified starch, PAA, PEG, NaCMC	Porcine attached gingiva	Modified tensile apparatus	31, 32
CP 934, PHEMA, Eu RL 100	Porcine intestinal mucosa	Modified Du Nouy tensiometer	33
CP, Hyaluronic acid	Porcine gastric mucin gel	Electronic digital microbalance	34
PAA, HPC	Porcine buccal mucosa	Tensile tester	35
Chitosan, polycarbophil, CMC, pectin, xanthan gum	Pig intestinal mucosa	Modified tensiometer	36
Alginate, CMC, chitosan	Intestinal tissue from Sprague–Dawley rats	Precise microbalance (dynamic contact analyzer)	37
CP 934, HPC-M, PVP, NaCMC	Hamster cheek pouch	Modified pan balance	38
Copolymers of dextran, poly acrylamide, PAA	Cellulose paper disk impregnated with porcine mucine gel	Tensile apparatus	39
Modified starch PAA	Porcine gingiva	Tensile tester	40
NaCMC, HPC	Rabbit stomach/intestinal tissue	Modified tensile tester	41, 1
CP 934, HPMC, chitosan, acacia	PVP/cellulose acetate hydrogel	Tensile tester	42, 43
Na alginate, PEG	Guinea pig ileum mucosa	Tensile apparatus (Instron, U.K.)	44
Chitosan, Na alginate	Rat peritoneum membrane	Spring tension gauge	45
CP 934, PVP	Bovine cheek pouch	Modified pan balance	46
Copolymer of ε-caprolactone and ethylene oxide	Rat duodenum mucosal tissue	Tensile tester	47
CP 934	Porcine gastric mucin	Dynamic contact analyzer	48

[a]PMA = polymethacrylic acid; PHEMA = polyhydroxyethyl methacrylic acid; Eu = Eudragit; PAA = polyacrylic acid.

flowed over the inner mucosal surface of a section of guinea pig intestine and the weight of the adherent particles was determined. Although the method was of limited value due to poor data reproducibility resulting from fairly rapid degeneration and biological variation of the tissue, it was possible for them to determine the effect of particle size and charge on the adhesion after 5 min contact with everted intestine.

Fluorescent Probe Method

Park and Robinson (54) studied polymer interaction with the conjunctival epithelial cell membrane using fluorescent probes. The study was done in an attempt to understand structural requirements for bioadhesion in order to design improved bioadhesive polymers for oral use. The membrane lipid bilayer and membrane proteins were labeled with pyrene and fluorescein isothiocyanate, respectively. The cells were then mixed with candidate bioadhesives and the changes in fluorescence spectra were monitored. This gave a direct indication of polymer binding and its influence on polymer adhesion.

Flow Channel Method

Mikos and Peppas (18) developed a flow channel method that utilized a thin channel made of glass and

Table 2

Bioadhesion Measurements by Shear Strength

Bioadhesive Material	Substrate	Instrument	Ref.
CP 934, NaCMC, HPMC, gelatin, PVP, acacia, PEG, pectin, tragacanth, Na alginate,	Mucus from guinea pig intestine	Wilhelmy plate method (microforce balance)	49
CP 934 ointment	Glass plates	Shearing stickiness test apparatus	51
Polyethylene gel, NaCMC, hydrolyzed gelatin	Polymethyl methacrylate	Instron model 1114	52
Ca polycarbophil, Na CMC, HPMC, Eudragit	Homogenized mucus from pig intestine	Modified wilhelmy plate surface tension apparatus	53

filled with 2% w/w aqueous solution of bovine submaxillary mucin, thermostated at 37°C. Humid air at 37°C was passed through the glass channel. A particle of a bioadhesive polymer was placed on the mucin gel, and its static and dynamic behavior was monitored at frequent intervals using a camera.

Mechanical Spectroscopic Method

Kerr et al. (55) used mechanical spectroscopy to investigate the interaction between glycoprotein gels and polyacrylic acid, and the effect of pH and polymer chain length on this.

Mortazavi et al. (56) used a similar method to investigate the effect of introduction of Carbopol-934p on the rheological behavior of mucus gel. They used a Carri-Med CSL 100 rheometer with a 4-cm parallel plate and 0.5-mm gap for their studies. They also investigated the role of mucus glycoproteins (57) and the effect of various factors such as ionic concentration, polymer molecular weight and its concentration, and the introduction of anionic, cationic, and neutral polymers on the mucoadhesive mucus interface (58).

Caramella et al. (59), using a Bohlin CS rheometer, investigated the interactions taking place at the polymer mucin interface. In spite of a number of methods for the determination of bioadhesion, a poor correlation has been found between the bioadhesive strength measured in vitro and the bioadhesive performance in vivo.

It has been found that two formulations exhibiting similar bioadhesive strength determined using the conventional "stress-strain" method in vitro exhibit different adhesion time in vivo. The difference might be due to different erosion resistance of the formulations or to premature dislodgement of the formulations due to excessive swelling and formation of slippary surface (60). Hence, there is a need for an effective in vitro method which would sufficiently mimic the in vivo bioadhesive performance of the formulations.

Falling Liquid Film Method

Teng and Ho (61) developed a falling liquid film method. Small intestine segments from rats were placed at an inclination of a tygon tube flute. The adhesion of particles to this surface was monitored by passing the particle suspension over the surface. A similar principle was used by Rao et al. (62) to determine the adhesive potentials of various polymers. By comparing the fraction of particles adherent to the tissue, the adhesion strength of different polymers can be determined.

Colloidal Gold Staining Method

Park (63) proposed the colloidal gold staining technique for the study of bioadhesion. The technique employed red colloidal gold particles which were stabilized by the adsorbed mucin molecules (mucin–gold conjugates). Upon interaction with mucin–gold conjugates, bioadhesive hydrogels developed a red color on the surface. Thus, the interaction between them could easily be quantified, either by the measurement of the intensity of the red color on the hydrogel surface or by the measurement of the decrease in the concentration of the conjugates from the absorbance changes at 525 nm.

Viscometric Method

A simple viscometric method was used by Hassan and Gallo (64) to quantify mucin–polymer bioadhesive bond strength. Viscosities of 15% w/v percine gastric mucin dispersions in 0.1 N HCl (pH 1) or 0.1 N acetate buffer (pH 5.5) were measured with a Brookefield viscometer in the absence or presence of selected neutral, anionic, and cationic polymers. Viscosity components and the forces of bioadhesion were calculated.

Thumb Test

The thumb test (13) is a simple test method which can be used to identify mucoadhesives. The adhesiveness is quantitatively measured by the difficulty of pulling the thumb from the adhesive as a function of the pressure and the contact time. It is most likely that any mucoadhesive system is adhesive to fingers, since most mucoadhesives are nonspecific and not mucin specific. Like mucin, the skin has many hydroxyl groups. Although the thumb test may not be conclusive, it provides useful information on mucoadhesive potential.

Adhesion Number

With a mucoadhesive in the form of small particles, the adhesion number (13) can be used as a parameter for mucoadhesion. The determination of adhesion strength for small particles would be difficult. The adhesion number is typically represented by the following equation:

$$N_a = (N/N_0) \times 100$$

where N_a is the adhesion number, N_0 is the total number of applied particles, and N is the number of particles attached to the substrate. As the adhesion strength increases, the adhesion number also increases.

Electrical Conductance

Bremecker used electrical conductance (13) as a parameter for testing semisolid mucoadhesive ointments. The adhesion of Orabase, Carbopol, Eudispert, guar gum, and methyl cellulose to artificial biomembranes in artificial saliva was studied by using a modified rotational viscometer capable of measuring electrical conductance. This parameter, measured as a function of time, was found to be influenced by the sample, the artificial saliva, and the artificial biomembrane. In the presence of adhesive material, the conductance was comparatively low. As the adhesive was removed, the value increased to a final value corresponding to the conductance of the saliva, which indicated the absence of adhesion.

