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Mucoadhesion: a review of characterization techniques

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Importance of the field: Mucoadhesive drug delivery vehicles attract much attention owing to benefits such as extended residence time of the drug at the site of application, a relatively rapid uptake of a drug into the systemic circulation, and enhanced bioavailability of therapeutic agents. Mucoadhesion, defined as the ability to adhere to the mucus gel layer covering organs that are exposed to the outer surface of the body yet are not covered with skin, such as the mouth and the respiratory tract, is a key element in the design of these drug delivery systems.

Areas covered in this review: This review focuses on the numerous experimental methods that have been proposed over the years for mucoadhesion characterization. These techniques are categorized into directs methods, which measure the force or time required to detach the mocoadhesive from a mucus, and indirect methods, which asses the interactions between the mucoadhesive and mucin type glycoproteins.

What the reader will gain: The comprehensive description of the available techniques could facilitate the selection of a characterization method that meets the requirements of a specific study. Moreover, a comparison between the results obtained in different laboratories is given whenever possible.

Take home message: The challenge of adopting a universal test method that could be used to compare data from different research groups and rank new mucoadhesion candidates has not yet been met.

Keywords: adhesion assay, bioadhesion, mucoadhesion, sustained release

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1. Introduction

Mucoadhesive polymers were pioneered by Prof. Joseph R Robinson in the early 1980s as a new strategy to design sustained drug delivery systems which are capable of attaching to the mucusal layer that covers epithelial cells. Mucoadhesive drug delivery systems offer several benefits over other delivery methods. These include extended residence time of the drug at the site of application, a rapid uptake of a drug into the systemic circulation owing to the relatively large permeability of the mucus membranes, and enhanced bioavailability of therapeutic agents resulting from the avoidance of some of the body's natural defense mechanisms [1]. Mucoadhesion is a key element in the design of these drug delivery systems.

The mucus layer covers organs that are exposed to the outer surface of the body yet are not covered with skin, such as the mouth and the respiratory tract. It is composed of 95% water and ~ 5% mucus glycoproteins, termed mucin, plus a large number of minor components [2]. Sulfide functional groups attached to neighboring glycoprotein molecules interact with each other to create a crosslinked polymer matrix [3,4]. Mucin type glycoproteins play an important role in the mucoadhesion process owing to their unique chemical structure and physical properties [5].

The adherence of mucoadhesive polymers is an outcome of their physical and/or chemical interactions with the mucin glycoproteins. Non-covalent bonds such as hydrogen bonds, van der Waals forces, ionic interactions and/or chain

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Article highlights.

- A description of various tensile techniques.
- A description of rotating cylinder and adhesion time of tissue/sample attached in stirred beaker.
- A description of various continuous flow instruments.
- A description of the use of AFM in mucoadhesion measurements.
- An evaluation of the mucoadhesion properties using *in vivo* studies performed on animals.
- An evaluation of the mucoadhesion properties in human volunteers.
- A description of rheology measurements used to evaluate mucoadhesion properties.
- A description of various spectroscopic methods such as FTIR, NMR and dielectric spectroscopy for evaluating mucoadhesion properties.
- A description of the use of surface energy to evaluate mucoadhesion properties.
- A description of several methods based on mucoadhesive sample adsorption on intestinal surface (everted intestinal sac assay) and mucin particles (zeta-potential).

This box summarises key points contained in the article.

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entanglements are the most common [6]. In addition, owing to the negative surface charge of the mucus, electrostatic interactions play an important role in the adhesion process. Attempts have been made to enhance mucoadhesion by means of chemical modification of the polymers. The modified polymers contain thiol groups, which are capable of forming covalent bonds (disulfide bond) with the mucin's glycoproteins [7-11].

Mucoadhesion is a specific example for the more general phenomenon of adhesion. The origin of the term 'adhesion' is the Latin word *adhaerere* (*ad* = to, *haerere* = stick) [12]. The classical definition of adhesion is an assembly made by the use of an adhesive material between two other material surfaces (substrate) that creates a joint resistant to separation [13]. Two forces act together to prevent breakage of an adhesion joint: adhesion and cohesion. The adhesion force is responsible for creating the intimate contact between the molecules of the adhesive and the atoms or molecules on the substrate surface. This process can be referred to as wetting where the adhesive material is spread on the substrate [13]. The cohesive force results from interactions between the adhesive's molecules, and can be expressed as the work that is required to break the adhesive material and create two new surfaces. Adhesives are typically applied on the surface in a liquid form to allow wetting, and then hardened by a chemical reaction, loss of solvent or water, and so on, to achieve good cohesion [13].

