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Review article

Mucoadhesives in the gastrointestinal tract: revisiting the literature for novel applications

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Abstract

This article investigates applying mucoadhesives to manipulate friction and to achieve locomotion of an alternative colonoscopic device through the large intestine. Considering that such an application of mucoadhesives is new, the authors recognised the need to revisit the different aspects of mucoadhesion in the gastrointestinal tract on the basis of the literature and to re-evaluate them according to the requirements for intestinal locomotion. First, the material properties, which are critical for the locomotion mechanism and specific categories of mucoadhesives characterised by those critical properties were identified. The next step was to examine the structural characteristics of those categories to specify which of the already synthesised mucoadhesives are promising candidates for friction manipulation. Then, the response of those mucoadhesives to a number of environmental stimuli was examined. At the end, two in vitro experiments were carried out to study the potential of mucoadhesives for intestinal locomotion. A comparative analysis of the role of mucoadhesives in drug delivery and in intestinal locomotion leads to the conclusion that the two applications can be approached to one extent with common principles, but crucial differences are present as well.

Keywords: Mucoadhesion; Gastrointestinal tract; Colon; Drug delivery; Locomotion; Friction

1. Introduction

In an effort to prevent colorectal cancer, a leading cause of death in Western civilisation, colonoscopic examinations are being carried out. The patient drinks a laxative fluid to empty the gastrointestinal tract, after which the endoscope is inserted into the rectum. The patient stays usually conscious to avoid the risk of complications caused by anaesthesia. Although the results of colonoscopic procedures are quite successful, the use of conventional flexible colonoscopes makes the examination unpleasant, since it frequently causes painful cramps to the patient. Additionally, although colonoscopy is regarded as a relatively safe procedure, it entails the risk of perforation of the intestinal wall [1,2]. For this reason, a new intestine inspection and intervention device is being developed at TU Delft. The device will be inserted into the rectum and will be able to move forward and backward through the colon. Pretreatment of the patient with commonly used sedatives which reduce the colonic motility can facilitate the locomotion of the device against the direction of the colonic peristaltic waves. The device will be connected with the outside world via a tube, so that it can be pulled back and removed when needed. The tip of the device will contain a camera with a light source and a biopsy channel that can be used to insert instruments for simple interventions.

The main challenge for the successful development of the intestine inspection and intervention device is its locomotion mechanism along the flaccid and slippery colonic wall. To achieve successful locomotion, the device should be able to manipulate the properties of the interface with the colonic surface. More precisely, the device should be able to generate *high friction* to ensure gripping and *low friction* to allow sliding. The device can grip on the colonic surface with high friction by interposing an *adhesive interlayer* between its body and the mucus layer. Before initiating sliding, the device should be able to change

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the properties of the interposed adhesive interlayer, e.g. by decreasing its viscosity, thus allowing unsticking and sliding.

The first step to implement the locomotion concept described above is to find an interlayer adherent to the lubricative mucus layer. *Mucoadhesives* adhere to the mucus and can therefore be used as the adhesive interlayer between the mucus and the device. Mucoadhesives can be prepared in several forms, such as hydrogels, tablets, particles, pellets, granules, or films [3]. It seems that films are most convenient, since they not only adhere to the colonic mucus, but can also be easily attached to the surface of the device. Furthermore, films hydrate and thus interact quickly after contact with mucus [4]. This parameter is significant for an intestine inspection and intervention device, since the device should be able to move through the colon relatively quickly to reduce the time needed for the medical investigation. The second step to implement the locomotion concept is to generate low friction in the presence of the mucoadhesive interlayer. A number of mucoadhesives have the ability to respond to external stimuli and to alter their material properties. Friction can be reduced and thus manipulated by controlling the behaviour of those environmental-sensitive mucoadhesives via alterations in the values of the external stimuli.

The device can consist of a number of cylinders with constant diameter connected together via extensors (Fig. 1). Each cylinder is coated with a mucoadhesive film which plays the role of the adhesive interlayer. The friction

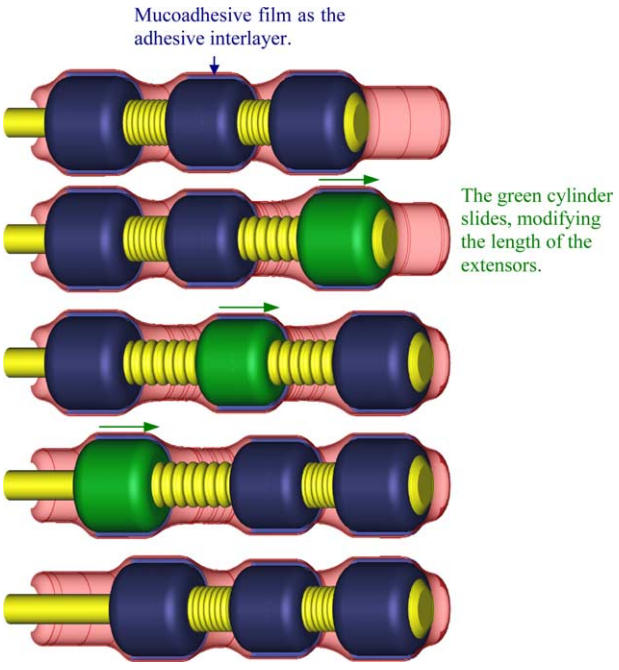

Fig. 1. Intestine inspection and intervention device with cylinders connected via extensors. All cylinders are coated with mucoadhesive films. The blue cylinders grip with high friction, whereas the green cylinder slides with low friction. The yellow tube connects the device with the outside world.

manipulation for safe grip and atraumatic sliding is realised as follows. In each stage, all cylinders (blue), except one (green), grip with high friction, since they are covered with mucoadhesive films. The green cylinder should unstick and slide forward with low friction. For this reason, an external stimulus is applied and the mucoadhesive film responds by changing its rheological properties or by disrupting the bonds with the mucus. In this way, the green cylinder becomes unstuck and is free to slide. The required advancement is produced by elongating and compressing the extensors.

To apply mucoadhesives as a medium for friction manipulation and intestinal locomotion, we should first identify which group of already synthesised mucoadhesives can be used as the adhesive interlayer and which external stimuli can be applied to alter the properties of these mucoadhesives. In this framework, a literature survey on mucoadhesion and mucoadhesives in the gastrointestinal tract in general and particularly in the colonic region, has been carried out. The existing literature of mucoadhesives focuses mainly on the requirements for successful controlled drug delivery. A new set of requirements for the use of mucoadhesives as a medium for friction manipulation has thus to be constituted. Considering that the set of requirements for intestinal locomotion is partly different from the set of requirements to deliver drugs, the authors recognised the need to revisit the different aspects of mucoadhesion in the gastrointestinal tract on the basis of the literature and to reconsider and re-evaluate these aspects according to the requirements for the locomotion mechanism. A comparative analysis of the role of mucoadhesives in drug delivery and in intestinal locomotion has been carried out as well. The aim was to determine to what extent a unified approach for both cases can be followed and to indicate in which points such a unified approach should be differentiated. After exploring which mucoadhesives and external stimuli seem to be the most promising candidates for friction manipulation, two in vitro experiments were carried out to study the potential of mucoadhesives for intestinal locomotion.

