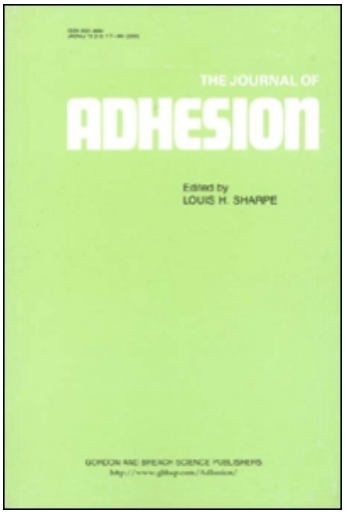

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Grip to the Colon by Means of Macroscopic Adhesion-Controlled Friction

Dimitra Dodou[a]; Freek Bedaux[a]; Raoul van Heffen[a]; Paul Breedveld[a]; Peter A. Wieringa[a]
[a] Department of BioMechanical Engineering, Faculty of Mechanical, Maritime and Materials Engineering, Delft University of Technology, Delft, The Netherlands

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Dimitra Dodou
Freek Bedaux
Raoul van Heffen
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Peter A. Wieringa
Department of BioMechanical Engineering, Faculty of Mechanical, Maritime and Materials Engineering, Delft University of Technology, Delft, The Netherlands

Manipulating friction without applying high normal forces is important for an intestine inspection and intervention device in order to eliminate the risk of tissue damage. One possible solution is to generate friction by means of adhesive forces. The adhesive forces should be high to offer sufficient grip without needing high normal forces. The generated friction is then called adhesion-controlled and depends on the size of the area in contact. Adhesion-controlled friction is well known to be dominant at microscopic and molecular levels. According to this paper, adhesion-controlled friction can be applicable on the macroscopic scale as well and, more specifically, within a range of forces in which friction is usually considered to be load-controlled. The intestine inspection and intervention device manipulates the friction with the colonic wall by means of mucoadhesive films. In this way, grip with high static friction is achieved without the need to apply high normal forces and friction is altered by changing the size of the area of the mucoadhesive film. Friction theories on different scales are revisited and considered in order to understand the dominant phenomena and the principles associated with this macroscopic adhesion-controlled friction.

Keywords: Adhesion-controlled friction; Colon; Friction manipulation; Mucoadhesive films

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Address correspondence to Dimitra Dodou, Department of BioMechanical Engineering, Delft University of Technology, Mekelweg 2, 2628 Delft, The Netherlands. E-mail: d.dodou@3me.tudelft.nl

INTRODUCTION

Colonoscopy is a standard medical procedure in which a long flexible endoscope is inserted into the rectum for inspection of the colon. Pushing the endoscope along the colon can cause painful cramps to the patient, and risks perforation of the colonic wall. The drawbacks of the conventional instrumentation have led to research into alternative intestine inspection and intervention devices. The main challenge for the development of such devices is their locomotion mechanism along the slippery, flaccid colonic tube.

Successful intestinal locomotion can be achieved by manipulating the friction with the colonic surface [1], *i.e.* by generating high friction for grip and low friction for sliding. At Delft University of Technology, a new method to manipulate friction inside the colon by means of mucoadhesives is being investigated (Fig. 1). Mucoadhesives are polymers that adhere with the mucus covering the colonic surface by forming bonds with the mucus proteins. Mucoadhesives are originally used as vehicles for controlled and local drug delivery, and they can be prepared in various semi-solid or solid forms, such as hydrogels, films, microspheres, sponges, tablets or microtablets.

In the literature, there is a lack of information about the frictional behaviour of mucoadhesives [2]. Researchers have tried to carry out friction measurements of mucoadhesives, but with limited success [3]. In a previous paper [4], the authors measured the friction generated by mucoadhesive films interposed between an intestine inspection device and the colonic surface and reported that high static friction can be generated. In this paper, the frictional behaviour

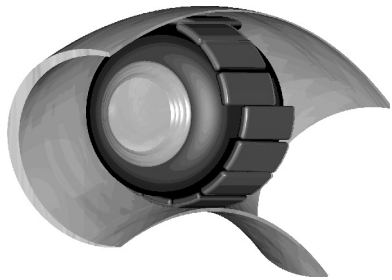


FIGURE 1 Design concept of an intestine inspection and intervention device. All pads are covered with mucoadhesive films. In each stage, only one single pad slides forward, while all the other pads grip to the colon due to their mucoadhesive content. As soon as all pads have slid one step forward, the cylinder moves forward as well, so that the device moves one step further.

of mucoadhesive films on the colonic surface is further investigated, to gain insight into the dominant phenomena and related friction theories.