Six theories describing the adhesion phenomenon and its relation to different exterior forces have been published [13-15]. Each of these theories is valid to some extent, depending on the nature of the material in contact and the condition of the process. Various types of force could be activated simultaneously depending on the observer's point of view. The physical adsorption theory of adhesion is the most widely used approach. This theory attributes the adhesion to van der Waals forces between permanent dipoles and induced dipoles across the interface. The chemical bonding theory of adhesion invokes the formation of covalent, ionic or hydrogen bonds across the inter-phase. The diffusion theory of adhesion is based on the assumption that the adhesion strength of polymers to themselves (autohesion) or to each other is induced as a result of mutual diffusion (inter-diffusion) of macromolecules across the inter-phase. The electrostatic theory was originally developed for metals where electrons transferred from one metal to the other form an electrical double layer that results in a force of attraction. According to the mechanical interlocking theory, adhesion occurs as a result of penetration of adhesive into the cavities, pores and asperities of the solid surface. The weak boundary layer theory proposes that clean surfaces can give strong bonds to adhesives, but some contaminants such as rust, oils or grease give a layer that is cohesively weak.

It is believed that the mechanisms involved in the mucoadhesion process are mostly surface energy thermodynamics, interpenetration/diffusion and chemical bonds. Thus, the mucoadhesion process is established first by wetting and adsorption on the mucus to create intimate contact followed by inter-diffusion or interpenetration of the mucoadhesive material. In some cases, the final bond formation is established by secondary chemical interactions that strengthen further the adhesive and the inter-phase bond [5].

The design of a mucoadhesives relies on two equally important features: its ability to function as a prolonged drug release matrix, and strong attachment to the mucus. This review focuses on the latter aspect and describes many of the experimental methods that have been proposed over the years for the evaluation of adhesion ability.

2. Methods for evaluating mucoadhesion strength

The first and probably the most crucial step in developing a new mucoadhesive system is verification of its ability to adhere to mucus. The literature describes numerous characterization methods that have been developed in different laboratories. Generally speaking, these techniques can be classified into direct ones that measure the force required to detach the mocoadhesive from a mucosa surface, and indirect methods that assess the interactions between the mucoadhesive and mucin type glycoproteins.

2.1 Direct methods

A direct determination of the mucoadhesion ability may involve a quantitative determination of the force required to detach the mucoadhesive from the surface. An alternative approach is the determination of another quantitative parameter such as the time required to detach the

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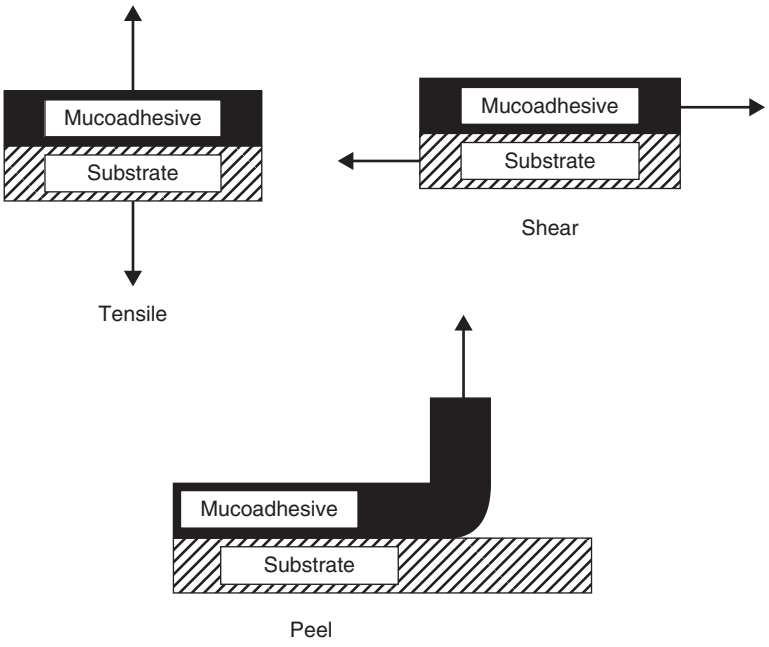

Figure 1. Types of force commonly applied in adhesion assays.

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mucoadhesive from the surface when the polymer is subject to a constant applied force. *In vitro* adhesion assays are commonly performed in tensile mode where the applied force acts in the axial direction, and in shear mode in which the force acts in the tangential direction (**Figure 1**). Use of a peel test, which requires that at least one of the substrates be made from a flexible material that can be peeled off the other surface (**Figure 1**), is rare in the field of mucoadhesion. The only documented example is in a study by de Vries and co-workers [16], who used the peel test to characterize the mucoadhesion of a hydrogel strip to porcine tissue. *In vivo* and clinical studies in this field typically focus on measuring the pharmacokinetics of drugs embedded in mucoadhesive matrices, thus providing indirect evidence of mucoadhesion. Only a few studies have evaluated the adhesion directly, as described in the following.

