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# Polymers for Mucoadhesive Drug Delivery System: A Current Status

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**To overcome the relatively short gastrointestinal (GI) time and improve localization for oral controlled or sustained release drug delivery systems, bioadhesive polymers that 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 in the GI tract, including the buccal cavity and rectum. This article lays emphasis mainly on mucoadhesive polymers, their properties, and their applications in buccal, ocular, nasal, and vaginal drug delivery systems with its evaluation methods.**

**Keywords** mucoadhesion; mucoadhesive polymers; buccal; nasal; ocular; vaginal; evaluation.

## INTRODUCTION

Bioadhesion may be defined as the state in which two materials, atleast one of which is of biological nature, are held together for extended periods of time by interfacial forces (Chickering & Mathiowitz, 1999). For drug delivery purposes, the term *bioadhesion* implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue, or the mucous coat on the surface of a tissue. If adhesive attachment is to mucous coat, the phenomenon is referred to as mucoadhesion (Ahuja, Khar, & Ali, 1997a).

The mucoadhesion may be defined as drug delivery systems that utilize property of bioadhesion of certain water-soluble polymers that become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time (Chowdary, & Srinivas, 2000; Jimenez-Castellanos, Zia, & Rhodes, 1993).

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The mucosal layer lines a number of regions of the gastrointestinal (GI) tract, the airways, the ear, nose, and the eye. These represent potential site for attachment of any bioadhesive system, and hence, the mucoadhesive drug delivery system includes the following (Khanna, Agrawal, & Ahuja, 1998).

1. Buccal delivery system
2. Oral delivery system
3. Vaginal delivery system
4. Rectal delivery system
5. Nasal delivery system
6. Ocular delivery system

### Mucoadhesive Polymers (Chowdary & Srinivas, 2000)

Mucoadhesive polymers are water-soluble and water-insoluble polymers, which are swellable networks, joined by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place. Mucoadhesive polymers that adhere to the mucin–epithelial surface can be conveniently divided into three broad classes.

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

### Characteristics of an Ideal Mucoadhesive Polymer (Patil, Murthy, Mahajan, Wagh, & Gattani, 2006)

1. The polymer and its degradation products should be nontoxic and should be nonabsorbable from the GI tract.
2. It should be nonirritant to the mucus membrane.

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

Robinson and his group (Park & Robinson, 1984), using the fluorescence technique, 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 with 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 carboxy methyl cellulose, gelatine, hyaluronic acid, carbopol, and polycarbophyl.

## Molecular Characteristics

Investigations into polymers with various molecular characteristics have led to a number of conclusions regarding the molecular characteristics required for mucoadhesion (Lee, Park, & Robinson, 2000).

The properties exhibited by a good mucoadhesive may be summarized as follows (Peppas & Buri, 1985):

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

Examples of some mucoadhesive polymers and their properties are enlisted in Table 1.

## Factors Affecting Mucoadhesion (Chen, & Cyr; Ch'ng, Park, Kelly, & Robinson 1985)

*Polymer-Related Factors*

*Molecular Weight (Duchene, Touchard, & Peppas, 1988).* The optimum molecular weight for maximum bioadhesion depends upon type of bioadhesive polymer at issue. It is generally understood that the threshold required for successful bioadhesion is atleast 100,000 molecular weight. For example polyethylene glycol (PEG), with a molecular weight of 20,000, has little adhesive character, whereas PEG with 200,000 molecular weight has improved and PEG with 400,000 has superior adhesive properties. The fact that bioadhesiveness improves with increasing molecular weight for linear polymers implies two things: (1) interpenetration is more critical for low molecular weight polymer to be a good bioadhesive, and (2) entanglement is important for high molecular weight polymers. Adhesiveness of a nonlinear structure, by comparison, follows a quite different trend. The adhesive strength of dextran, with a high molecular weight of 19,500,000, is similar to that of PEG, with a molecular weight of 200,000. The reason for this similarity may be that the helical conformation of dextran may shield many of the adhesive groups, which are primarily responsible for adhesion, unlike the conformation of PEG.

*Concentration of Active Polymer (Duchene et al., 1988; Gurny, Meyer, & Peppas, 1984).* There is an optimum concentration for bioadhesive polymer to produce maximum bioadhesion. In highly concentrated system, beyond the optimum level, however the adhesive strength drops significantly because the coiled molecules become separated from the medium so that the chain available for interpenetration becomes limited.

*Flexibility of Polymer Chains (Barrer, Barrie, & Wong, 1968).* Chain flexibility is critical for interpenetration and entanglement. As water soluble-polymers become cross-linked, mobility of an individual polymer chain decreases and thus the effective length of the chain that can penetrate into the mucus layer decreases, which reduces bioadhesive strength.

*Spatial Conformation (Ahuja et al., 1997a).* 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 PEG, 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.

*Swelling (Chen & Cyr, 1993; Gurny& Peppas, 1990).*

Swelling characteristics are related to the bioadhesive itself and its environment. Swelling depends on the polymer concentration, the ionic strength, and the presence of water. During the dynamic process of bioadhesion, maximum bioadhesion in vitro occurs with optimum water content. Overhydration results in the formation of a wet slippery mucilage without adhesion.

*Environment-Related Factors*

*pH of Polymer–Substrate Interface (Ch'ng et al., 1985; Park & Robinson, 1984, 1985b).* pH can influence the formal charge on the surface of the mucus as well as certain ionizable bioadhesive polymers. Mucus will have a different charge density depending on pH due to difference in dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. Some studies had shown that the pH of the medium is important for the degree of hydration of cross-linked polyacrylic acid, showing consistently increased

TABLE 1
Some Bioadhesive Polymers and their Properties

| Bioadhesive | Properties | Characteristics | Reference |
|---|---|---|---|
| Polycarbophil (polyacrylic acid cross-linked with divinyl glycol) | • MW = $2.2 \times 10^5$<br>• η 2,000–22,500 cps (1% aq.soln)<br>• 15–35 mL/g in acidic media<br>• (pH 1–3) 100 mL/g in neutral and basic media<br>• Viscous colloid in cold water | • Synthesized by lightly cross-linking divinyl glycol<br>• Swellable depending on pH, but insoluble in water<br>• Entangle the polymer with mucus on the surface of the tissue<br>• Hydrogen bonding between the non-ionized carboxylic acid and mucin | (Ch'ng et al., 1985) |
| Carbopol/carbomer (carboxy polymethylene) | • MW $1 \times 10^6$–$4 \times 10^6$<br>• η 29,400–39, 400 cps at 25°C with 0.5% aqs.soln.<br>• ρ 5 gm/cm$^3$ in bulk<br>• pH 2.5–3.0<br>• Φ water, alcohol, glycerine | • Synthesized by cross-linker of allyl sucrose or allyl penta erythritol<br>• Excellent thickening, emulsifying suspending gelling agent<br>• Common component in bioadhesive dosage form | (Ahuja, Khar, & Ali, 1997b) |
| Sodium carboxymethyl cellulose (cellulose carboxymethyl ether sodium salt) | • MW $9 \times 10^4$–$7 \times 10^5$<br>• η 1,200 cps with 1.0% soln.<br>• ρ 0.5 gm/cm$^3$ in bulk<br>• pH 6.5–8.5<br>• Φ water | • Sodium salt of a polycarboxy methyl ether of cellulose<br>• Emulsifying, gelling, binding agent<br>• Good bioadhesive strength | (Wallace, 1990) |

