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Silane surface modification for improved bioadhesion of esophageal stents

Mert Karakoy¹, Evin Gultepe¹, Shivendra Pandey¹, Mouen A. Khashab², and David H. Gracias^{1,*}

¹Department of Chemical and Biomolecular Engineering, The Johns Hopkins University, Baltimore, MD, USA

²Division of Gastroenterology and Hepatology, Department of Medicine, The Johns Hopkins University, Baltimore, MD, USA

Abstract

Stent migration occurs in 10-40% of patients who undergo placement of esophageal stents, with higher migration rates seen in those treated for benign esophageal disorders. This remains a major drawback of esophageal stent therapy. In this paper, we propose a new surface modification method to increase the adhesion between self-expandable metallic stents (SEMS) and tissue while preserving their removability. Taking advantage of the well-known affinity between epoxide and amine terminated silane coupling agents with amine and carboxyl groups that are abundant in proteins and related molecules in the human body; we modified the surfaces of silicone coated esophageal SEMS with these adhesive self-assembled monolayers (SAMs). We utilized vapor phase silanization to modify the surfaces of different substrates including PDMS strips and SEMS, and measured the force required to slide these substrates on a tissue piece. Our results suggest that surface modification of esophageal SEMS via covalent attachment of protein-binding coupling agents improves adhesion to tissue and could offer a solution to reduce SEMS migration while preserving their removability.

Keywords

Self-assembled monolayer; coating; proteins; gastrointestinal; pull-force

1. Introduction

Cancer of the esophagus is one of the most lethal cancers, which has a cure rate less than 50% and a five year survival rate of only 5-10% [1]. Chemoradiation, laser ablation therapy, brachytherapy and argon beam coagulation therapy with self-expanding stents have been widely used for palliative treatment of esophageal cancer [2,3]. Due to the advances in

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*Address correspondence to: dgracias@jhu.edu.

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minimally invasive medicine and the developments in interventional endoscopy, the use of stents for either treatment or alleviation of strictures in the gastrointestinal (GI) tract including the esophagus has become more prevalent [4]. There are a variety of commercially available self-expandable metal stents (SEMS) designed for different portions of the GI tract. These stents have different physical characteristics such as dimensions, material composition, expansion properties and are deployed using varied delivery methods depending on their manufacturer and the intended GI organ.

While endoluminal stenting is a common procedure, stent migration occurs in upto 40% of the patients, especially in those who are treated for benign disorders, such as benign strictures, leaks and fistulae; migration is a major drawback in esophageal stent therapy [5-10]. One of the main reasons that the migration rate is higher in benign disorders is that therapies for these conditions utilize removable SEMS. In contrast when SEMS composed of pure nitinol, which is a flexible shape memory metal alloy of nickel and titanium, are utilized, these stents expand, eventually embed into tissue and migrate less often. However, these uncoated SEMS have a higher risk of tumor ingrowth and they become nonremovable which makes them unsuitable for the treatment of benign disorders [11]. In an attempt to keep SEMS removable, they are partially or fully coated with silicone, which results in decreased ingrowth, but increases the possibility of stent migration [12]. It is possible to address this problem by introducing surface roughness which partially resolves both migration and ingrowth problems, but it also creates challenges in the retrieval of the stent [13-15].

In this paper, we investigated the possibility of increasing the adhesion strength of the SEMS to the surrounding tissue while preserving their removability by modifying the stent surface with self-assembled monolayers (SAMs). SAMs offer unique opportunities for surface modification of biomedical implants and are particularly attractive due to their commercial availability, ease of modification and tunability of head- and tail-groups, consequently altering the surface properties. SAMs of alkylalkoxysilanes spontaneously form on the surface of hydroxyl terminated silicone surfaces by chemisorption [16]. The activation of these silane coupling agents through hydrolysis is the driving force behind the silane-SAM formation. Specifically, reactive siloxane groups undergo condensation with water and with surface silanol groups ($-\text{SiOH}$) and neighboring siloxanes to form a cross-linked polysiloxane ($-\text{Si-O}-$)_n network. The cross-linking of such organic molecules through head-groups onto a substrate from either liquid or vapor phase is followed by a slow organization of tail-groups [17,18]. This phenomenon, the slow packing of the monolayer, is attributed to polysiloxane cross-linking and the van der Waal interactions between hydrocarbon chains.