2.1.1 *Tensile assays*

The detachment force in tensile assays is determined using either a commercially available instrument such as materials testing machines or texture analyzers, or various home-made apparatuses, for example the one shown in **Figure 2**. The results are usually presented as the maximum detachment force (MDF) and the area under the measured load–extension curve representing the total work of adhesion (TWA) [17-19]. The type of substrate is a crucial parameter affecting the measured values. The most obvious substrate is fresh mucosa surface from an animal source, which imitates the physiology environment [20-24]. However, its availability is limited and therefore the utilization of other surfaces is common. Frozen tissues are easy to store, although the effect of freezing and thawing on the tissue characteristics is not fully understood [17,25-28]. Commercially available mucin powders are widely used as received or in the form of a concentrated aqueous solution (gel) [29-31], as partially hydrated compressed disc [32], or partially hydrated film. Alternatively, mucin solution can be soaked into a filter paper disc [21,33,34].

Many variations of sample and test design exist: the mucoadhesive polymer can be dry, hydrated or semihydrated, but liquids or pastes cannot be tested. Sample geometries of tablets, films, powders or particles have been used. Tests are preformed in wet or dry environment. The operating mode also changes depending on parameters such as detachment speed, preload strength and contact time.

The initial water content of the polymer sample is a key element that affects both the drug release profile and the mucoadhesiveness [35,36]. Dry polymer samples are widely used [37]. Bernkop-Schnurch and co-workers [20,38] glued dry compressed polymer tablets to stainless steel grid attached to nylon thread fixed to a laboratory stand. A mucosa surface was glued to the lower platform, which came into contact with the polymer tablet. The test was performed by pulling the lower platform at a constant rate of 6 mm/min. As an example, MDF values of 10 and 70 mN and TWA of 20 and 100 μJ were obtained for alginate and alginate-thiol, respectively [38]. This experimental set up was modified further by placing polymer tablets between two fresh mucosa surfaces attached to both of the tensiometer arms for fixed time followed by detachment of the upper arm at a constant rate [40]. Another variation included gluing dry polymer powder directly to the instrument arm [21,26]. The same methodology was used to characterize the mucoadhesion ability of dry microparticles

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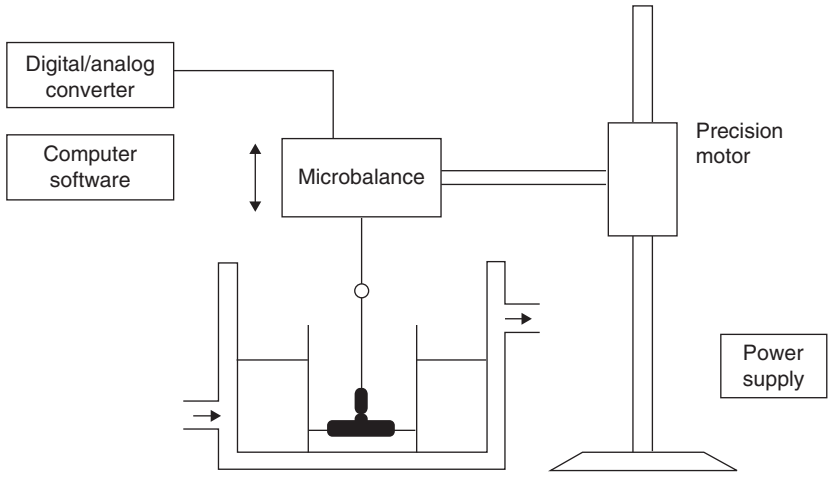

Figure 2. An example for the experimental set up for tensile measurements.
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prepared by a 'water-in-oil emulsification' method [27,41]. Dry polymer films were characterized in a similar manner. Samples were prepared by pouring a polymer solution on an inert surface [22,29,42] or into a mold [43], or immersing thin glass into the solution [44], followed by drying.

Semi-dry samples are usually dry samples that have been lightly hydrated by pouring a known amount of solvent on top of the sample surface before being contacted with mucosa surface [17,30,31,35]. The use of a dry or semi-dry polymer sample (i.e., not fully swollen) can enhance the adhesion because it allows diffusion and penetration of polymer chains into the mucus layer. However, dry polymers are not suitable for encapsulation of living cells for therapeutic treatment. With this application in mind, fully hydrated samples in the form of crosslinked hydrogels [1] were created and their adhesion to fresh mucosa surface was monitored. The hydrated hydrogel tablets were attached to the upper arm of a Lloyd tensile machine and the mucus was attached to the lower arm. Measurements were performed by raising the upper arm at a constant speed of 1 mm/min. MDF values ~ 40 mN for alginate and alginate-thiol were obtained, compared with the measured values of 10 and 70 mN for dry alginate and alginate-thiol [38]. The adhesion of hydrated polymer gel packed in a vessel was assessed by attaching a mucus sample to the upper arm of a tensiometer machine which was lowered until it came into contact with the gel vessel connected to the lower arm [23,25,28,30,32,45]. Caramella and co-workers [33,34] and, more recently, Edsman and co-workers [21] attached a filter paper disc soaked with polymer solution to the sample holder. The solution was contacted with mucosa surface for fixed time and then pulled away at constant rate.

