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Biodegradable Polymer Blend Based Surgical Sealant with Body Temperature Mediated Adhesion

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Supporting Information

Supporting Information including cell viability studies, videos corresponding to Figure 2C, Figure 2D, and videos of the burst pressure studies is available from the Wiley Online Library or from the authors.

Surgical care suffers from a lack of materials that enable patient specific intervention. Despite technical limitations, conventional suturing and tissue stapling remain the standard method of surgical tissue closure and sealing.^[1] The development of practical, efficient, and patient specific surgical sealants has the potential to enhance surgical competency and reduce the incidence of complications.

Clinically available surgical sealants include fibrin, glutaraldehyde, cyanoacrylate, and poly(ethylene glycol) (PEG) hydrogel based materials. All of the available formulations have significant limitations with regard to adhesive quality and/or method of application. Fibrin glues are high in cost, complex to prepare, and carry the risk of disease transmission.^[2] Glutaraldehyde-protein sealants are relatively low in cost, but suffer from toxicity issues that restrict their ultimate clinical potential.^[3] Cyanoacrylate glues induce significant inflammatory responses, are rigid, and have been associated with tissue toxicity, limiting the majority of their use to external applications.^[4] PEG hydrogel based sealants achieve adhesion with end group succinimidyl glutarate functionalization that covalently reacts with tissue.^[5] Even though they are not cytotoxic and do not involve the risk of disease transmission, they require multi-step preparations before application and can undergo excessive swelling after use that can cause tissue injury of the involved or neighboring anatomic structures.^[6] These shortcomings have encouraged the investigation of new approaches for the application and development of safe and effective surgical sealants.

Many current approaches utilize biomimetic strategies to promote tissue adhesion. This is accomplished through the use of reactive chemistries, components, or features found in a variety of aquatic animals^[7] and reptiles.^[8] Aquatic animals rely on adhesive chemistries to adhere to wet surfaces. For instance, marine mussels use a catechol containing post-translationally modified amino acid to covalently bind to amines and thiols under oxidative conditions.^[9] This functionalization has been investigated for use in surgical sealants in the form *in situ* forming hydrogels^[10] and coacervates.^[11] Sealants have also been designed to maximize interfacial adhesion by mimicking the high aspect ratio topographical features of gecko feet.^[8, 12] These micro- and nano-patterned surfaces have been used in combination with wet adhesive chemistries to improve utility in a surgically relevant environment.^[13]

An important consideration in the development of surgical sealants is the ease of use. Many approaches rely on a mixing and/or an initiation step that leads to a gelation or crosslinking event. Failure to optimize parameters such as cure time or solution viscosity can lead to poor performance due to clogging of the application device or inadequate sealant coverage. Shear-thinning hydrogels circumvent many of these problems by taking advantage of dynamic self-assembly.^[14] UV-curable sealants have also garnered wide interest.^[15] A rapidly curing hydrophobic light-activated adhesive based on poly(glycerol sebacate acrylate) recently demonstrated efficacy in cardiac procedures.^[16] Another promising strategy is the use of pre-formed polymer nanosheets.^[17] The nanometer-scale thickness of these films results in polymer-substrate interactions that promote adhesion. While promising, many of the aforementioned approaches are geometrically restricted by the limited coverage of the sealant material or the application device.

Here we report a body temperature activated surgical sealant that utilizes the thermal behavior of a biodegradable polymer blend to promote adhesion. The polymer blend is deposited with an airbrush using a technique called solution blow spinning.^[18] This method allows for a polymer fiber mat to be directly and rapidly fabricated onto any anatomical region of interest.^[19] After warming to a critical temperature ($\sim 31^\circ\text{C}$), the fiber mat consisting of a poly(lactic-co-glycolic acid) (PLGA)/PEG blend undergoes a fiber mat to film transition. During this transition, the sealant increases in adhesive strength and becomes transparent. While variations of PLGA and PEG have been incorporated into degradable sutures,^[20] surgical constructs,^[21] and hemostatic dressings,^[22] they only function as a structural component in these applications and do not typically take an active role in tissue adhesion on their own.