Our hypothesis is that modifying the surface of the silicone covered esophageal SEMS with silane coupling agents would improve adhesion of the SEMS to the surrounding tissue and thereby reduce its migration. Silane coupling is a well-known phenomenon that is based on a reversible hydrolytic bond mechanism between silane and a substrate with a stress relaxation capacity [19,20]. Under stress, the bonds between the silane and substrate break, allowing the system to slip across the substrate plane to reform bonds at new sites in the presence of

water. The reversible hydrolytic bond mechanism, i.e. spontaneously reforming the broken bonds, prevents any loss of adhesion in silane coupling [21,22].

For the initial experiments, we used polydimethylsiloxane (PDMS) strips to mimic the silicone coated stent surface and reduce the use of expensive commercial stents. We focused on silane coupling agents with epoxide and amine tail-groups, (3-Glycidyloxypropyl)trimethoxysilane (GPTMS) and (3-Aminopropyl)triethoxysilane (APTES) respectively, due to their affinity for amine- and carboxyl groups which are abundant in body [23-26]. Figure 1 shows the chemical structures of these silanes and the SAM formation on a silicone surface.

We developed a silanization technique which is applicable to silicone coated esophageal SEMS. After confirming the functionalization success using X-ray photoelectron spectroscopy (XPS), we tested the effect of the silane-SAM formation on the strength of the adhesion in *ex vivo* experiments. Importantly, we also measured the strength of adhesion with and without mucin gel to simulate adhesion in the presence of the mucus lining in the GI tract.

2. Materials and methods

2.1 Preparation of PDMS substrates

PDMS elastomer kit (Sylgard[®] 184; Dow Corning) was used to prepare PDMS substrates by vigorous mixing of 10:1 (w/w) ratio of the base polymer to the curing agent for 5 minutes. This mixture was then degassed under 700 mmHg vacuum for 35 min to remove all embedded bubbles. Once the bubbles were completely removed, the prepolymer mixture was pipetted into Fischer Scientific 47 mm petri dishes, which served as the mold, and the prepolymer was subsequently cured at 65 °C for 4 h in a gravity convection oven (Thermolyne[®]; Product #Z111007; Sigma-Aldrich).

2.2 Preparation of mucus gel

Mucin from porcine stomach (Type II) was purchased from Sigma-Aldrich (Product #M2378; Sigma-Aldrich). A 2% (w/w) mucin gel was prepared in PBS (Product #10010023; Life Technologies) to simulate the mucin content in the GI tract. The solution was placed on a stir plate at 550 RPM at room temperature for 45 min to ensure good, homogenous mixing. No heat was added to the system during gel preparation and a fresh batch of gel was made for each experiment to avoid protein aggregation and changes in protein conformation.

2.3 Surface modification protocols

PDMS substrates and the SEMS (Evolution, Cook Medical, Winston Salem, NC and Wallflex, Boston Scientific, Natick, MA) were exposed to an 18 W (at High setting) air plasma (Product #PDC-32G; Harrick Plasma) for 30 s after pumping down for four minutes in order to reach a background pressure of 200 mTorr. This low power plasma oxidation converts surface methyl groups to hydroxyl groups [27]. Post-activation, substrates were jetted with nitrogen gas and placed in a desiccator for vapor-phase silane deposition.

Control samples of both PDMS and SEMS were removed and the rest of the samples were silanized as follows. Silanes, APTES (99%) and GPTMS (98%) (Product #440140 and #440167; Sigma-Aldrich), were purchased and used without further purification. The substrates were positioned in the desiccator and a tiny droplet (0.1 mL) of the silane of choice was injected onto a petri dish via a 1 mL syringe. Silicone grease was applied to all the connection points to ensure good sealing and the chamber was degassed for 3.5 min under 700 mmHg vacuum. At the end of the 3.5 min, the vacuum valve was shut and the substrates were exposed to silane-vapor for 1 h. The chamber was then pumped down once again for another 3.5 min, followed by an additional hour of exposure. Since silane mono layers do not possess long term stability [28,29], once the functionalization was complete, samples were jetted with nitrogen gas and sealed with Parafilm under an inert atmosphere to preserve the quality of the SAM.

