PEG Hydrogel Coating of Medical Devices

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Abstract

It has been proposed to examine and optimize a procedure for applying hydrogels to material surfaces. The ultimate goal for this project is to be able to coat a urinary catheter with a hydrogel in order to limit the infections that often result from long term catheter use. Polyethylene glycol (PEG) based hydrogels were used to do this and the characteristics of adhesion and thickness were mainly focused on. The PEG hydrogel was tested on multiple materials with unique surface chemistries in order to learn about the interactions between the reaction's photoinitiator, actual hydrogel, and substrates. Experimental results reveal that the hydrogels formed were of non-uniform thicknesses ranging from zero to sixty microns. Also, the adherence of the hydrogels to the substrates was very poor. We hope some future changes in the hydrogel formation procedure will resolve the problems of non-uniform thickness and lack of adhesion. Before applying the hydrogel to a urinary catheter, the non-fouling properties of the hydrogel will also be tested.

Problem Statement

Our objective is to form a Polyethylene glycol based hydrogel microlayer on material surfaces in order to examine and improve upon their characteristics and biocompatibility. When referring to biocompatibility, we are mainly focusing on the hydrogel's non-fouling capabilities; meaning that no unwanted protein adhesion or interactions form when the hydrogel is placed in a physiological environment (1). The characteristics of greatest importance to the client, Arthur J. Coury, Vice President of Biomaterials Research at Genzyme Corp., are adhesion strength, biocompatibility, and a useable thickness. Adjustments to the existing Genzyme application process will be made in order to optimize these characteristics.

Motivation

The ultimate goal for this project is to coat a urinary catheter with a microlayer of PEG hydrogel that is approximately fifty microns thick, has very strong adherence, and is biologically inert with surface resistance to protein adhesion. We chose to coat this medical product because of the materials it is made out of, the current problems associated with its use, and the possible benefits of a PEG coating that are possible for a catheter.

Urinary catheters are tube systems that are used to drain and collect urine from the bladder. They are often used when people have difficulty urinating on their own, have urinary incontinence, or urinary retention problems. There are several problems associated with long term catheter use. Urinary tract infection, kidney infection, blood infections, urethra damage, and blood in the urine are complications that can result from

continuous catheter use (2). These problems often happen because proteins adsorb on to the catheter surface and the Vroman effect ensues. This effect describes sequential sorption of proteins from a mixture, one on top of another over time. Protein desorption is unlikely, being thermodynamically and energetically unfavorable (3). These proteins build up and crystallize around the catheter, causing obstruction, blockage, backflow, and bacteria buildup (4). Since PEG is biologically inert, it should not interact with proteins of the body. By coating a catheter with this hydrogel we hope to eliminate the problems associated with protein crystallization and the subsequent infections that follow.

Catheters are commonly made out of latex, silicon, polyvinyl chloride, and Teflon (2). Figure 1 shows pictures of multiple catheters including a straight catheter and a foley balloon catheter.

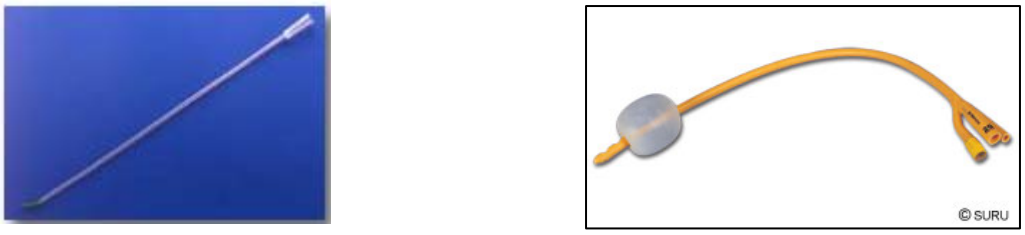

Figure 1: Left, a straight catheter, right, a Foley balloon catheter (12,13)

These materials work out well because latex and PVC are easily accessible resources that we can use for testing. PVC was obtained from blood bags donated by the American Red Cross. Latex will be obtained from non-powdered latex gloves. A common problem with catheters is that patients have an allergic reaction to latex catheters, which will hopefully be eliminated with a PEG coating. Catheters are currently coated with silver nitrates, antibiotics, and other materials in an effort to prevent infections and increase the catheter's operational time in vivo. A study done on a variety

of silver alloys and oxides showed that the antimicrobial property of silver reduced the number of infections, but only from 14% (uncoated treatment), to 12% (silver coated treatment) (5). Also, the study mentioned that silver coated catheters are seven dollars more expensive than the uncoated version. The current coatings seem to limit infections, but we have not discovered any PEG coated catheters and hope to find that this hydrogel greatly improves infection resistance without greatly increasing cost.