| | | | |
|---|---|---|---|
| Hydroxypropyl cellulose (cellulose 2-hydroxypropyl ether) | • MW $6 \times 10^4$–$1 \times 10^n$<br>• η 4,000–6,000 cps (2% aqs. soln.)<br>• ρ 0.5 g/cm*n* in bulk<br>• Φ soluble in water below 38°C, ethanol | • Partially substituted polyhydroxypropyl ether of cellulose<br>• granulating and film coating agent for tablet<br>• thickening agent, emulsion stabilizer, suspending agent in oral and tropical liquid soln. or suspension formulation | (Kumar & Banker, 1993) |
| Hydroxypropylmethyl cellulose (cellulose 2-hydroxypropylmethyl ether) | • MW $8.6 \times 10^4$<br>• η 15–4,000 cps (2% aqs. soln.)<br>• Φ cold water | • Mixed alkyl hydroxy alkyl cellulosic ether<br>• Suspending, viscosity-increasing, and film-forming agent<br>• Tablet binder and adhesive ointment ingredient | (Ahuja et al., 1997b) |
| Hydroxyethyl cellulose | • ρ 0.6 g/mL<br>• pH 6–8.5 | • Used as suspending or viscosity-increasing agent<br>• binder, film-former, thickener | (Ahuja et al., 1997b) |
| Alginate | • pH 7.2<br>• η 20–400 cps (1% aqs. soln.)<br>• Φ water | • stabilizer in emulsion, suspending agent, tablet disintegrant, tablet binder | (Wallace, 1990) |

η, viscosity; MW, molecular weight; pH, measured at 1.0% aqueous solution; α, absorption measured at water; Φ, soluble solvent; soln.,solution; aqs, aqueous.

hydration from pH 4 through pH 7, and then a decrease as alkalinity or ionic strength increases, for example polycarbophil does not show a strong bioadhesive property above pH 5 because uncharged, rather then ionized, carboxyl group reacts with mucin molecule, presumably through numerous hydrogen bonds. However at higher pH, the chain is fully extended due to electrostatic repulsion of the carboxylate anions.

*Applied Strength (Ahuja et al., 1997a).* To place a solid bioadhesive system, it is necessary to apply a defined strength. Whatever the polymer, poly(acrylic acid/divinyl benzene) or carbopol 934, the adhesion strength increases with the applied strength or with the duration of its application, up to an optimum. The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interactions with mucin.

*Initial Contact Time (Kamath & Park, 1994).* Contact time between the bioadhesive and mucus layer determines the extent of swelling and interpenetration of the bioadhesive polymer chains. More bioadhesive strength increases as the initial contact time increases.

*Physiological Factors*

*Mucin Turnover (Lehr, Poelma, Junginger, & Tukker, 1991).* The natural turnover of mucin molecules from the mucus layer is important for atleast two reasons. 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 chance to interact with the mucus layer. Surface fouling is unfavorable for mucoadhesion to the tissue surface. Mucin turnover may depend on the other factors such as the presence of food. The gastric 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. 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 the rate of 5 mm/min. The mucociliary clearance in the tracheal region has been found to be in the rate of 4–10 mm/min (Allen, Pain, & Robson, 1976).

*Disease State (Allen et al., 1976).* The physiochemical 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 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.

## Mucoadhesive Systems

The mucoadhesive systems are intended to extend the GI residence time by adhering them to the gastric mucous membrane. Bioadhesion on soft tissues of certain natural or synthetic polymers has been exploited to control as well as to prolong the gastric retention of the delivery systems (Ch'ng et al., 1985; Longer, Ch'ng, & Robinson, 1985). The adhesion of the polymers with the mucous membrane may be mediated by hydration, bonding, or receptor (Park & Robinson, 1984). In hydration-mediated adhesion, the hydrophilic polymers become sticky and mucoadhesive upon hydration.

Bonding-mediated adhesion may involve mechanical or chemical bonding. Chemical bonds may involve covalent or ionic bonds or Van der Waals forces between the polymer molecules and the mucous membrane. Receptor-mediated adhesion takes place between certain polymers and specific receptors expressed on gastric cells. The polymers could be anionic or cationic or neutral. The details of the classification are given below in Table 2.

## Drug Delivery via Oral Mucosa

Absorption of drug via the mucous membranes of the oral cavity can occur in the sublingual, buccal, or local regions. The local region includes all areas other than the former two regions. In general, the oral mucosa is classified as a somewhat leaky epithelium with a permeability rank order of sublingual > buccal > palatal, based on the thickness and degree of keratinization of the tissues (Harris & Robinson, 1992). Different regions of the oral cavity vary greatly in terms of their composition and their potential utility in drug delivery. The thin and highly permeable membrane of the sublingual tissue is a perfect target if a prompt onset is desired. Considerable surface area and high blood flow to this region provide a means for

TABLE 2
Classification of Bioadhesive Polymers (Talukdar & Fassihi, 2004)

| Anionic | Cationic | Neutral |
|---|---|---|
| Carboxymethylcellulose | Polylysine | Polyethylene glycol |
| Chondroitin sulfate | Polybrene | Polyvinyl pyrrolidone |
| Polyacrylic acid | | Dextran |
| Pectin | | |
| Carageenan | | |
| Chitosan | | |
| Alginic acid | | |

rapid access to the systemic circulation. However, if a retentive, sustained-release system is desired, the sublingual membrane fails to be an appropriate target tissue.

Local delivery in the oral cavity has had particular applications in the treatment of toothache, periodontal diseases, and bacterial infections. However, because of its specificity, local delivery does not have the broad range of applications that sublingual and buccal drug administration provides. The list of investigated buccal mucoadhesive tablets is given in Table 3.

The list of investigated buccal mucoadhesive patches is given in Table 4.

The list of investigated buccal mucoadhesive films is given in Table 5.

The list of investigated buccal mucoadhesive gels is given in Table 6.

## Ocular Drug Delivery (Ahuja et al., 1997a; Lee et al., 2000; Ludwig, 2005)

*Structure of the Ocular Globe*

The eyeball has a wall consisting of three layers: the outer coat or the sclera and cornea, a middle layer or uveal coat, and the inner coat or retina. The sclera is made of fibrous tissues shaped as segments of two spheres, the sclera and the cornea. The external part of the eye is covered by the mobile tarsal part of the eyelids. The thin skin of the lids folds easily over the eyeball and permits rapid opening and closing of the palpebral fissure. The eyelids are under involuntary (spontaneous or periodic blinking and reflex blinking) and voluntary control. They distribute the tear fluid over the eye, providing an optically smooth surface over the cornea. The shear rate during blinking is estimated to be about 20,000 $s^{-1}$ and influences the rheological properties of viscous ocular dosage forms instilled and consequently the bioavailability of the drug applied. The cornea is a clear, transparent, avascular tissue to which nutrients and oxygen are supplied by the lacrymal fluid and aqueous humor. It is composed of five layers: epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium. The epithelium consists of five to six layers of cells. The cells of the basal layer are columnar. As they are squeezed forward by the new cells, they differentiate and exfoliate from the epithelial surface as flattened polygonal cells. Replacement of the epithelial cells occurs by mitotic division of the basal layer. The average life of a polygonal cell is about 4 to 8 days.