Considering that the intestinal tube can be easily deformed and stretched outward, causing pain in the abdomen, intestine inspection and intervention devices should be able to generate high grip without the need to apply high normal forces. It would be preferable that the generated friction should be independent of the applied load and controlled by other parameters, such as the area of contact between the device and the colonic surface. The colonic surface is soft and flexible, creating a large number of contacts with the device. It is, therefore, expected that the generated friction between the device and the colonic surface depends on the area of contact. Moreover, if the device is coated with mucoadhesive films, the generated adhesive forces can be high enough to offer sufficient grip without needing high normal forces. It should be noted, however, that the action of the mucoadhesive films should be temporary and, thus, the generated forces should be lower than those generated by permanent surgical glues. In other words, the generated friction should be load-independent and area-controlled within a range of forces on the macroscale, which, in general, is supposed to be load-controlled [5].

In this paper, the influence of the *applied load* and the influence of the *area* of the mucoadhesive film on the static friction generated between the colonic surface and the device are investigated. We attempt to explain the observed dominating phenomena in terms of friction and adhesion on the macroscopic scale. For this reason, theories of adhesive friction on the microscopic and molecular scale, as well as theories on adhesive joints are revisited and considered, even if they are all originally applicable on different scales.

Real vs. Apparent Contact Area

A hydrated mucoadhesive film is a polymer semi-solid form, whereas the mucus is a protein semi-solid form. In an effort to define the area of contact between a mucoadhesive film and mucus, a number of theoretical aspects are considered. In 1954, Bowden and Tabor introduced the concept of real contact area in juxtaposition to the apparent contact area [6]. The basic idea is that between two solid surfaces in touch, only a limited number of asperities are microscopically in contact and determine the real contact area. The real contact area is, thus, smaller than the macroscopic apparent contact area. In contrast to solid contacts, in the case of polymer semi-solid forms, the real contact area can be equal to, or even larger than, the apparent contact

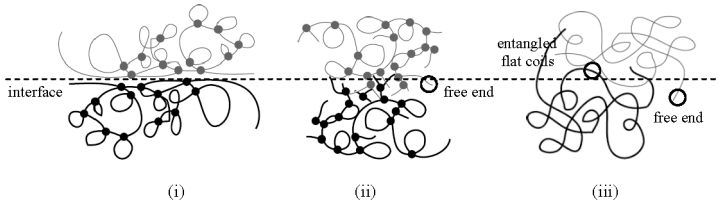


FIGURE 2 Interface of two (i) fully cross-linked polymers, (ii) polymers after scission, (iii) uncrosslinked polymers.

area, because of chain interpenetration [7]. A clearer picture of the consequences of polymer chain interaction on the generated adhesion and friction is given by Maeda *et al*. [8]. Those authors compared the friction force and the adhesion hysteresis generated by fully cross-linked polymer films, polymer films after scission (i.e., chemical reaction resulting in the local breaking of the polymer macromolecules) and uncrosslinked polymer films (Fig. 2). It was found that cross-linked polymers generated the lowest friction, because of their inability to interpenetrate and increase the contact area (Fig. 2(i)). The highest friction was generated by polymers after scission, because of the presence of free ends able to interact (Fig. 2(ii)). Uncrosslinked polymers generated lower friction than the polymers after scission because the former contains mainly flat coils which, even when interpenetrating, entangle like loops rather than free ends (Fig. 2(iii)).

For the case of a mucoadhesive in contact with a mucus layer, visualisation studies of the interface [9] showed that no serious interpenetration of free chains occurs on a microscopic range. The interface appeared as an irregular but sharp borderline. It can, thus, be assumed that in the case of mucoadhesive-mucus contact the real contact area is equal to the apparent contact area and, thus, equal to the area of the mucoadhesive film.

