Advances in Mucoadhesion and Mucoadhesive Polymers

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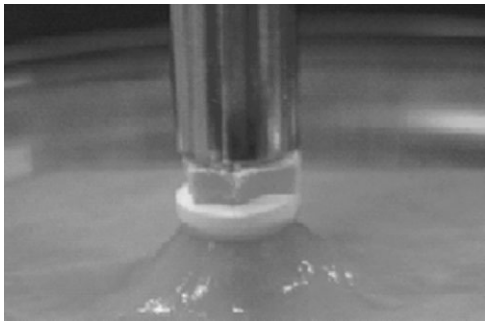
Mucoadhesion is the ability of materials to adhere to mucosal membranes in the human body and provide a temporary retention. This property has been widely used to develop polymeric dosage forms for buccal, oral, nasal, ocular and vaginal drug delivery. Excellent mucoadhesive properties are typical for hydrophilic polymers possessing charged groups and/or non-ionic functional groups capable of forming hydrogen bonds with mucosal surfaces. This feature article considers recent advances in the study of mucoadhesion and mucoadhesive polymers. It provides an overview on the structure of mucosal membranes, properties of mucus gels and the nature of mucoadhesion. It describes the most common methods to evaluate mucoadhesive properties of various dosage forms and discusses the main classes of mucoadhesives.



Introduction

Mucosal membranes are the moist surfaces lining the walls of various body cavities such as respiratory, gastrointestinal and reproductive tracts as well as the nostrils, the eyes and the mouth. They play an important role in protecting cellular epithelia from chemical and mechanical damage. Mucosal membranes also provide lubrication and wettability of the cell epithelial surface, and regulate its moisture content.[1]

Mucoadhesion is defined as attractive interaction at the interface between a pharmaceutical dosage form and a mucosal membrane. One of the first applications of mucoadhesive formulations dates back to 1947, when Scrivener and Schantz[2] reported the use of gum tragacanth mixed with dental adhesive to administer penicillin to the oral mucosa. Eventually this therapeutic application of mucoadhesives laid grounds for formulating Orabase.[3] The potential of mucoadhesion in drug delivery has been fully recognized in the early eighties, when Nagai and coworkers demonstrated the applicability of viscous gel ointments and mucoadhesive tablets for drug administration in the oral cavity[4,5] and polymer-mediated enhancement in the bioavailability of nasally administered peptide.[6]

Various administration routes, such as ocular, nasal, buccal and gingival, gastrointestinal (oral), vaginal and rectal, make mucoadhesive drug delivery systems attractive and flexible in dosage form development. Recent reports have suggested that the market for mucoadhesive drug delivery systems is expanding rapidly.[3,7,8] The advantages associated with the use of mucoadhesives in drug delivery include increased dosage form residence time, improved drug bioavailability, reduced administration frequency, simplified administration of a dosage form and termination of a therapy as well as the possibility of targeting particular body sites and tissues.[8] Moreover, the drugs administered via transmucosal non-oral routes often avoid the metabolism associated with its passage through the gastrointestinal tract and also benefit from better mucosal penetration compared to relatively low permeability of transdermal route.[9]

Mucoadhesive drug delivery systems may be formulated as tablets, lozenges, solid inserts, wafers, pessaries, films, gels, viscous solutions, micro- and nano-particulate

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suspensions, in situ gelling systems and sprays. The majority of these dosage forms incorporate polymeric excipients, which play a major role in their mucoadhesivity. Some mucoadhesive polymers can not only increase the dosage form residence time at the site of administration but also may enhance drug permeability through the epithelium by modifying the tight junctions between the cells.[10]

Despite several decades of research, mucoadhesion is still not fully understood. The complexity of interactions between various polymer-based mucoadhesive dosage forms and biopolymer-based viscoelastic mucus gel present on the surface of mucosal membranes continues to attract attention of researchers. Numerous studies on developing novel mucoadhesive polymers, mechanisms of their interactions with mucins and mucosal membranes, formulating and administering novel active ingredients via transmucosal routes increasingly appear in the literature.

In the present review we will consider the recent advances in mucoadhesion and mucoadhesive materials, focusing on the studies of mucoadhesive interactions, methods to evaluate mucoadhesive properties of polymers, and development of novel polymers.

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Structure and Functions of Mucosal Membranes

The epithelial cells of the mucosal tissues are coated by two types of mucins, membrane-bound and secreted (soluble) biomacromolecules forming a fully-hydrated viscoelastic gel layer (mucus). Soluble mucins are high-molecular-weight glycoproteins (0.5 — 40 MDa) composed of 500 kDa sub-units linked together by peptide linkages and intramolecular cystein–cystein disulfide bridges.[1,11] There are two models proposed to describe the macrostructure of mucins: non-linear and linear models (Figure 1).

Each mucin subunit consists of protein-based backbones and oligosaccharide-based grafted chains. The protein backbone constitutes about 12–17% of the total mucin

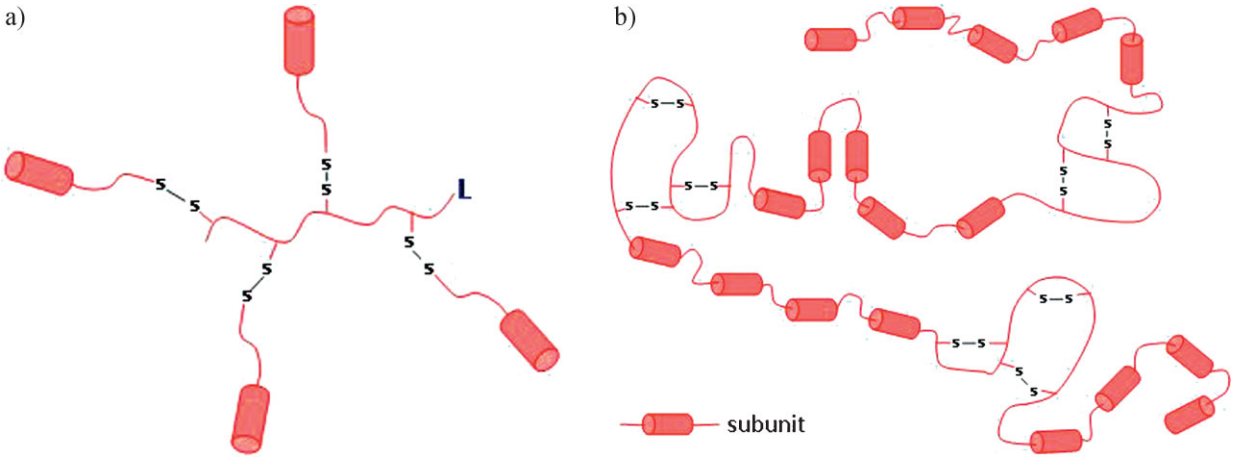

Figure 1. Proposed macromolecular structures for mucus glycoprotein: (a) the nonlinear model that may involve a link peptide (L) from which subunits branch off; (b) the linear model containing four groups of multiple subunit assembly. Adapted from ref.[1] with permission from CRC Press; permission conveyed through Copyright Clearance Center, Inc.

weight, the amino acid composition of which includes ≈70% serine, threonine and proline. The grafted chains of oligosaccharides are made of *N*-acetylgalactosamine, *N*-acetylglucosamine, galactose, fucose and *N*-acetylneuramic acid (sialic acid). The coverage of the protein backbone with oligosaccharide chains is over 63%, with the remainder being non-glycosylated.[1,12]

Most mucins carry a net negative charge due to the presence of carboxylate groups (sialic acid) and ester sulfates at the terminus of some sugar units (Figure 2). The approximate pK_a of these acidic groups is 1.0–2.6 resulting in their complete ionization under physiological conditions.[12]

There has been significant interest and progress in mucins research demonstrating their unique physicochemical behavior in diluted and concentrated solutions. For example, gastric mucins undergo pH-dependent sol-gel transitions from a viscoelastic solution at neutral pH to a soft gel at acidic pH. This property plays an important role in protecting stomach epithelium from acid self-digestion.[13–15] It was also demonstrated that pig gastric mucin is a lyotropic side-chain liquid-crystal polymer and at concentrations above 26 wt.-% it forms a liquid crystalline gel.[16] Mucins have also been found to reduce bacterial adhesion to surfaces.[17] For more detailed description of mucins, their structure and properties see a review by Bansil and Turner.[18]

The water content in most mucus gel types (i.e., lung, gastric, cervicovaginal) is typically 90–98%. In addition to mucins, mucus gel incorporates cells, bacteria, lipids, salts, proteins, macromolecules and cellular debris.[19]

The pH of a mucus gel may vary depending on the site in a human body.[9,19] The pH of mucus in the lung and nasal cavity is close to neutral or slightly acidic (pH = 5.5–6.5) and in the eye it is slightly basic (pH ≈ 7.8). In the mouth, the pH ranges from 6.2 to 7.4, whereas the gastric mucus shows wider pH variability: from the luminal pH of 1.0–2.0 to ≈7.0 at the epithelial surface. It is also greatly affected by the presence of food. Vaginal pH in an adult female varies between 4.0 and 5.0, depending on the particular stage of the menstrual cycle. During pregnancy the pH in the vagina decreases to 3.9–4.4, whereas in the postmenopausal state it increases to 7.0–7.4.