The basal cellsl are packed closely together like a pavement, forming not only an effective barrier to most microorganisms but also for drug absorption. The low permeability of the cornea suggests the presence of tight junctions between the cells. The tight junction complex includes two integral transmembrane proteins (claudin and occludin) and the membrane-associated protein ZO-1. Claudins also function as extracellular aqueous pores. The cellular calcium levels and actin filaments of the cytoskeleton probably play an important role in the integrity of the tight junctions. High extracellular and low intracellular calcium levels are required for the low permeability of the normal tight junction. The squamous flattened cells have on their surface microvilli of different types and dimensions depending on the maturity of the cells. These microvilli enhance the cohesion and stability of the tear film. The conjunctiva is a thin transparent membrane, which lines the inner surface of the eyelids and is reflected onto the globe. At the corneal margin, it is structurally continuous with the corneal epithelium. The membrane is vascular and moistened by the tear film.

To improve the ocular bioavailability of drugs, numerous natural and synthetic viscosifying agents were added to the vehicle in order to increase the viscosity of the preparation, to reduce the drainage rate, and subsequently to improve the therapeutic efficacy (Chrai & Robinson, 1974; Lee & Robinson, 1986; Patton & Robinson, 1976; Saettone, Giannaccini, Ravecca, La Marca, & Tota, 1984; Saettone, Giannaccini, Teneggi, Savigni, & Tellini, 1982; Trueblood, Rossomondo, Carlton, & Wilson, 1975;). No significant bioavailability enhancement was reported in humans, as was obtained in rabbits, due to differences in blinking frequency and tolerance (Saettone, Burgalassi, & Chetoni, 2005; Saettone, Giannaccini, Guiducci, Marca, & Tota, 1985). Moreover, rapid drug efflux out of the polymer network occurs (Chang, Chien, Bundgaard, & Lee, 1988). Besides the viscosity increase of the vehicle, Hui and Robinson demonstrated the utility of bioadhesion of polymers for reducing the drainage loss after instillation of ophthalmic formulations, hence improving drug absorption or local action (Hui & Robinson, 1985). Also, in the development of efficient artificial tears, a search for polymers that mimic mucus, retain water, and stay for a long time period in the precorneal area and therefore provide a protective effect by strengthening and/or substituting the mucus layer was undertaken (Calonge, 2001; Le Bourlais, Treupel-Acar, Rhodes, Sado, & Leverge, 1998). Polymer-related factors influencing mucoadhesion are hydration or degree of swelling, molecular weight, functional groups, molecular conformation or chain flexibility and mobility, and concentration (Lee et al., 2000; Mikos & Peppas, 1986). Polymer hydration results in the relaxation of stretched, entangled, or twisted macromolecules, exposing the adhesive sites.

Furthermore, chain interdiffusion is favored by polymer–water interactions dominating the corresponding polymer–polymer interactions. A critical chain length is necessary to obtain interpenetration and molecular entanglement between the polymer and the mucus layer. The threshold required for successful mucoadhesion is a molecular weight of at least 100,000 Da. Excessive cross-linking in the polymer, however, decreases the chain length available for interfacial penetration. Also, excessive formation of interchain physical entanglement and hydrogen bonding within the polymer itself can lead to conformation hindering polymer diffusion into the mucus network (Mortazavi & Smart, 1993). Viscosifying polymers screened for ocular mucoadhesive capacity are given in Table 7.

TABLE 3
List of Investigated Buccal Mucoadhesive Tablets

| Active Ingredient | Polymers Used | Reference |
|---|---|---|
| Acitretin | CP 934P and HPMC | (Gaeta et al., 2000) |
| Carbamazepine | HPMC and CP | (İkinci et al., 2000) |
| Cetylpyridinium chloride | Sodium CMC and HPMC | (Ali, Khar, Ahuja,& Kalra, 2002) |
| Cetylpyridinium chloride | HMPC, PC, or CP 974P | (Minghetti, Pacchetti, Montanari, Ronchi, & Berlati, 1997) |
| Cetylpyridinium chloride | HPC and CP 934 | (Collins & Deasy, 1990) |
| Chlorhexidine diacetate | Chitosan and sodium alginate | (Giunchedi, Juliano, Gavini, Cossu, & Sorrenti, 2002) |
| Chlorpheniramine maleate | Hakea gum from Hakea gibbosa | (Alur, Pather, Mitra, & Johnston, 1999a, 1999b) |
| Chlorpheniramine maleate | Polyoxyethylene | (Tiwari, Goldman, Sause, & Madan, 1999) |
| Cyanocobalamin | Polyoxyethylene | (Tiwari, Goldman, Town, Sause, & Madan, 1999) |
| Danazol | PC or HPMC | (Jain, Aungst, & Adeyeye, 2002) |
| Diltiazem HCl | CP 934P and HPMC | (Singh & Ahuja, 2002) |
| Diltiazem HCl | CP 934 with HPC, HPMC, or PVP K30 | (Ahuja, Dogra, & Agarwal, 1995) |
| Ergotamine tartrate | Carboxyvinyl polymer and HPC | (Tsutsumi et al., 2002) |
| Fluoride | Not mentioned in the article (subject to a patent) | (Bottenberg, Cleymaet, Röhrkasten, & Lampert, 2000) |
| Fluoride | CP, HPMC, and gelatin | (Vivien-Castioni, Gurny, Baehni, & Kaltsatos, 2000) |
| Glucagon like peptide (GLP)1 | Poly(ethylene oxide) and CP | (Gutniak et al., 1996, 1997) |
| Hydrocortisone acetate | HPMC, CP 974P, or PC | (Ceschel, Maffei, Biogia, & Ronchi, 2001) |
| Insulin | CP 934 with HPC or HPMC | (Hosny, Elkheshen, & Saleh, 2002) |
| Insulin | CP 934 and HPC | (Ishida, Machida, Nambu, & Nagai, 1981) |
| Lactoferrin | Sodium alginate | (Kuipers et al., 2002) |
| Leu-enkephalin | Thiolated PC | (Langoth, Kalbe, & Bernkop-Schnürch, 2003) |
| Lignocaine HCl | CP 934P, sodium CMC, and PVP K30 | (Parvez, Ahuja, & Khar, 2002) |
| Luteinizing hormone-releasing hormone (LHRH) | PVP K30, PVP K90, CP 934P | (Nakane, Kakumoto, Yukimatsu, & Chien, 1996) |
| Metronidazole | HPMC, sodium CMC, and CP 934P | (Ahuja, Khar, & Chaudhry, 1998) |
| Metronidazole or benzydamine | Gelatin/HPC, gelatin/HPMC, and gelatin/sodium CMC | (Parodi, Russo, Gatti, Cafaggi, & Bignardi, 1999) |
| Metronidazole | HEC, HPC, HPMC, or NaCMC combined with CP940, | (Perioli et al., 2004) |
| Miconazole nitrate | Mixtures of HPMC, sodium CMC, CP 934P, and sodium Alginate | (Mohammed, & Khedr, 2003) |
| Miconazole nitrate | Thermally modified maize starch (drum-dried waxy maize)/PAA mixtures | (Bouckaert, Lefebvre, Colardyn, & Remon, 1993; Bouckaert, Lefebvre, & Remon, 1993; Bouckaert, Remon, 1993; Bouckaert, Schautteet, Lefebvre, Remon, & van Clooster, 1992) |
| Miconazole nitrate | Not mentioned in the article | (Van Roey, Haxaire, Kamya, Lwanga, & Katabira, 2004) |
| Morphine | Not mentioned in the article | (Beyssac et al., 1998) |