Load-Controlled vs. Adhesion-Controlled Friction

According to Amontons' second law, friction is independent of the area of contact. For adhering surfaces, Amontons' second law is violated [10–12], and the contribution of the adhesive forces should be added to the law in the form of an internal load [12]. Friction can be then expressed as $F = \mu L + \sigma A$, in which F is the friction force, μ the friction coefficient, L the applied load, σ the critical shear stress (at which slipping starts) and A the real contact area. At sufficiently high loads [11], the contribution of the load, μL, dominates and the friction is called

load-controlled. The contribution of the adhesive forces, σA, becomes more important when zero or negative loads are imposed on molecularly smooth adhering surfaces. The friction is then called adhesion-controlled. In other words, even though the van der Waals interactions at each contact point are weak, they add up to an adhesive force which makes the load contribution negligible [11]. Adhesion-controlled friction is more likely to occur on the microscopic and molecular scale, where molecularly smooth surfaces exist, whereas friction on the macroscopic scale remains load-controlled [13].

The intestine inspection and intervention device should be able to generate adhesion-controlled and load-independent friction within a range of applied loads compensating for the intra-abdominal pressure. The applied normal force varies, therefore, within 0.1–1 N for areas between 3–12 cm^2. The range of areas was selected so that it corresponds to the surface area of the developing intestine inspection and intervention device. If the adhesive forces were limited strictly to weak van der Waals forces, the contribution of such an applied load could not be neglected. The use of mucoadhesive films, however, can lead to stronger hydrogen and ionic bonds, which can eliminate the influence of the load and introduce adhesion-controlled friction on the macroscale.

EXPERIMENTS

The aim of the experiments described below was to investigate whether applied loads between 10–100 g for areas between 3–12 cm^2 influence the friction generated by mucoadhesive films on the colonic surface, and to what extent the friction depends on the area of the mucoadhesive films. All the experiments were carried out *in vitro* using porcine colons.

Materials

As a mucoadhesive polymer, Carbopol 971P NF (CP971) was used. Carbopol® is the commercial name of high molecular weight cross-linked polymers of acrylic acid, developed by the company Noveon. Carbopols seem to be promising candidates for friction manipulation, since they are attached to the mucus *via* physical bonds (ionic, hydrogen and van der Waals) that are formed instantaneously. CP971 has a medium degree of cross-linking and molecular weight of 1,250,000 [14–15]. Triethanolamine (TEA) was used to neutralize the Carbopol dispersions and Polyvinylpyrrolidone (Plasdone® K-90D) (PVP) was used as a film-casting polymer. Propylene glycol

was used to strengthen the films and to prevent them from breaking during decasting and storage. Methylene blue was used to stain the film and assist the observation of their behaviour during the experiments.

CP971 was a gift from the company Noveon Inc. (Cleveland, OH, USA) and PVP was a gift from the company ISP Technologies Inc. (Waalwijk, The Netherlands). TEA and Methylene blue were purchased from the company Sigma-Aldrich Chemie BV (Zwijndreclit, The Netherlands). All animal procedures were performed using institutionally approved protocols.

Preparation of Mucoadhesive Films

Mucoadhesive films were prepared according to a method described by Eouani *et al*. [16]. A 0.3% w/w mucoadhesive hydrogel was prepared by slowly sifting CP971 into the vortex of distilled water while stirring at 800 rpm. After the entire quantity of dry polymer was introduced, stirring continued for 15 minutes at moderate speed (600 rpm) to avoid air entrapment into the dispersion. Then, a small quantity of TEA was added dropwise under mild stirring (500 rpm), until neutralization of the dispersion [16]. In this way, transparent, lump-free hydrogel dispersions were obtained.

A 10% w/w PVP aqueous solution was prepared under stirring at 800 rpm for 15 min. A volume of 0.6% w/w propylene glycol solution equivalent to the volume of the PVP solution was prepared. The hydrogel dispersion, the PVP solution, and the propylene glycol solution, were mixed under stirring at 800 rpm for 15 min. The produced dispersions were kept overnight at 4°C to complete hydration and release any entrapped air. The dispersions were then returned to room temperature and poured into Petri dishes. Next, the produced samples were dried in an oven at 38°C for 24 h and the obtained films were removed from the Petri dishes. The thickness of the films was measured and they were stored at room temperature for at least 48 h before use. The thickness of the films was in all cases 5 ± 0.5 microns.