In Vivo Methods

In vivo techniques for measuring the bioadhesive strength are relatively few. Some of the reported methods are based on the measurement of the residence time of bioadhesives at the application site (13). The GI transit times of many bioadhesives have been examined using radioisotopes.

Ch'ng et al. (19), in order to investigate the gastrointestinal transit of bioadhesive beads, developed an in vivo method in rats, inserting ^{55}Cr-labeled bioadhesive material in the stomach and measuring the radioactivity in cut segments of the intestine.

Duchene et al. (16) described the method used by Davis, which involved the scintigraphic method to study the gastrointestinal transit of a bioadhesive form.

Khosla et al. (65) studied the gastric emptying of ^{99m}Tc-labeled polycarbophil pellets in humans using γ scintigraphy.

BIOADHESIVE POLYMERS

To overcome the relatively short gastrointestinal time and improve localization for oral-controlled or sustained-release drug delivery systems, bioadhesive polymers which adhere to the mucin/epithelial surface are effective and lead to significant improvement in oral drug delivery. Improvements are also expected for other mucus-covered sites of drug administration. Bioadhesive polymers find application in the eye, nose, and vaginal cavity as well as the gastrointestinal tract, including the buccal cavity and rectum (54).

Polymers that adhere to the mucin–epithelial surface can be conveniently divided into three broad categories: (*a*) polymers that become sticky when placed in water and owe their bioadhesion to stickiness; (*b*) polymers that adhere through nonspecific, noncovalent interactions which are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant); (*c*) polymers that bind to specific receptor sites on the cell surface. All three polymer types can be used for drug delivery. Polymers which can adhere to either hard or soft tissue have been used for many years in surgery and dentistry. Among these "superglues," polymers and monomeric alpha-cyanoacrylate esters have been most frequently investigated and used. Other synthetic polymers such as polyurethanes, epoxy resins, polystyrene,

acrylates, and cements from natural products were also extensively investigated, as were glues.

An ideal polymer for a mucoadhesive drug system should have the following characteristics (1,66).

1. The polymer and its degradation products should be nontoxic and nonabsorbable from the gastrointestinal tract.
2. It should be a nonirritant to the mucous membrane.
3. It should preferably form a strong noncovalent bond with the mucin–epithelial cell surfaces.
4. It should adhere quickly to moist tissue and should possess some site specificity.
5. It should allow easy incorporation of the drug and offer no hindrance to its release.
6. The polymer must not decompose on storage or during the shelf life of the dosage form.
7. The cost of the polymer should not be high, so that the prepared dosage form remains competitive.

Robinson and his group (54), using the fluorescence techinque, concluded that:

1. Cationic and anionic polymers bind more effectively than neutral polymers.
2. Polyanions are better than polycations in terms of binding/potential toxicity; and further, that water-insoluble polymers give greater flexibility in dosage form design compared to rapidly or slowly dissolving water-soluble polymers.
3. Anionic polymers with sulfate groups bind more effectively than those with carboxylic groups.
4. Degree of binding is proportional to the charge density on the polymer.
5. Highly binding polymers include carboxymethyl cellulose, gelatin, hyaluronic acid, carbopol, and polycarbophyl.

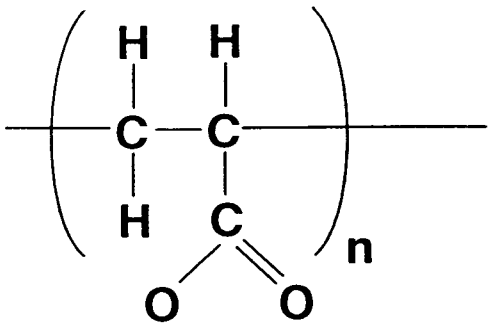
Role of pH on bioadhesion is of great importance, with maximum adhesion being observed from pH 5 to 6.

Rao and Buri (62) showed that polycarbophil and sodium carboxymethyl cellulose adhered more strongly to mucus than hydroxypropyl methyl cellulose, methylcellulose, or pectin. Better adhesion occurred in the stomach than in the intestine.

Properties of some of the important bioadhesive polymers commonly used are described in the following sections.

Carbopol/Carbomer

Carbopol/carbomer (67,68) is a synthetic, high molecular weight, cross-linked polymer of acrylic acid copolymerized with allyl sucrose or allyl pentaerythritol. The carboxyl groups provided by the acrylic acid backbone of the polymer are responsible for many of the product characteristics.



Chemical name: carboxy polymethylene.
Empirical formula: $(C_3H_4O_2)_x$ $(-C_3H_5\text{-sucrose})_y$
Grades: 907, 910, 934, 934P, 940, 941, 971P 974P, 980, and 981.

- Carbopol: 934P, 971P and 974P are the only pharmaceutical grades of the resin intended for internal use.
- Carbopol 934 P is a high molecular weight polymer of acrylic acid cross-linked with allyl ethers of sucrose and polymerized in benzene.
- Carbopol 974 P is polymerized in ethyl acetate and is slightly treated with a potassium base.

Description: white, fluffy, acidic, hygroscopic powder with a slight characteristic odor.
Molecular weight: 1×10^6 to 4×10^6.
Density, bulk: 5 g/cm^3.
Density, tapped: 1.4 g/cm^3.
Viscosity: 29,400 to 39,400 cps at 25°C (0.5% neutralized aqueous solution).
pH: 2.5–3.0 (1% aqueous solution).
Solubility: soluble in water, alcohol, and glycerin.
Stability: Gel loses viscosity on exposure to sunlight. It is relatively unaffected by temperature variations, not subjected to hydrolysis or oxidation and is resistant to bacterial growth.
Safety: It is safe and nontoxic. No primary irritation or any evidence of allergic reactions has been observed in human beings following topical application. It is not absorbed in the body and is excreted unchanged. It contributes no off-taste and

in some cases may mask the undesirable taste of the formulation.

Incompatibility: It is observed with phenols, cationic polymers, high concentration of electrolytes, and resorcinol.

Applications: It is an excellent thickening, emulsifying, suspending, and gelling agent. It is used as a tablet binder in sustained-release formulations affording zero- to near-zero-order release. It is used as the bioadhesive component in muco-adhesive ointments, gels, and tablets.

Sodium Carboxymethyl Cellulose

Sodium carboxymethyl cellulose (SCMC) (67,69) is the sodium salt of a polycarboxymethyl ether of cellulose.

Chemical name: cellulose carboxymethyl ether sodium salt.

Empirical formula: $[C_6H_7O_2(OH)_{3x}\ (OCH_2\text{-}COONa)_x]_n$.

Grades: carboxymethyl cellulose H, M, L.

Description: white to faintly yellow, odorless, hygroscopic powder or granular material having a faint paper-like taste.

Molecular weight: 90,000–700,000.

Density, bulk: 0.75 g/cm^3.

Viscosity: 1200 cps (1% aqueous solution).

pH: 6.5–8.5 (1% aqueous solution).

Solubility: It is soluble in water at all temperatures, giving a clear solution; it is practically insoluble in most organic solvents.

Stability: Sterilization in both the dry state and in solution causes a decrease in viscosity. Irradiation of solutions will also cause a drop in viscosity. The bulk material is stable on storage.

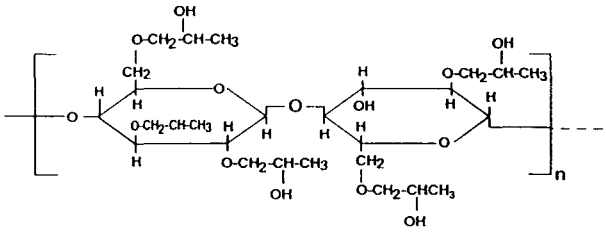
Safety: Generally recognized as safe.

Incompatibility: It is incompatible with strongly acidic solutions and with soluble salts of iron, mercury, zinc, and aluminum.

Applications: It is used as an emulsifying, gelling, and binding agent. It has been found to possess a good bioadhesive strength.

Hydroxypropyl Cellulose

Hydroxypropyl cellulose (HPC) (67,70) is partially substituted poly(hydroxypropyl) ether of cellulose.