A wet environment is used during the mucoadhesion test because of its similarity to physiological conditions, where mucus-covered surfaces are constantly hydrated. Several studies have described tensile tests where both the polymer and the mucus were immersed in liquid [20,22,24] during measurements. Typical TWA values were in the range 27 – 740 µJ [20], depending on the polymer type. For example, alginate displayed TWA in the range 34 – 47 µJ [20], which is higher than the values obtained in dry environment. The adhesion assay is similar to the one used for dry samples and used a conventional tensile machine.

An interesting alternative to material testing machine is a Cahn dynamic contact angle analyzer (CAHN), an instrument intended for measuring contact angle or surface tension [46-50]. This instrument includes an accurate and sensitive microbalance, thus it was modified to serve as a micro-bioadhesive instrument. The experimental procedure included placing a tissue in buffer at a constant temperature on the mobile stage, attaching a single polymer microsphere to the balance, and contacting the polymer and the tissue while submerged in the buffer for a fixed time before separating the surfaces in a tensile mode. Tensile work of adhesion in the range 25 – 350 nJ was obtained for various polymer samples, in particular the alginate sample performed tensile work of 70 nJ [46].

2.1.2 *Dynamic assays under shear forces*

2.1.2.1 *Mucoadhesion time duration*

Bernkop-Schnurch and Steininger [51] were the first to propose the rotating cylinder method (**Figure 3**) for evaluating the ability of mucoadhesive formulations (solids or semisolids) to maintain contact with mucosa surface under shear forces. This assay also assesses the sample cohesiveness in wet environment. Dry compressed tablets are attached to fresh mucosa surface that is being spun on a stainless steel cylinder. The cylinder is fully immersed in buffer solution and agitated at a constant speed, typically 250 r.p.m. The quantitative measured parameter is the time until detachment, disintegration and/or erosion of the tablets is observed. Adhesion time in the range

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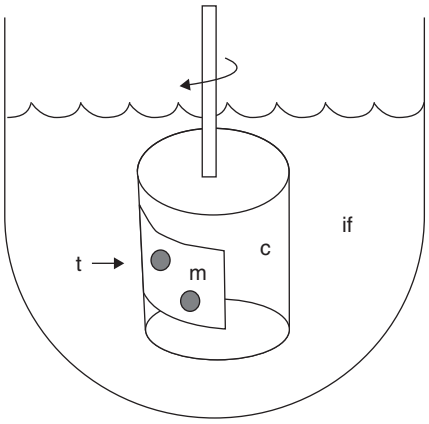

Figure 3. Schematic representation of the set up used for the rotating cylinder method.
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c: Stainless steel cylinder; if: Intestinal fluid; m: Porcine mucosa; t: Tablet.

0.05 – 161 h was obtained for various polymer samples. The rotating cylinder method was used further in several studies by the same group, in most cases in addition to tensile test measurements [52-58]. Grabovac *et al.* [20] compared those two methods for various polymer samples and found an agreement between the rank order for adhesion time and TWA in most cases. Hagesaether *et al.* [59] modified the rotating cylinder methods for the characterization of mucoadhesive zinc-pectinate hydrogel beads. The results were expressed as the percentage of beads remaining attached to the fresh intestine at the end of each experiment.

In a similar approach [60-62], porcine buccal tissue is fixed to the internal side of a beaker; afterwards the mucoadhesive sample is attached to the tissue. The experiment involves stirring the fluid inside this beaker until detachment is achieved. Another variation was performed by attaching fresh mucosa to a glass slide where a mucoadhesive formulation was pasted to it by applying a light force. The whole apparatus was immersed in a phosphate buffer container for 2 min, and stirred further at fixed rate [63].

2.1.2.2 Continuous flow assay

Continuous flow assays quantify the ability of a polymer to maintain binding with the mucosa surface under shear forces subjected as a continuous flow. This method was first introduced by Rao and Buri in 1989 [64], **Figure 4** and was used recently by Blegamwar *et al.* [58]. Glass spheres were coated with the tested polymer and a known amount of particles was placed on fresh mucus attached to the floor of the flow cell for a fixed time at humid environment to allow hydration of the polymer and prevent drying of the tissue. The experiments were performed by washing the mucosa surface with flowing phosphate buffer or dilute HCl solution at a constant rate for a fixed time. The tip of the eluted syringe was placed 2 – 3 mm above the tissue to ensure an even distribution of the liquid over the subjected mucosa surface. The percentage of beads washed away was determined by weighing the wash solution after drying, and the results were expressed as an index of mucoadhesion calculated from the percentage of particles retained on the tissue.