Methods

The colon of a pig was extracted, rinsed and preserved in Ringer's lactate solution at 4°C. Just before the experiment, a colonic segment was cut, opened longitudinally and stabilised on a heating pad to maintain the temperature at 37°C with the inner surface up (Fig. 3) [1]. A mucoadhesive film was fixed to a rectangular Plexiglas® plate. The edges of the Plexiglas plate were rounded, since sharp edges can cause

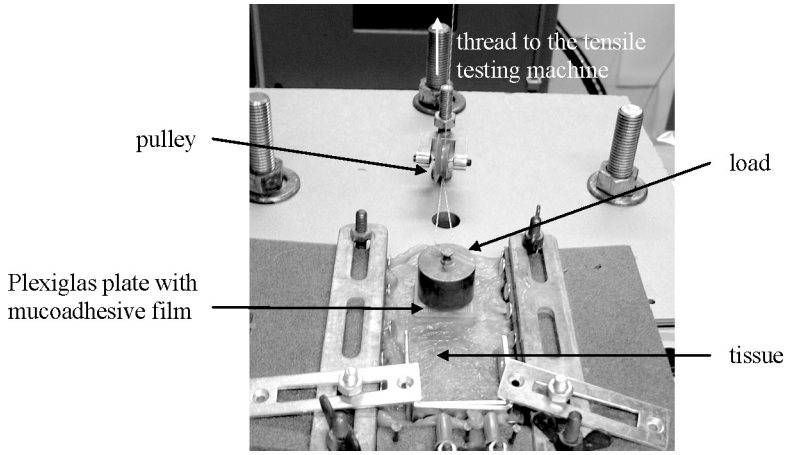


FIGURE 3 Experimental setup for measuring friction between the inner colonic surface and a Plexiglas plate.

damage to the colonic wall. The Plexiglas plate was loaded with a weight and connected *via* a thread and pulley to a tensile testing machine (Zwick 1484, Zwiek GmbH & Co. KG Ulm, Germany). The tensile testing machine pulled the Plexiglas plate forward with constant speed (60 mm min^{-1}) and recorded the trace of the generated friction force (sample frequency 50 Hz) [4]. All measurements were carried out within a short and fixed time of 2 min after the tissue stabilization on the heating pad, in order to avoid excessive drying of the mucus.

Experiment 1: Effect of the Applied Load

In the framework of Experiment 1, the effect of the applied load on the friction generated by Plexiglas plates and mucoadhesive films was investigated. Plexiglas was chosen since it is hydrophobic and, therefore, is repulsed by the hydrophilic mucus, leading to decrease of eventual adhesion to the mucus layer. First, the friction generated on the colonic surface by 25×25 mm Plexiglas plates under applied loads of 10 and 100 g including the weight of the Plexiglas plate was measured. The loads were selected such that the pressure on the colonic surface is within the range of values of the intra-abdominal pressure [17–18]. Each measurement was repeated five times. One intestinal segment was used for all measurements (animal weight 30 kg). Then, mucoadhesive films were fixed on 25×25 mm Plexiglas

plates and their friction with the colonic surface was measured under loads of 10 and 100 g including the weight of the Plexiglas plate.

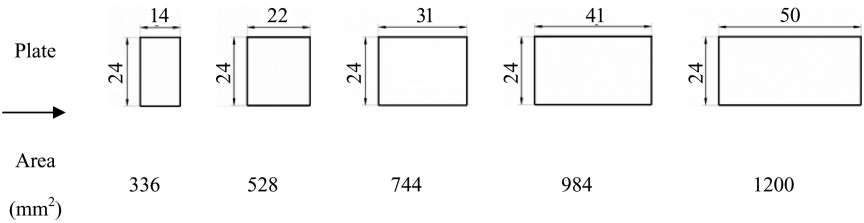
It has been shown from previous experiments [4] that the motion of a mucoadhesive film sticking on the colonic surface is initiated by cohesive failure of the film. As a consequence, fragments of the film remain on the colonic surface. For this reason, a different segment of tissue was used for each measurement, since the presence of the mucoadhesive film may influence the properties of the mucus. Each measurement was repeated five times, using different intestinal segments, all extracted from the animal used in the case of Plexiglas plates as well. It should be noted that mucoadhesives are non-toxic. Moreover, considering that the turnover time of intestinal mucus is estimated in the order of a few hours [19], eventual leftovers of mucoadhesive will be quickly washed away. For a device moving along the colon by means of mucoadhesive films, fragments of the films are, thus, not considered to be harmful for the colonic surface.