Chemical name: cellulose, 2-hydroxypropyl ether.

Empirical formula: $(C_{15}H_{28}O_8)_n$.

Grades: Klucel EF, LF, JF, GF, MF, and HF.

Description: white to slightly yellowish, odorless powder.

Molecular weight: 60,000 to 1,000,000.

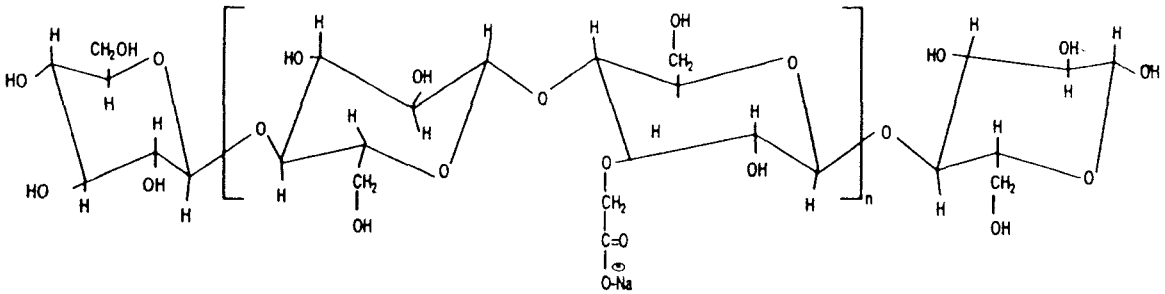
Density, bulk: 0.5 g/cm^3.

Viscosity: Klucel MF, 4000–6500 cps (2% aqueous solution); Klucel LF, 75–150 cps (5% aqueous solution).

pH: 5.0–8.0 (1% aqueous solution).

Solubility: Soluble in water below 38°C. Also soluble in many polar organic solvents such as ethanol, propylene glycol, dioxane, methanol, isopropyl alcohol (95%), dimethyl sulfoxide, and dimethyl formamide. Insoluble in hot water.

Stability: Aqueous solutions of hydroxypropyl cellulose possess the best viscosity stability when the pH is maintained between 6.0 and 8.0, and the solutions are protected from light, heat, and the action of microorganisms. Aqueous solutions of HPC are susceptible to both chemical and biological degradation.



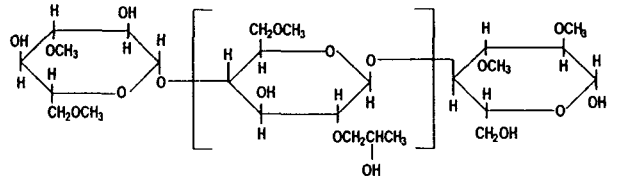
Safety: It is physiologically inert. The results of repeat insult patch tests on humans disclose no evidence of skin irritation or sensitization. It is not metabolized in the body.

Incompatibility: HPC may not tolerate high concentrations of other dissolved materials and tends to be "salted out." In solution, it demonstrated some incompatibility with substituted phenol derivatives, such as methyl and propyl parahydroxybenzoate.

Applications: It is used as a granulating and film coating agent for tablets. It is also used as a thickening agent, emulsion stabilizer, and suspending agent in oral and topical liquid solution or suspension or suspension formulations.

Hydroxypropylmethyl Cellulose

Hydroxypropylmethyl cellulose (HPMC) (67,71) is a mixed alkyl hydroxyalkyl cellulosic ether and may be regarded as the propylene glycol ether of methyl cellulose.



Chemical name: cellulose, 2-hydroxypropyl methyl ether.

Empirical formula: $C_8H_{15}O_6$-$(C_{10}H_{18}O_6)_n$-$C_8H_{15}O_5$.

Grades: Methocel—E5, E15, E50, E4M, F50, F4M, K100, K4M, K15M, K100M.

Description: An odorless, tasteless, white or creamy-white fibrous or granular powder.

Molecular weight: Approx. 86,000.

Density: 0.25–0.70 g/cm^3.

Viscosity: HPMC E15, 15 cps (2% aqueous solution); HPMC E4M, 4000 cps (2% aqueous solution); HPMC K4M, 4000 cps (2% aqueous solution).

pH: 6.0–8.0 (1% aqueous solution).

Solubility: Soluble in cold water, forming a viscous colloidal solution; insoluble in alcohol, ether, and chloroform, but soluble in mixtures of methyl alcohol and methylene chloride. Certain grades are soluble in aqueous acetone, mixtures of methylene chloride, and isopropyl alcohol and other organic solvents.

Stability: Very stable in dry conditions. Solutions are stable at pH 3.0–11.0. Aqueous solutions are liable to be affected by microorganisms.

Safety: Human and animal feeding studies have shown HPMC to be safe.

Incompatibilities: Extreme pH conditions, oxidizing materials.

Applications: It is a suspending, viscosity-increasing, and film-forming agent. It is also used as a tablet binder and as an adhesive ointment ingredient. The E grades are generally suitable as film formers while the K grades are used as thickeners.

Guar Gum

Guar gum (GG) (69) is a substance obtained from the ground endosperms of the seeds of *Cyamposis tetragonolobus* (family Leguminosae). It consists chiefly of a high molecular weight hydrocolloid polysaccharide composed of galactan and mannan units combined through glycosidic linkages.

Chemical name: galactomannan polysaccharide.

Empirical formula: $(C_6H_{12}O_6)_n$.

Description: white to yellowish white, odorless powder with a bland taste.

Molecular weight: approx. 220,000.

Viscosity: 2000 to 22,500 cps (1% aqueous solution).

Solubility: It forms viscous colloidal solution when hydrated in cold water. The optimum rate of hydration is between pH 7.5 and 9.0.

Stability: It is stable in solution over a pH range of 1.0–10.5. Prolonged heating degrades viscosity. Bacteriological stability can be improved by the addition of a mixture of 0.15% methyl paraben or 0.1% benzoic acid.

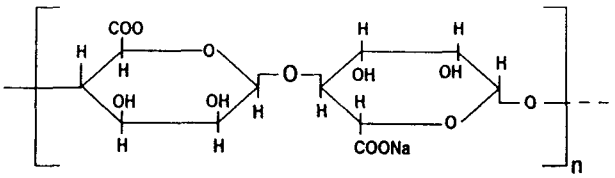
Safety: Guar gum is recognized by the FDA as a substance added directly to human food and has been affirmed as generally recognized as safe.

Incompatibility: It is incompatible with acetone, tannins, strong acids, and alklalis. Borate ions, if present in the dispersing water, will prevent hydration of guar.

Applications: Used as a thickener for lotions and creams, as tablet binder, and as emulsion stabilizer.

Sodium Alginate

Sodium alginate (ALG) is the purified carbohydrate product extracted from brown seaweed by the use of dilute alkali. It consists chiefly of the sodium salt of alginic acid, a polyuronic acid composed of β-D-mannuronic acid residues.



Empirical formula: $(C_6H_7O_6Na)_n$.

Description: It occurs as a white or buff powder which is odorless and tasteless. The powder may be coarse or fine.

Viscosity: 20 to 400 cps at 20°C (1% aqueous solution).

pH: 7.2 (1% aqueous solution).

Solubility: It is slowly soluble in water, forming a viscous, colloidal solution. It is insoluble in alcohol and in hydroalcoholic solutions in which the alcohol content is greater than 30% by weight. It is also insoluble in other organic solvents and acids where the pH of the resulting solution falls below 3.0.

Safety: Numerous studies have indicated sodium alginate to be quite safe. Allergy tests have shown it to be nonallergenic.

Incompatibility: It is incompatible with acridine derivatives, crystal violet, phenyl mercuric nitrate and acetate, calcium salts, alcohol in concentrations greater than 5%, and heavy metals.

Applications: Used as a stabilizer in emulsions, as a suspending agent, tablet disintegrant, and tablet binder. It is also used as a hemostatic agent in surgical dressings.