Nielsen *et al.* [42] developed this procedure further by placing the flow cell in a temperature-controlled container and analyzing the polymer concentration in the effluent by reversed phase high-performance liquid chromatography (HPLC). Recovery of at least 70% w/w of the applied polymer sample on the mucosa surface was taken as indication of mucoadhesion ability, thus the results were regarded as an 'all or none' test. Batchelor *et al.* [65] used a similar instrument; however, the washing solution was split into four channels to improve the liquid distribution. The polymer sample was labeled to allow accurate direct determination of the percentage of polymer retained on the mucosa surface. The use of spectrophotometeric analysis to monitor the concentration of the polymer in the effluent was also adopted by Le Ray *et al.* [66], who used a slightly different set up of flow cell based on an open glass tube that can allow free circulation of liquid. The mucosa surface was introduced into the glass tube and fixed at its upper and lower ends. Mikos and Peppas [67] used a rectangular channel flow device equipped with a lid. After placing the particles on the surface and allowing contact for 5 min, the flow rate was gradually increased until detachment of the particle occurred. Alternatively, the flow rate was maintained constant and the time required for detachment was measured.

Flow cells can also be used to monitor adhesion of cells and nanoparticles to various surfaces. In the literature one can find various cell flow designs based on laminar or turbulent flow where the adhesion strength was evaluated by means of continuous flow equations [68].

2.1.3 Atomic force microscope

The atomic force microscope (AFM) can allow molecular and surface forces to be measured on a near molecular scale [69] and is therefore suitable for the monitoring of mucin–polymer interaction on the molecular level. AFM was used to determine the adsorption and binding of macromolecules from solution onto mucosa surface [41,70] and to measure the force–distance curve between a polymer microsphere attached to an AFM cantilever and mucus surface [69,71,72].

The use of AFM technology was expanded further to characterize mechanical contact between cells. Such analysis could provide an adequate measurement of adhesion strength down to the molecular level. The experiments were performed by immobilizing a single cell, coated bead or monolayer of cells on the force sensor itself. The adhesion strength was evaluated by scanning the sensor tip with varied surface layers [73].

2.1.4 In vivo studies

Lehr *et al.* [22] evaluated the mucoadhesive properties of microspheres coated with different polymer types in a rat

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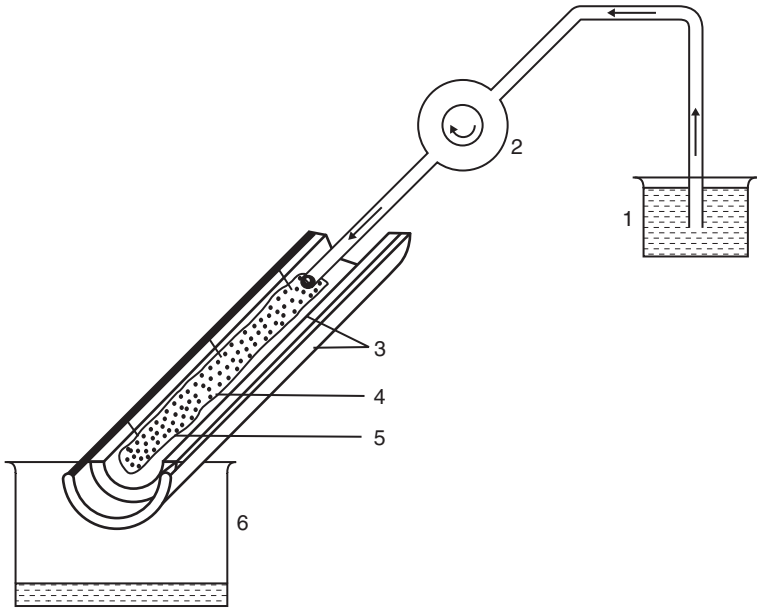

Figure 4. Schematic illustration of the experiment set up used for the microparticle mucoahesion study of Rao and Buri [64].
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model. Rats were subject to an invasive surgery where an isolated internal loop was connected to their intestine cavity. Microspheres were inserted to the inlet side and their amount and residence time were measured at the outlet side. Another surgical model included inserting labeled polymer dose directly into the animal stomach. In this experiment the subjects were recovered from the surgery and sacrificed at selected time intervals in order to inspect radioactivity of the stomach and the small intestine. Such analysis evaluated the polymer residence time and levels through the gastrointestinal cavity [74].