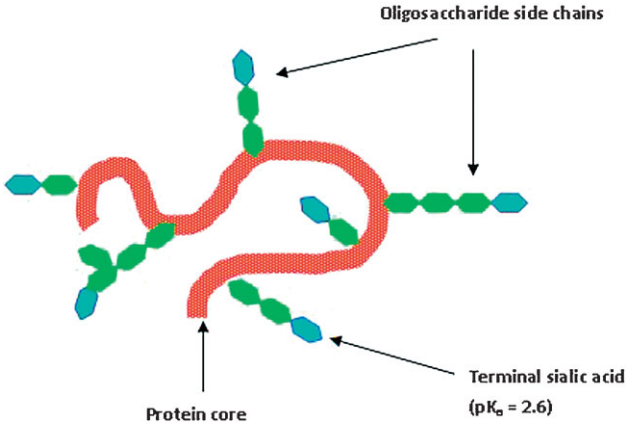

Figure 2. Schematic structure of mucin subunits.

Mucus gel is a dynamic system that is reformed continuously through the secretion of mucins from the goblet cells. It has a relatively short life time, with a clearance period varying from 5.0–7.7 min in the eye, 10–20 min in the respiratory tract to 4–6 h in the gastrointestinal tract.[19] The thickness of the mucus layer is determined from the balance between the rate of its secretion and the rate of degradation and shedding.[20] It ranges from 1 to 400 μm with a mean of 200 μm in humans.[12] Toxic and irritating substances can stimulate mucus secretion, leading to its thickening and facilitating efficient removal of irritants from the epithelium.

Mucosal membranes act as an efficient semi-permeable barrier system allowing the diffusion of water, nutrients, gases, selected small molecules and ions through the mucus gel, which remains impermeable to most bacteria and many other pathogenic microorganisms.[20] While acting as a unique and efficient protective system, the mucus gel also hampers diffusion of many drug molecules and nanomedicines.[21]

Theories of Mucoadhesion

Mucoadhesion is a complex phenomenon that is not fully understood.[11,12,22] There are several general theories that have been used to explain mucoadhesion phenomena:

(i) The *electronic theory* is applicable when the mucoadhesive polymer and the mucus have different electronic characteristics and transfer of electrons occurs resulting in formation of electrical double layer and electrostatic attraction between oppositely charged surfaces.[23,24]

(ii) The *adsorption theory* considers that the attraction between the mucus and the mucoadhesive polymers is achieved via specific interactions such as hydrogen bonds and van der Waals forces.[25] Hydrophobic effects may also play an important role especially when the mucoadhesive polymers have an amphiphilic nature. The adsorption theory also considers the possibility of chemisorption, when strong covalent bonds are formed between the mucoadhesive polymer and mucins.

(iii) The *wetting theory* correlates the surface tension of the mucus and the mucoadhesive polymer with its ability to spread on the mucus layer.[26] This theory is mainly applicable to liquid mucoadhesive forms. Better ability of polymers to spread on the surface

of mucosal tissues is usually associated with excellent mucoadhesive performance.

(iv) The *diffusion theory* considers the penetration of mucoadhesive macromolecules into the mucus gel and diffusion of soluble mucins into the dosage form, resulting in formation of an interpenetration layer.[11,25] This process is driven by the gradient of concentrations and is dependent on the molecular weight of mucoadhesive macromolecules, their hydrodynamic size and mobility. The depth of interpenetration depends also on the diffusion coefficient and the time of contact.[27] Efficient adhesion is normally achieved when the thickness of interpenetration layer reaches 0.2–0.5 μm.

(v) The *fracture theory* relates the difficulty of separation of two surfaces after adhesion to the adhesive bond strength.[28] This theory is considered to be appropriate for calculating the fracture strength of adhesive bonds involving solid and rigid mucoadhesive materials.

(vi) The *mechanical theory* considers the effect of surface roughness, which favors the adhesion due to an increased contact area.[12,27] The contribution of the mechanical theory effects into mucoadhesion becomes more important for rough and porous materials.

In isolation, none of these theories can explain mucoadhesion by the many and varied pharmaceutical formulations that have been developed. Indeed, mucoadhesion probably results from combinations of several mechanisms. Consequently, some researchers prefer to divide the adhesion process into sequential phases, each of which is associated with a different mechanism.[29] First, the dosage form wets and swells (wetting theory), after which non-covalent (physical) bonds are created within the mucus/polymer interface (electronic and adsorption theories). Then, the polymer and protein chains interpenetrate (diffusion theory) and entangle together, to form further non-covalent (physical) and covalent (chemical) bonds (electronic and adsorption theories) (Figure 3).

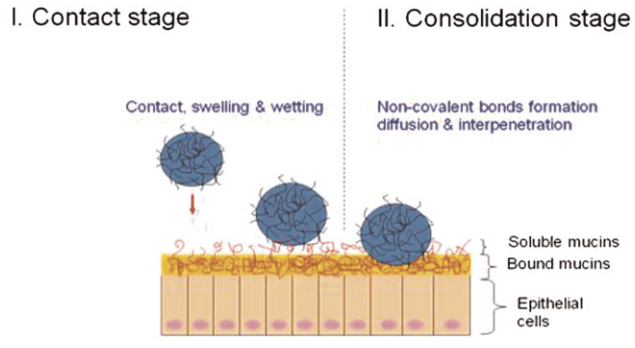

Figure 3. Contact and consolidation stages of mucosal adhesion. Adapted from ref. [29] with permission from Elsevier.

Methods to Study Mucoadhesion

The assessment of mucoadhesive properties is fundamental to the development of novel drug delivery systems. The mucoadhesive properties of dosage forms have traditionally been evaluated by in vitro methods including tensile studies, visual detachment/dissolution time methods and flow retention techniques. Additionally a number of various physical techniques such as rheological, optical and spectroscopic have been applied to evaluate the nature and intensity of mucoadhesive interactions. Below we will consider some of these methods.

Tensile (Detachment) Method

In tensile studies, the formulation is brought in contact with mucosal tissue and the force that is required to break the adhesive bond is measured. The instruments typically used for this testing are modified balances or tensile testers. One of the most convenient approaches to test detachment of a dosage form from a mucosal tissue (substrate) involves the use of an automatic tensile machine, for example, Texture Analyzer (Stable Microsystems, UK). Variants of this method have been developed and applied for different kinds of formulations: dry tablets, discs, powder/granules/particles and semisolid vehicles. Depending on the nature, geometry and physical properties of the dosage form as well as the substrate different ways of performing experiments and securing the dosage form and the substrate have been developed and some of the accessories for fixing the materials are available commercially (e.g., mucoadhesion rig from Stable Microsystems, UK). If a solid dosage form such as a tablet or a disc is to be tested then it may be secured on a mobile metallic probe by a double sticky tape and the biological tissue can be fixed in a mucoadhesion rig (Figure 4). Alternative arrangement is also possible when the biological tissue, for example, the pig eye is fixed on a mobile metallic probe and the dosage form (polymeric film or gel) are used as a substrate. The detachment experiment performed on an automatic tensile machine allows recording a detachment profile, i.e., changes in the force applied versus the distance between the dosage form and the substrate.