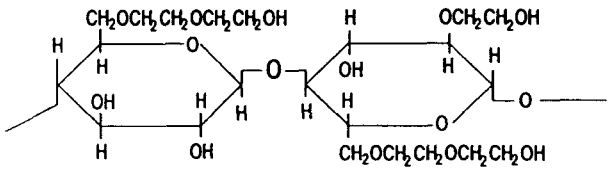
Polycarbophil

Polycarbophil is a synthetic polymer composed of polyacrylic acid loosely cross-linked with 0.5–1% (w/w) divinyl glycol (3,4-dihydroxy 1,5-hexadiene). It consists of particles that swell but are insoluble in water. The particles are also insoluble but may swell to varying degrees in common organic solvents, strong mineral acids, and bases. Swelling characteristics in water depend on the pH and the ionic strength of the test solution, with swelling increasing as pH increases. At low pH (pH 1–3), polycarbophil absorbs 15–35 ml of water per gram of resin, whereas in neutral or basic media it can absorb approximately 100 ml per gram. This compound is approved for use in humans in antidiarrheal and laxative products since concerns about the toxicity of the polymer are minimal. This polymer undergoes swelling in water and this permits entanglement of the polymer chains with mucus on the surface of the tissue. The nonionized carboxylic acid groups bind to the mucin molecule by means by hydrogen bridges.

Many researchers used a mixture of carbopol 934 and hydroxypropyl cellulose, but carbopol was the bioadhesive agent and the cellulosic derivative was the hydrophilic matrix.

Hydroxyethyl Cellulose

Hydroxyethyl cellulose (67) is the idealized structure of hydroxyethyl cellulose.



Description: light tan or cream to white powder, odorless and tasteless. It may contain suitable anticaking agents.

pH: (1 in 100) = 6–8.5.

Bulk density: 39 lb per ft^3 (0.6 g/ml).

Functional category: It is used as a suspending and/or viscosity-increasing agent. It is also a binder, film former, and a thickener.

EVALUATION OF MUCOADHESIVE DOSAGE FORMS

Two important evaluating parameters of mucoadhesive drug delivery systems are release rate in vitro and in vivo, and bioadhesive strength. Release rate studies are reviewed in this section.

In Vitro Release Studies

No standard in vitro method has yet been developed for dissolution studies of buccal formulations. Different workers have used apparatus of varying designs, depending on the shape and application of the dosage form developed. Machida and Nagai (72), in 1977, used a J.P. IX disintegration tester without the attached disk, with 800 ml of the dissolution medium for dissolution rate measurement of directly compressed tablets of *dl*-isoprotenol hydrochloride, meant for controlled release.

Nagai et al. (73), in 1978, prepared disk-like dosage forms for the treatment of uterine cancer and measured the dissolution rate using a Toyamo–Sangyo TR-553

dissolution tester. For this, 900 ml of purified water was used as dissolution medium, rotating the basket at 100 rpm. This apparatus was used for the evaluation of oral mucosal dosage forms of insulin.

Ishida et al. (74), in 1981, used an apparatus similar to that used for the evaluation of insulin dosage forms, with a slight modification of providing a water jacket for the maintenance of temperature. This apparatus was used for the dissolution rate measurement of mucosal adhesive dosage forms of lidocaine for toothache.

Collins and Deasy (75) studied the release of cetyl pyridinium chloride into the simulated saliva (isotonic phosphate buffer, pH 6.6) in an apparatus consisting of a water jacket and an internal compartment containing 50 ml of the dissolution medium. The compact formulated was placed in a metal die sealed at the lower end by paraffin wax; hence the drug could be released only from the upper convex face of the device. The medium was stirred with rotating stirrer at a rate of 250 rpm.

The methods used for in vitro release rate studies are listed in Table 3.

In Vivo Release Studies

Various techniques of in vivo testing have been reported to quantitatively evaluate drug absorption through the mucosal membrane (76).

A buccal absorption test which involves swirling a buffered drug solution around the mouth has been established. After a known time period the solution was expelled and the subjects rinsed their mouth with buffers. Drug solution and the buffers were then combined and analyzed for drug content, and the amount of drug absorbed estimated from the difference between the entered and recovered.

An improvement over this traditional buccal absorption test, which enables kinetic data to be collected in a single 15-min trial, has also been reported. This method involved multiple samples being withdrawn from the mouth using a positive displacement pipetter.

A method for investigating the transport of water and ions through known regions and fixed areas of the oral mucosa has been used. A similar method to study steroid absorption across keratinized and nonkeratinized oral mucosa sites has been investigated. A closed perfusion cell apparatus to study the transport of flubiprofen across the human buccal membrane has been developed.

In 1991 Rathbone (80) described a buccal perfusion cell apparatus which offers larger areas over which drug transfer can take place, has no leakage problem, and provides continuous monitoring of drug loss as a function of time.

Recently drug permeability using hamster cheek pouch has been investigated. A sophisticated approach to in vivo animal studies of buccal absorption has been investigated. A 2 cm^2 glass circulating perfusion chamber, developed for use in dogs, produces sufficiently precise data for use in physical modeling.

Veillard et al. (85), in 1987, conducted some preliminary studies on buccal absorption using a small perfusion on mongrel dogs.

IN VIVO ABSORPTION STUDIES DONE ON MUCOADHESIVE DOSAGE FORMS

Schurmann et al. (86) studied the buccal absorption characteristics and physicochemical properties of β-adrenoceptor blocking agents. The time course of absorption suggests membrane storage of lipophilic compounds. The in vivo partition coefficient of non-ionized propranolol relative to the mucous membrane could be calculated.

Tanaka et al. (87) studied the absorption of salicylic acid through the oral mucous membrane of hamster cheek pouch. Ointments containing salicylic acid were applied to the cheek pouch of the hamster and the influence of the type of base on drug absorption at the mucous membrane of the oral cavity was examined. The absorption of salicylic acid applied to the cheek pouch of the hamster and the influence of the type of base on drug absorption at the mucous membrane of the oral cavity was examined. The absorption of salicylic acid into the blood was closely related to drug retention in the tissue of the mucous membrane. The results of in vitro membrane permeation experiments corresponded very well with the results of the absorption experiments in vivo.

Ishida et al. (74) studied the in vivo absorption of lidocaine from the human gingiva with various mixing ratios of FD-HPC/CP to lidocaine. Buccal absorption of Protirelin was also studied. This study also evaluated buccal protirelin as a diagnostic tool.

Nagai (88) studied bioavailability of insulin when given by nasal route.

Saettone et al. (34) studied the in vivo activity of ophthalmic vehicles based on hyaluronic acid and on polyacrylic acid containing pilocarpine.

Collins and Deasy (75) studied the release of a three-layered device containing cetyl pyridinium chloride in

Table 3

In Vitro Release Rate Study Methods

Drug	Dosage Form	Apparatus	Testing Medium	Agitation Conditions	Ref.
Insulin	Tablet	Rotating basket immersed in a beaker	1/15 M phosphate buffer pH 7.38 (50 ml)	100 rpm	23
Lidocaine	Tablet	Tablet was kept in a holder which was immersed in a flask	Chloroform (50 ml)	Magnetic stirring	74
Tretinoin	Ointment	0.5 g ointment was filled in a cellulose tube, containing 5 ml saline which was immersed in a Nessler test tube	Saline (30 ml)	Mechanical shaker	77
Metronidazole	Tablet	Dissolution apparatus (Dissolutest, France)	0.1 N aqueous HCL solution, pH 1.0 (1000 ml)	50 rpm	27, 28
Cetylpyridinium chloride	Tablet	Paddle method with tablet in a metallic die at bottom	McIlvaine buffer, pH 6.6 (50 ml)	250 rpm	75
Sodium fluoride	Tablet	USP paddle device	Isotonic phosphate-buffered saline	70 rpm	31
Propranolol HCl	Tablet	USP rotating basket method	Phosphate buffer, pH 6.8	50 rpm	78
Propranolol HCl	Disk	USP type II apparatus	Phosphate buffer, pH 3.5 or 6.8 (250 ml)	75 rpm	35
Verapamil HCl	Tablet	Tablet was held in a Teflon block which was kept at the bottom of a cylindrical flask	Isotonic phosphate buffer, pH 6.6 (100 ml)	50 rpm	79
Triamcinoloacetonide (encapsulated)	Ointment	Franz diffusion cell apparatus with a synthetic membrane	Phosphate-buffered saline pH 7.2	Magnetic stirring	81
Metoclopramide	Disk	Modified USP type II method	Distilled water (500 ml)	100 rpm	82
Nifedipine	Tablet	USP dissolution apparatus I	Methanol and water (3.7) (100 ml)	—	83
Buprenorphine	Patch	Patches affixed to Plexiglass sample blocks and placed in a flask	Phosphate buffer, pH 7 (100 ml)	—	42, 43
Ketoprofen	Tablet	JP XII dissolution test apparatus	Distilled water (1000 ml)	150 rpm	45