(*Continued*)

TABLE 3
(*Continued*)

| Active Ingredient | Polymers Used | Reference |
|---|---|---|
| Morphine sulfate | HPMC with CP | (Anlar et al., 1994) |
| Nalbuphine | CP 934 and HPC | (Han, Fang, Sung, & Hu, 1999) |
| Nicotine | CP 934 and HPC | (Park & Munday, 2002) |
| Nicotine | CP 974P, sodium alginate, and HPMC | (İkinci, Şenel, Wilson, & Şumnu, 2004) |
| Nifedipine | CMC and CP | (Varshosaz, & Dehghan, 2002) |
| Nifedipine | Sodium alginate, PVP, and PEG | (Save, Shah, Ghamande, & Venkitachalam, 1994) |
| Nifedipine or Propranolol HCl | Chitosan with or without anionic cross-linking polymer (PC, sodium alginate, gellan gum) | (Remuñán-López, Portero, Vila-Jato, & Alonso, 1998) |
| Omeprazole | Sodium alginate, HPM | (Choi et al., 2000; Choi & Kim, 2000; Yong, Jung, Rhee, Kim, & Choi, 2001) |
| Pentazocine | CP 974 and HPMC | (Agarwal & Mishra, 1999) |
| Pindolol | CP 934 and sodium CMC (bioadhesive polymers); HPMC and HPC (matrix-forming polymer) | (Dortunç, Özer, & Uyanik, 1998) |
| Piroxicam | HPMC and CP 940 | (Jug & Bećirević-Laćan, 2004) |
| Propranolol | PAA, HPMC, and HPC | (Çelebi & Kişlal, 1995) |
| Propranolol HCl | HPMC and PC | (Akbari et al., 2004) |
| Prosidol | N/A (article in Russian) | (Osipova et al., 1994) |
| Salmon calcitonin | Hakea gum from Hakea gibbosa | (Alur, Beal, Pather, Mitra, & Johnston, 1999) |
| Sodium fluoride | Eudragit® and/or EC | (Diarra, Pourroy, Boymond, & Muster, 2003) |
| Testosterone | Starch-g-PAA copolymers or starch/PAA mixtures | (Ameye et al., 2002) |
| Testosterone | Drum-dried waxy maize (DDWM) and CP974P | (Voorspoels, Remon, Eechaute, & De Sy, 1996) |
| Testosterone | Not mentioned in the article | (Ross et al., 2004) |
| Theophylline | Starch–acrylic acid graft copolymers | (Geresh et al., 2004) |
| Triamcinolone acetonide | CP 934P and sodium CMC | (Ali, Khar, & Ahuja, 1998) |
| Zinc sulfate | EC and Eudragit® | (Diarra, Pourroy, Muster, Zingraff, & Boymond, 1998) |

CP, carbopol; HPMC, hydroxypropylmethyl cellulose; CMC, carboxymethyl cellulose; HPC, hydroxypropyl cellulose; CP, crospovidone; PVP, polyvinylpyrrolidone; HEC, hydroxyethylcellulose; PAA, poly(acrylic acid); PEG, poly(ethylene glycol); EC, ethyl cellulose.

### Polymers in Vaginal Delivery (Ahuja et al., 1997; Lee et al., 2000; Valenta, 2005)

For drugs that are susceptible to gut or hepatic metabolism or that cause GI side effects, vaginal delivery may offer 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 principles of bioadhesion.

The vagina is a fibromuscular tube connecting the uterus to the exterior of the body. In adults, length of vagina varies from 6–10 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 lamina propria. The surface area of vagina is increased by numerous folds in the epithelium and by micoridges covering the epithelial cell surface. The vaginal wall is devoid of glands but is usually covered by a surface film of moisture. This consists of mainly cervical mucous and of fluid exuded from the rich, vascular lamina propria. The pH of the vagina is usually between 4 and 5, and is maintained by the action of bacteria which converts glycogen into lactic acid. Menstrual blood, cervical and uterine

TABLE 4
List of Investigated Buccal Mucoadhesive Patches

| Active Ingredient | Polymers Used | Reference |
|---|---|---|
| Acyclovir | Copolymers of acrylic acid and PEG monomethylether monomethacrylate (PEGMM) | (Shojaei, Berner, & Li, 1998; Shojaei, Zhuo, & Li, 1998) |
| Buprenorphine | CP 934P, polyisobutylene, and polyisoprene | (Guo, 1994; Guo & Cooklock, 1996) |
| Cetylpyridinium chloride | PVA, HEC, or chitosan | (Nafee, Boraie, Ismail, & Mortada, 2003) |
| Lignocaine | Proprietary mucoadhesive support system | (Brook, Tucker, Tuckley, & Boyes, 1989) |
| Melatonin | CP 934P and polyisobutylene | (Bénès et al., 1997) |
| Metoprolol tartrate | Eudragit® NE40D with HPMC, sodium CMC/CP | (Wong, Yuen, & Peh, 1999) |
| Miconazole nitrate | Sodium CMC, chitosan, PVA, HEC, HPMC | (Nafee, Ismail, Boraie, & Mortada, 2003) |
| Protirelin | HEC, HPC, PVP, or PVA | (Anders & Merkle, 1989) |
| Oxytocin | CP 974P | (Li, Bhatt, & Johnston, 1996, 1997) |
| Terbutaline sulfate | CP 934, CP 971, HPMC, HEC, or sodium CMC | (Mohamed & Mortada, 2000) |
| Thyrotropin-releasing hormone (TRH) | Organic polymers | (Li, Koch, Raul, Bhatt, & Johnston, 1997) |
| Thyrotropin-releasing hormone (TRH) | Not mentioned in the article | (Schurr, Knoll, Ziegler, Anders, & Merkle, 1985) |
| Triamcinolone acetonide | CP, poloxamer, and HPMC | (Chun, Kwak, & Choi, 2003) |

PEG, poly(ethylene glycol); CP, carbopol; PVA, poly(vinyl alcohol); HEC, hydroxyethyl cellulose; HPMC, hydroxypropyl methylcellulose; CMC, carboxymethyl cellulose; HPC, hydroxypropyl cellulose; PVP, poly(vinyl alcohol).