The tensile test reproduces the processes similar to those occurring in vivo to some extent, however, tensile detachments are relatively rare because shear forces or rather a combination of forces are likely to act on the vehicle.[22] Nevertheless, tensile testing may give information on the relative mucoadhesiveness of dosage forms and allows classifying mucoadhesives by their performance. It should be noted that the force applied to a tablet to establish an initial contact with mucosal tissue (contact force), testing speed and tablet-mucosa contact environment (e.g., amount of liquid present, solution pH and

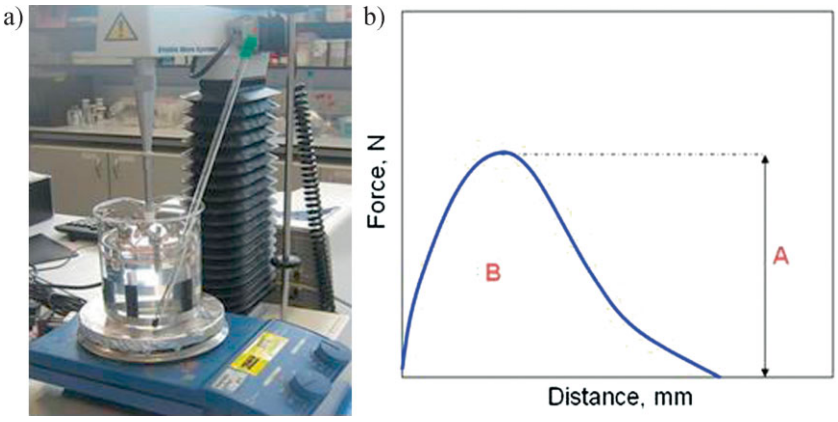

Figure 4. (a) Application of Texture Analyzer for studying mucoadhesion properties of tablets to animal mucosa; (b) Detachment profile (force/distance curve). *A* is the maximal detachment force and *B* (area under the curve) is the total work of adhesion.

temperature) have all been shown to affect the results of detachment.[30]

The earlier studies on characterization of various mucoadhesives by detachment test have often reported the use of detachment forces only (maximal force required to detach a dosage form from a biological substrate) to describe the performance of various materials.[31–33] Later, it was realized that the detachment is a complex physical process that depends not only on the adhesiveness but also on the deformation and mechanical properties of both the dosage form and the substrate. This has resulted in a more reliable description of the mucoadhesive performance of dosage forms through a combination of two important parameters–the maximal detachment force and the total work of adhesion (area under the detachment curve). Some researchers have reported a linear correlation between the maximal detachment force and the total work of adhesion,[34] however, the experiments performed in our laboratory on various dosage forms and substrates have demonstrated more complex dependence that cannot be described by a linear relationship (unpublished results).

The substrates used to study mucoadhesion are often taken from animals (cows, pigs, rabbits, dogs, guinea pigs, rats, mice and hamsters). Although the majority of mucoadhesive studies reported the use of animal tissues obtained from slaughterhouses, numerous reports can be found where mucosal tissues were directly taken after sacrificing laboratory-bred animals (see refs. [31,35,36] as examples). Besides, the results obtained from these studies are often characterized by relatively poor reproducibility due to variable properties of biological substrates.[37] Therefore, the development of an alternative testing method, which does not involve animal experiments in assessment of mucoadhesives, is of significant importance and several attempts have been made to identify a synthetic substitute of animal mucosal tissues. Wet glass surface was tested by Shojaei et al.[38] as a substrate to evaluate mucoadhesive properties of tablets and compared with porcine buccal mucosa. However, it was demonstrated that the forces of adhesion generated on the glass surface were an order of magnitude different than those from contact with porcine buccal mucosa. In experiments performed by Mortazavi[34] the mucoadhesive polymer discs were found to adhere to the poly(vinyl chloride) tape stronger than rat's small intestine. Choi and coworkers[39] studied the adhesion of polymeric compositions to a poly(propylene) plate. They claimed that there was a relatively good correlation between the adhesive force of the polymeric dosage form to pig intestinal mucosa and that of the dosage form to the poly(propylene) plate. It should be noted that in all these cited studies the possibility of using synthetic and semi-synthetic substrates as mucosal mimic was evaluated through determination of the maximal detachment force.

An adequate correlation between the detachment of a dosage form from a semi-synthetic substrate (tanned leather) and from bovine sublingual mucosa has also been reported by Blanco-Fuente[40] He has compared the values of the total work of adhesion for various tablets to a biological mucosa and tanned leather and established that an exponential or a linear correlation may be achieved depending on the way experiments were conducted. The exponential correlation was observed when the detachment experiments were performed in the presence of a limited amount of water (25 μL) used to moisturize the area of contact. The linear correlation was achieved in experiments when both the dosage form and the substrate were fully submersed in an excess of water.

Recently we have realized a potential of synthetic hydrogels to mimic biological mucosa and provide a synthetic substitute for animal tissues. Hydrogels or three-dimensionally cross-linked networks of hydrophilic polymers are soft, elastic and porous materials capable of imbibing large quantities of water and resembling the properties of biological tissues.[41] Hydrogels can be synthesized using a number of different approaches including three-dimensional polymerization of hydrophilic monomers[42,43] or cross-linking of ready-made water-soluble polymers.[44,45] To develop a synthetic hydrogel substitute for mucosal tissues suitable as a substrate for evaluating mucoadhesive properties of tablets we have used two approaches: (i) layer-by-layer deposition of hydrogen-bonded interpolymer complexes of poly(acrylic acid) and methylcellulose on the surface of chemically modified glass with subsequent cross-linking of dry

multilayered coatings by thermal treatment at 120 °C;[46] and (ii) three-dimensional copolymerization of 2-hydroxyethyl methacrylate with various co-monomers (2-hydroxyethyl acrylate, *N*-vinylpyrrolidone, sorbitol methacrylate and *N*-acryloylglucosamine).[47] The first approach has resulted in ultrathin multilayered hydrogel coatings tightly bound to the surface of glass slides, whereas the second one led to bulk hydrogels.

The thickness of the multilayered hydrogels was controlled by a number of polymer deposition cycles and the swelling properties were regulated by varying the thermal treatment time (2, 4 and 6 h).[46] These multilayered hydrogels were used as substrates to evaluate adhesiveness of Carbopol940 tablets and compared to porcine buccal tissue as well as unmodified glass slides and poly(propylene) (Figure 5). It was established that these coatings have a potential to mimic the total work of adhesion observed for the detachment of mucoadhesive tablets from porcine buccal mucosa but fail to exhibit identical detachment profiles. The experiments with multilayered hydrogel coatings allowed concluding that even a combination of the detachment force and the total work of adhesion values does not provide a complete description of mucoadhesiveness for a particular dosage form. A more detailed characterization of a mucoadhesiveness can be achieved only through a comparison of detachment profiles, which can be considered as a unique 'signature' of mucosal adhesion.[46]

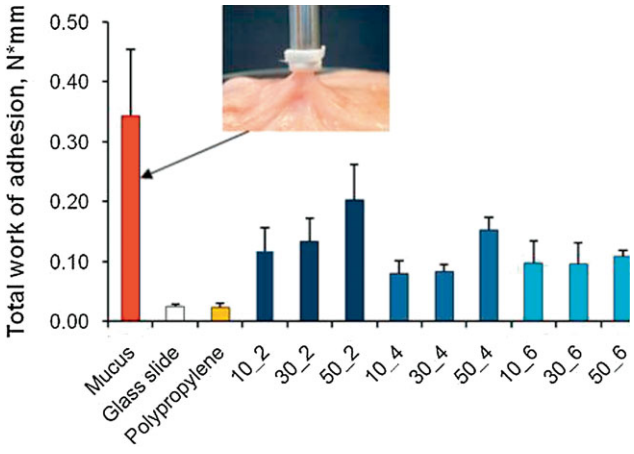

Figure 5. Total work of adhesion of Carbopol®940 tablets to porcine buccal mucus, glass slide, polypropylene plate and glass slides with hydrogel coatings. The first number in a sample code shows the number of deposited monolayers, the second number is the time of the material thermal treatment in hours (for example, 50_2 means that 50-monolayers were deposited and were cross-linked by thermal treatment for 2 h). Each detachment experiment was performed with at least 4–5 samples and the results are presented as a mean ± standard deviation. Inset: Image showing a detachment of Carbopol®940 tablet from buccal mucosa. Reproduced from ref. [46] with permission from the Royal Society of Chemistry.

In the second approach we have synthesized a range of hydrogel samples by three-dimensional copolymerization of 2-hydroxyethyl methacrylate (HEMA) with 2-hydroxyethyl acrylate, *N*-vinylpyrrolidone, sorbitol methacrylate and *N*-acryloylglucosamine (AGA).[47] These materials were tested as substrates for mucosal adhesion of tablets prepared by direct compressing Carbopol940/hydroxypropylcellulose mixtures at various polymer ratios and the results were compared with detachment from porcine buccal and stomach mucosa. It was established that the degree of the hydrogels swelling as well as their mechanical properties and chemical nature of co-monomers have a strong effect on the ability of these materials to mimic biological mucosa. The best detachment profiles with a nearly perfect similarity to a biological tissue were achieved when HEMA-AGA hydrogels were used as substrates.

It is also important to mention a recent study by Laulicht et al.[48] looking into the correlation between the detachment of quickly eroding polyanhydrides [e.g., poly(adipic anhydride)] and slowly eroding hydrophobic polymers such as polycaprolactone from a freshly excised rat stomach tissue (in vitro experiment) and a stomach tissue of a live anesthetized animal accessed through a gastric cannula (in vivo experiment). It was demonstrated that no significant difference was found for the fast eroding polymers compared to the slow eroding polymers when the detachment experiments were conducted in vivo. However, when these polymers were tested in vitro, the expected difference was observed. The authors concluded that standard in vitro mucoadhesion testing conditions do not adequately reflect in vivo environment and the lack of in vitro/in vivo correlation may be related to a difference in the depth to which the polymers penetrate upon contact with mucosa.