For each measurement, a different film was used, since films lose their adhesive ability as soon as they have slid once along the colonic surface. In other words, as soon as motion is initiated, the device can slide along the colonic with low dynamic friction, without being disturbed by the presence of mucoadhesive films.

Experiment 2: Effect of the Area of the Mucoadhesive Film

In the framework of Experiment 2, the effect of the area of the mucoadhesive film on the generated friction was investigated. The films were fixed on five Plexiglas plates with the dimensions given in Table 1. All plates were loaded so that the total load on the colonic surface was 100 g. For each measurement, a different intestinal

TABLE 1 Plexiglas Plate Dimensions and Areas in Experiment 2. Dimensions are in mm. The Arrow Indicates the Direction of Shearing



segment was used. Each plate was tested on five animals, using three tissue segments of each animal (two animal of 30 kg and three animals of 80 kg). Each plate was, thus, tested in total fifteen times.

RESULTS

Experiment 1

The maximum static friction was measured for mucoadhesive films and Plexiglas plates under loads of 10 and 100 g (Table 2, Fig. 4). It appears that the friction of the mucoadhesive films does not depend on the applied load (Wilcoxon rank sum test: $p = 1$, $h = 0$) within the studied range, whereas the friction of the Plexiglas plates does (Wilcoxon rank sum test: $p = 0.0079$, $h = 1$). The figure shows that large dispersion of the results occurs in the case of mucoadhesive films (the interquartile range was 0.66 for 10 g and 0.47 for 100 g). In the case of Plexiglas plates, there was no need to use different tissue segments, since there was no mucoadhesive film and, thus, no fragments. The dispersion of the results was considerably smaller (the interquartile range was 0.01 for 10 g and 0.02 for 100 g).

Experiment 2

Maximum static friction was measured for five Plexiglas plates of different dimensions (Table 1) coated with mucoadhesive films. The resulting values were plotted against the corresponding areas of mucoadhesive film (Fig. 5). The results show a significant increase of friction with the area (ANOVA: $p = 8.1823 \cdot 10^{-6}$). The figure shows also that large dispersion of the results occurred for all areas (the interquartile range was 1.66, 1.04, 1.48, 2.59, and 2.26 for areas 3.36, 5.28, 7.44, 9.84, and 12.00, respectively).

TABLE 2 Experimental Data for Experiment 1

	Plexiglas plates		Mucoadhesive films	
Load	10 g	100 g	10 g	100 g
Measured friction (N)	0.05	0.16	3.81	2.25
	0.06	0.16	2.34	2.74
	0.06	0.18	1.76	2.00
	0.05	0.17	2.47	2.52
	0.06	0.19	2.54	2.63