Solution blow spinning was utilized for polymer fiber deposition. Rapidly coating non-uniform surfaces with polymer fiber mats has been previously demonstrated with this technique in non-medical^[23] and medical applications,^[24] including deposition *in situ*.^[19] The ability to deposit polymer fiber mats directly onto the tissue of interest circumvents the limitations associated with pre-fabricating sealant materials without knowledge of specific procedural or anatomical details. Additionally, since the material reaches the tissue surface as a solid, there is no activation or gelation step. Fiber formation is accomplished when a combination of solution and deposition requirements are met. The major considerations are solution concentration with respect to polymer chain entanglement and solvent. Fibers will not be formed if the solution concentration is below the polymer chain overlap condition.^[25] More dilute solutions will result in the deposition of materials with corpuscular or beads on a string morphologies.

Polymer fiber mats were deposited from solutions containing 10%(wt/v) PLGA and 0–5% (wt/v) PEG dissolved in acetone, herein referred to by the PEG composition. These polymers are commonly investigated for a wide variety of biomedical applications such as drug delivery^[26] and tissue engineering.^[27] This broad usage can be attributed to their biocompatibility and bioabsorbability.^[28] A commercially available airbrush connected to a compressed CO_2 source was used as the solution blow spinning apparatus in all cases without modification (Figure 1). Higher PEG content led to increased fiber diameter, ranging from $0.57 \pm 0.03 \mu\text{m}$ for the 0%(wt/v) PEG solution to $2.42 \pm 0.15 \mu\text{m}$ for the 5%(wt/v) PEG solution (Figure 1F). The change in fiber morphology is potentially a factor of multiple variables including solvent evaporation rate, total polymer concentration, and solution viscosity.^[29]

When deposited onto a warm substrate (over $\approx 31^\circ\text{C}$), the polymer fiber mats with higher PEG content (3%(wt/v) and 5%(wt/v)) undergo a melting transition between 31°C and 32°C (Figure 2A). This is in agreement with the melting temperature of the crystalline domains of PEG alone. This melting event occurs at a temperature that is below both topical and internal body temperatures. Similar thermal behavior in polymer blends has been previously exploited to create porous tissue engineering scaffolds^[30] and injectable cell delivery systems.^[31] Upon reaching the crystal melting temperature the fibers weld together and PLGA and PEG become miscible, creating a homogenous, transparent polymer film (Figure 2C,D). This opaque to translucent transition, as observed on the palm of a hand

(Figure 2E), results in a decrease in sample thickness from $160 \pm 30 \mu\text{m}$ to $90 \pm 10 \mu\text{m}$ after heating to 37°C for a $500 \mu\text{L}$ sample. During film formation the polymer blend homogenizes and displays a single glass transition temperature (T_g) ($T_g = -18.1^\circ\text{C}$ for 5% (wt/v) PEG). This softening transition results in increased polymer-substrate interaction at the application temperature (between room and body temperature), as depicted in Figure 2G, and is characterized by a decrease in elastic modulus from $2.21 \pm 0.29 \text{ MPa}$ to $0.03 \pm 0.01 \text{ MPa}$ after heating to 37°C (Figure S3). After the initial melting event the recrystallization of PEG is suppressed in all cases except for the pure PEG sample (Figure 2B).