Rotating Disc Method

The rotating disc method has been developed and successfully used to study mucoadhesive properties of solid dosage forms by Bernkop-Schnurch and coworkers.[49] This method allows estimating the time of detachment/dissolution/disintegration of a dosage form attached to a mucosal tissue in a dynamic environment, mimicking physiological conditions of gastrointestinal tract to some extent. In a typical experiment, mucoadhesive dosage forms (tablets, discs or films) are attached to a mucosal tissue glued to a stainless steel cylinder (one of the commercially-available accessories typically used for studies of tablet dissolution in Pharmacopoeia testing). This cylinder is then placed into a dissolution apparatus and the system is completely immersed into a dissolution medium at 37 °C. The cylinder can be rotated at a speed of 125 rpm and the changes in the position and state of a dosage form are registered regularly

through visual observations. The time of complete detachment, dissolution or disintegration of a dosage form is then registered as an indication of mucoadhesive strength of the studied formulations and can be compared with the values obtained in experiments with reference mucoadhesive materials. Some other researchers have used different experimental set-ups and experimental conditions for assessing mucoadhesive properties of dosage forms by rotating disc method,[45,50] which makes a direct comparison between the results reported by different research groups rather difficult.

Table 1 shows some experimental data recorded for detachment/dissolution of various tablets from porcine stomach mucosa as an example. Depending on the mucoadhesive properties and solubility of the copolymers in the dissolution medium time values can be registered. The best mucoadhesive performance in this particular experiment was observed for the tablets prepared by direct compression of two powders, copolymer of 2-methacryloyloxyethyltrimethylammonium chloride with butyl acrylate (MAD-BA) (73:27 mol-%)/poly(acrylic acid) (PAA), giving the longest detachment time of 900 ± 50 min. This improved mucoadhesive ability is likely related to the formation of insoluble polyelectrolyte complex between cationic copolymer and anionic PAA upon hydration. The formation of the polyelectrolyte complex inhibits quick dissolution of the copolymer and results in tablet slow swelling, whilst attached to the mucosal tissue.

The rotation disc method may provide useful information on the mucoadhesive properties of solid dosage forms. The ranking orders of polymers mucoadhesivity estimated by this technique often correlate well with the data obtained by tensile studies.[49]

Flow-Through Method

This method was first described by Rango Rao and Buri[52] and is often used for estimating mucoadhesive properties of dosage forms administered in the regions of the human body, where mucosal tissues are highly affected by a flow of biological fluids. For example, it is applicable for testing gastrointestinal, ocular, nasal or vaginal formulations and it involves simulation of a biological flow which washes off a dosage form from the surface of a mucosal tissue. This technique can also be used for evaluating mucoadhesive properties of micro- and nano- as well as semi-solid formulations (e.g., gels and creams) that cannot be easily tested with a tensile approach. The principle of the flow-through test is schematically shown in Figure 6. In a typical experiment, a mucosal tissue is secured on a surface of a 'slide' and covered with a product to be tested. A flow of a simulated body fluid is maintained to wash off a formulation from the surface of mucosal tissue. The dosage form retention can be monitored by analyzing the content of a drug, a model die or a mucoadhesive polymer in the collected perfusate. The analysis can be performed either spectrophotometrically (UV-Vis or fluorescence) or by using chromatographic techniques (high-performance liquid chromatography or gel permeation chromatography). Additionally, the amount of a dosage form remaining on the mucosal tissue could also be monitored.

The correct selection of experimental conditions used for flow-through evaluation of mucoadhesive dosage forms is very important[53,54] and ideally should mimic the biological environment of a particular route of administration. The most important factors to consider are temperature at

Table 1. Detachment/dissolution time registered for tablets attached to porcine stomach mucosa (dissolution medium: 1 L, pH = 2.0, 37 °C). Tablets were prepared by compression of powder blends. Data was taken from ref. [50]

Tablet	Detachment/dissolution time	Comment
	min	
MAD-BA (93:7 mol-%)[a)]	12 ± 4	dissolved
MAD-BA (83:17 mol-%)	13 ± 2	dissolved
MAD-BA (73:27 mol-%)	12 ± 2	dissolved
MAD-BA (63:37 mol-%)	13 ± 4	dissolved
MAD-BA (73:27 mol-%)/PAA[b)] 1:3 (w/w)	900 ± 50	dissolved
PAA	295 ± 12	dissolved
MAD-BA (63:37 mol-%)/L-HPC[c)] 1:3 (w/w)	1 ± 0.3	disintegrated

[a)]Random copolymer prepared by free-radical copolymerization of 2-methacryloyloxyethyltrimethylammonium chloride with butyl acrylate. The ratio of monomeric units in the copolymers is shown in parentheses. The details on copolymer synthesis can be found in ref. [51]; [b)]PAA is poly(acrylic acid) with $\overline{M}_w = 450$ kDa; [c)]L-HPC is low-substituted hydroxypropylcellulose (insoluble in water).

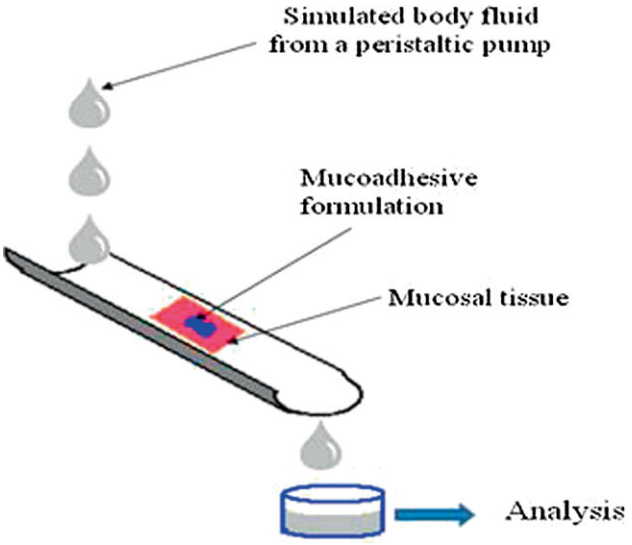

Figure 6. Flow-through experimental setup for evaluating mucoadhesive properties.

the mucosal surface in the human body, humidity, content of a simulated biological fluid and its flow rate.

Rheological Method

The rheological approach first described by Hassan and Gallo[55] has been suggested to evaluate the strength of interactions between mucus gels and polymers. In this method the interpenetration layer is simulated by mixing the polymer solution or dispersion with a mucin solution. Polymers with strong mucoadhesive ability are expected to have a greater viscosity in mixtures with mucins compared to the sum of polymer and mucin viscosities and this rheological synergism may be used to evaluate their adhesive properties. Viscosity or elasticity is experimentally determined for their mixture and the data are compared with the rheological properties of the polymer and the mucin separately. The viscosity of the mixture (η_{total}) can be expressed through the following relationship:

$$\eta_{total} = \eta_{mucin} + \eta_{polymer} + \eta_{mucoad} \quad (1)$$

where η_{mucin} and $\eta_{polymer}$ are the individual viscosities of mucin and polymer, respectively. η_{mucoad} is a factor evolving from the mucoadhesive interaction between mucin and polymer and is termed as viscosity component of mucoadhesion. Consequently, the force of mucoadhesion (F) represents the additional intermolecular frictional force per unit area and is defined by the following equation:

$$F = \eta_{mucoad} \times \sigma \quad (2)$$

where σ is the shear rate (s^{-1}). The term η_{mucoad} is based on experimental viscosity values determined at the same concentration, temperature, time and shear rate.

Hassan and Gallo[55] have determined the values of the force of mucoadhesion for poly(ethylene glycol) (4 kDa), bovine serum albumin, dextran (71.5 kDa), polybrene or 1,5-dimethyl-1,5-diazaundecamethylenepolymethobromide (4.5 kDa), cationic gelatin (193 kDa), chitosan (652 kDa), poly(aspartic acid) (35 kDa), heparin (48.5 kDa) and poly(acrylic acid) (90 kDa) in mixtures with commercial porcine gastric mucin at pH = 1.0 (0.1 N HCl) and pH = 5.5 (0.1 N acetate buffer). The highest F values were observed for chitosan and poly(acrylic acid) at pH = 5.5 with polymer concentrations of 1 and 2.5% w/v, respectively. Very poor mucoadhesive properties were observed for polymers having relatively low molecular weights such as poly(ethylene glycol), polybrene, poly(aspartic acid) and heparin.

Madsen et al.[56] have used the rheological method to study mucoadhesive interactions between freshly isolated porcine gastric mucin and four mucoadhesive polymers (two polymeric derivatives of acrylic acid, Noveon and Pemulen TR-2, as well as carrageenan and sodium carboxymethylcellulose). It was demonstrated that, with the exception of sodium carboxymethylcellulose, mixing mucoadhesive polymers with mucus gels results in a high degree of rheological synergism, indicating the presence of intermolecular interactions between the polymers and mucins. The strength of these interactions was found to be dependent on temperature and solution pH.