Table 3 Continued

Drug	Dosage Form	Apparatus	Testing Medium	Agitation Conditions	Ref.
Isosorbide dinitrate	Film	JP XII dissolution test apparatus	Buffered Clark–Lubs solution (500 ml)	100 rpm	84
Diltiazem HCl	Tablet	Tablet was held in a Teflon block which was kept at the bottom of a cylindrical glass beaker	Isotonic phosphate buffer (pH 6.6) (100 ml)	50 rpm	46

a nonadhesive and flavored waxy exposed layer using high-performance liquid chromatography (HPLC) and showed that the release was not affected by location within the mouth.

Yamahara et al. (89) developed an in situ perfusion system for oral mucosal absorption in dogs. The utility of the perfusion system with a circulating perfusion chamber was investigated using three drugs: salicyclic acid, sulfadimethoxine, and diltiazem. The oral mucosal absorption of the drugs could be adequately described by first-order rate processes.

Rathbone and Hadgraft (15) have discussed several methods to study the rate and extent of drug loss from human oral cavity. These include the buccal absorption test, disk methods, and perfusion cells. These methods have provided information on the mechanisms by which drugs are transported across oral cavity membranes and suggest that passive diffusion or carrier-mediated transport systems may be involved.

Sveinsson and Holbrook (81) studied the in vitro release of the oral mucosal adhesive ointment containing liposomal corticosteroid.

Nozaki et al. (90) developed a new transmucosal therapeutic system. Following gingival application of TYB-3215, each containing 10 mg of ISDN spiked with ^{14}C-ISDN, to each beagle dog, the plasma concentrations of the radioactivity was observed.

Bottenberg et al. (32) tested two formulations, each containing 0.1 mg of fluoride. Salivary fluoride was measured with a fluoride-specific electrode. The formulations were tested for irritation and release.

Hosny and Al-Meshal (91) investigated the relative bioavailability of a bioadhesive-containing directly compressed tablet formulation against the commercial indomethacin capsules.

Save et al. (83) studied the pharmacodynamics of nifedipine administered via the oral mucosa in hypertensive patients. The effect of two buccoadhesive formulations, tablets, and films, was compared with commercially available sublingual capsule in a complete crossover study in 6 patients. Analysis of variance indicated that although time-dependent differences in the formulations were suggested, there was no significant difference in the overall effect produced by the three formulations. The results of the study suggest that the buccoadhesive formulations of nifedipine were comparable in performance with the sublingual capsule.

MUCOADHESIVE DRUG DELIVERY SYSTEMS

Gastrointestinal Bioadhesive Drug Delivery Systems

A primary objective of using mucoadhesive formulations orally would be to achieve a substantial increase in length of stay of the drug in the gastrointestinal tract. Stability problems in the intestinal fluids can be overcome. Therapeutic effect of drugs insoluble in the intestinal fluids can be improved, especially in the case of drugs acting locally.

In 1985 Longer et al. (92) studied albumin beads containing chlorthiazide mixed with equal-sized particles of polycarbophil at a ratio of 3:7 (w/w). The beads were administered orally in the form of capsules to rats. Their in vitro release studies showed that the albumin beads and bioadhesive dosage form offered sustained release for $\leq$8 hr. In vivo studies showed that nearly 90% of the beads in the polycarbophil–albumin bead dosage form remained in the rat stomach. In the absence of polymer, the majority of beads moved at least half-way down the small intestine, with some moving further.

When these experiments (7) were repeated in dogs, less satisfactory results were obtained. The explanation for the difference in findings stems from the difference

in the amount of soluble mucin in the stomach of rat versus that of the dog.

The influence of the putative bioadhesive polycarbophil on the gastric emptying of a pellet formulation was investigated by Khosla and Davis in 1987 (65). The gastric emptying of pellets, labeled with a gamma-emitting radionuclide, was measured in human subjects, using the technique of gamma scintigraphy. Similar rates of emptying for polycarbophil formulation and control formulation indicated that their admixture with polycarbophil did not retard the gastric emptying of pellets in fasted subjects. On the other hand, Russell and Bass (93) reported that 50% of a 90-g polycarbophil meal emptied within 4 hr in canine gastric acid.

Ito et al. (94) developed magnetic granules containing ultrafine ferrite, brilliant blue FCP, and bioadhesive polymers (10:1:9 w/w), surmising a possible application for targeting therapy for esophageal cancer. When 5 mg of granules containing a mixture of HPC and carbopol 934 (6:4 w/w) was flushed into an agar gel tube with 20 ml of 0.65% HPC solution, about 90% of the granules were held in the region of the applied magnetic field when the granules were administered to rabbits with about 2 ml of 0.65% HPC solution via catheter and without anesthesia; nearly all of the granules were held in the region 2 hr after administration with magnetic guidance for the initial 2 min.

Aiache (95) mixed morphine sulfate with a natural protein, Prosobel L85 (>50%) and a hydrophilic polymer, HPMC (0.5–1%), then wet granulated and compressed the dry granules (with lubricants and other excipients) into tablets to prepare a sustained-release mucoadhesive dosage form.

Decrosta et al. (96) used carbopol 934P as mucoadhesive substance to prepare captopril sustained-release tablets. Captopril mixed with carbopol 934P and stearic afcid (as lubricant) and tableted could sustain the release of the drug for upto 16 hr or more.

Matharu and Sanghavi (97) also used carbopol 934P and poly(acrylic acid) cross-linked with 0.001% ethylene glycol, to prepare mucoadhesive tablets for captopril.

Vaginal Bioadhesive Drug Delivery Systems

For drugs which are susceptible to gut or hepatic metabolism or which cause GI side effects, vaginal delivery may offer a number of advantages over the other routes of administration. However, in common with other mucosal sites, such as mouth, nose, and rectum, the bioavailability and local action of drugs administered vaginally is generally very low and may be increased by use of principle of bioadhesion.

In recent years vaginal bioadhesive preparations have been developed as a new type of controlled-release form for the treatment of both topical and systemic diseases. The greatest advantage of such dosage forms is the possibility of maintaining them in the vagina for extended periods of time including daytime and nighttime, thereby enabling lower dosing frequencies. Among the polymers, polyacrylic acid (PAA) and hydroxypropyl methyl cellulose (HPMC) are the ideal excipients in bioadhesive vaginal preparations due to their high bioadhesive strength.

The vagina is a fibromuscular tube connecting the uterus to the exterior of the body. In adults, length of the vagina varies from 6 to 10 cm, with the posterior wall approximately 1.5–2.0 cm longer than the anterior wall. The vaginal epithelium is a stratified squamous epithelium resting on a lamina proporia. The surface area of the vagina is increased by numerous folds in the epithelium and by microridges covering the epithelial cell surface (98). The vaginal wall is devoid of glands but is usually covered by a surface film of moisture. This consists of mainly cervical mucus and of fluid exudate from the rich, vascular lamina propria. The pH of the vagina is usually between 4 and 5, and is maintained by action of bacteria which converts glycogen into lactic acid. Menstrual blood, cervical and uterine secretions, and semen act as alkalinizing agents and increase the vaginal pH. The pH tends to be lowest during pregnancy and at ovulation, when estrogen level reaches a peak and glycogen accumulation is maximal (99).