The reviewed information in this paper is systemised in four fundamental questions that are tightly interrelated:

1. *What are the theories* that describe the mechanism of mucoadhesion?
   Theories of mucoadhesion, derived by the classical theories of metallic and polymer adhesion, have already been established 30 years ago. However, the authors considered revisiting them to summarise the basic principles of adhesion between a polymer (mucoadhesive) and a protein (mucus) layer.
2. *What material properties* can be influenced to obtain effective mucoadhesion, according to these theories?
   The aim of reviewing the material properties was to evaluate which of them play the most critical role in intestinal locomotion. The re-evaluation is required,

considering that the critical material properties for the locomotion mechanism differ from the related properties for drug delivery.

3. *What mucoadhesives* have been developed according to these material properties?
   This question has to be answered, since the main goal of the literature search was to identify which group of already synthesised mucoadhesives can be used as the interlayer between the intestine inspection and intervention device and the colonic surface. The mucoadhesives were categorised in four basic groups according to the different types of bonds which can be developed with the mucus. It seems that the favourable mucoadhesives for intestinal locomotion can be different from the mucoadhesives which are favourable for drug delivery.
4. *What factors* influence the material properties of these mucoadhesives?
   There are several ways to influence one or more material properties of the mucoadhesives. *Intrinsic factors* are structural characteristics that can be affected during the polymerisation process of a mucoadhesive. *External factors* are environmental stimuli that can be activated to alter the properties of a mucoadhesive. A comparative analysis of the factors and their preferable values for successful drug delivery or intestinal locomotion leads to the conclusion that, though common principles can be established for both applications, differences are present as well.

2. Drug delivery vs. intestinal locomotion: requirements of the mucoadhesive

A mucoadhesive used in oral drug delivery should meet the following requirements [5]:

- Adhesiveness with the mucus layer, to provide adequate contact.
- Ability to swell and allow drug release.
- Ability to prolong the residence time of the drug at the site of administration.
- Lack of interaction with the active drug, to allow the drug to be released and absorbed through the mucosal surface.
- Biocompatibility with the mucosal surface, to avoid cytotoxicity or other irreversible alterations of the mucosal surface.
- Biodegradability, to allow the physical clearance of the mucosal surface.

A mucoadhesive used as an interlayer between the colonic surface and an intestine inspection and intervention device should meet the following requirements:

- Adhesiveness with the mucus layer, to provide strength within the interlayer-mucus interface and thus high friction.
- Ability of the mucoadhesive to respond to alterations of the external stimuli.
- Quick interaction of the mucoadhesive with the mucus, to reduce the time needed for the medical investigation.
- Cohesiveness, to provide strength inside the interlayer.
- Biocompatibility with the mucosal surface, to avoid cytotoxicity or other irreversible alterations of the mucosal surface.
- Biodegradability, to allow the physical clearance of the mucosal surface.

Table 1
Requirements that a mucoadhesive should meet for drug delivery and for intestinal locomotion

Drug delivery	Intestinal locomotion
Adhesiveness with the mucus layer	Adhesiveness with the mucus layer
Swelling and allowing drug release	Response to external stimuli
Prolonged residence time	Quick mucus–mucoadhesive interaction
Lack of interaction with the drug	Cohesiveness
Biocompatibility	Biocompatibility
Biodegradability	Biodegradability

As shown in Table 1, the set of requirements for drug delivery through the mucosal surface and the related set for locomotion along the mucosal surface show common points as well as differences. For instance, the quick interaction of the mucoadhesive with the mucus is a crucial parameter for intestinal locomotion, but not for drug delivery. In the case of drug delivery, the presence of the mucoadhesive vehicle should not impede the action of the loaded drug, whereas, the absence of drug in the case of intestinal locomotion recalls all the requirements concerning eventual interactions between the drug and the mucoadhesive.

3. Theories of mucoadhesion

A number of researchers worked out theories that explain the mechanisms with which mucoadhesives adhere to the mucus layer. The theories of mucoadhesion are based on the classical theories of metallic and polymer adhesion. There are four main theories that describe the possible mechanisms of mucoadhesion: the *electronic*, the *adsorption*, the *wetting* and the *diffusion* theory.

- The *electronic theory* [6,7] assumes that transfer of electrons occurs between the mucus and the mucoadhesive due to differences in their electronic structures. The electron transfer between the mucus and the mucoadhesive leads to the formation of a double layer of electrical charges at the interface of the mucus and the mucoadhesive. This results in attraction forces inside the double layer.
- The *adsorption theory* [8–12] concerns the attraction between the mucus and the mucoadhesive achieved via molecular bonding caused by secondary forces such as

hydrogen and van der Waals bonds. The resulting attractive forces are considerably larger than the forces described by the electronic theory.

- The *wetting theory* [13–18] correlates the surface tension of the mucus and the mucoadhesive with the ability of the mucoadhesive to swell and spread on the mucus layer and indicates that interfacial energy plays an important role in mucoadhesion. By calculating the interfacial energy from the individual spreading coefficients of the mucus and the mucoadhesive or by calculating a combined spreading coefficient, predictions about the mucoadhesive performance can be obtained. The wetting theory is significant, since spreading of the mucoadhesive over the mucus is a prerequisite for the validity of all the other theories.
- The *diffusion theory* [9,19–25] concerns the interpenetration to a sufficient depth and physical entanglement of the protein and polymer chains of the mucus and the mucoadhesive, depending on their molecular weight, degree of cross-linking, chain length, flexibility and spatial conformation.

None of these theories gives a complete description of the mechanism of mucoadhesion. The total phenomenon of mucoadhesion is a combined result of all these theories. Some of the researchers prefer to divide the mucoadhesion process into sequential phases, each of which is associated to a different mucoadhesion mechanism [3,26]. First, the polymer gets *wet* and *swells* (wetting theory). Then, *non-covalent* (*physical*) *bonds* are created within the mucus–polymer interface (electronic and adsorption theory). 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 theory).

4. Material properties of mucoadhesives

Mucoadhesives are characterised by material properties that contribute to good adhesiveness, according to one or more theories of mucoadhesion. Such material properties are the ability of mucoadhesives to *swell*, their ability to form *molecular bonds* (covalent and non-covalent) with the mucus layer and their *spatial conformation* due to the entanglement of chains. The creation of molecular bonds and the entanglement of chains lead to changes of the rheological behaviour of the mucoadhesives. The *rheological properties* of mucoadhesives can therefore be used as an indication of the extent of molecular bonding and spatial conformation. The *cohesiveness* of mucoadhesives contributes indirectly to their adhesive ability, since it concerns the internal strength of the mucoadhesive. All these properties are discussed below with regard to the requirements for successful drug delivery or intestinal locomotion. A re-evaluation is required, since the critical material properties appear to be different in these two applications.

4.1. Swelling

The ability of mucoadhesives to swell is a prerequisite for mucoadhesion, since it concerns wetting, uncoiling and spreading of the polymer over the mucus (wetting theory). This spreading process, controlled by the interfacial energies of the mucus and the mucoadhesive, allows intimate contact at the mucus–mucoadhesive interface, thus governing the formation of bonds [17,18]. Over-hydration, however, forms a slippery mucilage deteriorating mucoadhesion [27]. Furthermore, swelling is a key-parameter for environment-sensitive drug delivery [28], where drug release can be achieved by a reversible volume change of an environmental-sensitive polymer with controlled swelling–deswelling ability [29]. Swelling is a crucial parameter for intestinal locomotion as well, since intimate mucus–mucoadhesive contact is important and controlled swelling–deswelling ability can lead to on–off switching between high and low friction.