Rossi et al.[57,58] have evaluated the rheological behavior in mixtures of chitosan with porcine gastric mucin at different polymer concentrations and polymer/mucin ratios. They reported two types of rheological interactions: one was characterized by a minimum in viscosity and was typical for higher polymer/mucin ratios; the other type resulted in positive rheological synergism and was observed for mixtures with excessive mucin content. It was emphasized that the second type of rheological behavior causes a 'strengthening' of the mucoadhesive interface and responsible for formation of adhesive joints.

The rheological approach is a useful technique allowing easy evaluation and comparison of mucoadhesive properties of various polymers; however, it is not always reliable and has to be often used in conjunction with other techniques. Care must be taken when interpreting rheological results as depending on the polymer and mucin concentrations the outcome of mucoadhesive interactions may be either a rheological synergism or a decrease in viscosity of the mixture.

Methods to Study Mucoadhesive Interactions

Peppas and Huang[59] have emphasized the importance of studying the nature of mucin/polymer interactions to get a

further understanding of mucoadhesion phenomena. Numerous studies have been reported on evaluation of interactions between various polymers and mucins in solutions. A number of reports were published demonstrating that native mucins, freshly isolated from animals, exhibit some biophysical properties which are partially lost upon their purification and storage.[60] However, the majority of studies evaluating mucoadhesive interactions have reported the use of commercially-available lyophilized porcine gastric mucin[51,57,58,61–64] and bovine submaxillary gland mucin.[17,65–67] Although, these products may differ from the native mucins they often show less batch-to-batch variability and give more reproducible results.

Commercially-available porcine gastric mucin can be easily dispersed in water and form colloidal suspensions, suitable for application of various physicochemical methods to evaluate polymer/mucin interactions. Mucin particles within these suspensions are usually highly polydisperse and negatively charged (Figure 7). The surface charge of particles is highly dependent on pH. Zeta-potential values for porcine gastric mucin dispersed in a medium with pH = 7.0 are around –19.4 mV. The negative charge of mucin particles decreases upon acidification and approaches electroneutrality at around pH = 2.0.[63]

Rossi et al.[57], Fefelova et al.[51], Sogias et al.[63] and Thongborisute and Takeuchi[68] have used a turbidimetric technique as a simple and reliable method to study the interactions between aqueous mucin dispersions and polycations such as chitosan and cationic methacrylate polymers. They found that formation of mucin/polymer complexes is accompanied by an increase in solution turbidity due to the aggregation of mucin particles caused by polymer adsorption at their surfaces and bridging effects (Figure 8). When excess of polymer is added to the aggregates it results in their de-aggregation leading to a further decrease in turbidity.[51,63]

Takeuchi et al.[61] have also suggested the use of dynamic light scattering and zeta-potential measurements to characterize the strength of interactions between porcine gastric mucin and various water-soluble polymers. The surface charge of mucin particles was found to change upon addition of mucoadhesive polymers due to their adsorption and changes in zeta-potential values may be used as an indication of mucoadhesive properties. The addition of cationic polymers to mucin particles resulted in increase of zeta-potential from -19 ± 1 mV to positive values[51,61,63] confirming their direct interactions and mucoadhesiveness. Negatively-charged Carbopol polymers also showed good affinity to mucins resulting in accumulation of further negative charge at particle surfaces. Zeta-potential values of mucin particles dropped from -19 ± 1 to -31 ± 1 mV in the presence of 1% of Carbopols (971P and 974P) at pH = 6.8.[61] When hydroxypropylmethylcellulose (HPMC) was added to mucin dispersion instead of chitosans and Carbopols, the zeta-potential of particles remained unchanged, indicating poor mucoadhesive affinity of this non-ionic polysaccharide.[61]

In a series of publications Harding and coworkers[69–72] have reported the use of analytical centrifugation to probe mucoadhesive interactions between freshly isolated mucins and various polymers in solution mixtures. They demonstrated that interactions between mucins and mucoadhesive polymers result in the changes of the sedimentation velocity and molecular weights due to the formation of large complex aggregates.

Another physical technique pioneered by Takeuchi and coworkers[61,68] is based on the use of surface plasmon resonance (SPR) with a Biacore instrument. This method allows monitoring changes in refractive index for solutions passing through a sensor chip. Prior to the Biocore experiment, the sensor chip should be modified by covalent attachment of mucin particles. When polymer solutions are passed through this system, mucoadhesive component binds to immobilized mucin particles resulting in the changes in SPR response. The amplitude of SPR response may be used as a quantitative measure to assess mucoadhesive ability of different polymers. For example, the authors[61,68] have demonstrated that chitosan with higher molecular weight (150 kDa) binds stronger to mucins compared to its lower molecular weight analogue (20 kDa); Carbopols 971 PNF and 974 PNF have shown an intermediate binding potential compared to low and high molecular weight chitosans; and the lowest mucoadhesivity was observed for non-ionic polymers such as poly(vinyl alcohol) and hydroxypropylcellulose.

Several other techniques have been used to provide insights into mucoadhesion mechanism. Patel et al.[73] have used infrared (IR), ^{1}H and ^{13}C NMR, X-ray

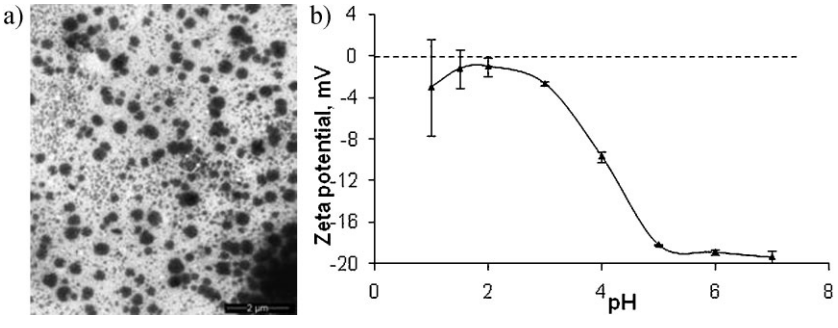

Figure 7. (a) Transmission electron microscopy image of 1 mg · mL^{-1} porcine gastric mucin aqueous dispersion at pH = 6.8. Reproduced from ref. [51] with permission from Elsevier. (b) Zeta potential of 0.1% w/v porcine gastric mucin dispersion as a function of pH. Reproduced from ref. [63] with permission from the American Chemical Society.

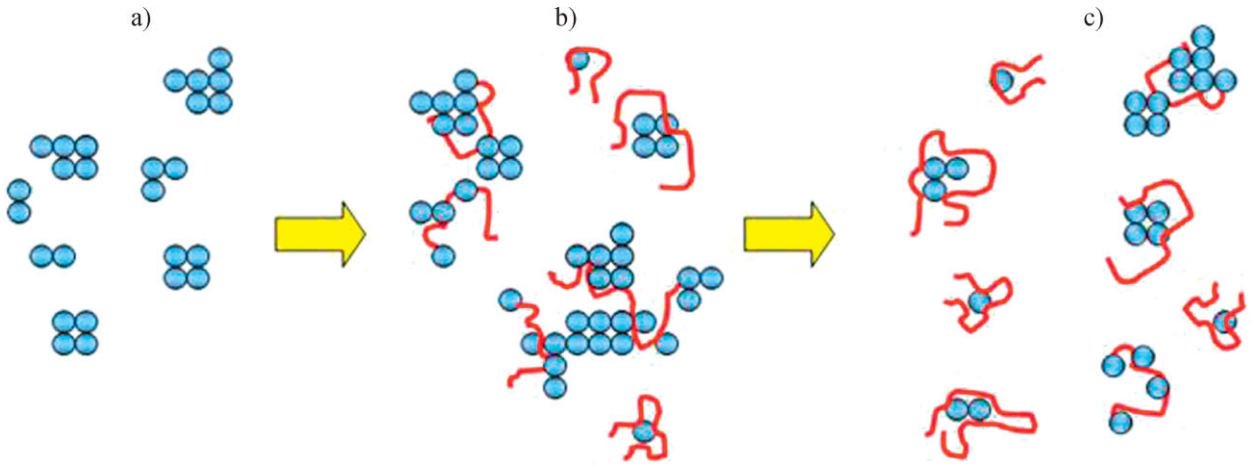

Figure 8. Aggregation/de-aggregation of mucin particles in the presence of a cationic polymer: (a) mucin dispersion in the absence of a polymer; (b) mucin dispersion in the presence of a small portion of a polymer; (c) mucin dispersion in the presence of excess polymer. Reproduced from ref. [51] with permission from Elsevier.

photoelectron spectroscopy (XPS) and DSC to study the interactions between poly(acrylic acid) and the glycoprotein components of mucus. The formation of hydrogen bonds between mucus and poly(acrylic acid) has been shown by the displacement of IR absorption bands and by NMR resonances. XPS results indicated that, in mixtures, the mucus tend to encapsulate the polymer. Qaqish and Amiji[65] have used fluorescence polarization technique to probe interactions between bovine submaxillary mucin and chitosan labeled with fluorescein isothiocyanate (FITC). A growth in the degree of fluorescence polarization usually indicates an increase in the molecular volume of the fluorophore upon association. In the presence of mucin the degree of polarization of FITC-chitosan (mucin/chitosan molar ratio of 19:1) was found to result in 61% increase in polarization, suggesting that more than one mucin can associate with each chitosan macromolecule. The use of fluorescence polarization allowed the authors[65] to study the effects of pH and ionic strength on the interactions between FITC-chitosan and mucin and conclude that hydrogen bonding and/or hydrophobic effects also contribute to mucoadhesion of chitosan in addition to electrostatic interactions.