The volume, viscosity, and pH of the cervical mucus also vary with menstrual cycle. At the time of ovulation, mucus secretion is increased and the mucus is clear, thin, and alkaline. After ovulation, the mucus produced is scanty and viscous. The volume, viscosity, and pH of vaginal fluids may also affect the vaginal absorption of drugs. Semen volume averages 3.3 ml and has a greater buffering capacity than vaginal secretions associated with sexual arousal, which are at a more physiological pH.

A number of animal models have been employed in the study of vaginal absorption of drugs, including cats, dogs, mice, rats, rabbits, and sheep. In several of these models, the permeability of the vaginal epithelium and the vaginal absorption of drugs may vary during the estrus or menstrual cycle, and extent of absorption may vary between the species. The vaginal cavity has traditionally been used for the delivery of locally acting

drugs such as antibiotics and antifungal compounds, or for the delivery of systematically acting contraceptives and prostaglandins. When a continuous infusion of the drug over an extended period is essential, vaginal delivery systems such as vaginal rings, microcapsules, and pessaries are used. The main factors that govern the drug release rate over a predetermined time period from controlled-release bioadhesive matrices are concentration of the polymer and drug in the tablet, drug solubility and diffusion coefficient, and matrix porosity and tortuosity (100).

Machida et al. (101) developed a topical, disk-like dosage form for carcinoma colli. Flat-faced disks were prepared containing a mixture of biomycin hydrochloride and a combination of HPC and other water-soluble polymers. A combination of HPC and CP-934 was chosen as the vehicle, and the amount of BLM released from the preparation increased remarkably with an increase in concentration of HPC.

Lejoyeux et al. (28) developed a bioadhesive tablet of metronidazole for oral or vaginal administration, containing 50% drug, 37.5% HPC, and 12.5% carbopol 934P. It seems that the presence of a large quantity of mucus at the interface protects the bioadhesive system from the effects of the surrounding medium.

Prostaglandin F_2 given intravaginally or intracervically has been widely used to induce ripening of the cervix. It has been found that the shelf life of this drug, which is 7 days to 2 months at 4°C, can be extended to 4 months to a year at room temperature, if formulated with cross-linked water-insoluble polymer (12).

Nagai and his group improved their vaginal preparations for the treatment of carcinoma coli for treating tumor cells inside the cervical canal. They prepared stick-like preparation containing bleomycin, carboquone, or 5-fluorouracil in a mixture of hydroxypropyl cellulose and carbopol 934. Such a system showed an advantage over suppositories of bleomycin with Witepsol, and the percentage of complete disappearance of carcinoma cells increased in clinical studies (12).

Ocular Mucoadhesive Drug Delivery Systems

The physiology of the eye is as follows:

- *Eyelids*: The main functions of the eyelids are to protect and to replenish the tear film over the exposed globe through the blinking mechanism. Located on the temporal area above each eye is the lachrymal gland, which provides the bulk of the aqueous fluid that constitutes tears.
- *Conjuctiva*: The conjuctiva is the mucous membrane that lines the lids. It is a multilayered nonkeratinized columnar epithelium covering the highly vascularized substantial proporia.
- *Lacrimal gland*: It is located beneath and behind the upper lid, and is responsible for secretion of the major volume portion of the tear film.
- *Cornea*: The cornea is a unique three-layered membrane, because the special arrangement of cells, vascularity, and smoothness of epithelium make it transparent.
- *Tear film*: The tear film is a crucial part of the preocular area with respect to conventional and adhesive dosage forms, since it is the major carrier of debris away from the eye. Normal tear flow would facilitate drug release from the precorneal dosage form by providing a constant flow of dissolving fluid and preventing the accumulation of drug in the vicinity of the vehicle. The pH of the tears normally ranges between 7.3 and 7.7, and is buffered by inorganic salts in the aqueous layer. Reflex tearing can result from instillation of solution outside this range. Tears are poorly buffered, especially at higher pHs.

The major reason for failure of conventional ocular drug delivery systems is the drainage of the drug before adequate absorption can occur. Approximately 2 μl is pumped from the tear film in each blink (102). Therefore, for a 50 μl drop, with 20–30 μl lost from overflow and immediate drainage and 2 μl/blink lost continuously, only about one third of the dose remains available for absorption after few seconds. Hence loss of drug via drainage, short residence time, tear turnover, and protein binding are some of the problems associated with ocular administration of drug.

Hui and Robinson (103) showed (using progesterone as the model drug) that the area under the curve of an aqueous humor drug concentration versus time plot was 4.2 times greater than conventional suspension in rabbits.

Nasal Bioadhesive Drug Delivery Systems

The nasal route appears to be an ideal alternative to the parenterals for administering drugs intended for systemic effect, in view of the rich vascularity of the nasal membranes and the ease of intranasal administration. Besides avoidance of hepatic first-pass elimination, the rate and extent of absorption and the plasma concentration versus time profile are relatively comparable to

those obtained by IV medication. Nasal membranes are characterized by existence of a highly rich vasculature and a highly permeable structure for absorption. However, there are some factors which could potentially influence the efficacy of nasal absorption of drugs, such as method and technique of administration, the site of deposition, and rate of clearance (142). Nasal mucosa is a thin vascular tissue with a surface area of about 150 cm^2.

Nasal Passage

The nasal passage, which is 12–14 cm in depth, runs from the nasal valve to the nasopharynx. The three distinct functional zones in the nasal cavity are named the *vestibular, respiratory*, and *olfactory* areas. The nasal passage is composed of a horizontally skin lined vestibule with the passages being directed upward and backward, and is separated by cartilagenous bony nasal septum. The septum ends at the nasopharynx and the airways merge into one.

Nasal Epithelium

The nasal membrane can be classified into olfactory and nonolfactory epithelia. The former is pseudostratified columnar in type and consists of specialized olfactory cells, supporting cells, and both the serous and mucous glands. There are two types of mucus covering the surface of the mucous membrane; one adheres to the tips of cilia and the other fills the space among the cilia. Adequate moisture is necessary to maintain the normal functions of the nasal mucosa. Dehydration of the mucous blanket increases the viscosity of secretions and reduces the ciliary activity.

Nasal Secretion

In a clean, noninfected, nonallergic nose, the mucosa is covered by a thin layer of mucus, which is moved posteriorly by the ciliary beat at a rate of about 1 cm/min, so that the nasal mucus is renewed approximately every 10 min (143). A total of approximately 1500–2000 ml of mucus is produced daily, which contains 90–95% water, 1–2% salt, and 2–3 % mucin. In addition to mucous glycoproteins, nasal secretions contain a variety of other proteins, enzymes, and antibodies. The presence of excessive mucus has direct implications on the development of nasal bioadhesive drug delivery systems.

The normal pH of the nasal secretions in the adults ranges approximately from 5.52 to 6.5, whereas in infants and young children it ranges from 5 to 6.7. It is obvious that the distribution of the drug in the nasal cavity is an important factor for nasal medication. Because the method of delivery will affect drug distribution in the nose, it will subsequently influence the site of deposition and efficacy of drug. It is important that the integrity of the nasal clearance mechanisms should be kept intact so that it can remove dust, allergens, and bacteria. However, the mechanism can be influenced by drug and excipients in the formulation.

Nasal Dosage Forms

In recent years intranasal administration, which might be useful for many compounds which are not absorbed orally, has received a great deal of attention. Nagai et al. (104) in their study of dogs with powder dosage forms of insulin using a freeze-dried powder with carbopol 934, obtained the same blood concentration of insulin as with an intravenous injection of three times higher dosage.

Morimoto et al. (105) developed a bioadhesive system for nasal administration of nifedipine, using a mixture of drug (10 μg/ml), PEG 400, and carbopol 931 (50:50). They obtained a relatively high and sustained drug plasma concentration.