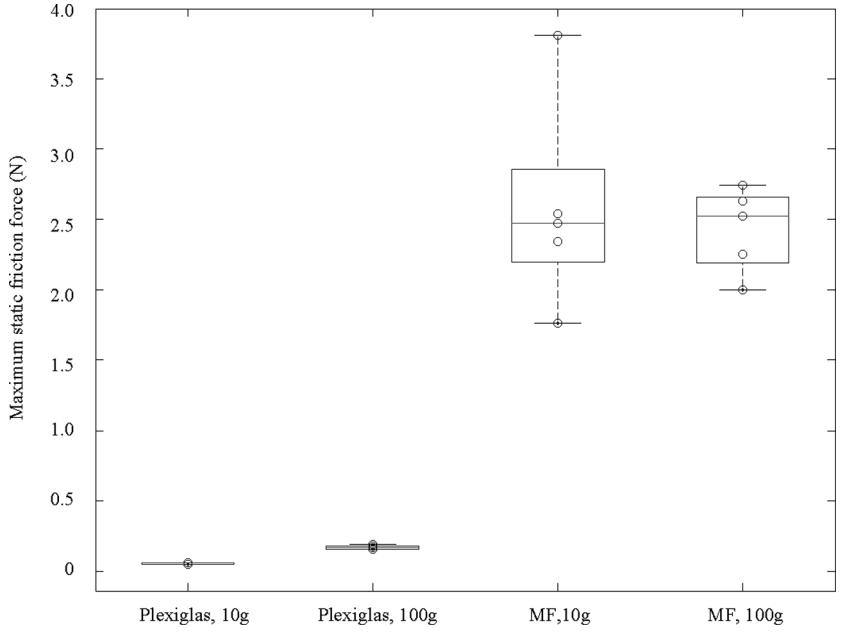


FIGURE 4 Box plots and experimental data of the maximum static friction force generated by Plexiglas plates and mucoadhesive films on the colonic surface under loading of 10 and 100 g (Experiment 1). The line in the middle of the box is the sample median. The lower and upper lines of the box indicate the interquartile range. The whiskers extending out of the box indicate the spread. Non-centred boxes indicate skewness in the results. MF: mucoadhesive film.

DISCUSSION

Mucoadhesive Film on Mucus: Macroscopic Adhesion-Controlled Friction

It seems that the friction of mucoadhesive films can be adhesion-controlled within a range of loads (10–100 g) and generated friction forces (1-8 N) which, in general, is supposed to be controlled by the load. This occurs because the mucoadhesive films create ionic and hydrogen bonds. These bonds are stronger than the van der Waals bonds, which can play important role mainly on nano and microscale, but weaker than the chemical bonds, present in adhesive joints, which lead to irreversibly high forces (Table 3). Moreover, the friction of mucoadhesive films depends on their area. As already discussed in the introduction, the friction dependence on the area can be explained by the high deformability of the colonic surface. Friction dependence

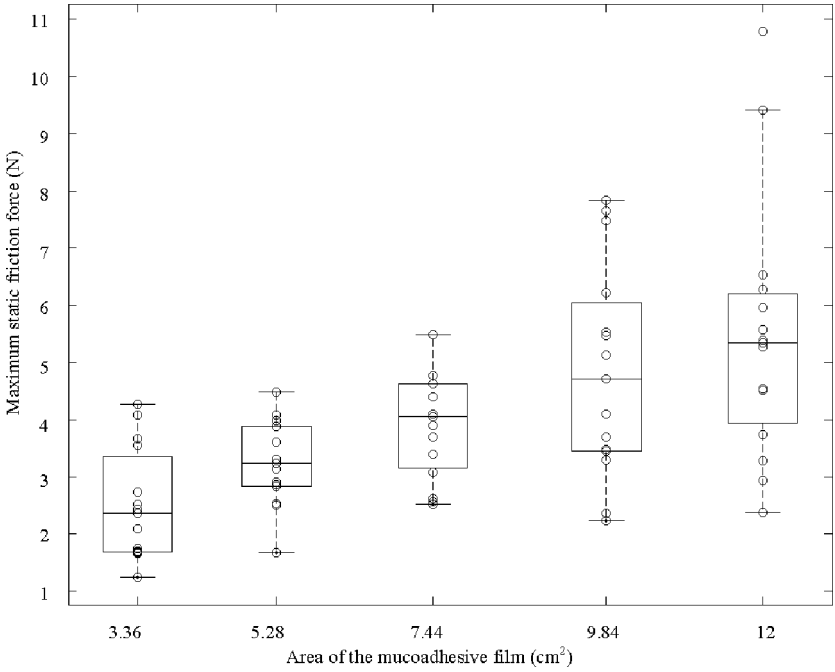


FIGURE 5 Box plots and experimental data of the maximum static friction force generated by mucoadhesive films on the colonic surface *vs*. the area of the mucoadhesive film (Experiment 2). The line in the middle of the box is the sample median. The lower and upper lines of the box indicate the interquartile range. The whiskers extending out of the box indicate the spread. Non-centred boxes indicate skewness in the results.

is, thus, likely to be present even without using mucoadhesive films. This can be seen from the experimental data derived for Plexiglas plates: an increase of the load 10 times did not lead to a 10 times