4.2. Molecular bonding

The presence of suitable molecular groups in the mucoadhesive leads to the formation of covalent bonds (e.g. disulfide bonds), as well as non-covalent bonds (e.g. ionic, hydrogen and van der Waals bonds) with the mucus layer. These molecular bonds contribute considerably to good adhesion, according to the electronic and the adsorption theory. Covalent bonds are stronger than non-covalent bonds and therefore lead to higher mucoadhesive forces [30,31]. However, covalent bonds require time to be created, whereas non-covalent bonds are formed immediately as soon as the mucus and the mucoadhesive come in contact. The delay time which is required for covalent bonding does not play an impending role in drug delivery, in which maintaining the delivery system at a particular location for an extended period of time ($\sim$3 h in oral delivery [3,5]) is advantageous. This is the reason why research in drug delivery focuses on the synthesis of mucoadhesives that form strong covalent bonds with the mucus, even if this formation requires time. In the case of an intestine inspection and intervention device, delay time is a crucial parameter, since the device should accomplish the medical investigation in a short time. It is thus preferable in that case to use mucoadhesives which interact with mucus only with non-covalent bonds that can be activated immediately after the two materials come in contact.

4.3. Spatial conformation

The interpenetration rate of the mucus–mucoadhesive chains depends on the diffusion coefficient and the chemical potential gradient of the interacting macromolecules [32].

The flexibility and mobility of the mucoadhesive chains as well as the expanded form of the mucoadhesive network control the effective chain length which can penetrate into the mucus [3]. In this way, spatial conformation is critical for the interpenetration of mucus–mucoadhesive chains. It should be noted, however, that spatial conformation is a time-dependent phenomenon, since the interpenetration of the mucus and mucoadhesive chains requires a certain amount of time. This is the reason why spatial conformation is not expected to contribute significantly to a short-time application such as the locomotion of a device through the colon.

4.4. Rheological properties

The chain entanglement and the molecular bonding which occur between the mucus and the mucoadhesive lead to changes in the rheological behaviour of the two materials [33]. Since changes in the rheological properties reflect the degree of interaction between mucus and mucoadhesive, rheological methods constitute a common way to evaluate mucoadhesion. For instance, mucus–mucoadhesive systems with a high elastic component show good mucoadhesiveness [34,35]. Moreover, a high viscosity and viscoelasticity of the system mucus–mucoadhesive indicates improved cohesiveness and resistance to deformation [36]. A number of authors measured that the viscosity of the system mucus–mucoadhesive can be larger than the sum of the separate viscosities from the mucus and the mucoadhesive. This phenomenon is named ‘rheological synergism’ [32,36–38]. High rheological synergism indicates extensive chain entanglement (diffusion theory) and molecular bonding (adsorption theory) and thus good mucoadhesive ability. Therefore, rheological synergism refers to a state in which the interpenetration between mucoadhesive and mucus has been already achieved and is not simply an interfacial phenomenon. Although rheological synergism reflects satisfying mucoadhesion in drug delivery, it cannot be used as an indication for good mucoadhesion in the case of intestinal locomotion. However, the non-Newtonian character of both the mucus and the mucoadhesive (i.e. the alteration of rheology as a function of the applied shear rate and the time) can be employed in both cases of drug delivery and intestinal locomotion as a medium for controlled mucoadhesion in correlation with the parameters of time and pressure.

4.5. Cohesiveness

Mucoadhesives exhibit high adhesiveness at their interface with the mucus layer, but should exhibit sufficient cohesiveness as well, to prevent internal fracture of the mucoadhesive. Solid forms of mucoadhesives show in general satisfying cohesiveness. A number of solid mucoadhesive dosage forms for drug delivery in the gastrointestinal tract, such as tablets, micro- and nanoparticles, granules, pellets, and capsules, have been studied in vitro and in vivo [39]. They showed satisfying mucoadhesive performace, even if in vitro/in vivo testing cannot always predict the mucoadhesive performance in humans [40]. In the case of an intestine inspection and intervention device, the mucoadhesive can be transferred and administered on the spot and not via the oral route. In this case, the mucoadhesive can thus be applied even in forms that are not applicable in colonic drug delivery, such as films or patches. Another aspect of the correlation between cohesiveness and mucoadhesive ability is pointed out by Hägerström et al. [41] who investigated the mucoadhesiveness of common polymers to several kinds of mucins. It turned out that too high interaction between the polymer and the mucin led to weakening instead of strengthening of the gel, since the increased interaction at the interface disturbed the internal cohesive structure of the polymer network.

Fig. 2 visualises the interrelation between the theories of mucoadhesion (red circles) and the material properties of mucoadhesives (blue circles). The overlapping areas between the circles indicate how and to what extent the mucoadhesive theories are connected to the material properties. As visualised in Fig. 2, first the mucoadhesive swells (wetting theory) and then molecular bonding (electronic and adsorption theories) occurs as the formation of non-covalent bonds within the mucus–mucoadhesive interface. Next spatial conformation (diffusion theory) is introduced to achieve interpenetration between the mucus and mucoadhesive. Then molecular bonding continues as the formation of new non-covalent and covalent bonds inside the mucus–mucoadhesive interface. The rheological properties are visualised as an overlapping circle, since they are an indication of the extent of covalent molecular bonding and spatial conformation.

5. Chemicals with mucoadhesive ability

A considerable amount of chemicals with mucoadhesive ability is cited in the bibliography. A basic distinction can be made according to the different side groups that the polymers contain and that lead to different bonding with the mucus. Four groups can be distinguished:

- Polyacrylates and cellulose derivatives (anionic, non-covalent bonding).
- Thiolated polymers of polyacrylates and cellulose derivatives (anionic, covalent bonding).
- Chitosan (cationic, non-covalent bonding).
- Thiolated polymers of chitosan (cationic, covalent bonding).

Fig. 3 illustrates typical cases of molecular bonding between side groups of the mucoadhesives and mucin macromolecules.

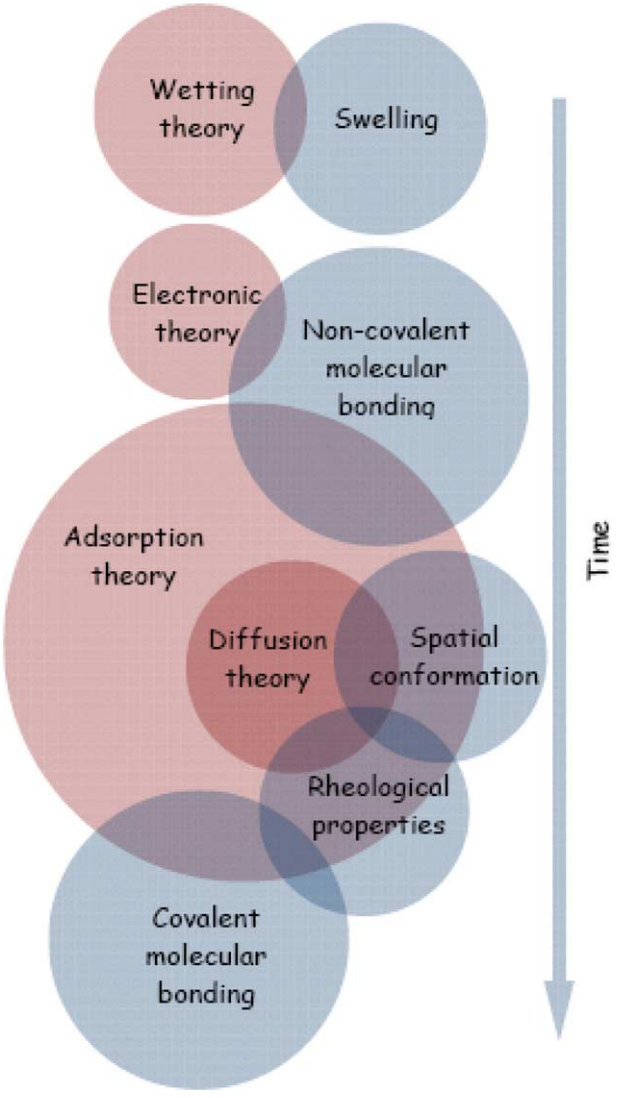

Fig. 2. Theories of mucoadhesion (red circles) and material properties of mucoadhesives (blue circles). The overlapping areas between the circles of the material properties and the mucoadhesive theories indicate how and to what extent the former are connected to the latter.