Illum et al. (106,107) demonstrated the bioadhesive properties of severe microsphere (albumin, starch, and DEAE-dextran microspheres) for nasal use. The half-life of clearance for starch microspheres was found to be in the order of 240 min, compared to 15 min for the liquid and powder control formulations.

Nagai (12) has published works on the development of a powder called "Rhinocort" containing beclomethazone dipropionate and hydroxypropyl cellulose for the treatment of allergies.

Rectal Bioadhesive Drug Delivery Systems

Hydrogels administered rectally have proven to be useful for drug delivery. Leede et al. (108) proposed that hydrogels using hydroxyethyl methacrylate cross-linked with ethylene glycol dimethacrylate and including antipyrine and theophylline as model drugs provided rate-controlled drug delivery. A good correlation between in vitro and in vivo results with antipyrine was obtained.

Buccal Bioadhesive Drug Delivery Systems

Overview of Oral Mucosa

The oral mucosa is a complex series of tissues demonstrating a range of permeabilities. The oral cavity is

lined with stratified squamous epithelium below which lies the basement membrane; that membrane is supported by a connective tissue lamina propria which consists of collagen fibers, a supportive layer of connective tissue, blood vessels, and smooth muscle. The major artery supplying blood to the oral cavity is the external carotid artery. The venous backflow goes through the branches of capillaries and veins, and is finally taken up by the jugular vein (123).

The stratified squamous epithelia consists of a mitotically active basal cell layer, progressing through a number of differentiating intermediate layers to the superficial layer, where the cells are shed from the surface of the epithelium. These regions represent the major absorption sites in the oral cavity. An important issue is the turnover of cells. Unlike the skin, which has a complete turnover period of 30 days, the oral mucosa has a turnover time in the range of 3–8 days. The buccal epithelium is composed of approximately 40–50 cell layers, while sublingual layer consist of fewer cell layers. In humans, dogs, and rabbits, the buccal mucosa measures 500–800 μm in thickness. The surface of the mucous membrane is continuously washed by a stream of about 0.5 to 2 liters of saliva daily, which is produced by the salivary glands comprised of three pairs of parotid, submaxillary, and sublingual glands. In addition, the buccal and palatal regions contain minor salivary glands. Absence of keratized tissue (buccal and sublingual) makes the oral mucosa more permeable than skin. This improved permeability of the oral mucosa, as compared to skin, holds for a wide variety of drugs. Both the gut and the oral mucosa are kept moist all the time. However, the GI tract is lined with columnar epithelia, highly specialized for its absorptive functions. Hence, one might expect the oral mucosa to be less permeable than the gut and to have permeability characteristics between that of the gut and skin, and closer to the former.

Substances can be transported across various epithelial membranes by means of simple diffusion, carrier-mediated diffusion, active transport, or other specialized mechanisms such as endocytosis. While cells of the oral epithelium are capable of taking up material by endocytosis, particularly in the basal and prickle layer (109), it does not seem likely to be a transport mechanism across an entire stratified epithelium. There is considerable evidence suggesting that most substances passing across the oral mucosa move by simple Fickian diffusion (110). Two potential routes across the oral mucosa can be classified as nonpolar and polar. The nonpolar route involves lipid elements of the mucosa by partitioning of the drug into the lipid bilayer of the plasma membrane or into the lipid of intracellular matrix. The polar route involves the passage of hydrophilic material through the aqueous pores in the plasma membrane of individual epithelial cells, or ionic channels in the intracellular spaces of the epithelium. The rate at which a given drug will pass across the oral mucosa is determined by its partitioning between lipid and water. Substances with high lipid solubility will be transported through the lipid-rich plasma membranes of the epithelial cells, while water-soluble substances will pass through the intracellular spaces.

Buccal Dosage Forms

With a better understanding of the mechanism(s) of bioadhesion, several bioadhesive dosage forms have been reported. Because of the presence of a smooth and relatively immobile surface for placement of a bioadhesive dosage form, the buccal region appears to be more suitable for sustained delivery of therapeutic agents using a bioadhesive system.

Since there is a limit to the size of the bioadhesive dosage form, only a limited amount of drug can be used in these systems. In general, any drug with a daily requirement of 25 mg or less is suitable for buccal delivery. Drugs with short biological half-lives; requiring a sustained effect; and exhibiting poor permeability, sensitivity to enzymatic degradation, and poor solubility may be successfully delivered via a bioadhesive oral delivery system. Relevant bioadhesive dosage forms in the buccal cavity include adhesive tablets, adhesive gels, adhesive patches, and adhesive ointments.

Adhesive Tablets. Unlike conventional tablets, bioadhesive tablets allow drinking and speaking without major discomfort. Triamcinolone acetonide (12) has been formulated as a bioadhesive tablet for the treatment of aphthous stomatitis. This is a small, thin, and double-layered tablet, currently marketed in Japan under the trade name Aftach. Schor in 1983 (112) developed nitroglycerin bioadhesive tablet, susadrin for angina pectoris.

Adhesive Gels. Bioadhesive gels may be used to deliver the drug via the buccal mucosa with the possibility of prolonging residence time and improve bioavailability. Polyacrylic acid and polymethylmethacrylate have been used as gel-forming polymers.

Adhesive Patches. Bioadhesive patches may range from simple erodible and nonerodible adhesive disks to laminated systems (113) in the size range of 1–16 cm^2. These can be designed to provide either unidirectional or bidirectional release of the drug.

As early as in 1947, gum tragacanth and dental adhesive powders were used to incorporate penicillin for application in dentistry. In the late 1950s orahesive and orabase were developed as mucoadhesives for the oral cavity orahesive bandage composed of gelatin, sodium carboxymethyl cellulose, and polyisobutylene backed by a layer of polyethylene film on one side and a layer of removable paper on the other. The research in bioadhesion was continued in 1970 by Chen and Cryr (114). Machida and Nagai (72), in 1978, developed a new peroral controlled-release dosage form using HPC-L and lactose for directly compressed tablets of *dl*-isoproterenol hydrochloride.

Nagai's group (87) in 1981 developed a new oral mucosal dosage form of insulin with a view to solving the problem of administration by injection, using HPC-H and carbopol-934 (1:2) and sodium glycocholate. Absorption of insulin was about 0.5% compared with amount absorbed on intramuscular injection when tested in beagle dogs. Later, in 1982 (74), they attempted to develop a multilayered bioadhesive tablet containing a local anesthetic for toothaches, using lidocaine as a model drug in hydroxypropyl cellulose and carbopol-934. This dosage form could afford a long-acting local anesthetic action, especially if lidocaine could be replaced by dibucaine in order to obtain a better anaesthesia.

Ointments. In 1982 the above scientists (51) developed an ointment-type oral mucosal dosage form of prednisolone for the treatment of aphthae; it contained carbopol-934 and white petrolatum served as the base. It was found that the release of prednisolone from the ointment containing 30% carbopol was better than the original base.

Bremecker, Strempel, and Klein (77) formulated a novel mucosal adhesive ointment containing tretinoin (vitamin A acid) for the treatment of lichen planus, using neutralized polymethacrylic acid methyl ester; this caused neither any local initiation inhuman buccal mucosa nor any systemic side effects. With twice daily treatment the macroscopic lesions disappeared after an average of 3–4 weeks in 15 to 18 patients. This new form of mucosal adhesive ointment could be applied to all types of mucous membranes and could also be used for incorporation of other drugs.

Buccoadhesive Formulations

Nagai's group (115), in 1987, developed a bilayered bioadhesive tablet for aphthous stomatitis containing triamcinolone acetonide as the active ingredient. This tablet, commercially available under the same AFTACH, resulted in the award of the Japan National Invention Prize to Professor Nagai in 1984.

In 1989 Lejoyeux et al. (28) developed a bioadhesive tablet of metronidazole using carbopol-934 and HPMC-K4M (1:3) as bioadhesive component. Bioadhesion was found to be a function of pH and presence of ions.