TABLE 3 Adhesion-Controlled Friction on Different Scales. μ is the Friction Coefficient, L the Applied Load, σ the Critical Shear Stress at Which Slipping Starts, A the Real Contact Area and F the Friction Force

μL	+	σA	=	F
Load range (kg)		Required adhesive forces to make load contribution negligible		Generated friction (N)
$\rightarrow 0$		Physical (van der Waals)		10^{-9}–10^{-6}
10^{-1}		Physical (ionic and hydrogen)		10^{0}–10^{1}
10^{5}		Chemical		10^{5}

increase of the generated friction. The importance of using mucoadhesive films is that they generate high adhesive forces and the generated friction can then be adhesion-controlled. In other words, the presence of mucoadhesive films scales up the generated friction to a level such that the dependence of friction on the area is considerable and, therefore, suitable for applications on a macroscopic scale. It should be further noted that the friction dependence on the area does not seem to be linear and that smaller plates appear to perform better for their size. This implies that not only the area but also other geometric parameters can influence the friction of the films on the colonic surface.

When testing *in vivo*, it can be expected that the absolute values of friction are not identical to those derived from *in vitro* testing. The generated friction can be lower *in vivo*, because of the presence of floating mucus or excessive moisture. However, the load should be once more considered not of influence, because of the high flexibility of the colonic tube that cannot sustain significant normal forces.

Friction of Mucoadhesive Films vs. Shear Strength of Adhesive Joints

The geometry of the experiments described above (Fig. 6(i)) seems comparable with that of a finite-size doubler bonded to a base and subjected to shear loading (Fig. 6(ii)). Bonded doublers are adhesive joints which serve often as a reinforced hard point for component attachment, such as an antenna on an aircraft fuselage [20]. The maximum static friction of a mucoadhesive film on mucus corresponds to the shear strength of an adhesive joint. The friction of a mucoadhesive

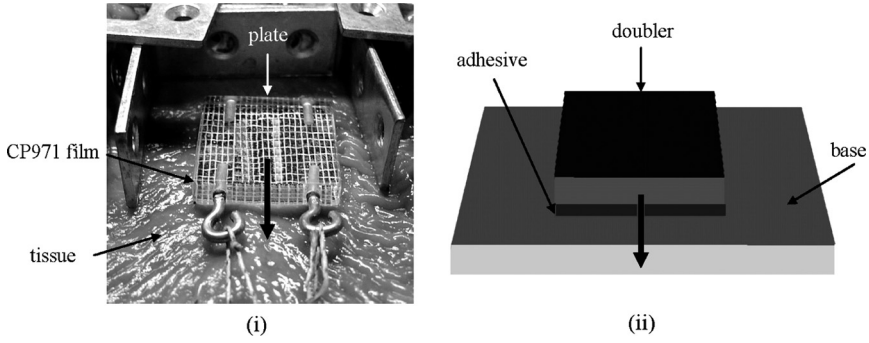


FIGURE 6 (i) Shearing of mucoadhesive film on the colonic surface. (ii) Shearing a doubler bonded on a base.

film depends on the area with the mucus, whereas the shear strength of an adhesive joint depends strongly on the size of the overlap. The friction of a mucoadhesive film is controlled by the created adhesive bonds rather than the applied loads, similar to the shear strength of an adhesive joint. Following this line of reasoning, one could imply that a mucoadhesive film on mucus can be considered as an adhesive joint or, more specifically, a bonded doubler. Two main differences, however, inhibit this correlation. First, CP971 creates only physical bonds with the mucus, whereas adhesive joints create strong chemical bonds with the in-contact surfaces. The friction is, in that case, controlled by adhesion because of the range of the created adhesive forces which lead to maximum stresses in the range of MPa or GPa. Second, adhesive joints concern solidified laps, whereas mucoadhesive films should be hydrated in order to activate the bonding process. This leads to a case with considerably different material properties. As a result the theories of adhesive joints cannot be directly applied to the case of mucoadhesive films.