2.4 XPS measurements

XPS analysis was performed using an X-ray photoelectron spectrometer (Model 5400; PHI XPS System). Each measurement was made over 10 sweeps with a non-monochromatized Mg K_α radiation source (1253.6 eV, 15 kV, 300 W). The binding energies were referenced to O (1s) at 532.0 eV [30]. The emission angle of electrons was set at 45° with respect to the sample normal.

2.5 Force measurements

The measurement of bioadhesive force between the stents and tissue represents a challenge due to the relative roughness of the interfaces, presence of mucus, stent pattern and the heterogeneity of tissue. We developed an approach to measure the bioadhesion using a force meter to measure the lateral pull-off force which represents the important criterion for testing lateral migration of the stent. We used the approach with flat samples and stents while measuring the influence of the presence of mucus using a simulated mucin gel.

2.5.1 Adhesion of surface modified PDMS samples on PDMS substrates—

Functionalized PDMS surfaces were removed from the petri dishes by cutting out a disk with a scalpel. The disks were then cut into half-disks and 4 μL of 2% (w/w) mucus gel was dropped on the bottom half-disk for the samples; control samples without the mucus gel were also studied. While pairing the half-disks, 0.5 cm was left skewed from each other to allow the attachment of force meters. Once the disks were paired and placed in a petri dish, a uniform weight of 32.2±0.2 g was placed on each pair to ensure good contact between the surfaces. Samples were then left out at room temperature to crosslink overnight. Upon collection, samples were carefully placed on a double sticky tape. A force meter was attached to the top half-disk and was pulled until it migrated. The amount of force required to displace the sample or the lateral pull-off force was recorded as the adhesive force. Figure 2 shows the schematic representation of our experimental procedure. The force meter was calibrated so that it agreed with the weighing scale measurements within a 3% error margin. A minimum of four samples in each group were measured. It is important to mention that the force meter had to be oriented parallel to the bottom disk during force measurements in order to reduce angular errors in the adhesion measurement.

2.5.2 Bioadhesion of surface modified SEMS on tissue—The SEMS were cut in two in order to fit them in the desiccator chamber. Then their surfaces were modified using the same protocols as the PDMS samples, described previously. The esophagus pieces were cut open and their muscle layer was removed to eliminate the non-uniform stress in tissue samples before they were soaked in 2% mucus gel. Each stent piece was wrapped in a piece of esophagus in such a way that the tip of the stent was left open so that it could be connected with the force meter without disturbing the setup. The samples were kept at 10°C overnight. The shape of the SEMS did not allow a stable or uniform weight distribution, so to avoid non-uniformity in measurements no external weight was used. The force required to move the stent inside the tissue was measured as explained previously. The force meter was calibrated so that it agreed with the weighing scale measurements within a 1% error margin. We measured a minimum of three samples in each group.

3. Results

We used two samples from each batch of functionalized PDMS samples for the XPS study. Figure 3 shows the structural changes due to SAM formation on the surface of PDMS. Both PDMS and the silane coupling agents are comprised of Si, C, and O; but the primary amine at the tail APTES introduces the N (1s) peak, which is therefore unique to the functionalized substrates. The binding energy of the N (1s) peak at 398.63 eV in Figure 3(A) is in agreement with the literature value assigned to N (1s), which is 398.65 eV [31].

On the other hand, both PDMS and GPTMS are comprised of Si, C, O, and lack N so the XPS spectra looked very similar. However, when the spectra for unmodified and modified samples were overlaid, we observed differences in the intensity of the O (1s) region [Fig. 3(B)] since the introduction of epoxide functional groups directly translates into a dramatic increase in the oxygen concentration of the surface. From these spectra, we determined the oxygen concentrations for pristine PDMS and GPTMS treated samples as 29.7% and 51.3%, respectively.

Following the confirmation of the SAM formation on the PDMS surface, we proceeded with the quantification of the adhesive force. We observed a statistically significant increase in the adhesive force, by over a factor of two, for silane modified samples as compared to controls, and this adhesive force increased further in the presence of mucus gel as compared to non-mucinated samples (Fig. 4), confirming enhanced affinity of the silanes to the proteins in the gel and consequently enhanced bioadhesion.