5.1. Polyacrylates and cellulose derivatives

The term polyacrylates includes synthetic, high molecular weight polymers of acrylic acid (polyacrylic acid or PAA) (Fig. 4(a)) that are also known as Carbomers. They are either linear or cross-linked polymers that are broadly applied in pharmaceutical and cosmetic industry. Cross-linked Carbomers, manufactured by the Performance Materials Segment of the B.F. Goodrich Company under the commercial name Carbopols and Polycarbophils (PCPs), are commonly used as mucoadhesives [42]. Polyacrylates interact with mucus by *hydrogen* and *van der Waals bonds*, created between the carboxylic groups of polyacrylates and the sialic acid residues of mucin glycoproteins. Cellulose derivatives contain carboxylic side groups as well. A typical example of cellulose derivative is sodium carboxymethyl cellulose (NaCMC) (Fig. 4(b)) that interacts with mucus by *hydrogen* and *van der Waals bonds*. NaCMC has weaker interaction with mucus than polyacrylates. Polyacrylates seem to be a promising candidate for intestinal locomotion, since they are attached to the mucus via non-covalent bonds and they can be prepared easily in various forms.

5.2. Chitosan

Chitosan is a natural polycationic hydrophilic polymer, derived from polysaccharide chitin (Fig. 4(c)). Chitosan exhibits strong mucoadhesive properties due to the formation of *hydrogen* and *ionic bonds* between the positively charged amino groups of chitosan and the negatively charged sialic acid residues of mucin glycoproteins [43]. Furthermore, chitosan enhances drug permeability through the mucosal surface [44–46] and is non-toxic, since it cannot be absorbed due to its high molecular weight [47–50]. By polymerising acrylic acid in the presence of chitosan, Ahn et al. [51] synthesised recently a novel mucoadhesive conjugate of PAA and chitosan.

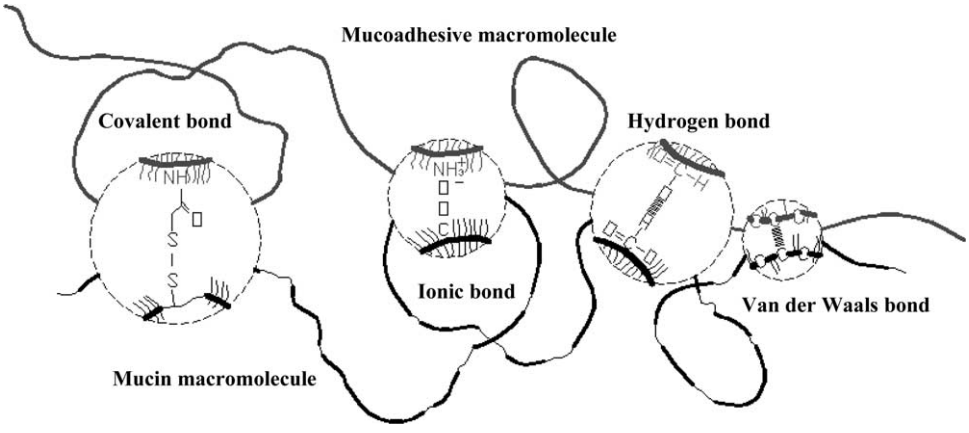

Fig. 3. Molecular bonds between mucin and mucoadhesive macromolecules.

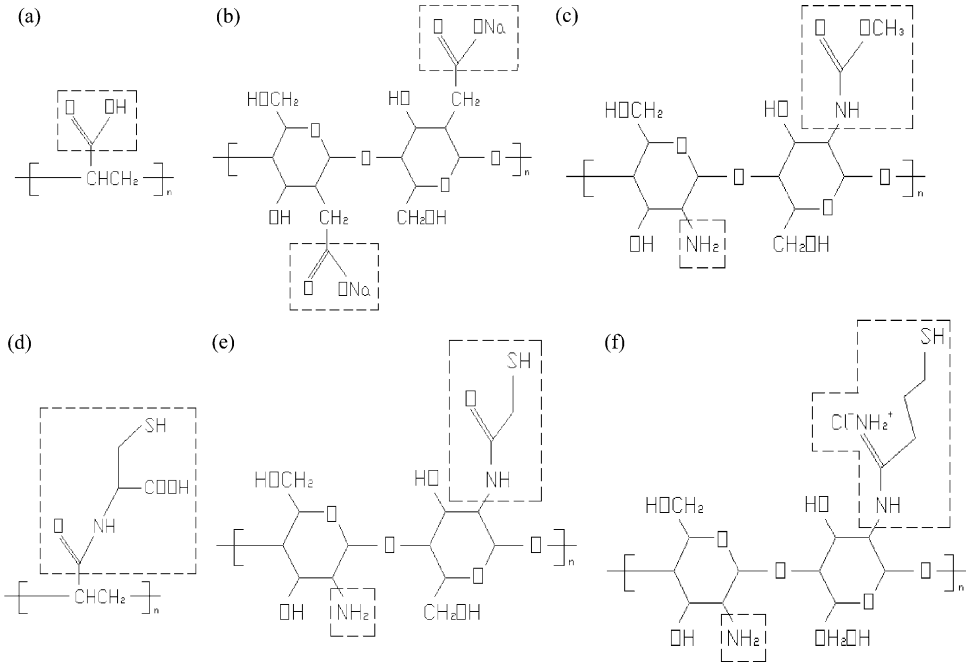

Fig. 4. Structural formulas of mucoadhesives: (a) PAA, (b) NaCMC, (c) chitosan, (d) thiolated polymer of PAA, (e) chitosan–TGA conjugate and (f) chitosan–2-iminothiolane conjugate. The dashed boxes indicate the side groups that are responsible for mucoadhesiveness.

The conjugate contains hydrogen bonds between the carboxylic group of PAA and the hydroxyl or amino groups of chitosan. The conjugate shows strong mucoadhesive ability due to *ionic, hydrogen* and *van der Waals bonds*. However, chitosan is a weak base with a pK_a value of about 5.5 and, thus, insoluble at neutral and basic environments such as in the large intestine and colon. Chitosan can therefore not be used as an absorption enhancer in these environments [52,53]. In these cases, chitosan solubility can be achieved by trimethylasing its primary amino groups [54]. Trimethylated chitosan can therefore play an important role in colonic drug delivery.