Classes of Mucoadhesive Polymers

Mucoadhesivity of dosage forms is usually achieved by the use of hydrophilic polymers in formulations, which often demonstrate good ability to stick to mucosal membranes. Excellent mucoadhesive performance is typically observed for polymers possessing charged groups or non-ionic functional groups capable of forming hydrogen bonds with mucosal surfaces. Some of the polymeric structural characteristics necessary for mucoadhesion can be summarized as follows: (i) strong hydrogen bonding groups, e.g., carboxyl, hydroxyl, amino- and sulfate groups, (ii) strong anionic or cationic charges, (iii) high molecular weight, (iv) chain flexibility, (v) surface energy properties favoring spreading onto mucus.[26,74] Below we will consider different classes of mucoadhesive polymers in relation to their chemical structure and functionality.

Anionic Polymers

The mucoadhesiveness of weakly anionic carboxyl-containing polymers such as poly(acrylic acid), poly(methacrylic acid), carboxymethylcellulose, sodium alginate and poly[(maleic acid)-*co*-(vinyl methyl ether)] has often been related to the ability of carboxylic groups to form hydrogen-bonds with oligosaccharide chains of mucins. A number of studies have been published on evaluating the mechanism of mucoadhesive interactions of poly(acrylic acid) or/and its weakly cross-linked derivatives Carbopols and Carbomers with mucins.[31,73,75,76] Park and Robinson[31] have synthesized a series of weakly cross-linked hydrogels by copolymerizing acrylic acid with acrylamide in the presence of a cross-linker and systematically examined the effects of solution pH, copolymer composition and cross-linking density on adhesiveness of these polymers to freshly excised stomach tissue. They established that the strongest mucoadhesive properties are observed under acidic conditions and adhesion force drops sharply at pH above 4.0. This clearly suggested that carboxylic groups in acidic form provide excellent mucoadhesion, which may be related to their hydrogen bonding with mucins. The copolymers containing lower levels of acrylic acid showed poorer mucoadhesive performance confirming the major role of carboxylic groups in adhesive bonding.

The mucoadhesive performance of the copolymers was also found to decrease with the concentration of a cross-linker in the monomeric mixture. This was related to decreased chain flexibility and poorer ability of the polymer to form interpenetration layer with mucins. Degim and Kellaway[75] studied the swelling of poly(acrylic acid) microspheres in solutions of pig gastric mucin at various pHs. They demonstrated the formation of interfacial film through adsorption of mucin at the solid/liquid interface, which exhibited pH dependent resistance to the diffusion of water. The lowest diffusion of water was observed at pH = 4.0 and 5.0 indicating the formation of impermeable interfacial film under these conditions. Nikonenko et al.[76] have applied visible and IR spectroscopic ellipsometry to study the adsorption of bovine submaxillary mucin on poly(acrylic acid)-*block*-poly(methyl methacrylate) and poly(methyl methacrylate) surfaces at various pHs (3.0, 7.0 and 10.0). They established that the greatest thickness of adsorbed mucin layer is observed when the experiment was conducted at pH = 3.0. The IR ellipsometry experiments have confirmed that the highest density of hydrogen bonding involving carboxylic groups is observed for mucin layers deposited on block copolymers at pH = 3.0.

In addition to mucoadhesive properties, some anionic polymers such as Carbopols exhibit unique gelation behavior, which can be easily triggered by changes in solution pH. For example, Carbopol 71G forms slightly viscous 0.5% w/v solution in deionized water but undergoes a rapid gelation upon increase in pH (Figure 9). The gelation of Carbopols triggered by changes in solution pH and their mucoadhesive properties open excellent opportunities for formulating in situ gelling dosage forms for ocular drug delivery. These dosage forms may be instilled into the eye as a liquid and form a gel sticking to ocular mucosal surfaces and providing an improved dosage form retention.[77]

Cationic Polymers

Cationic polymers such as chitosan[63] and some synthetic polymethacrylates[51,78] have been reported to show excellent mucoadhesive performance. Chitosan is a linear polysaccharide, consisting of β-(1→4)-linked 2-amino-2-deoxy-D-glucose residues, and it is produced commercially by alkali *N*-deacetylation of chitin, the main constituent of crustacean exoskeletons. Chitosan has a number of unique physicochemical and biological characteristics including its cationic nature and film forming ability, antimicrobial and wound healing properties, the ability to bind lipids and fatty acids and to enhance penetration through mucosal membranes.[79] Mucoadhesive properties of chitosan and its derivatives have been widely exploited to develop pharmaceutical formulations for oromucosal,[80] oral,[81] ocular[82] and nasal[83,84] routes of administration.

The excellent mucoadhesive properties of chitosan have often been related to its ability to interact with negatively charged mucins via electrostatic attraction. However, some authors also highlighted the complexity of chitosan's mucoadhesive interactions and suggested that hydrogen bonding and hydrophobic effects may also play a certain role.[65,70] Recently, we also studied the contribution of different physical interactions involved in mucoadhesiveness of chitosan through manipulating with its chemical structure via partial acetylation and adding NaCl, ethanol or urea.[63] We demonstrated that mucoadhesive interactions between chitosan and mucin have a complex nature with contributions from electrostatic attraction, hydrogen bonding and hydrophobic effects. Electrostatic attraction appears to be the major mechanism for chitosan mucoadhesion but is also reinforced by contributions from hydrogen bonding and hydrophobic effects. Solution pH as well as the presence of other chemicals can change the relative contributions of each physical interaction.

The presence of active functional groups such as amines and hydroxyls in chitosan opens wide opportunities for its chemical derivatization. There are a number of well-established chitosan derivatives; some of these are even available commercially. The most important chitosan derivatives relevant to pharmaceutical applications include trimethyl chitosan, glycol chitosan, carboxymethylchitosan and half-acetylated chitosan. Numerous papers have been published on the use of chitosan-based polymers and their further derivatives for formulating drugs for transmucosal administration (see refs.[85–87] as examples); however, there are only few systematic studies available on elucidation of the structure–mucoadhesive property relationship for various chitosans.

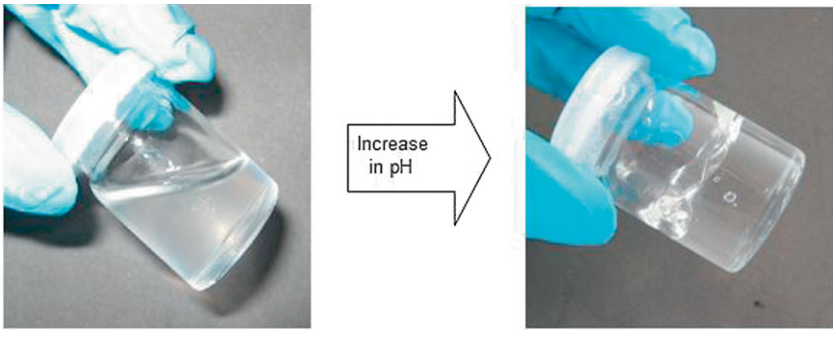

Figure 9. Gelation of 0.5% w/v Carbopol 71G solution triggered by changes in pH.

Non-Ionic Polymers

Non-ionic polymers typically exhibit poorer mucoadhesive performance compared to polyelectrolytes.[88] The specific interactions between non-ionic polymers

and mucin are usually very weak and often cannot be registered by conventional physicochemical techniques.[61,68] Mucoadhesive performance of formulations based on non-ionic polymers may be achieved predominantly through diffusion of their macromolecules and formation of interpenetration layer with mucus gel.