We also tested commercial silicone covered esophageal SEMS to measure the effect of surface functionalization. The surface treated SEMS also required significantly higher force to move on the tissue surface, 60% and 70% higher for GPTMS and APTES silanization respectively, compared to non-functionalized SEMS (Fig. 5). During the *ex vivo* experiments, we observed no tissue damage during the removal of the stents, proving that the enhanced adhesion due to the silanization is in fact reversible and the stents are removable. We note that although the standard deviation is high on measurements with real tissue samples, which we attribute to the heterogeneity of tissue, our results are statistically significant as depicted by the p-values.

4. Discussion

The goal of this study was to investigate a new approach for stent surface modification in order to improve tissue attachment of the stents. The advantage of surface functionalization with SAMs is that there are a large number of commercially available SAMs that can be tailored to increase affinity to specific molecules in bodily fluids such as mucus as well as epithelial layers in the mucosa. Additionally, this kind of surface modification can be done post-processing of the stent with relative ease in a small number of steps using vapor phase processes that reduce contamination. This approach should be contrasted with other surface modification methods such as polymer grafting, polymer blending or the inclusion of additives [32], which can change the bulk mechanical properties or cause toxicity concerns. On the other hand, the biocompatibility of silane treatment has been reported in several biomedical applications such as in development of novel dental composites used as fillers [33], orthopedic fixators [34], bone substitutes [35], metallic microdevices [36], thromboresistant coatings for medical devices [37], and silanized nanoparticles for tumors [38].

To realize our goal, it was necessary to choose a cross-linking agent with affinity to both the stent and the tissue surface. We chose GPTMS and APTES because their functional groups are known for binding proteins. APTES, for instance, is known for binding mucin proteins, building blocks of the mucus gel, to immobilize them on mica surface for AFM measurements [26]. Surface modification with APTES produces an amine group on the surface which creates covalent coupling with proteins [39]. On the other hand, the epoxy ring in GPTMS, can form either an amine-epoxy bond with the proteins under physiological conditions [24,25], or it can react with carboxylic acid in proteins resulting with bioconjugation [23].

The driving force for the surface functionalization is the activation of the silane coupling agent. This activation is achieved by hydrolysis of the alkoxy groups. Hence, the presence of surface hydroxyl groups is crucial for the ordered formation of the silane-SAM. There are various ways of hydroxylation; the most popular and frequently used methods include air/oxygen plasma treatment, application of piranha solution or strong base, or ultra violet (UV) exposure [27,40,41]. A popular protocol utilizes organics such as piranha solutions to remove unbound and adsorbed surface contaminants before surface activation and after silane treatment. However, organic treatments can deform the silicone coating of the stents, and these could also contaminate the stent. In this study, we demonstrated that we can successfully functionalize the silicone surface and introduce silanes with epoxide and primary amine tail groups without the use of organics or water by utilizing an air plasma treatment and vapor silanization which involves no contact with solvents or other liquids.

We used PDMS samples to initially test the hypothesis before proceeding with either tissue or commercially coated stents. We chose PDMS as a substitute due to its similar chemical structure to silicone, low cost, and conformal contact with various substrates. Moreover, as compared to the silicone coatings on commercial stents, many of which include proprietary compounds, Sylgard PDMS is well characterized in the literature and thus represents a model silicone surface. PDMS is also extensively used for surface functionalization through

formation of silane based self-assembled monolayers (SAMs) for a variety of biological applications [42]. In Figure 3, we used plasma treated PDMS disks with mucus gel sandwiched in between as the control. No experiments were conducted for plasma treated PDMS without mucus gel since it is already well established that upon contact these oxidized PDMS surfaces irreversibly bond with each other [43]. We tested both silanes in the presence and absence of mucus gel in order to be able to differentiate between the resulting adhesive forces. It is apparent in Figure 3 that there is a significant increase in the adhesive force for the functionalized PDMS disks (with and without mucus gel) when compared to the controls.

The lining of the GI tract is constantly coated with a mucus gel layer, varying up to ~ 100 μm to 800 μm in thickness *in vivo* [44]. This gel coating keeps the tissue surface lubricated and wet, and it is essential to simulate the same condition when we investigate the surface interactions. Although we tried to minimize the time between procurement of the tissue pieces and our experiments, there was still approximately a day lag between the death of the animal and our *ex vivo* experiments. Since the drying of the esophagus pieces during this waiting time poses a potentially significant challenge, we re-hydrated the tissue pieces with 2% mucin gel prior to the experiments. We chose a two hours hydration time in mucin gel after experimentation and observing that the tissue pieces were still wet and slimy at the end of the experiments.