5.3. Thiolated polymers of polyacrylates and cellulose derivatives

Thiolated polymers are synthesised by immobilizing thiol groups on polyacrylates or cellulose derivatives (Fig. 4(d)) [30,31,55,56]. Typical examples of such thiolated polymers are PAA–cysteine and NaCMC–cysteine conjugates. The immobilized thiol moieties are capable to form *strong covalent disulfide bonds* with the cysteine domains of mucins, improving mucoadhesion significantly. Those thiolated polymers show improved cohesiveness as well [55], thus meeting the main requirements for satisfying drug delivery. Thiolated polymers can be used for intestinal locomotion as well, although it is possible that the covalent molecular bonds cannot be activated within the required short mucus–mucoadhesive contact time.

5.4. Thiolated polymers of chitosan

Chitosan can be modified by introducing thioglycolic acid (TGA) and forming amid bonds (Fig. 4(e)) [57,58]. The formed thiolated polymer shows highly improved mucoadhesiveness in comparison with chitosan due to the formation of strong covalent disulfide bonds with the cysteine domains of mucins. Chitosan–TGA conjugates have the advantage of keeping their mucoadhesive ability at physiological pH values (∼7) [59]. For this reason, chitosan–TGA conjugates can be applied on the intestinal epithelia, where unbound chitosan is ineffective. The action of chitosan–TGA conjugates has recently been verified in in vivo experiments [60], showing satisfactory mucoadhesive ability in physiological pHs. Recently, further improvement of mucoadhesiveness has been achieved by the synthesis of chitosan–2-iminothiolane conjugates (Fig. 4(f)) [61]. This conjugate has the advantage that, on the one hand, 2-iminothiolane introduces cationic amidine substructures, while, on the other hand, thiol groups are immobilized. This conjugate offers therefore a double way to affect the functional groups of mucin glycoproteins. As a result, mucoadhesiveness appears to be significantly improved. The disadvantage of chitosan–TGA conjugates and chitosan–2-iminothiolane conjugates in the case of intestinal locomotion is that they are very stable in the colonic environment and thus time is required to activate the mucoadhesive performance.

The mucoadhesive selection criteria for drug delivery and for intestinal locomotion are different. On the one hand, researchers nowadays synthesise new

mucoadhesive conjugates to achieve improved drug delivery. On the other hand, it seems that polyacrylates, broadly produced and used during the last 20 years, can offer a promising solution for intestinal locomotion. Thiolated polymers of polyacrylates seem to be useful for successful intestinal locomotion as well. Chitosan appears to be less promising, because of its insolubility in neutral and basic environments, whereas the stability of thiolated polymers of chitosan inhibits their quick activation in the colonic environment.

6. Factors that influence the material properties of mucoadhesives

There are several ways to influence one or more material properties of mucoadhesives to improve their adhesive ability. Section 6.1 reviews the *intrinsic factors* that can be affected during the polymerisation process to obtain improved material properties. Section 6.2 reviews the *external factors* that can be affected to obtain improved material properties, in the case of polymers responding to environmental alterations. The reviewed information for each factor is systemised into the four categories of mucoadhesive chemicals, as defined in Section 5. In cases that no information was found in the literature, these categories are omitted in the text. Tables 2–5 connect the intrinsic and external factors with the affected material properties and provide a comparative analysis of the critical values for drug delivery and intestinal locomotion.

6.1. Intrinsic factors

Intrinsic factors are structural characteristics that can be affected during the polymerisation process of a chemical to obtain improved mucoadhesiveness. Commonly used intrinsic factors are the *molecular weight*, the *cross-linking*, the presence of *functional groups* and the *concentration* of the mucoadhesive dispersion. The aim of Section 6.1 is to define and compare the optimum values of structural characteristics for drug delivery and for intestinal locomotion and to specify which of the already commercially available mucoadhesives can be used to achieve *high friction and grip* of a moving device with the colonic surface.

Table 2
Suitable values of each intrinsic factor for improved mucoadhesion in the cases of drug delivery and intestinal locomotion

Intrinsic factors	Drug delivery	Device locomotion
Molecular weight	$\sim 10^3$ kDa	$\sim 10^3$ kDa
Cross-linking	Present but weak	Present but weak
Functional groups	High amount for covalent and non-covalent bonding	High amount for non-covalent bonding
Concentration	2–10% for Carbopols, 12–15% for NaCMC	

Table 3
Material properties that can be affected by intrinsic factors and the related bibliographic references for drug delivery

Intrinsic factors	Affected material properties	Drug delivery
Molecular weight	Molecular bonding	[63]
	Spatial conformation	[30,55,62,64]
	Rheological properties	[63]
	Cohesiveness	[62]
Cross-linking	Swelling	[65]
	Molecular bonding	[4,62,63,66]
	Spatial conformation	[55,62,67]
	Rheological properties	[4,63,66]
Functional groups	Swelling	[36,55,57,70–72]
	Molecular bonding	[36,68–72]
	Spatial conformation	[47]
	Rheological properties	[36,59,61,70–72]
Concentration	Molecular bonding	[26,33,43,66,73,74]
	Spatial conformation	[26]
	Rheological properties	[26,33,43,66,73,74]

6.1.1. Molecular weight

6.1.1.1. Polyacrylates and cellulose derivatives. Advantages of high molecular weight are that it reinforces the cohesiveness of the mucoadhesive material [62], contributes to the rheological synergism [63] and indicates longer mucoadhesive chains which can penetrate deeper into the mucus layer. A disadvantage of high molecular weight is that it reduces the flexibility of the macromolecular chains [62,64], inhibiting their diffusion. As a result, there is a range of high molecular weights ($\sim 10^3$ kDa) that offers satisfactory cohesiveness, rheology, chain length and flexibility of the polymer.

6.1.1.2. Thiolated polymers of polyacrylates and cellulose derivatives. Bernkop-Schnürch and co-workers [30,55] synthesised thiolated polymers of polyacrylates and cellulose derivatives by conjugating linear PAA, PCP, and NaCMC with cysteine, similar to polyacrylates and cellulose derivatives. The authors found out that high molecular weight conjugates have satisfactory mechanical resistance and length of macromolecular chains, but restricted flexibility.

6.1.2. Cross-linking

6.1.2.1. Polyacrylates and cellulose derivatives. In polyacrylates and cellulose derivatives, cross-linking between chains occurs when two acid groups in the polymer react and form an anhydride. High cross-linking restricts the mucoadhesive ability by decreasing the amount of free macromolecular chains able to diffuse in the mucus layer [62]. High cross-linking restricts the swelling ability of the polymer as well, since it leads to tighter structures [65]. Hägerström and Edsman [66] found out that high

Table 4
Suitable values of each external factor for improved mucoadhesion in the cases of drug delivery and intestinal locomotion

External factors	Drug delivery	Device locomotion
pH	Questionable; >6.4 (pH at distal colon)	Questionable; >7.0 (pH at descending colon)
Time	Contact for >180 s	Not applicable
Temperature	CGP between 20 and 37 °C	CGP around 37 °C
Shear rate	Suitable values for colon filled with luminal contents	Suitable values for empty colon

CGP, critical gelation point.

cross-linking leads to weakening of the mucoadhesive structure, since mucin macromolecules fill the interstitial space of the mucoadhesive. Riley et al. [63] showed, however, that the mucoadhesive properties of *weakly* cross-linked Carbopols are improved in comparison with linear polyacrylic acids, due to positive rheological synergism. In consequence, weakly cross-linked polymers appeared to compromise all demands for unrestricted swelling, positive rheological synergism, and diffusion [4].