Similar methodology was used to evaluate the residence time of microspheres [58,75,76] and suspensions [76] in rat. The formulation dose was given orally, the subjects were killed, the gastrointestinal regions were exposed, and the amount of adsorbed polymer was determined by counting the microspheres at each region or by measuring the gamma radiation in the case of suspension. A microsphere formulation could also be monitored in a non-invasive procedure by including a radiopaque marker; feces collection and X-ray inspection provided a real-time method for monitoring total gastrointestinal residence time [49]. Another non-invasive method is based on the use of magnetic resonance images (MRI), which directly monitor the capsule's movement through the gastrointestinal tract [77]. MRI images were also used to localize the point in the intestine at which a thiomer was released from the sample's form.

2.1.5 *Clinical studies*

Clinical studies with human volunteers are not common in the literature. Several studies describe assessment of buccal mucoadhesion ability by attaching dry tablet to the region of the upper canine in the mouth [78-80] or gums [60-62]. The volunteers were asked to record the permanence time, the event that caused end of adhesion (erosion or tablet's detachment), mucosal irritation, comfort, and smarting sensation in mouth and the buccal cavity. The adhesion time and formulate behavior were also determined by gamma camera in human volunteers [81,82]. In those experiments the subjects were asked to swallow a labeled formulate capsule with known amount of water; afterwards the subjects were monitored continuously by collecting gamma camera images.

2.2 Indirect methods

2.2.1 *Rheology*

Polymer entanglements, penetration, chain diffusion and chemical interactions were found to be the key elements promoting mucoadhesion. When mucin is added to a solution of mucoadhesive polymer, the same type of interactions between the components exist. Therefore, the use of rheology, a technique used for the study of flow and deformation of materials [83], offers a straightforward means to monitor the strength of the interaction and predict the mucoadhesion ability. Two types of rheology experiment are commonly used: viscosity measurements, and determination of the frequency dependence of the storage and loss modulus.

The viscosity of mucin solution represents the total resistance to flow exerted by chain entanglements, non-covalent bonds such as hydrogen, electrostatic and hydrophobic bonding and covalent bonds such as disulfide bridges. These interactions are also the ones participating in mucin/polymer mucoadhesion [84] and therefore can be monitored by viscosity

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changes. Hassan and Gallo [84] proposed the following empirical equation:

$$\eta_t = \eta_m + \eta_p + \eta_b \quad (1)$$

where η_t is the viscosity of a solution containing both mucin and polymer, η_m and η_p are the individual viscosity of mucin and polymer, respectively, and η_b is the contribution that appears to be an outcome of molecular interaction. The mucoadhesion ability of various polymers could be screened using their η_b values. A similar approach was used to monitor disulfide interactions created between thiolated alginate and mucin type glycoproteins [1]. Rossi *et al.* [33] fitted the flow curves to the Cheng-Evans equation to estimate the low shear viscosity η_0 and high shear viscosity η_∞. On the basis of change in those parameters, the characteristics interactions between chitosan and mucin were determined.

The storage moduli, G', represent the energy stored and recovered per deformation cycle and therefore reflect the solid-like component of viscoelastic material, whereas the loss moduli, G'', represent the energy lost per deformation cycle and therefore reflect the liquid-like component [33,83,85,86]. An increase of storage moduli of a polymer solution on adding mucin was claimed to give a quantitative measure to the strength of the interactions between the components, as G' reflects the resistance to elastic deformation [30]. G'' also increases in the presence of mucin [5]. Other parameters that were used to quantify the interactions were the loss tangent and rheological synersism parameters [86]. The loss tangent, tan δ, is known to be a simple indicator for the overall viscoelasticity of a sample and can be calculated from the ratio of G'' to G'. A tan δ value smaller then unity represents a solid (gel)-like response, whereas a value higher then unity reflects a liquid-like response. Thus, decrease in tan δ reflects an increase in the sample elasticity. Another type of analysis uses the values of the relative rheological synergism parameters, defined as the relative increase in the values of the storage modulus and the loss modulus, normalized with respect to their initial value [34,87]:

$$\frac{\Delta G'}{G'} = \frac{\Delta G'}{(G'_{\text{polymer}} + G'_{\text{mucin}})} = \frac{G'_{\text{mix}} - (G'_{\text{polymer}} + G'_{\text{mucin}})}{(G'_{\text{polymer}} + G'_{\text{mucin}})} \quad (2)$$

$$\frac{\Delta G''}{G''} = \frac{\Delta G''}{(G''_{\text{polymer}} + G''_{\text{mucin}})} = \frac{G''_{\text{mix}} - (G''_{\text{polymer}} + G''_{\text{mucin}})}{(G''_{\text{polymer}} + G''_{\text{mucin}})}$$

This type of analysis was also used to investigate pectin–mucin mixture [88], where an increase in dynamic moduli and a decrease in loss tangent were attributed to significant interactions between the mucin and pectin. The same methodology was adopted by Ceulemans and co-workers [89].