Amphoteric Polymers

Mucoadhesive properties of polyampholytes, i.e., polymers simultaneously bearing cationic and anionic functional groups in their chains, have been explored only in few studies. The most common polyampholytes that were used in mucoadhesive formulations are gelatin and *N*-carboxymethylchitosan. Gelatin was reported to exhibit relatively poor mucoadhesive properties similar to non-ionic polymers,[12] which may be explained by its amphoteric nature and self-neutralization of cationic and anionic charged within its structure. On the contrary, aminated derivative of gelatin has shown a considerable gastric mucoadhesion both in vitro and in vivo in rats.[89] N-carboxymethylchitosan was used by Thanou et al.[90] to enhance the intestinal absorption of low-molecular-weight heparin across intestinal epithelia both in vitro and in vivo; however, in the study reported by Di Colo et al.[91] the same polymer failed to show an enhancement effect for intraocular penetration of ofloxacin.

Polyampholytes have a number of unique features[92,93] that have to be taken into consideration when analyzing their mucoadhesive and penetration-enhancing properties. Depending on solution pH and their specific isoelectric point (pI) amphoteric polymers may exist in three different states (positively charged, neutral and negatively charged). The viscosity of polyampholytes in solutions is typically minimal at the isoelectric pH and increases when pH is higher or smaller than pI. Polyampholytes with significant proportion of hydrophobic groups in their structure often precipitate or crystallize at or near the isoelectric pH. In the presence of inorganic salts the viscosity of polyampholytes in their cationic or anionic forms tends to decrease, whereas under isoelectric conditions it increases. All these pH-induced structural and physicochemical transformations are expected to affect the mucoadhesive and penetration-enhancing properties of polyampholyte-based formulations but have not yet been studied systematically.

Polymeric Thiomers

Thiomers can be defined as polymers containing side chains with thiol-bearing functional groups.[94] These polymers can be prepared by conjugating conventional mucoadhesive polymers with molecules carrying thiol functionality. Typical examples of polymeric thiomers include the following conjugates: poly(acrylic acid)/cystein,[95] chitosan/*N*-acetylcystein,[96] alginate/cystein,[97] chitosan/thioglycolic acid[98] and chitosan/thioethylamidine.[99] The mucoadhesive properties of polymeric thiomers have been extensively studied by Bernkop-Schnurch and coworkers.[49,94] They established that these polymers are capable of forming covalent bonds (disulfide bridges) with cystein-rich sub-domains of mucus glycoproteins either via thiol/disulfide exchange reactions or through a simple oxidation of free thiol groups (Figure 10).

Due to the formation of covalent bonds with mucins, thiolated polymers exhibit significantly enhanced mucoadhesive properties in comparison with conventional mucoadhesives.[49] For example, a lyophilized chitosan/4-thiobutylamidine conjugate containing up to 243 ± 54 μmol/g of thiol groups exhibits the total work of adhesion of 740.0 ± 146.7 μJ for its detachment from freshly excised porcine small intestinal mucosa compared to 40.9 ± 12.4 μJ observed for unmodified chitosan under identical conditions.[49]

It is interesting to mention a recent study by Davidovich-Pinhas et al.[100], who synthesized thiolated alginate and studied the adhesiveness of hydrated polymer discs to

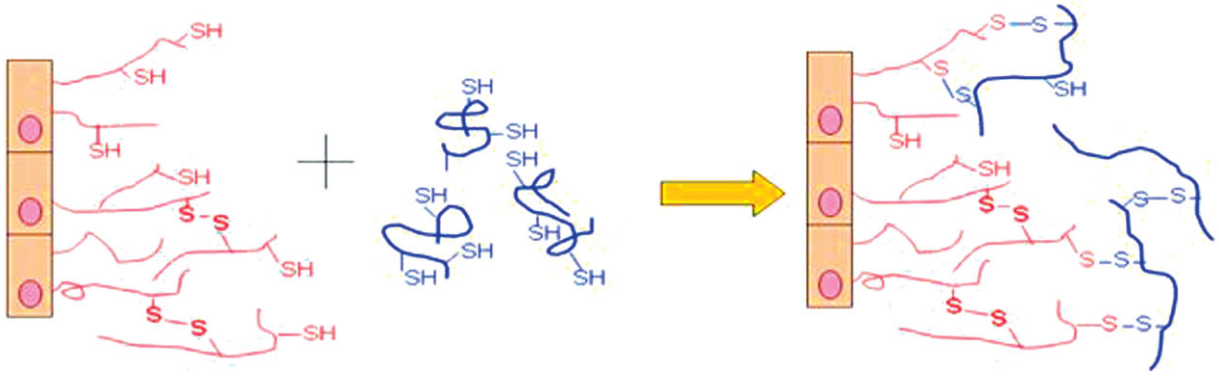

Figure 10. Formation of disulfide bridges between polymeric thiomers and cystein-rich domains of the mucus gel. Adapted from ref. [88] with permission from Elsevier.

porcine small intestine tissues. They demonstrated that hydrated thiolated alginate does not show any benefit of thiolation for mucoadhesive properties, previously reported for dry tablets.[97] This result was explained by the formation of intermolecular disulfide junctions.

Further studies will be required to evaluate and compare the mucoadhesive properties of thiolated polymers both in solid and hydrated states. It would also be useful to have a further expansion of a range of polymeric thiomers. Particularly, the development of novel derivatization approaches to thiolate non-ionic polymers may offer an excellent way to improve their poor mucoadhesive performance.

Polymers with Acrylate End Groups

An interesting class of mucoadhesive polymers capable of forming covalent bonds with mucins similarly to polymeric thiomers has recently been proposed by Davidovich-Pinhas and Bianco-Peled.[101] They demonstrated that poly(ethylene glycol) diacrylate is able to react with thiol groups present in freshly extracted porcine small intestinal mucin through Michael addition under physiological conditions and form stable covalent linkages. This reaction was confirmed by ^{1}H NMR spectroscopy and rheological measurements of polymer/mucin mixtures. The adhesion of poly(ethylene glycol) diacrylate samples to a fresh small intestinal surface was studied by means of a tensile technique and revealed mucoadhesiveness comparable to thiolated alginate. Although this study utilized just one poly(ethylene glycol) diacrylate sample and provided an incomplete characterization of mucoadhesive properties (only detachment force was measured), it may potentially lead to the development of a novel class of mucoadhesive polymers. Further studies will be required to assess mucoadhesive properties of various polymers with numerous pendant acrylate and methacrylate groups to prove their superior adhesive properties compared to unmodified analogues.

Dendrimers

Dendrimers are monodisperse well-defined macromolecules with regular and highly branched three-dimensional structures consisting of a core, branches and end-groups. Due to their unique structure and properties dendrimers have attracted a lot of attention of pharmaceutical scientists and current areas of their potential application include vectors for gene delivery,[102] excipients for enhancing aqueous solubility of poorly-soluble drugs,[103] antimicrobial agents[104] and drug conjugates.[105]

Only few papers were published on evaluation and use of dendrimers as mucoadhesives. Vandamme and Brobeck[106] have reported the use of poly(amidoamine) (PAMAM) dendrimers carrying various functional groups (amino, carboxylate and hydroxyl surface groups) for ocular delivery of pilocarpine nitrate and tropicamide (Figure 11).

The mucoadhesive properties of these dendrimers were studied by evaluating the rheology of dendrimer/mucin mixtures and comparing with the behavior of individual components in solutions at neutral pH, mimicking the ocular environment. It was established that the strongest mucoadhesive interactions are observed for 2.0% solutions of G2 and G4 dendrimers with amino group surface functionality, which may be related to their interaction with negatively charged mucins due to electrostatic attraction. The dendrimers with COOH surface groups (G1.5 and G3.5) exhibited the weakest mucoadhesive interactions similar to Carbopol 980 NF 0.2% solution, which was used as a control in these experiments. The