6.1.2.2. Thiolated polymers of polyacrylates and cellulose derivatives. Linear PAA–cysteine conjugate exhibits better mucoadhesiveness than PCP– and NaCMC–cysteine conjugates. This is because linear PAA–cysteine conjugate contains more free chains that are able to diffuse within the mucus network [55]. Cross-linked poly(acrylic acid)–cysteine conjugates, however, display high cohesive properties, thus improving the mucoadhesive performance [67].

6.1.3. Functional groups

6.1.3.1. Polyacrylates and cellulose derivatives. According to the adsorption theory, mucoadhesion can occur as a result of the formation of bonds between the polymer and the mucus. Thus, a strong adhesive polymer should contain groups that are able to interact with the mucus gel. Mortazavi [68] verified the correlation between the amount of hydrogen bonds in Carbopols and the mucoadhesive ability, by disrupting the hydrogen bonds with potassium thiocyanate (KCNS) and urea and measuring the rheological characteristics. The author found out that the disruption of hydrogen bonds decays mucoadhesiveness. Patel et al. [69] measured the adhesion of polyacrylates to buccal cells in the human oral mucosal surface and found out that both non-covalent and covalent bonds between cationic charges of the polymer and anionic charges of the mucus are significant for improved mucoadhesion. Madsen et al. [36] defended that secondary hydrogen and van der Waals bonds contribute to the swelling ability of polymers, which favours the presence of rheological synergism and leads to improved mucoadhesion.

6.1.3.2. Chitosan. Patel et al. [69] experimented with chitosan and measured its adhesion to buccal cells. The authors concluded that bonding between cationic charges of the polymer and anionic charges of the mucus contributes positively to mucoadhesion. However, chitosan remains insoluble and inactive at the high pH values of the colonic region, since the chitosan macromolecules keep a coiled spatial conformation which inhibits the exposure of the functional groups and the formation of bonds with the mucin macromolecules [47].

6.1.3.3. Thiolated polymers of polyacrylates and cellulose derivatives. The increased amount of immobilised sulfide groups in thiolated polymers of polyacrylates leads to positive rheological synergism and promotes the ability of the polymer to swell, contributing to good mucoadhesiveness [55,70–72].

6.1.3.4. Thiolated polymers of chitosan. Chitosan–TGA conjugate contains a large amount of immobilized thiol groups. For this reason, it shows improved viscoelasticity in comparison with unbound chitosan. Additionally, the covalent attachment of chitosan–TGA conjugate does not deteriorate the good swelling ability of its chitosan part [57,59,61]. The presence of immobilized thiol groups leads therefore to improved mucoadhesion in comparison with unbound chitosan.

6.1.4. Concentration

6.1.4.1. Polyacrylates and cellulose derivatives. Mortazavi [73] measured the mucoadhesive force of three Carbopols in several concentrations. It was found that 2% w/v concentration gives good mucoadhesion due to optimum viscosity of the mucoadhesive. Higher concentrations of mucoadhesives contain larger amounts of functional groups to form molecular bonds, thus improving mucoadhesion

Table 5
Material properties that can be affected by external factors and the related bibliographic references for drug delivery

External factors	Affected material properties	Drug delivery
pH	Swelling	[30,59,63,72,77–82]
	Molecular bonding	[30,59,63,72,77–82]
	Spatial conformation	[73,77]
	Rheological properties	[63,71,76,77]
Time	Swelling	[88,89]
	Molecular bonding	[59,89]
	Rheological properties	[4,90]
Temperature	Molecular bonding	[28,77]
	Rheological properties	[28,77]
Shear rate	Molecular bonding	[76,91–93]
	Rheological properties	[76,91–93]

even more. Solomonidou et al. [26] found similar optimum values of Carbopol concentrations 2–10%, but also that higher concentrations can lead to decreased mucoadhesivess. In high concentrations, the polymer chains interact strongly with each other. This leads to an inflexible conformation of polymer coils that cannot participate actively in the adhesion with mucin macromolecules. The last remark is in agreement with Hägerström's hypothesis about the phenomenon of negative rheological synergism [66]. The mucoadhesive performance of NaCMC depends on the concentration as well, showing a maximum at about 12–15 wt% [74].

6.1.4.2. Chitosan. Rossi et al. [33,43] calculated the rheological synergism, as a measure of mucoadhesiveness for mixtures with several HCS/mucin weight ratios. The results showed that positive rheological synergism and therefore improved mucoadhesion occurs for HCS/mucin weight ratios equal to 1:10 in distilled water and 1:5 in 0.1 M HCl. The authors concluded that the rheology of HCS/mucin mixtures depends on the hydration media, indicating that the phenomenon is connected with the parameter of molecular bonding.

6.1.5. Conclusion

Table 2 summarises the values of each intrinsic factor for improved mucoadhesion. The affected material properties and the related bibliographic references are cited in Table 3. As shown in these tables, intrinsic factors affect more than one material property. The influence on the material properties is similar for all four categories of chemicals, making it possible to generalise the effect. The suitable values for mucoadhesion in the case of drug delivery and intestinal locomotion follow common principles. Hence, a unified approach can be assigned. Such a unified approach should be differentiated only at the point which concerns the incorporation of functional groups, since, in the case of intestinal locomotion, functional groups that form covalent bonds do not contribute positively to the required short-term mucoadhesive performance.

According to Section 5, polyacrylates and their thiolated polymers appear to be promising candidates for the interlayer between a moving device and the colonic surface. Based on the structural characteristics summarised in Table 2, a suitable polyacrylate should have molecular weight $\sim 10^3$ kDa, be weakly cross-linked and contain functional groups able to form non-covalent bonds with mucus. Carbopols have a molecular weight between 1.25 and 4×10^3 kDa. They are weakly cross-linked via small molecules, such as allyl sucrose and allyl pentaerythritol [42]. Moreover, they form non-covalent bonds with the mucin macromolecules and remain active at the high pH values of the colonic region [42]. Thiolated polymers of polyacrylates, such as cross-linked poly(acrylic acid)–cysteine conjugates can be prepared so that they meet the required structural characteristics [67] for successful intestinal locomotion. In the two in vitro experiments described below, however, it was decided to use *Carbopols* to test the potential of mucoadhesives for intestinal locomotion, since Carbopols do not only show satisfying mucoadhesion, but are also commercially available and easily handled.

6.2. External factors

External factors are environmental stimuli that can be affected and alter the behaviour of environmentally responsive polymers. Commonly used external factors are the *pH*, the *time*, the *temperature* and the *shear rate*. The aim of Section 6.2 is to define and compare the optimum values of the environmental characteristics for drug delivery and intestinal locomotion and to specify which of those external factors can be used to achieve *controlled alterations of friction* between a moving device and the colonic surface.

6.2.1. pH

Although pH-sensitive hydrogels have been used to design colonic drug delivery systems, pH remains still a questionable stimulus for delivery in the colon. The basic concept for pH responsive colonic drug delivery is that the mucoadhesive vehicle should stay inactive at the low pHs that dominate the upper parts of the gastrointestinal tract and be activated only after reaching the high pH environment ($pH > 6.4$) of the colon. The first problem of this concept is that the pH in the proximal colon (~ 6.4) is lower than that of the distal small intestine (~ 7.5). This can lead to premature activation of the mucoadhesive vehicle at the distal small intestine and indicates a deficiency of pH responsive drug delivery [75]. In the case of intestinal locomotion through the colon, however, there is no risk of premature inactivation, since the device administers the mucoadhesive on the spot. A second problem, not only for pH responsive colonic drug delivery but also for intestinal locomotion, is connected to the fact that, in cases of diseases such as the ulcerative colitis, the colon exhibits significantly lower pH values. Therefore, pH appears to be an unreliable stimulus for controlled colonic drug delivery and for intestinal locomotion.