The literature demonstrates large variation in the rheology results, which can be due to differences in mucin type [90], mucin and polymer concentrations, and different measurement configurations (parallel plate, cone and plate or concentric cylinder) [33,34,86]. In addition, the selection of the quantitative parameter seems to affect the final conclusion [23].

Therefore, Hagerstrom and co-workers [23,91] concluded that rheology should not be used as a standalone method for detecting mucoadhesive properties of polymer–mucin mixtures.

2.2.2 Spectroscopic methods

Similarly to rheology, spectroscopic methods detect mucus–polymer interaction at the molecular level. A Fourier transform infrared spectrometer with an attenuated total reflectance accessory (FTIR-ATR) was used to analyze interfacial interactions or interpenetration between polymer film and hydrated mucin samples [79,92-94]. Those studies demonstrated that chain inter-diffusion occurred at the interface of the polymer film and the mucin solution, which, according to the diffusion theory of adhesion, is expected to contribute to mucoadhesion. Xiang and Li [95] immersed a prehydrated polymer film in mucin solution and monitored changes in the FTIR spectrum occurring as a result of molecular interactions between the polymer and mucin. The FTIR spectrum of a freeze-dried mixture of mucin glycoproteins and polymer was compared with that of the mixture's components; peaks shift and location allude to molecular interaction [96].

Interactions between glycoproteins and polymers were also observed by ^{1}H or ^{13}C nuclear magnetic resonance (NMR) experiments. The spectrum from the mixture is compared with the spectra of the components. Changes in the electronic environment appear on molecular interaction, thus alluding to chemical shift changes and peak broadening [96,97].

Dielectric spectroscopy was used to study adhesion properties in terms of a compatibility factor obtained from mucus and mucus-gel samples. The movement of charged particles resulting from applying a sinusoidal voltage to a sample is evaluated, and the current response is recorded. The current response can be expressed as a complex frequency-dependent capacitance,

$$C(w) = C_{\text{Real}}(w) + iC_{\text{Im}}(w) \quad (3)$$

where i is the imaginary number and w is the angular frequency. This equation can be developed further to give the complex relative permittivity, ε, and complex total impendance, Z. Both parameters are used to analyze the measured response. The mucoadhesion is obtained as a measure of the ease in which a charged particle passes a barrier between the gel and the mucus. A low barrier indicates a high compatibility between the two samples and vice versa.

The compatibility factor CF is calculated from the high-frequency resistances of the gel, mucus and their combined system.

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Table 1. Summary of mucoadhesion techniques reviewed in the paper.

Direct methods	Indirect methods
Tensile Tensiometer [17-32] Cahn dynamic contact angle analyzer [46-50]	*Rheology* [1,5,23,30,33,34,83-86,88-91]
Dynamic assays under shear forces Mucoadhesion time duration Rotating cylinder [20,51-59] Tissue + sample in beaker [60-63] Continuous flow assay [58,64-68]	*Spectroscopic methods* Fourier transform infrared spectrometer [79,92-96] Nuclear magnetic resonance [96,97] Dielectric spectroscopy [98-100]
Atomic force microscope [41,69-73]	*Surface energy* [44,48,93,101-104]
In vivo [22,58,74-77] Clinical studies [60-62,78-82]	*Adsorption of mucoadhesive* Zeta-potential [105,106] Everted intestinal sac [50,101,107]

$$CF = \frac{(\overline{R}_{hf}^{gel} + R_{hf}^{mucus}) - R_{hf}^{gel+mucus}}{R_{hf}^{mucus}} \quad (4)$$

where R_{hf} is the high frequency resistance of a sample. The value of the compatibility factor reflects the potential for intimate surface contact, which is considered to be the first step in the mucoadhesion process [98-100]. However, a comparison with tensile measurements has led to the conclusion that dielectric spectroscopy could not give direct information related to the mucoadhesive bond formation rather than an assessment of the likelihood of intimate surface contact between the gel and the mucus [98].

2.2.3 *Surface energy*

Contact angle measurements can predict the mucoadhesive nature owing to the role of surface energy in the mucoadhesion process. Larger contact angle is indicative of better wetting and believed to be an indication of adhesion enhancement [44,48,93,101-103]. Contact angle analysis was also used to calculate the work of adhesion of adhesive-water and adhesive-mucus surfaces [104].

2.2.4 *Adsorption of mucoadhesives*

The ability of mucosa surface to adsorb mucoadhesive polymers is considered to be a measure of mucoadhesion. For example, mucin particles were suspended in buffer and mixed further with polymer solution [105,106]. Change in the particles' surface properties due to polymer absorption was detected by zeta-potential measurement and attributed to the mucoadhesive properties of the polymers.