Client Requirements

Dr. Coury would mainly like us to deliver a detailed procedure for applying a hydrogel to a material with the desired thickness and adherence. The client would like a uniform microlayer between 25 and 100 microns. The adhesion strength should be as high as possible, meaning strong force can be applied with a metal spatula and most of the hydrogel will remain adhered to the material. An illustrative example of this would be trying to remove the sticky label off a plastic soda bottle and not being able to get it all off. The client would also eventually like us to expose the hydrogels to physiologically imitated environments. In an effort to do this, we created all solutions at a pH of 7.35, which is the pH of the human body. We plan to expose the hydrogels to bovine albumin, which would show the interaction between the hydrogels and the most abundant protein in blood, accounting for roughly 60% of the plasma proteins (6).

Hydrogels

A Hydrogel is formed by networking polymer chains, commonly through crosslinking. The chains are water-soluble, and have remarkable absorption properties. In

some gels, over 99% of the weight is composed of water. Because of this water content, hydrogels maintain a great deal of flexibility, which mimics natural tissue. Common uses for hydrogels include contact lenses, disposable diapers, breast implants and medical electrodes (7).

Polyethylene Glycol

Polyethylene glycol is a commercially important polymer used in a wide variety of biological situations due to its non-toxic properties. It has the chemical formula $C_{2n}H_{4n+2}O_{n+1}$ and its structure is clearly seen in Figure 2.

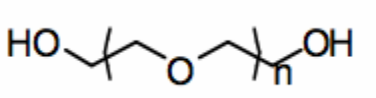

Figure 2: Polyethylene glycol's monomer (9).

In water, the polymer forms a helical structure and is repulsive of charged molecules. Due to its excellent biocompatibility it is used in many materials in vivo, including drug delivery matrices, food additives, wound dressings, and soft tissue replacement. PEG's ability to absorb water when crosslinked is responsible for it's application in slow dosing medications.

Substrate Materials

Several materials were used to test the hydrogel coating process. Each of the materials has distinct properties that make them applicable to biomaterials. The surface

properties were most heavily concentrated on since the surface properties of the materials would have the greatest effect on the adhesion of eosin Y and consequently on the hydrogel coating.

Poly vinyl chloride (PVC) is a polymer that has very hydrophobic surface properties and tends to be very biologically inert. A monomer unit of PVC is shown in Figure 3.

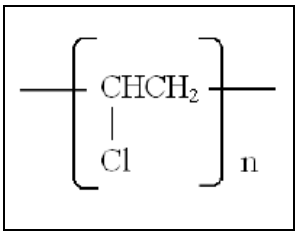

Figure 3: PVC monomer unit (16).

PVC's biologically inert property makes it a great candidate for a negative control when looking at non-fouling. We can test PVC both with and without the hydrogel coating. If it is found that protein adhesion increases when the hydrogel coating is applied, then it can be assumed that the hydrogel is not having the desired effect. In biomedical applications, PVC is used to make a variety of tubing. PVC is used in tubing for dialysis, blood transfusion, and feeding. It is also used to make blood bags. As stated previously, the source of PVC used in trials was obtained from expired blood bags.

Another material used as a substrate for coating was the polymer polystyrene. A monomer unit of polystyrene is shown in Figure 4.

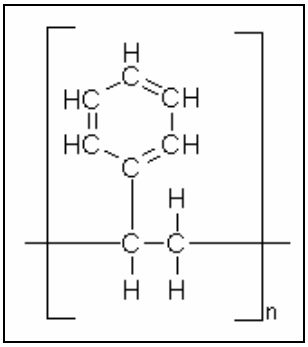

Figure 4: Polystyrene monomer unit (17).

Polystyrene also has a hydrophobic surface; however, polar groups can be added to introduce ionic or dipole-dipole interactions. Polystyrene is used to make Petri dishes and tissue culture wells, thus providing a good material for testing cell adhesion. The polystyrene that was used in the coating trials were pieces of Petri dishes available in the lab.

Glass was also used as a substrate for hydrogel coatings. Glass has a hydrophilic and negatively charged surface which offered good contrast to the other two hydrophobic surfaces. Glass is used in chemical ware, tissue culture flasks, and also for optics in endoscopy. The glass used for the coating trials was obtained from standard microscopy slides.

Procedure

To create a microlayer of PEG based hydrogel on the surface of the substrate (interfacial polymerization) a thin layer of the photoinitiator must be adhered onto the surface of the material to be coated. The photoinitiator used in this experiment was eosin Y, which has an orange-pink color and is used widely as a stain for cytoplasm, collagen and muscle fibers (8). Eosin Y absorbs light in the visible region, with a maximum absorption at 514 nm. When excited by the energy at this wavelength, eosin Y will become a radical and is able to propagate a reaction by free-radical propagation. In the reaction used in this experiment, eosin Y will create a radical in another compound known as triethanolamine (TEOA) as shown in Figure 5.