Correspondingly, adhesive strength drastically increases for the high PEG content blends after incubation at 37°C because of the homogenization. 3% (wt/v) and 5% (wt/v) PEG blends reached adhesive pull-off strengths of $6.1 \pm 1.2 \text{ N/cm}^2$ and $11.6 \pm 0.9 \text{ N/cm}^2$, respectively (Figure 2F). This is in contrast to the adhesive strength of PLGA alone at either room temperature ($0.2 \pm 0.1 \text{ N/cm}^2$) or 37°C ($0.4 \pm 0.1 \text{ N/cm}^2$) and to the same blends at room temperature ($2.2 \pm 0.5 \text{ N/cm}^2$ for 3% and $1.4 \pm 0.1 \text{ N/cm}^2$ for 5%). PEG alone was also deposited and tested but resulted in no measurable adhesive pull-off strength. PEG at the tested molecular weight and concentration is unable to form fibers and rapidly dissolves under aqueous or *in vivo* conditions (Figure S1). When used in a blend with PLGA, PEG persists for at least 30 days *in vitro* and the blend remains homogenized over this timeframe without drastically influencing the *in vitro* degradation profile of PLGA (Figure S4).

A cecal intestinal anastomosis mouse model was used to assess the clinical potential of this polymer blend and deposition method. Intestinal anastomosis can be technically complex and suffers from significant morbidity and mortality when complications of leakage occur.^[32] A high-risk model was adapted from other groups^[33] in which the use of a sub-clinical number of sutures leads to a high incidence of mortality. The solution blow spun PLGA/PEG sealant (5% (wt/v) PEG) was used to supplement the sutures (Figure 3A–C). Performance was compared to a suture-only control and to sutures supplemented with a commercially available fibrin glue or PEG hydrogel sealant. In an initial study, burst pressure at the site of anastomosis was measured at 24 hours (Figure 3D). The PEG/PLGA sealant supplemented sutures were exceptionally resistant to leakage, with burst pressure reaching $71.4 \pm 11.3 \text{ mmHg}$. The intestine completely fills with fluid, and significantly distends before any minor leakage occurs (Figure 3E,H). This is in contrast to the other 3 groups tested in which significantly lower burst pressures were measured. These substantial differences in leakage are visually observable in videos of the burst pressure experiment (Supporting Information).

The same cecal intestinal anastomosis model was used in a 7-day survival study (Figure 3I). As mentioned previously, the less than adequate sub-clinical number of sutures used in this model resulted in a high incidence of anastomotic leakage. This cecal leakage is reflected in the suture-only control having a 50% ($n = 10$) mortality rate over the 7-day time period, with all deaths occurring before day 3. The sutures supplemented with the PEG hydrogel sealant saw a similar mortality rate at 60% ($n = 10$). One additional mouse from the PEG hydrogel group survived the 7 days but failed to thrive due to abscess formation as identified during necropsy. The use of either the solution blow spun PLGA/PEG sealant or the fibrin glue resulted in only a 10% mortality rate ($n = 10$), representing a 40% improvement over the suture-only control. The combination of the adhesive pull-off strength, the *in vivo* burst

pressure, and survival rate are representative of the ultimate clinical potential of this technique and material. Histological observation of the intestine for animals surviving to day 7 showed normal physiology of the serosa and mucosa with no evidence of an elevated inflammatory response relative to the 4-suture control (Figure 3F,G). This is in agreement with *in vitro* assays that showed only moderate differences in cell viability at 24 hours (Figure S5).

In summary, we have developed a body temperature responsive surgical sealant that is easily applied with a process that allows for targeted conformal polymeric material deposition directly onto the tissue of interest during open surgery. Further investigation of this technique is focused on adapting the apparatus design for use in minimally invasive surgery. The surgical sealant was comprised of a polymer blend composed simply of PLGA and PEG. The sealant transitioned from a fiber mat to film by taking advantage of the thermal behaviors of the polymer blend. This transition resulted in increased polymer substrate interaction that promoted adhesion. When utilized in a high-risk intestinal anastomosis model, the PLGA/PEG sealant was able to significantly improve the burst pressure and survival rate in comparison to the suture only control.

Experimental Section

Polymer Deposition

A commercially available airbrush (Master Airbrush G22-SET, 0.2 mm nozzle diameter) was used to deposit all polymer fiber mats. The airbrush was connected to a compressed CO₂ tank equipped with a regulator through a gas flow meter. Polymer solutions were composed of 10%(wt/v) PLGA (IV=0.86 dL/g in hexafluoroisopropanol, 50:50, Lactel) in combination with 0–5%(wt/v) PEG (M_n= 950–1050 g/mol, Sigma Aldrich) in acetone.