6.2.1.1. Polyacrylates and cellulose derivatives. Taberner et al. [76] correlated the pH-dependence of the mucoadhesive ability with the pH-dependence of the gelation point of polymers. It turned out that the maximum consistency of Carbopols appears when gelation happens. This occurs at an optimum pH region between 6 and 8. Mortazavi et al. [73] proposed a more narrow optimum pH region between 6.2 and 7.1. The authors explained the pH-dependence by the fact that at pH values between 6 and 7 the carboxylic groups in the polymer are in their ionised form, repulsing each other and forming an expanded viscoelastic network. According to other researchers, however, mucoadhesiveness is

improved at *acid* pHs (3–5), where rheological synergism (see Section 4.4) occurs [63]. These contradictions in the bibliography were mentioned also by Madsen et al. [77], who propose an optimum *weakly acid* pH region for which both the polymer and the mucus have their optimum spatial conformation and thus improved viscoelasticity.

6.2.1.2. Chitosan. Chitosan has strong mucoadhesive properties, but till recently its applications were limited, because it is a weak base and thus soluble only in an acid environment. In order to overcome this problem, Junginger and co-workers synthesised the novel chitosan derivative *N*-trimethylchitosan chloride (TMC; Fig. 5) which can be solubilized at *neutral* and *basic* pH levels [78–82].

6.2.1.3. Thiolated polymers of polyacrylates and cellulose derivatives. Kast and Bernkop-Schnürch [72] synthesised several thiolated polymers by conjugating PAA or NaCMC with cysteine or cysteamine. By investigating the influence of the pH on the mucoadhesive ability, the authors found different results for each conjugate:

- PCP–cysteine and NaCMC–cysteine conjugates turned out to be strongly influenced by pH: only at pH 5, the mucoadhesiveness was improved. At pH > 7 or < 4, the adhesive ability decayed. This phenomenon is caused by the formation and disruption of disulfide bonds: at very low pH values, the bonds are stable and therefore inactive. At pH > 7, disulfide bonds are created within the conjugate, already before it comes in interaction with mucus. As a result, there are no more remaining thiol groups to react with the mucin glycoproteins and to form bonds. NaCMC–cysteine conjugates show high mucoadhesion at pH 5 (similarly to PCP–cysteine) and further improvement of mucoadhesion at pH values between 4 and 5. The reason is that these conjugates can bind to the mucin glycoproteins not only with disulfide but also with esther bonds [30].
- Linear PAA–cysteine conjugates showed high viscosity and positive rheological synergism with mucin at pH > 6, because of the presence of sulfide groups [71]. NaCMC– and neutralised PCP–cysteamine conjugates showed good mucoadhesiveness at pH > 6 as well. According to disintegration measurements, the polymer was very cohesive at this pH region due to the formation of disulfide bonds [72].

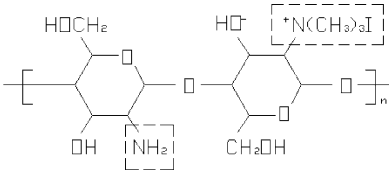

Fig. 5. Structural formula of *N*-trimethylchitosan chloride. The dashed boxes indicate the side groups that are responsible for mucoadhesiveness.

6.2.1.4. Thiolated polymers of chitosan. Chitosan–TGA conjugate is very sensitive to pH changes: rheological studies performed by Hornof et al. [59] indicated an optimum pH value at 5.5. In this *weakly acid* environment, the elasticity of chitosan–TGA conjugate is significantly increased, because of the high amount of active thiol groups.

6.2.2. Time

Time is an external stimulus that can be used to release a drug in the colon. Researchers have already suggested time responsive drug delivery systems which incorporate a time lag of 5 h before being activated [83–86]. Such a time lag coincides with the transition time of the delivery system from the mouth to the colon. In this way, the drug release is activated after the delivery system has already reached the colon. Furthermore, the contact time between a mucoadhesive and a mucosal surface affects the generated adhesive force [87]. In the case of intestinal locomotion, time cannot be used as a stimulus for friction manipulation due to the reasons already discussed in Section 2.

6.2.2.1. Polyacrylates and cellulose derivatives. Rillosi and Buckton [88] measured the detachment force of several Carbopols in different dissolvers (intestinal, gastric and saline fluid) after different times of contact of the Carbopols with the dissolver. After 1 min of contact, the highest detachment force was found in strongly acid gastric fluid (pH 1.2). This occurred because in this acid environment, the *ionisation* of both the polymer and the mucus was intensive. After 5 min of contact, the dominant phenomenon was not anymore the ionisation, but the *hydration* of the polymer. The detachment forces were higher for all hydration media in comparison with the forces after 1 min and the highest value was found in weakly acid saline fluid (pH 6.4). The authors further noticed that the time profile of mucoadhesiveness coincides with the hydration profile of Carbopols. Hydration appears therefore to be the dominant phenomenon of the change of mucoadhesive behaviour with time. Moreover, the time-dependence of mucoadhesion can occur because both mucus and mucoadhesives exhibit non-Newtonian thixotropic behaviour, which means that their viscosity decreases with time under shearing [4]. Wong et al. [89] measured the work of adhesion and the peak detachment force of Carbopol 974 on chicken pouch for different contact times (from 10 to 600 s). The authors found out that both the work of adhesion and the peak detachment increase significantly when the contact time increases. The reason is that the contact time affects the degree of hydration, swelling, interpenetration and formation of non-covalent bonds which in turn influence the mucoadhesive performance. Mortazavi [90] connected the contact time (15, 60 and 120 min) of different Carbopols on mucus with changes in the rheological properties of the mucoadhesive, which indicate gel strengthening due to chain interpenetration, physical entanglement and non-covalent bonding and thus improved mucoadhesion.

6.2.2.2. Thiolated polymers of chitosan. Chitosan–TGA conjugates show improvement of their rheological properties within the first 2 h of their contact with mucus. This behaviour indicates that the mixtures of mucin and chitosan–TGA conjugate form a physically entangled system and that 2 h are required to complete the cross-linking of the system [59].

6.2.3. Temperature

Mucoadhesive thermosensitive gels (MTG) have been already developed but not for the colonic region. Such formulations are Newtonian at 20 °C but non-Newtonian at 37 °C [28]. The idea to design MTG for colonic drug delivery as well as for intestinal locomotion is challenging, since it can lead to precise and elegant ways of control. In the case of intestinal locomotion, the mucoadhesive should have a critical gelation point close to the body temperature.

6.2.3.1. Polyacrylates and cellulose derivatives. Although many researchers consider the behaviour of mucoadhesives as temperature-independent, Madsen et al. [77] pointed out that the mucus–mucoadhesive interface shows differences in its viscoelastic behaviour within a temperature range between 10 and 50 °C. The authors found out that PAA showed a dramatic decrease of viscoelasticity at high temperatures, whereas the rheology of NaCMC is only slightly changed in the temperature range between 10 and 50 °C. In this context, it seems interesting to optimise and apply PAA as a MTG.