Collins and Deasy (75) studied the release of cetyl pyridinium chloride from two- or three-layered bioadhesive flavored device in six healthy human volunteers. It was observed that in comparison with a proprietary lozenge, the device produced more uniform and effective level of drug (20 μg/ml), with adequate comfort, taste, and nonirritancy over a period of 3 hr. Bouchaert and Remon (40) developed a buccal releasing device in the form of tablets of thermally modified starch and polyacylic acid containing miconazole, hence overcoming the shortcomings of buccal gel currently in use for this purposes.

Nozaki et al. (90) developed a new transmucosal therapeutic system for controlled systemic delivery of isosorbide dinitrate. It consisted of a fast-release layer of D-mannitol PVP, which provided a rapid release (20%) of drug in 15 min and created a prompt rise in blood concentration to reach therapeutic level; and a sustained-release layer of PVP and polyacrylic acid, which released the rest of 80% of drug to maintain therapeutic levels up to 12 hr.

Gupta et al. (79,116) developed a buccal delivery system for verapamil hydrochloride using a freeze-dried mixture of HPC-M and carbopol-934 (2:3) in the form of a three-layered tablet. The release studies were carried out across rabbit buccal mucosa. Ahuja et al. (24,46) studied the release of diltiazem hydrochloride from a carbopol 934 and PVP k-30 (1:4) matrix containing 6% cetric acid and 12% PEG 4000. In vitro release of 86% and a 7% release across bovine cheek pouch were observed.

Yotsuyanagi et al. (117) designed a mucoadhesive, moderately water-soluble polymeric film containing analgesics and antibiotics for the treatment of lesions and also to ease the accompanying pain. The film consisted of hydroxypropyl cellulose-M and contained tetracaine, thiamphenicol, and triacetin.

Ponchel et al. (28), developed a bioadhesive tablet of metronidazole containing hydroxypropylmethyl cellulose and poly(acrylic acid), and studied its release behavior and bioadhesive performance with respect to sublingual bovine mucus. The system containing 50% by weight metronidazole was found to exhibit non-Fickian release

behavior. The bioadhesive strength depended on the polyacrylic acid content.

Anders et al. (118) developed and evaluated laminated mucoadhesive patches of protirelin for buccal drug delivery. The patches consisted of two-ply laminates of an impermeable backing layer and a hydrocolloid polymer layer containing the drug. The duration of mucosal adhesion in vivo was found to be dependent on the type of polymer used, its viscosity grade, the polymer load per patch, and drying procedure for the preparation.

In 1991 Bottenburg et al. (31) developed a bioadhesive fluoride-containing slow-release tablet from modified starch, polyacrylic acid, polyethylene glycol, and sodium carboxymethyl cellulose. The fluoride release from the tablet was evaluated in healthy human volunteers. It was found that fluoride levels were sustained significantly longer than those obtained with the administration of a toothpaste containing four times the fluoride content.

Young et al. (119) tried to develop a transbuccal delivery system for low molecular polysaccharides (heparin), peptides, and proteins based on a hydrogel polyether urethane. They found that the delivery of low molecular weight agents was feasible from the hydrogel system, which exhibited high loading capabilities and sensible release profiles over 12-hr periods.

Save et al. (83) prepared and standardized a novel buccoadhesive erodible carrier consisting of sodium alginate, mannitol, and polyethylene glycol 6000 for the buccal delivery of nifedipine. They also formulated mucoadhesive buccal film of nifedepine (120) consisting of sodium alginate, methyl cellulose, poly(vinyl pyrrolidone), mannitol, PEG-6000, and glycerol.

Dinsheet (121) prepared a multilayered buccal tablet of hydralazine HCl using lyophilized blends of carbopol-934 and carboxymethyl cellulose, and containing citric acid, mannitol, and PEG 4000. The tablet exhibited satisfactory drug release properties in vitro and in vivo.

Recently a mucoadhesive film dosage form for isosorbide dinitrate (84) was prepared using hydroxypropyl cellulose and hydroxypropylmethyl cellulose phthalate. The film exhibited a sustained release of drug for up to 6 hr. Addition of glycyrrhizic acid increased the dissolution of the drug.

Bouckaert and Remon (40) developed a bioadhesive buccal tablet of miconazole using drum-dried waxy maize starch and polyacrylic acid. They compared the salivary miconazole concentration after administration of the bioadhesive tablet and an oral gel (122), and found that although the amount of drug administered via the bioadhesive tablet was sixfold lower than when the gel was used, the salivary miconazole levels were higher and remained above the MIC (minimum inhibitory concentration) value of *Candida albicans* for more than 10 hr.

A bioadhesive polymer patch formulation for buprenorphine controlled delivery (43)—consisting of polyisobutylene, polyisoprene, and carbopol-934P—was prepared using a two-roll milling method. It was observed that the milling process did not change the thermal, rheological, or viscous properties of the individual polymers used. A sustained delivery of buprenorphine with the ultimate release of nearly 75% of the drug was obtained over a 24-hr period. Patch swelling seemed to be the major mechanism of buprenorphine release.

Beyssac et al. (137), in 1994, developed bioadhesive buccal tablet of Piribedit. The bioavailability of the drug increases in vivo in human plasma. Voorspoelo et al. (144), in 1994, developed bioadhesive buccal tablets of testosterone and testosterone esters. Greater bioavailability was obtained and the system could sustain the testosterone levels within therapeutic plasma levels.

Rani et al. (138), in 1995, developed a buccoadhesive drug delivery system of propranolol to sustain drug release. Sodium CMC patches showed higher mucoadhesion and zero-order release.

Rajesh et al. (139,140) developed mucoadhesive buccal tablets and films of clotrimazole for oral candida infection. Drug released was found to be microbiologically active. In vivo evaluation of the optimized tablets in healthy human volunteers gave satisfactory results.

Sublingual Bioadhesive Drug Delivery Systems

The sublingual region generally shows higher drug permeability than the buccal region. This route has been extensively used for delivery of drugs which require a rapid onset of action, for example, nitroglycerine. The latest developments have been applied to the treatment of angina pectoris, cancer, and in the cure of smoking.

Using the principle of bioadhesion, Gurney et al. (52) attempted to deliver febuverine sublingually. The bioadhesive polymer system was prepared from a polyethylene gel containing various amounts of sodium carboxymethyl cellulose as the adhesive, and hydrolyzed gelatin as the water-sensitive material to ensure rapid swelling. They found that the relative adhesive bond strength of the various formulations was dependent on the concentration of NaCMC, showing a maximum at about 20 wt%. Also, optimal drug release rate was

Table 4

Commercial Mucoadhesive Dosage Forms

Name and Form	Drug	Application Site	Ref.
Aftach tablet	Triamcinolone acetonide	Oral cavity	2, 88, 124
Susadrin tablet	Nitroglycerin	Buccal	16, 112, 125
Buccostem tablet	Prochlorperazine maleate	Buccal	16, 125
Salcoat powder spray	Beclomethasone dipropionate	Oral cavity	126
Soloseryl paste	—	Gingival	126
Orabase gel	—	Oral cavity	52, 114, 127, 128
Orahesive bandage	—	Oral cavity	52, 114, 127, 128
Rhinocort powder spray	Beclomethasene dipropionate	Nasal	129
Replens gel	—	Vaginal	130
Sucralfate	Aluminum hydroxide	Gastrointestinal ulcers	131–136

achieved in formulations with NaCMC concentration in the range of 12–15 wt%.

CONCLUSIONS

Mucosal adhesive dosage forms are now at the starting line. The advantages are tremendous, which make further study in this field extremely important. The formulation of these drug delivery systems depends on the development of suitable polymers with excellent mucosal adhesive properties, stability, and biocompatibility. Many mucoadhesive drug delivery systems are already on the market, as shown in Table 4. Moreover, research in this field is becoming very active. Therefore, we hope that in the near future these dosage forms will be a reality for use and become an alternative to controlled-release dosage forms for the treatment of both topical and systemic diseases.

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