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. The volume, viscosity, and pH of the cervical mucus also vary at the time of 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.

Several bioadhesive polymers have been reported for different mucosal sites such as the buccal cavity, stomach, and intestine (Ahuja et al., 1997a). An increasing interest has been shown for vaginal bioadhesive tablets (Valenta, 2005). With respect to their facilitated and shorter registration, the polymers that were already in use as pharmaceutical excipients were tested for their mucoadhesive properties. The necessary assemblies have been designed to measure the bioadhesion characteristics of polymers and formulations in a mucus environment.

Smart, Kellaway, and Worthington, (1984) published a list of mucoadhesive polymers together with a rank order of their mucoadhesive force. Their in vitro test system consisted of homogenized mucus, which was obtained by scraping guinea-pig intestines. The force required to detach a glass plate coated with the test polymer from this mucus gel was measured. In general, the polymers had a high molecular weight and hydrophilic functional groups. Several groups of polymers have been tested as vaginal delivery systems. Details of the polymers are given in Table 8.

## Nasal Bioadhesive Drug Delivery (Ahuja et al., 1997a; Jimenez-Castellanos et al., 1993; Lee et al., 2000; Ugwoke, Agu, Verbeke, & Kinget, 2005)

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 with those obtained by intravenous medication. Nasal membranes are characterized by existence of a highly rich vasculature and highly permeable structure for absorption. However, there are some factors that could potentially influence the efficiency of nasal absorption of drugs, such as method and techniques of administration, the site of deposition, and the rate of clearance. The 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*,

TABLE 5
List of Investigated Buccal Mucoadhesive Films

| Active Ingredient | Polymers Used | Reference |
|---|---|---|
| Acyclovir | Chitosan HCl and PAA sodium salt | (Rossi, Sandri, Ferrari, Bonferoni, & Caramella, 2003) |
| Chitosan | Chitosan | (İkinci et al., 2002) |
| Chlorhexidine diacetate | EC | (Jones, & Medlicott, 1995) |
| Chlorhexidine digluconate | Chitosan | (Şenel et al., 2000) |
| CMV-β-gal plasmid DNA or β-gal protein | PC and Eudragit® S-100 | (Cui & Mumper, 2002a) |
| Dipotassium glycyrrhizate | PC, HPC, and EC | (Rhee, Lee, Sin, & Park, 1999) |
| Glibenclamide | Chitosan and PVP | (Ilango, Kavimani, Mullaicharam, & Jayakar, 1997) |
| Insulin | Gelatin and CP 934P | (Ritschel, Ritschel, Forusz, & Kraeling, 1989) |
| Lidocaine | HPC | (Okamoto, Nakamori, Arakawa, Iida, & Danjo, 2002; Okamoto, Taguchi, Iida, & Danjo, 2001) |
| Nifedipine | Sodium alginate, MC, PVP, and PEG | (Save et al., 1994) |
| Nifedipine or Propranolol HCl | Chitosan with or without an anionic cross-linking polymer (PC, sodium alginate, gellan gum) | (Remuñán-López et al., 1998) |
| Salmon calcitonin | PC and Eudragit® S-100 | (Cui & Mumper, 2002b) |
| Testosterone | PC and Eudragit® S-100 (polymethacrylic acid-co-methyl methacrylate) | (Jay, Fountain, Cui, & Mumper, 2002) |
| Tetracaine, miconazole, ofloxacin, guaiazulene, and triacetin | HPC | (Oguchi et al., 1998) |
| Tetracycline | Atelocollagen | (Minabe, Takeuchi, Tamura, Hori, & Umemoto, 1989) |
| Thiocolchicoside | Gelatin and CMC | (Artusi, Santi, Colombo, & Junginger, 2003) |

PAA, poly(acrylic acid); EC, ethyl cellulose; PC, polycarbophil; HPC, hydroxypropylcellulose; PVP, polyvinylpyrrolidone; CP, carbopol; MC, methylcellulose; PEG, poly(ethylene glycol); CMC, carboxymethylcellulose.

*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 cartilaginous 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 pseudo-stratified columnar in type and consists of specialized olfactory cells, supporting cells, and both the serous and mucous glands. There are two types of mucous 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 mucous blanket increases the viscosity of secretions and reduces the ciliary activity.

*Nasal Secretion*

In a clean, non-infected, non-allergic 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. A total of approximately 1,500–2,000 mL of mucus is produced daily, which contains 90–95% water, 1–2% salt, and 2–3% mucin. In addition to mucous glycoprotein, nasal secretions contain a variety of other proteins, enzymes, and antibiotic. 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 5.5 to 6.5, whereas in infant 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 effect drug distribution in the nose, it will subsequently influence the

TABLE 6
List of Investigated Buccal Mucoadhesive Gels

| Active Ingredient | Polymers Used | Reference |
|---|---|---|
| Arecoline | CP 934P | (Strickland, Veena, Houghton, Stanford, & Kurpad, 2003) |
| Chitosan | Chitosan | (İkinci et al., 2002) |
| Chlorhexidine | Collagen | (Vinholis et al., 2001) |
| Chlorhexidine | HEC, PVP, and PC | (Jones et al., (2000); Jones, Woolfson, & Brown, 1997) |
| Chlorhexidine digluconate | Chitosan | (Şenel, 2000) |
| Denbufylline | Palmitoyl glycol chitosan (GCP) | (Martin, Wilson, Koosha, & Uchegbu, 2003) |
| Diclofenac sodium | Hydroxyethyl Methacrylate (HEMA) | (Cassidy et al., 1993) |
| Ergotamine tartrate | PVA | (Tsutsumi, Obata, Nagai, Loftsson, & Takayama, 2002) |
| Flurbiprofen | HEC, PVP, and PC | (Jones, Irwin, Woolfson, Djokic, & Adams, 1999) |
| Lidocaine | PEG, CP 934P, and PVP | (Tan, Peh, & Al-Hanbali, 2000) |
| Propolis | HPC | (Ceschel, 2002) |
| Recombinant human epidermal growth factor-h (TGF-h) | Eudispert hv, PC 974P | (Park, Yoon, Li, Moon, & Han, 2003) |
| Tetracycline | HEC, PVP, and PC | (Jones, Woolfson, Djokic, & Coulter, 1996; Jones et al., 2000) |
| Transforming growth factor-h (TGF-h) | Chitosan | (Giunchedi, Juliano, Gavini, Cossu, & Sorrenti, 2002) |
| Triamcinolone acetonide | Poloxamer 407 and CP 934 | (Shin, Bum, & Choi, 2000; Shin & Kim, 2000) |

CP, carbopol; HEC, hydroxyethyl cellulose; PVP, polyvinyl pyrrolidone; PC, polycarbophil; PVA, poly(vinyl alcohol); PEG, poly(ethylene glycol); HPC, hydroxypropyl cellulose.

sight of deposition and efficacy of drug. It is important that the integrity of 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.