Morphology Characterization

Fiber mat samples were prepared by solution blow spinning 50 or 500 µL of polymer blend solutions onto 1 inch cover slips. For scanning electron microscopy (SEM), samples were sputter coated with gold before imaging (SEM, JEOL JSM-6390LV). Nanofiber diameter was measured using ImageJ (National Institutes of Health). Average fiber diameter and distribution were determined from 100 random measurements from 3 SEM micrographs. For optical microscopy, each sample was placed on a Mettler FP82HT hot stage controlled by a Mettler FP90 Central Processor and heated from room temperature to 37 °C at a rate of 1 °C per minute. For thickness measurements, 500 µL of the 10%(wt/v) PLGA 5%(wt/v) PEG polymer blend was deposited onto a glass slide via solution blow spinning and measured before and after incubation at 37 °C (n = 3).

Differential Scanning Calorimetry

Approximately 10 mg samples of fiber mats were sealed in aluminum hermetic pans (TA Instruments) using a sample encapsulation press. DSC measurements were made on a TA Instruments DSC Q100. Samples were held isothermal at –50 °C for 5 minutes and then heated and cooled from –50 °C to 80 °C to –50 °C, at a rate of 3 °C per minute, ± 0.20 °C amplitude, with a modulation period of 60 seconds for two continuous cycles.

Adhesion Testing

Pull-off strength measurements were made with an Instron E3000 mechanical tester equipped with an environmental chamber, using an experimental design adopted from Lang et al.^[16] 1 mL samples were deposited onto the face of a 1 square-inch custom machined aluminum stand by solution blow spinning. The samples were then incubated for 10 minutes in compression with another 1 square inch aluminum face at either room temperature or 37 °C before testing. The crosshead speed was set to 5 mm per minute for all samples. Each sample type was replicated 5 times (n = 5).

Cecal Intestinal Anastomosis Survival and Burst Pressure Studies

All animal experiments and care were approved by the Institutional Animal Care and Use Committee (IACUC) of Children's National Medical Center on October 30th 2014 and were in accordance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (National Institutes of Health publication 85-23, revised 1996). 16-week old C57BL6/J mice were anesthetized using 100 mg/kg ketamine and 10 mg/kg xylazine. A mini-laparotomy incision was made, and the cecum was exposed. The cecum was transected, leaving the mesenteric sidewall intact in order to preserve the blood supply. The cecum was then re-anastomosed using 4 interrupted 7-0 vicryl sutures. 40 anastomoses were performed on 40 mice with 10 mice in each of 4 groups (n = 10). The groups included a control group that underwent the sutured anastomosis without any additional sealant and 3 experimental groups that underwent the sutured anastomosis and received additional sealant. One group was supplemented with the solution blow spun 5% (wt/v) PEG blend, sprayed directly on the suture site. The two remaining groups were supplemented with applications of Coseal (PEG hydrogel, Baxter International Inc.) or Tisseel (Fibrin glue, Baxter International Inc.). The commercial sealants were prepared and applied to the anastomoses in accordance to the product insert directions. Following a set time of 2 minutes for all groups, the bowel was placed into the abdomen and the skin was closed using 4-0 vicryl suture in a running fashion. All surgeries were performed by one surgeon who was blinded to the treatment groups. Surgical Loupes were used for magnification in all cases.

Each animal was weighed preoperatively, and weights were taken every other day until day of sacrifice. Animals were allowed to survive for 7 days and were sacrificed after necropsy and harvest of the anastomosed bowel segment. Animals were monitored daily and were sacrificed prior to 7 days if they showed signs of extreme distress due to sepsis. Necropsy was performed to determine the cause of sepsis or death. The anastomosed bowel segment was harvested, inspected, and rinsed in phosphate buffered saline, fixed in 4% paraformaldehyde and embedded in paraffin blocks. After 10 µm sections were made, hematoxylin and eosin (H&E) staining was performed.