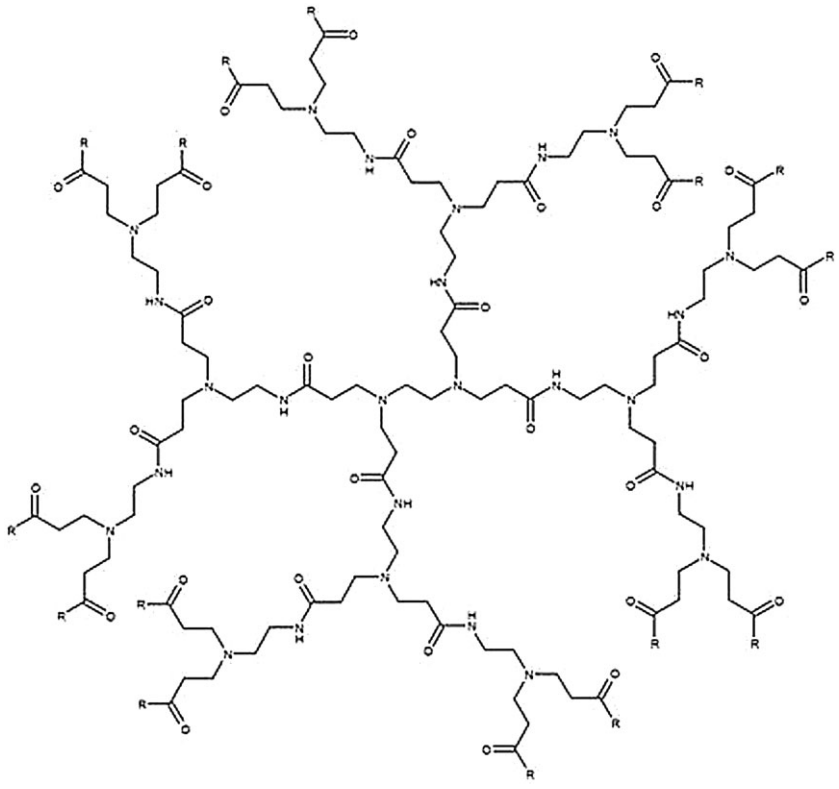

Figure 11. Structure of PAMAM dendrimers. The increase in generation number (Go, G1, G2, etc.) results in an incremental increase in size, molecular weight, and number of amine or carboxylate or hydroxyl surface groups. G1.5: R = OH; G2: R = $-NH-(CH_2)_2-NH_2$; G2(OH): R = $-NH-(CH_2)_2-OH$.

authors related the weak strength of interactions observed for anionic dendrimers and Carbopol 980 NF to their inability to form hydrogen bonds with mucins at neutral pH, where carboxylic groups of both the dendrimers or Carbopol 980 NF and the mucins are fully ionized and cause a repulsion. The dendrimers with hydroxyl surface groups displayed the mucoadhesive interactions of intermediate strength. However, when in vivo experiments were performed in rabbits using fluorescein as a model drug to evaluate dendrimer-mediated ocular residence, the best performance was found for dendrimers carrying hydroxyl functionality [G2(OH) and G4(OH)]. These dendrimers were shown to induce longer corneal residence time (up to 300 ± 0 min) compared to 100 ± 61 min and 203 ± 84 min, observed for formulations containing amino-groups surfaces (G2.0 and G4.0, respectively).

Griffiths et al.[64] have applied pulsed-gradient spin-echo NMR (PGSE-NMR) and small-angle neutron scattering (SANS) to evaluate the solution interactions of porcine gastric mucin with a series of PAMAM dendrimers (G2.0, G3.5, G4.0, G5.5) and compared them with branched polyethyleneimine, linear poly(ethylene glycol)s and dextrin. It was demonstrated that PAMAM dendrimers exhibit strong electrostatic attraction with mucins under pH conditions where PAMAM and mucin bore opposite charge. When pH was changed to reverse the charges either on mucins or dendrimer the attractive interaction may be 'switched off'. It was also indicated that different mechanisms are operating for mucoadhesive interactions involving full- and half-generation PAMAMs.

The limited number of studies involving dendrimers as mucoadhesives is likely due to relatively high costs of these chemicals compared to conventional polymeric excipients. Further systematic studies would be required to clarify the relationship between the structure/functionality of various dendrimers and their performance as mucoadhesives both in vitro and in vivo.

Boronic Acid Copolymers

Recently Ivanov et al.[107] have utilized the ability of water-soluble polymers containing phenyl boronate functional groups to form complexes with carbohydrates and suggested boronic acid copolymers as a novel class of mucoadhesives. They established that the copolymers of *N*-acryloyl-*m*-aminophenylboronic acid with *N,N*-dimethylacrylamide (up to 15 mol-% *N*-acryloyl-*m*-aminophenylboronic acid to ensure their solubility in aqueous environment) are capable to form insoluble complexes with porcine stomach mucin at $pH = 9.0$ and ionic strength of solution above 0.1 M. These complexes could be re-dissolved in the presence of fructose, a carbohydrate capable of competing with oligosaccharide moieties of mucins for binding to boronate groups. It was demonstrated that these copolymers may facilitate the retention of poly(vinyl alcohol)/borax gels in mucosal lumens providing their temporary occlusion. The authors also discussed the applicability of boronic acid copolymers as mucoadhesives for the routes of drug administration with neutral and weakly basic pHs 7.0–9.0, where their complexation with mucins is most pronounced. The nasal, ocular and buccal mucosa were highlighted in this study as a possibility for dosage form administration but no steps have been taken to evaluate the applicability of novel mucoadhesives for drug delivery via these routes yet.

Synthetic Glycopolymers

Glycopolymers are defined as polymers containing sugar moieties as pendant groups.[108] This class of polymers has attracted considerable attention of researchers due to their hybrid properties typical for both polysaccharides and synthetic polymers. The advantage of synthetic glycopolymers over the conventional water-soluble polysaccharides is the possibility for easy manipulation in their architecture and physicochemical properties, which can be performed through homo- and copolymerization with monomers of different nature.

The applicability of synthetic glycopolymers as mucoadhesives has been reported by Rathi et al.[35] They synthesized a series of novel glycopolymers by free-radical copolymerization of *N*-(2-hydroxypropyl)methacrylamide with various sugar-containing monomers such as *N*-methacryloylglycylglycylgalactosamine, *N*-methacryloylglycylglycylfucosylamine, *N*-methacryloylglycylglycylglucosamine and *N*-methacryloylglycylglycylmannosamine. The mucoadhesive properties of these copolymers were studied in vitro using small intestinal and colonic tissues taken from guinea pigs. The animal tissues were incubated for 30 min in solutions containing radio-labeled copolymers and then were intensively washed and their radioactivity was measured and expressed as a percentage of radioactivity per gram of biological tissue. Fucosylamine containing copolymers were found to adhere selectively to the colon in vitro and stronger adhesion was observed for copolymers containing larger quantities of sugar moieties. It was also established that this binding can be inhibited in the presence of free fucose and fucosamine-free copolymer did not exhibit any noticeable adhesion. The authors[35] hypothesized that this adhesion is related to the binding of sugar-moieties of the copolymers to specific receptors present in the colonic epithelium. The adhesion of these glycopolymers to small intestinal mucosa was less pronounced and less sensitive to fucosamine in the copolymers.

Polymeric Blends and Complexes

Simple blending of polymers is an easy way of achieving new materials with required properties and functionality, without the recourse to their chemical derivatization. Blending of polymers may be used to adjust mucoadhesive properties of dosage forms, to optimize their mechanical characteristics, to modulate their swelling behavior or to improve their biocompatibility. New mucoadhesive materials may be prepared by blending of pharmaceutical polymers in solid state or in solution.

Solid state blending may be realized through mixing of powdered excipients and their subsequent compression into mucoadhesive tablets or discs[30,32,109] or through hot-melt extrusion.[110] When two mucoadhesive polymers are mixed as powders and compressed into a dosage form, its mucoadhesive properties will depend on the strength of specific interactions occurring between both components upon hydration. If the specific interactions between the polymers are not very strong and do not lead to the formation of insoluble polycomplexes, then the mucoadhesive properties of a dosage form will often be intermediate between the adhesiveness of each individual components. For example, tablets prepared by compression of poly(acrylic acid) (Noveon AA1, Belgium) and HPMC powders at various component ratios show a composition dependent mucoadhesive properties.[111] The highest mucoadhesiveness was observed for tablets consisting of pure poly(acrylic acid) and addition of HPMC to the formulation results in gradual reduction of this property, which is related to a dilution of a more adhesive excipient [poly(acrylic acid)] with weaker non-ionic mucoadhesive (HPMC).

Blending of various functional polymers in solutions in a common solvent may be used for preparation of liquid and semi-solid mucoadhesives.[77,112] Alternatively solution mixtures may be dried on flat surfaces resulting in mucoadhesive polymeric films[45,113] or spray-dried yielding microparticulate formulations.[114] The control of specific interactions between polymers in a common solvent is of paramount importance as insoluble complexes are often formed and it affects the properties of final dosage forms. Further consideration of the effects of specific interactions between polymers on the properties of dosage forms including their mucoadhesive performance can be found in our recent review. [115]

Conclusion

Mucoadhesive polymers have been exploited for several decades by pharmaceutical scientists to formulate novel dosage forms for various routes of drug administration (buccal, oral, nasal, ocular and vaginal). The research in this area continues to develop very quickly with more than hundred new papers being published each year. The current efforts in this area are focused on the design of mucoadhesive polymers with improved performance, development and validation of new physical techniques to study mucoadhesion and formulation of novel dosage forms for mucosal administration. In this feature article we attempted to provide an overview of existing knowledge about mucosal membranes and mucins, mucoadhesion and mucoadhesive polymers, techniques used to characterize mucoadhesive properties of various dosage forms and also highlighted some recent developments in novel classes of mucoadhesive polymers.

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