Though on a different scale, it is expected that the friction of a mucoadhesive film on mucus meets some characteristics of the behaviour of adhesive joints. Such similarities can contribute in gaining insight into the phenomena present during shearing of a mucoadhesive film on mucus. The profile of the shear stress along an adhesive joint, for instance, indicates that there is a concentration of stresses near the edges, and particularly near the front and back part of the joint (Fig. 7(i)) [21,22]. It seems that the areas near the edges draw the zones of perturbed stresses and resist the delamination of the joint. The importance of the geometry has been further pointed out by other researchers who compared elliptical and rectangular

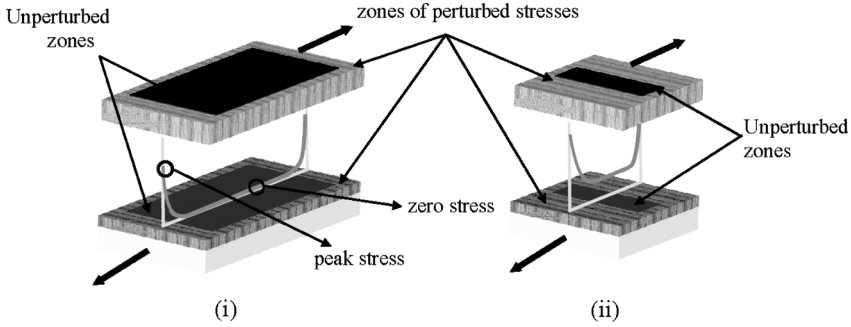


FIGURE 7 Zones and profile of perturbated stresses inside a (i) large joint, (ii) small joints [22].

geometries with the same size of overlap and found that shear strength in the first case can be up to eight times as high [23]. Similar to these examples, it is expected that the geometry of the film influences the friction and that the main stresses are indeed concentrated near the edges rather than inside the bond. The influence of the geometry on the friction deserves further investigation, since it not only enables friction manipulation by altering the device shape or surface geometry, but also because it can reveal shapes which generate high grip despite their small size, leading to a decrease in the overall size of the device.

The role of an adhesive joint size on the joint stress profile can help in recognizing the sizes of the mucoadhesive films which lead to optimal design solutions for the intestine inspection and intervention device. More precisely, researchers found that if the nominal size of an adhesive joint is high, the perturbed zones near the edges do not interact. In this case, it is thus possible that the shear stress inside the joint is zero and it is up to the borders to keep the joint from delamination (Fig. 7(i)) [22]. For smaller joints, however, the inside area contributes to the shear strength as well, while the peak stresses near the edges are often higher, the smaller the joint is (Fig. 7(ii)). Similar to these examples, it seems apparent that there is a critical size of area of the mucoadhesive film, at which the behaviour of the film changes. Narrowing down such a critical size might determine the turning point in which the presence of borders starts playing a more important role in the generated friction than the size of the area, thus offering useful information about the design criteria of device.

(Not)-Jumping Within Different Scales

When introducing adhesion-controlled friction on the macroscale, attention should be paid to possible scaling effects involved. A number of researchers have pointed out that friction coefficients on the nanoscale are much lower than those on the micro and macroscale [24]. This has to do with the fact that several parameters involved with friction are scale dependent, such as the roughness of the surfaces in contact, their average shear strength, and the adhesion contribution [25]. According to Maeda *et al*. [8], however, the reduced adhesion hysteresis and friction of crosslinked compared with uncrosslinked polymers at the molecular level are consistent with data about the friction of rubber at the macroscopic level. Those authors conclude that there is, therefore, every reason to expect that the phenomena observed at the molecular interface can be applicable to macroscopic

interfaces as well. Quantifying the involved scale effects, however, remains a challenge.

CONCLUSIONS

According to this paper, mucoadhesives ensure grip and manipulate the friction with the colonic surface, without needing to apply high normal forces. Since the colonic surface is soft and highly deformable, friction is expected to depend on the size of the area in contact. In order to exploit this property and be able to manipulate friction on the macroscale, we should first scale up the generated static friction so that the effect of altering the size of the area will lead to considerable differences on the generated forces. This can be achieved by means of mucoadhesive films. Our experiments show that mucoadhesive films on the colonic surface appear to generate macroscopic adhesion-controlled and load-independent friction within a range in which friction is usually load-controlled. In this way, the use of mucoadhesive films on the colonic surface can lead to high grip and friction manipulation without applying high normal forces.

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