In the anastomotic burst pressure study, separate mice underwent the same procedure outlined above (n = 4–6). These mice were allowed to survive for one day, at which time they were re-anesthetized. After performing an exploratory laparotomy, the anastomotic segment was identified, and burst pressures were determined. A digital pressure monitor was attached to a three-way stopcock, allowing for a saline solution containing 0.05% (wt/v)

methylene blue to be infused through the third port. After clamping the small bowel at the ileocecal junction, an angiocatheter with tubing attached to the three-way stopcock was placed distal to the anastomosis in a water-tight fashion. Burst pressure was measured as the highest pressure reached prior to leakage of methylene blue solution from the site of anastomosis.

Statistical Analysis

Data is expressed as mean $\pm$ standard error. Where appropriate, statistics were performed using SAS Version 9.3 (SAS Institute). ANOVA single factor analysis with Tukey's test for multiple comparisons was used. Relevant statistical relationships are reported on the figures and $p < 0.05$ is considered significant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. SEM images of solution blow spun PLGA/PEG blends showing changes in fiber mat morphology with increasing PEG content. (A) 0% (wt/v), (B) 1% (wt/v), (C) 3% (wt/v), and (D) 5% (wt/v) PEG blend. Scale bars represent 20 μm. (E) Nozzle of commercial airbrush while solution blow spinning the 5% (wt/v) PEG blend. (F) Average fiber diameter corresponding to polymer blend content. Fiber diameter increases with increasing PEG content. Error bars represent standard error (n = 100). Statistical significance amongst all groups is denoted by (*).

Figure 2.

Differential scanning calorimetry (DSC) of the first heating cycle (A) and second heating cycle (B), exothermic up. During the first cycle, high PEG content blends exhibit melting transitions. The second cycle shows the suppression of recrystallization as well as homogenization of the PLGA/PEG blends as evidenced by a single T_g . Optical micrograph of (C) 5% (wt/v) PEG solution blow spun sample showing fibrous morphology at room temperature and (D) after heating to 37 °C showing film morphology. Scale bars represent 100 μm and 25 μm in the inset. (E) Shows the transition from the opaque as deposited fiber mat (left) to a translucent film (right) on the palm of a hand. (F) Adhesive pull-off strength of various PLGA/PEG compositions demonstrating the influence of PEG content and temperature on adhesive strength. Error bars represent standard error ($n = 5$). Statistical significance amongst all groups is denoted by (*). Statistical significant amongst the same temperature set is denoted by (†). (G) Schematic of fiber mat to film transition resulting in increased polymer-substrate interaction.

Figure 3.

(A) Image of the 4-suture cecal anastomosis. A sub-clinical number of sutures was utilized to increase the incidence of complication. (B) Image of the blow spun PLGA/PEG sealant being deposited onto the sutured anastomosis. Intestine highlighted by black circle. (C) Image showing the thermal transition of the PLGA/PEG sealant after 2 minutes. (D) Burst pressure experimental set up. An angiocatheter was used to supply fluid and was attached to a pressure monitor. The black arrow indicates the site of anastomosis. (E) Image of the PLGA/PEG supplemented anastomosis, showing resistance to burst. Methylene blue solution was injected into the intestinal lumen to help identify the leakage. (F, G) Hematoxylin and Eosin staining of the cecum at 7 days post procedure. Both the 4-suture control (F) and the PLGA/PEG sealant (G) show normal physiology and no evidence of an elevated inflammatory response. The white arrow indicates the serosa and the black arrow indicates the mucosa. Scale bars represent 100 μm . (H) Burst Pressure study at 24 hours. Error bars represent standard error ($n = 4-6$). Statistical significance amongst all groups is denoted by (*). (I) 7-day cecal anastomosis survival study ($n = 10$).