6.2.4. Shear rate/pressure

Shear rate or pressure responsive mucoadhesives have been applied in ophthalmic controlled drug delivery, but the knowledge about their mucoadhesive performance in the gastrointestinal tract is still in its infancy and deserves to be explored. In this perspective, the increase in pressure due to the adsorption of water by the luminal contents of the colon can be exploited. This method was recently applied in colonic drug delivery but without incorporation of a mucoadhesive formulation [91]. In the case of intestinal locomotion, exerting pressure to alter the properties of the mucoadhesive interlayer and to manipulate friction is a triggering issue which can lead to an accurate locomotion mechanism. The main difference between exerting pressure for drug delivery and intestinal locomotion is that, in the second case, the colon is empty so that different ranges of pressures are applicable. The range of the exerting pressure, however, should be kept at low levels, to avoid cramp during the medical examination.

6.2.4.1. Polyacrylates and cellulose derivatives. Many researchers [76,92,93] testified the non-Newtonian pseudoplastic character of Carbopols, determined originally by the B.F. Goodrich Company [42]. This means that the viscosity of Carbopols decreases in high shear rates. Under high shear rates, disentanglement and disruption of the polymer structure occurs, decreasing the rheological synergism and decaying mucoadhesion.

6.2.5. Conclusion

Table 4 summarises the critical values of each external factor to control the delivery of a drug or to alter the friction values in the colon. The affected material properties and the related bibliographic references are cited in Table 5. As shown in these tables, external factors can affect simultaneously more than one material property. Although the influence of the external factors on the material properties depends on the specific chemical, an attempt was made to generalise the phenomenon. A comparative analysis of the suitable values of the external factors applicable for drug delivery or intestinal locomotion was realised.

It seems that the critical environmental stimuli for controlled drug delivery are different from those for manipulating friction in the case of intestinal locomotion. For example, exerting pressure to alter the properties of a mucoadhesive can lead to successful locomotion. However, there is always the risk of cramp during the colonoscopic procedure. Besides, the flaccidity and high deformability of the colonic tube create questions and doubts about the effectiveness of this locomotion mechanism. Therefore, a new method to alter friction should be found.

According to the adhesive theories of friction [94–97], when an adhesive is interposed between two bodies, friction depends on the contact area. Since the mucoadhesive interlayer is adhesive, the friction through the colon is expected to be dependent on the contact area. It seems therefore feasible to switch between high and low friction values by altering the size of the contact area between the intestine inspection and intervention device and the colonic surface.

7. Experimental verification

7.1. Carbopol films for high friction

In order to verify whether Carbopols increase the friction between an intestine inspection and intervention device and the colonic wall, the authors carried out two in vitro experiments in which the shear force between Carbopol films and a segment of a porcine colonic surface was measured [98].

Carbopol 971P NF mucoadhesive films were prepared according to the method described by Eouani et al. [4]. The colon of a pig was extracted, opened longitudinally and stabilised on a heating pad with the inner surface upto maintain the temperature at 37 °C. A mucoadhesive film was fixed to the bottom of a rectangular rigid plate. The plate was loaded with 100 g weight and connected via a thread and pulley to a tensile testing machine (Zwick 1484). The load was selected so that the pressure on the plate was

within the range of values of the intra-abdominal pressure (0.02–2.16 kPa) [99,100]. The tensile testing machine pulled the plate forward with constant speed and recorded the trace of the generated friction force.

To verify the effectiveness of mucoadhesive films in generating grip with the colonic surface, their static friction was compared with the static friction of conventional materials, such as Plexiglas, smooth glass, and ground glass, with the colonic surface. Each measurement was repeated four times. Friction forces measured with Plexiglas plates were very low (0.1 N on average), since Plexiglas is hydrophobic whereas mucus is hydrophilic. The Plexiglas plates were thus repulsed by the mucus layer and slid with very low friction. Glass is a hydrophilic material which can explain the higher friction values measured. Friction was higher for a ground glass plate (0.5 N on average) than for a smooth glass plate (0.25 N on average), because the contact area and thus the surface tension between the ground glass plate and the wet mucus layer was larger. The friction values reached with a mucoadhesive film (5.67 N on average) were almost 20 times higher than for Plexiglas and glass, showing the strong benefits of using mucoadhesive films to increase friction. Carbopol films appear thus to be a promising solution to create high grip with the mucus layer of the colon.

7.2. Contact area alterations for friction manipulation

In order to verify whether and to what extent the friction of mucoadhesive films with the colon depends on the contact area, friction forces were measured for Carbopol 971P NF mucoadhesive films. The films were fixed on six plates with various dimensions and their friction with the inner porcine colonic surface was measured [101]. Each measurement was repeated seven times. The results showed a significant dependence of friction on the contact area, ranging from 1.7 N in average for a contact area of 2.4 cm^2–6.9 N in average for a contact area of 25.5 cm^2. It seems therefore feasible to manipulate the friction with the colonic surface by altering the contact area of the mucoadhesive film.

As an alternative method for friction manipulation, the response of mucoadhesives to more than one factor *simultaneously* deserves to be explored. A combined action of *shear rate*, *time* and *temperature* could lead to better manipulation of the mucoadhesive rheology. *Temperature–pH* sensitive polymers, which are already applied in tumour hyperthermic treatments, can respond as well to the combined changes of these two dependent factors. The role of other environmental factors such as *light, vibrations*, *electric charge* and *magnetic fields* on the mucoadhesive performance needs further exploration. These issues can offer new ways to control the behaviour of 'smart polymers' for drug delivery and for intestinal locomotion.

8. Discussion

This article investigates introducing mucoadhesives to manipulate friction and to achieve successful locomotion of an intestine inspection and intervention device along the colonic surface. The aim is to identify which groups of mucoadhesives and what environmental stimuli are suitable for this application. Since mucoadhesives have been developed for drug delivery, it was needed to revisit and re-evaluate the literature with regard to a new set of requirements for intestinal locomotion.

By investigating the structural characteristics of already synthesised mucoadhesives, it appears that the material properties of the mucoadhesives can be initially controlled by influencing intrinsic factors during the polymerisation process. The suitable values of those intrinsic factors are similar for both drug delivery and intestinal locomotion so that a unified approach for both applications can be assigned. Such a unified approach should be differentiated only at the point which concerns the incorporation of functional groups, since in the case of intestinal locomotion, functional groups that form covalent bonds do not contribute positively to the required short-term mucoadhesive performance. By investigating the response of environmental-sensitive mucoadhesives to external stimuli, it appears that the material properties of those mucoadhesives can be altered according to their environment. It seems, however, that the critical external stimuli for controlled drug delivery are different from those for manipulating friction in the case of intestinal locomotion.

In the experiments described above, shear forces were measured. Measuring shear forces instead of detachment forces can provide us with useful information for the mucoadhesive performance in drug delivery applications as well, since mucoadhesives are frequently subjected to shear forces through the gastrointestinal tract. The shear strength of mucoadhesives differs significantly from the commonly measured tensile strength. Researchers have already tried to carry out shear stress measurements of mucoadhesives. The experiments showed limited success [102] due to difficulties of measuring shear forces with satisfying precision and reproducibility.

A new method for locomotion along the colonic surface by manipulating friction can offer a useful alternative for conventional colonoscopes. By affecting only the mucus layer and not the intestinal wall itself, it can eliminate pain as well as a risk of potentially fatal perforation. The feasibility of friction manipulation by means of a mucoadhesive expands the area of mucoadhesion and initiates a new research field on the borderline between drug delivery and mechanical design.

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