An everted intestinal sac experiment was originally developed to study the transport of substances from the mucosal surface to the serosal surface [107]. A modified version of this method was developed to evaluate the mucoadhesive interaction of polymer microspheres with everted intestinal tissue surface [50,101]. A segment of intestinal tissue from a rat was everted, legated at the ends and filled with saline. The sac was introduced into a tube containing a known amount of microspheres and saline. The sac and spheres were incubated for 30 min to promote polymer–mucus interactions, during which the tube was rotated constantly. The sac was then removed, the attached microspheres were washed and lyophilized and the percentage of binding was determined by subtraction of the weight of the residual spheres from the original weight.

3. Conclusion

Numerous techniques, summarized in **Table 1**, have been developed for evaluating mucoadhesive properties of polymers. In this review it was proposed to classify the test methods into two categories, direct and indirect methods. Generally speaking, direct techniques measure the force required to detach the mucoadhesive from a mucosa surface, or the duration of attachment to the mucosa under constant force. Indirect methods assess the interactions between the mucoadhesive and mucin type glycoproteins.

Despite the larger number of techniques available for researchers, it is still impossible to point to the most appropriate one because even the few studies that compared different methods demonstrate inconsistency between the conclusions drawn from them.

4. Expert opinion

Drug delivery systems based on mucoadhesive polymers are a promising platform that offer benefits such as prolonged residence time of pharmaceuticals localized in the vicinity of the mucosal surface, a rapid uptake of drugs into the systemic circulation through the relatively permeable mucus membranes, and enhanced bioavailability of therapeutic agents that becomes possible owing to avoidance of some to the natural defense mechanisms of the body. Despite these advantages, the number of commercial mucoadhesive products is still limited. One of the reasons hindering the development of new products is the extremely complicated nature of mucoadhesion. Numerous parameters, ranging from the physicochemical properties of the polymers to the

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biological characteristics of the mucus covering different organs, affect dramatically the ability of polymers to attach to the mucosa. This complexity makes predictions of the performance of drug delivery systems practically impossible. *In vivo* studies and subsequent clinical studies are an excellent option, but are costly and subject to ethical constrains. Therefore, it was realized long ago that developing reliable *in vitro* methods for screening polymers and an educated selection of the best candidates for further *in vivo* studies are essential for exploiting the full potential of mucoadhesive polymers. This understanding has motivated researchers to suggest various experimental approaches for evaluating mucoadhesion. However, in many cases investigators choose to develop a new method or alter the test conditions instead of adopting an existing measurement technique. Unfortunately, this approach makes a comparison between the results obtained in different laboratories very problematic. The rare papers that compare different methods for evaluating mucoadhesion demonstrate the inconsistency between the conclusions drawn from them. As an example, linear poly (acrylic acid)–cystein conjugates having different molecular masses were tested using tensile measurements and the rotating cylinder method [55]. The results for tensile strength were not sensitive to the molecular mass: the maximum detachment force was almost constant, and the work of adhesion of low-molecular-mass polymers (2 and 45 kDa) was similar. On the contrary, the duration of adherence as determined by the rotating cylinder method increased with elevated molecular mass. Thus, in this case the rotating cylinder method offered a better way to probe the influence of the polymer's properties. A comprehensive study ranked 19 commonly used mucoadhesive polymers using both tensile assays and the rotating cylinder method [20]. The results presented in this paper clearly highlight the fact that ranking according to each of the methods leads to different conclusions. Comparison between the rheology and direct mucoadhesion tests is also controversy. Tamburic and Craig [30] found a good correlation between the rheological and texture analysis data for different poly(acrylic acid) samples. However, Caramella *et al.* [34], who worked with several natural, semisynthetic and synthetic products, did not find direct correlation between the rheological parameters and work of adhesion obtained from tensile measurements. These authors concluded that the tensile test mimics the *in vivo* condition more closely but is affected easily by experimental conditions such as contact time, preload force and instrument set up, whereas rheology measurements are more accurate and reproducible therefore shed light on the mucoadhesion mechanisms.

Thus far, more than 40 years after introducing the first mucoadhesive polymers, there is no universal *in vitro* testing method that is generally accepted. Such a method, or possibly a set of ASTM tests, could be used to compare data from different research groups and rank new potential candidates to the more traditional mucoadhesive polymers such as Carbopol or alginate. The best way to define a universal method is most probably to correlate the results of *in vitro* and *in vivo* studies. Unfortunately, investigations combining systematic *in vivo* and *in vitro* studies are scarce and therefore the challenge of defining the best way to evaluate mucoadhesion has not yet been met.

Declaration of interest

The authors state no conflicts of interest and have received no payment in the preparation of this manuscript.

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