*Polymers in Nasal Delivery*

Initial research on nasal mucoadhesion employed polymers manufactured for other purposes in the pharmaceutical and food industries. As shown in Table 9, several different types of polymers have been employed for delivery of different types/classes of drugs. In many cases, very encouraging results were obtained to the extent that marketed products could be developed. In a lot of other cases, only marginal or even no success was obtained. Further examination of the causes of failure pointed to issues such as

1. Delivery from devices and deposition in the appropriate region of the nasal cavity,
2. Lack of tissue specificity with respect to adhesion,
3. Reduced adhesion time,
4. Lack of permeation enhancement capability,
5. Interaction between drug and polymer leading to decreased release of the drug from the dosage form, increased drug instability, etc., and
6. Toxicity induced by the polymer.

Efforts to overcome such problems have led researchers to develop new polymers, the so-called second-generation mucoadhesives, a lot of which have been developed and tested for oral drug delivery. Even though the mechanism of adhesion is the same at nasal or GI tract sites, the functionalization of the polymers lead to more tissue/organ specificity. As a result, this part of the review will deal primarily with the functionalized polymers that have been tested for nasal drug delivery (NDD), but also make relevant references to other studies.

## EVALUATION METHODS TO STUDY MUCOADHESION

Buccoadhesive polymers can be characterized by testing their adhesion strength by in vitro and in vivo tests. These tests are necessary not only for screening a large number of candidates

TABLE 7
Viscosifying Polymers Screened for Ocular Mucoadhesive Capacity (Greaves & Wilson, 1993; Kaur & Smita, 2002; Krisnamoorthy & Mitra, 1993; Le Bourlais et al., 1998; Le Bourlais et al., 1995; Lee et al., 2000; Saettone, Bargalassi, & Chetoni, 1999)

| Polymer | Charge | Mucoadhesive Capacity |
|---|---|---|
| Poly(acrylic acid) (neutralized) | A | +++ |
| Carbomer (neutralized) | A | +++ |
| Hyaluronan | A | +++ |
| Chitosan | C | ++ |
| Na carboxymethylcellulose | A | ++(+) |
| Poly(galacturonic acid) | A | ++ |
| Na alginate | A | ++(+) |
| Pectin | A | ++(+) |
| Xanthan gum | A | + |
| Xyloglucan gum | A | + |
| Scleroglucan | A | + |
| Poloxamer | NI | +(+) |
| Hydroxypropylmethylcellulose | NI | + |
| Methylcellulose | NI | + |
| Poly(vinyl alcohol) | NI | + |
| Poly(vinyl pyrrolidone) | NI | + |

Charge: A, anionic; C, cationic; NI, non-ionic.
Mucoadhesive capacity: +++, excellent; ++, good; +, poor/absent.

TABLE 8
List of investigated Mucoadhesive Polymers in Vaginal Delivery

| Polymers | Reference |
|---|---|
| Poly(acrylates) | (Dittgen, Durrani, & Lehmann, 1997) |
| Chitosan | (Bernkop-Schnürch, Hornof, & Zoidl, 2003; El-Kamel, Sokar, Naggar, & Al Gamal, 2002) |
| Cellulose-derivatives | (Smart, Kellaway, & Worthington, 1984) |
| Hyaluronic acid and derivatives | (Honda, 1998; Richardson & Trevor, 1999) |
| Pectin and traganth | (Bombart, 1992) |
| Starch | (Richardson & Illum, 1992) |
| Poly(ethylene glycol) | (Smart, Kellaway, & Worthington, 1984) |
| Sulfated polysaccharides | (Witvrouw & De Clercq, 1997) |
| Carrageenan | (Maguire, Zacharopoulos, & Phillips, 1998; Zacharopoulos, & Phillips, 1997) |
| Sodium alginate | (Owen, Dunmire, Plenys, & Katz, 1999) |
| Gelatin | (Digenis et al., 1999; Meignant, Vieillard-Baron, & Verdier, 1999) |

for mucoadhesive but also to study their mechanisms. The various methods reported are as follows.

## In Vitro/Ex Vivo Methods

In vitro tests were initially designed to screen potential bioadhesives with a view to in vivo testing, if successful. Presently, more emphasis is being placed on elucidating the precise mechanisms of bioadhesion because an evaluation of bioadhesive properties is fundamental to the development of new bioadhesives. The most commonly employed in vitro techniques are given below.

*Methods Based on the Measurement of Tensile Strength (Park & Robinson, 1985a; Sam, Van Dan Heuij, & Tukker, 1989)*

Methods using tensile strength usually measure the force required to break the adhesive bond between a model membrane and test polymers. The instruments usually employed are modified balances or tensile testers. A typical example is the method employed by Robinson and his group. In this method, the force required to separate the bioadhesive sample from excised rabbit stomach tissue was determined using modified tensiometer. A section of 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 information regarding the effects of charge density, hydrophobicity, and experimental conditions such as pH, ionic strength, mucocytic agents, and applied pressure on bioadhesion. The list of polymers tested is given in Table 10.

*Methods Based on the Measurement of Shear Strengths (Smart et al., 1984)*

Shear stress is a measure of force that causes the bioadhesive to slide with respect to the mucus layer in a direction parallel to the plane of contact. An example is the Wilhelmy plate method reported by Smart. The method uses a glass plate suspended from a microbalance that 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. The list of tested polymers is given in Table 11.

TABLE 9
Summary of Some Nasal Drug Delivery Studies Where Mucoadhesive Excipients Were Employed