We note that although vapor phase silanization is not new, to our knowledge this is the first time that it has been applied to silicone coated SEMS and further optimization may be possible for even higher bioadhesion with more reactive groups and / or optimized processing conditions. Also, the SEMS we used in this study were deployed prior to surface modification. This was done so that we could access the stents from within the package to be able to silanize them. Prior deployment of the SEMS significantly lowered the radial force they applied to the tissue but it should be noted that we prepared the SEMS in the control group in the same way as the silanized ones which allowed for a valid comparison between the forces required to migrate both groups. Because the SEMS were pre-deployed and the esophagus pieces were not as tightly compressed as would likely occur under *in vivo* condition, the absolute values of the pull-forces are likely to be different under *in vivo* conditions, but we expect the trends to hold and bioadhesion could increase after compression of the SEMS with the tissue. Further studies are needed to incorporate silanization protocols prior to packaging of the SEMS.

5. Conclusions

In this paper, we presented a new method to increase the adhesion strength of SEMS on tissue surfaces and consequently reduce the risk of stent migration. We verified that it is possible to create silane-SAMs on stent surfaces by functionalization to their silicone coating. The force comparison experiments showed significantly increased reversible surface adhesion between the modified SEMS and esophagus surface compared to non-modified ones. It may be possible to further increase the adhesion force by optimizing the silanization procedure during the fabrication of the SEMS. Due to the similarity in the epithelium structure and the consistent presence of mucus gel in the GI tract, we can apply

the results obtained in this paper to the SEMS designated for other parts of the GI tract while further studies are needed to assess long term applicability of this approach *in vivo*.

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Abbreviations

APTES	(3-Aminopropyl)triethoxysilane
GI	gastrointestinal
GPTMS	(3-Glycidyloxypropyl)trimethoxysilane
SAMs	self-assembled monolayers
SEMS	self-expandable metallic stents
PDMS	Polydimethylsiloxane
XPS	X-ray photoelectron spectroscopy

Highlights

- Convenient vapor silanization methodology to reduce migration of stents
- Approach to measure bioadhesion of gastrointestinal stents
- Surface coating for improving bioadhesion of implants

Figure 1. Schematic of the molecular structure of the two silanes utilized and the formation of SAMs at an oxidized silicone interface

Chemical structures of (A) APTES and (B) GPTMS. (C) Schematic representation of the APTES SAM formation on a PDMS surface.

Figure 2. Schematic of the experimental protocol used for silanization and force measurements (A) The surface of the samples (PDMS disks or stents) were cleaned using an air plasma. (B) The samples were placed in a desiccator along with a droplet of a silane for SAM formation. (C) The surface of the samples was wet with mucus gel to simulate the *in vivo* environment in contact with the stent. (D) The surface modified samples was placed on top of the substrates (PDMS disks or tissue) and incubated for 24 h. (E) After incubation, the lateral pull-off force required to slide two surfaces over each other, i.e. to break the bond, was measured with a force meter.

Figure 3. XPS spectra of PDMS compared to APTES and GPTMS treated PDMS
 (A) Pristine PDMS compared to PDMS treated with APTES. The red circle highlights the N (1s) peak at 398.63 eV, specific to APTES. (B) Pristine PDMS compared to PDMS treated with GPTMS; the inset shows the O (1s) peak, circled with red in the full spectrum, which is referenced to literature value of 532.0 eV [30].

Figure 4. Results of adhesive force measurements of surface modified PDMS samples in contact with PDMS strips

Silanized samples express higher bonding strength, more than 100% higher, with the presence of mucin; * represents p-value of 0.05 while ** represents p-value of 0.01.

Figure 5. Bioadhesion of surface modified SEMs on esophagus samples

(A) The experimental setup where a piece of esophagus is wrapped around a stent. The arrow represents the direction of the pulling force. (B) Silanized samples express significantly higher bonding strength; more than 60% and 70% for GPTMS and APTES respectively; * represents p-value of 0.05 while ** represents p-value of 0.03.