| Drugs | Mucoadhesive Excipients | Dosage Forms | Reference |
|---|---|---|---|
| Apomorphine | Carbopol 971P | Powder | (Ugwoke, Sam, Van Den Mooter, Verbeke, & Kinget, 1999) |
| Apomorphine | Polycarbophil | Powder | (Ugwoke et al., 1999) |
| Apomorphine | Carboxymethylcellulose | Powder | (Ugwoke, Kaufmann, Verbeke, & Kinget, 2000) |
| Apomorphine | Degradable starch microspheres | Powder | (Ugwoke et al., 2000) |
| Budesonide | (P(MAA-g-EG)) | Powder | (Nakamura et al., 1999) |
| Pentazocine | Chitosan microspheres | Powder | (Sankar, Rani, Srivastava, & Mishra, 2001) |
| Dopamine | Hydroxypropyl cellulose | Solution | (Ikeda, Murata, Kobayashi, & Noda, 1992) |
| Dopamine | Hydroxypropyl cellulose+azone | Liquid | (Ikeda et al., 1992) |
| Ketorolac tromethamine | MCC, pH 5.95 | Spray | (Quadir, Zia, & Needham, 2000) |
| Ketorolac acid | MCC, pH 3.2 | Spray | (Quadir et al., 2000) |
| Ketorolac acid | MCC, pH 6.0 | Spray | (Quadir et al., 2000) |
| Ketorolac acid | MCC | Powder | (Quadir et al., 2000) |
| Ketorolac tromethamine | MCC | Powder | (Quadir et al., 2000) |
| Metoprolol tartrate | Alginate microspheres | Liquid | (Rajinikanth, Sankar, & Mishra, 2003) |
| Midazolam | SβbCD/HPMC | Spray | (Loftsson et al., 2001) |
| Morphine hydrochloride | Chitosan glutamate | Spray | (Illum et al., 2002) |
| Morphine hydrochloride | Chitosan microspheres | Powder | (Illum et al., 2002) |
| Morphine hydrochloride | SMS + LPC | Powder | (Illum et al., 2002) |
| Morphine hydrochloride | Chitosan glutamate | Liquid | (Illum et al., 2002) |
| Morphine hydrochloride | Chitosan glutamate | Powder | (Illum et al., 2002) |
| Nicotine | Amberlite resin | Powder | (Cheng et al., 2002) |
| Oxyprenolol | Gelatin/polyacrylic microspheres | Powder | (Preda, & Leucuta, 2003) |
| Gentamicin | Hyaluronan | Powder | (Lim, Forbes, Martin, & Brown, 2001; Lim, Martin, Berry, & Brown, 2000) |
| Gentamicin | Chitosan | Powder | (Lim et al., 2001; Lim et al., 2000) |
| Gentamicin | Hyaluronin/chitosan | Powder | (Lim et al., 2001; Lim et al., 2000) |
| Leuprolide | HPC/MCC | Powder | (Suzuki & Makino, 1999) |
| Calcitonin | HPC/MCC | Powder | (Suzuki & Makino, 1999) |
| Calcitonin | Chitosan free amine | Liquid | (Sinswat & Tengamnuay, 2003) |
| Ciprofloxacin | HPMC | Gel | (Ozsoy et al., 2000) |
| Ciprofloxacin | HEC | Gel | (Ozsoy et al., 2000) |
| Ciprofloxacin | MC | Gel | (Ozsoy et al., 2000) |
| Ciprofloxacin | HEC + Tween80 | Gel | (Ozsoy et al., 2000) |
| Ciprofloxacin | MC + Tween80 | Gel | (Ozsoy et al., 2000) |
| FD4 | HPC/MCC | Powder | (Suzuki & Makino, 1999) |
| FD4 | Ethyl cellulose | Powder | (Ishikawa et al., 2002) |

(*Continued*)

TABLE 9
(*Continued*)

| Drugs | Mucoadhesive Excipients | Dosage Forms | Reference |
|---|---|---|---|
| Cyanocobalamin | SD-MCC | Powder | (Garcia-Arieta, Torrado-Santiago, Goya, & Torrado, 2001) |
| Cyanocobalamin | SD-CP | Powder | (Garcia-Arieta et al., 2001) |
| Cyanocobalamin | SD-DM | Powder | (Garcia-Arieta et al., 2001) |
| Insulin | Chitosan glutamate | Liquid | (Hamman, Stander, & Kotze, 2002) |
| Insulin | Chitosan glutamate | Liquid | (Hamman et al., 2002) |
| Insulin | Chitosan complex | To check | (Hamman et al., 2002) |
| Insulin | Chitosan nanoparticles | To check | (Hamman et al., 2002) |
| Insulin | DSM | Powder | (Illum, Fisher, Jabbal-Gill, & Davis, 2001) |
| Insulin | DSM + GDC + STDHF | Powder | (Illum et al., 2001) |
| Insulin | DSM + STDHF | Powder | (Illum et al., 2001) |
| Insulin | DDWM | Powder | (Callens, & Remon, 2000) |
| Insulin | DDWM/Carbopol 974P | Powder | (Callens, & Remon, 2000) |
| Insulin | Maltodextrin DE 8/Carbopol 974 | Powder | (Callens, & Remon, 2000) |
| Insulin | Maltodextrin DE 22 | Powder | (Callens, & Remon, 2000) |
| Insulin | Maltodextrin DE 22/Carbopol | Powder | (Callens, & Remon, 2000) |
| Insulin | Maltodextrin DE 38 | Powder | (Callens, & Remon, 2000) |
| Insulin | Maltodextrin DE 38/Carbopol | Powder | (Callens, & Remon, 2000) |
| Glucagon | MCC | Powder | (Callens, Pringels, & Remon, 2003) |
| Desmopressin | MCC | Spray | (Harris, Ohlin, Svensson, Lethagen, & Nilsson, 1989) |
| Desmopressin | DSM | Powder | (Critchley, Davis, Farraj, & Illum, 1994) |
| Desmopressin | DSM/LPC | Powder | (Critchley et al., 1994) |
| Mannitol | TMC-12, pH 6.2 | Liquid | (Hamman et al., 2002) |
| Mannitol | TMC-22, pH 6.2 | Liquid | (Hamman et al., 2002) |
| Mannitol | TMC-36, pH 6.2 | Liquid | (Hamman et al., 2002) |
| Mannitol | TMC-48, pH 6.2 | Liquid | (Hamman et al., 2002) |
| Mannitol | TMC-59, pH 6.2 | Liquid | (Hamman et al., 2002) |
| Mannitol | TMC-12, pH 7.4 | Liquid | (Hamman et al., 2002) |
| Mannitol | TMC-22, pH 7.4 | Liquid | (Hamman et al., 2002) |
| Mannitol | TMC-36, pH 7.4 | Liquid | (Hamman et al., 2002) |
| Mannitol | TMC-48, pH 7.4 | Liquid | (Hamman et al., 2002) |
| Mannitol | TMC-59, pH 7.4 | Liquid | (Hamman et al., 2002) |

(P (MAA-g-EG)), polymethacrylic acid and polyethylene glycol; MCC, microcrystalline cellulose; SβbCD, sulfobutylether β cyclodextrin; HPMC, hydroxypropylmethyl cellulose, SMS, cross-linked eldexomer starch microspheres; LPC, l-α-lyso phosphatidyl choline; HPC, hydroxypropyl cellulose; HPMC, hydroxypropyl methyl cellulose; HEC, hydroxyethyl cellulose; SD-MCC, spray-dried microcrystalline cellulose; SD-CP, spray-dried; SD-DM, spray-dried dextran microspheres; DSM, degradable starch microspheres; GDC, deoxyglycocholate; STDHF, sodiumtaurodihydrofusidate; DDWM, drum-dried waxy maize starch; TMC, trimethyl chitosan chloride.

*Adhesion Weight Method*

Smart and Kellaway (1982) developed a test system where suspensions of ion exchange resin particles 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 adhesion after 5 min contact with averted intestine.

*Fluorescent Probe Method (Park & Robinson, 1984)*

Park and Robinson 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

TABLE 10
Bioadhesion Measurement by Tensile Strength (Ahuja et al., 1997; Jimenez-Castellanos et al., 1993; Lee et al., 2000)

| Bioadhesive Polymer | Substrate | Instrument |
|---|---|---|
| CP934, HPC | Mouse peritoneal membrane | Spring balance |
| Cross-linked PAA, PHEMA | Rabbit stomach tissue | Modified surface tensiometer |
| PAA, HPMC | Bovine sublingual mucosa | Tensile apparatus (Instron, UK) |
| Modified starch, PEG, NaCMC | Porcine attached gingeva | Modified tensile apparatus |
| CP, hyaluronic acid | Porcine gastric mucin gel | Electronic digital microbalance |
| Chitosan, polycarbophyll, CMC, pectin, xanthan gum | Pig intestinal mucosa | Modified tensiometer |
| Chitosan, sodium alginate | Rat peritoneum membrane | Spring tension gauge |
| Copolymer of è-caprolactone and ethylene oxide | Rat duodenum mucosal tissue | Tensile tester |
| CP934 | Porcine gastric mucin | Dynamic contact analyzer |

PMA, polymethyl acrylic acid; PHEMA, polyhydroxy ethyl methacrylic acid; PAA, polyacrylic acid; NaCMC, sodium carboxymethyl cellulose; CMC, carboxymethyl cellulose; CP, carbopol; HPC, hydroxypropyl cellulose; HPMC, hydroxypropylmethyl cellulose; PEG, polyethylene glycol.

TABLE 11
Bioadhesion Measurements by Shear Strength (Ahuja et al., 1997; Jimenez-Castellanos et al., 1993; Lee et al., 2000)

| Bioadhesive Material | Substrate | Instrument |
|---|---|---|
| CP934, NaCMC, HPMC, Gelatine, PVP, Acacia, PEG, Pectin, Tragacanth, Sodium alginate | Mucus from guinea-pig intestine | Wilhelmy plate method (micro force balance) |
| CP934 ointment | Glass plate | Shearing stickiness test apparatus |
| Polyethylene gel, NaCMC, hydrolysed gelatin | Polymethyl-methacrylate | Instron model 1114 |
| Polycarbophyll, NaCMC, Eudragit | Homogenized mucus from pig intestine | Modified Wilhelmy plate, surface tension apparatus |

NaCMC, sodium carboxymethyl cellulose; CMC, carboxymethyl cellulose; CP, carbopol; HPC, hydroxypropyl cellulose; HPMC, hydroxypropyl methyl cellulose; PEG, polyethylene glycol; PVP, polyvinyl pyrrolidone.

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 bioadhesive, 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 (1990) developed a flow channel method that utilized a thin channel made of glass and filled with 2% (wt/wt) 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. The static and dynamic behavior was monitored at frequent intervals using a camera.

*Mechanical Spectroscopic Method*

Mortazavi, Carpenter, and Smart (1994) used a similar method to investigate the effect of introduction of carbopol-934P on the rheological behavior of mucus gel. They used Carri-Med CSL100 rheometer with a 4-cm parallel plate 0.5 mm gap for their studies. They also investigated the role of mucus glycoprotein and the effect of various factors such as ionic concentration, polymer molecular weight, its concentration, and the introduction of anionic, cationic, and neutral polymers on the mucoadhesive mucus interface.

*Falling Liquid Film Method*

Teng and Buri (1987) 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 particles suspensions over the surface. By comparing the fraction of particles adherent to the tissue, the adhesion strength of different polymers can be determined.

*Colloidal Gold Staining Method*

Park (1989) proposed the colloidal gold stain technique for the study of bioadhesion. The technique employed red colloidal gold particles, which were stabilized by the adsorbed mucin molecule (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.

*Viscometeric Method*

A simple viscometric method was used by Hassan and Gallo (1990) to quantify mucin–polymer bioadhesive bond strength. Viscosities of 15% (wt/vol) percine gastric mucin dispersion in 0.1 N HCl (pH 1) or 0.1 N acetate (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.

*Electrical Conductance*

Bremecker (Asane, Rao, Bhosale, & Nirmal, 2007) used electrical conductance 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 the electrical conductance. This parameter, measured as a function of time, was found to be influenced by the sample, artificial saliva, and 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 adhesive.

## In Vivo Methods

The most common in vivo techniques to monitor bioadhesion include the following:

*Use of Radioisotopes*

Ch'ng et al. (1985) in order to investigate the GI transit of bioadhesive beads developed in vivo methods in rats, inserting Cr-55 (isotope) labeled bioadhesive material in the stomach and measuring the radioactivity in cut segments of intestine.

*Use of Gamma Scintigraphy (Krishnaiah, Kondala Rao, Rama Prasad, & Satyanarayana, 1998)*

It is a valuable tool used in the development of pharmaceutical dosage forms. With this methodology, it is possible to obtain information noninvasively. This technique gives information in terms of oral dosage forms across the different regions of GI tract, the time and site of disintegration of dosage forms, the site of drug absorption, and also the effect of food, disease, and size of the dosage form on the in vivo performance of the dosage forms.

The various factors to be considered for studying in vivo behavior of solid dosage forms using gamma scintigraphy involves selection of radioisotopes, radio labeling, and choice of imaging device. Examples of radioisotopes are Technetium ($^{99m}$Tc) and Indium ($^{111}$In).

*Use of Pharmacoscintigraphy (Singh, Bhardwaj, & Bhatnagar, 2004)*

Gamma scintigraphy is especially useful in exploring sources of intersubject variation, especially in examining food effects in pharmacokinetic estimations and establishing windows of absorption from oral delivery. As a tool to examine drug delivery to the lung and to the eye, scintigraphy is the method of choice. It is the technique of today which need to be exploited to the maximum for its potentials in the evaluation of new molecular entities, drug delivery systems, and therapeutic drug monitoring.

*Use of Electron Paramagnetic Resonance (EPR) Oximetry*

Petelin, Pavlica, Bizimoska, and Sentjure (2004) performed the in vivo study of different ointments for drug delivery into oral mucosa by electron paramagnetic resonance (EPR) oximetry. Three ointments with bioadhesive properties, orabase, carbopol 935P, and polymethyl methacrylate, and the ointment Miglyol without such properties were used. Benzyl nicotinate was used as an active ingredient that causes hyperemia. The kinetics of the drug action was measured by EPR oximetry in vivo using the paramagnetic probe (lithium phthalocyanine) implanted beneath the epithelium of the buccal mucosa in rats.

*X-ray Studies*

Chary, Vani, and Rao (1999) performed the in vivo adhesion testing of barium sulfate matrix tablet containing polymer and drug by X-ray study in rabbits, and it was found that the tablet was mucoadhesive even after 8 h. Enteric coating did not show any effect on mucoadhesion after passing from the stomach.

## CONCLUSION

Current use of bioadhesive polymers to increase contact time for a wide variety of drugs and routes of administration has shown dramatic improvement in both specific therapies and more general patient compliance. Almost all the commercially useful bioadhesive polymers had other uses too and were

"drafted" for their use as bioadhesives. The general properties of these polymers for purpose of sustain release of chemicals are marginal in being able to accommodate a wide range of physicochemical drug properties. Moreover, when special functions of these polymers, ranging from tissue permeability enhancement to cell communication, are added to the basic bioadhesive function, it is clear that multifunctional special polymers will be needed.

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