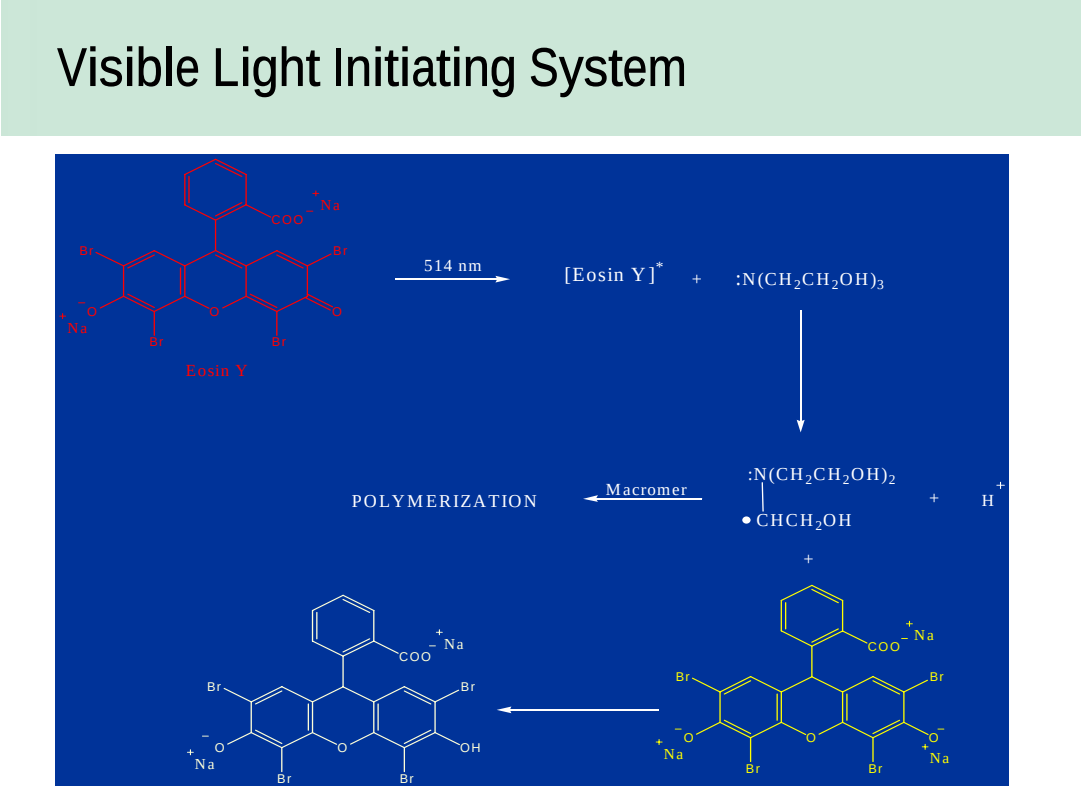

Figure 5: Diagram of chemistry involved in light initiating reaction (10).

This compound will continue the reaction by interacting with the polymer to be crosslinked, PEG. Once the crosslinking has occurred, a complex web of polymer exists that is capable of enormous water absorption and retention.

To create this reaction we created three solutions: an eosin Y stain, 10x buffer, and a PEG macromer solution. The Eosin Y stain was created using 50 mg of Eosin Y dissolved in 1 liter of phosphate buffered saline (PBS) solution. This creates a solution that is 50 ppm eosin Y.

The 10x buffer solution was made by dissolving 5.35g of TEOA and 5.1g of potassium phosphate into 50ml of distilled water. This solution's pH was then altered using 2N hydrochloric acid to create a pH of 7.35.

Our final solution contained the PEG macromer. This solution contained the following compounds:

Materials (5 mL Batch)	Weight (g)
3.35KL5A2	1.500
Distilled Water	2.970
10X Buffer	0.50 mL
Vinylcaprolactam	0.025
Fructose	0.005
Fe-Sulfate	0.00025
Total	5.0

Figure 6: Reagents and amounts used in PEG macromer solution (10).

Commonly this formula was increased 4-fold; this made the Fe-Sulfate much easier to weigh accurately and also increased our solution yield so that more experiments could be administered.

Our substrates, which included polystyrene (PS), polyvinylchloride, and glass, were immersed and left to equilibrate in the eosin Y solution for times ranging from two hours to one week. This was done to allow the eosin Y to come out of solution and stain the material, hopefully forming a thin layer of eosin Y on the material. This will allow the polymerization to propagate only near the surface of the substrate and thus form a thin layer of gel adhered to the substrate.

Next, our substrates were rinsed using a distilled water spray. The rinses were varied from no rinse, light rinse, heavy rinse, and a bath. Light rinsing involved sraying each side of the material with water for two seconds repeated two times, and then repeating for a total of three rinses one each side of the substrate. Heavy rinsing involved the same procedure, but was repeated five times. The bath had the substrate immersed into a distilled water bath and moved back and forth, thus maximizing the vigor of the rinse.

After the rinsing stage, the stained specimens were placed into the macromer bath, where a xenon light source of 514 nm was applied for 40 seconds. The light source causes the reaction previously stated to initiate and forms the crosslinked polymer on the surface of our substrate. After the light was administered, the substrate was left in the macromer bath for an additional 10 seconds to allow the reaction to proceed to completion. It was then moved into cell culture well filled with PBS to equilibrate before viewing and testing.

To measure the thickness we compared the gel on the substrate to six micron polystyrene beads while viewing under an optical microscope at 40X magnification. The widths of the beads were verified under a powerful and accurate microscope as shown in Figure 7.

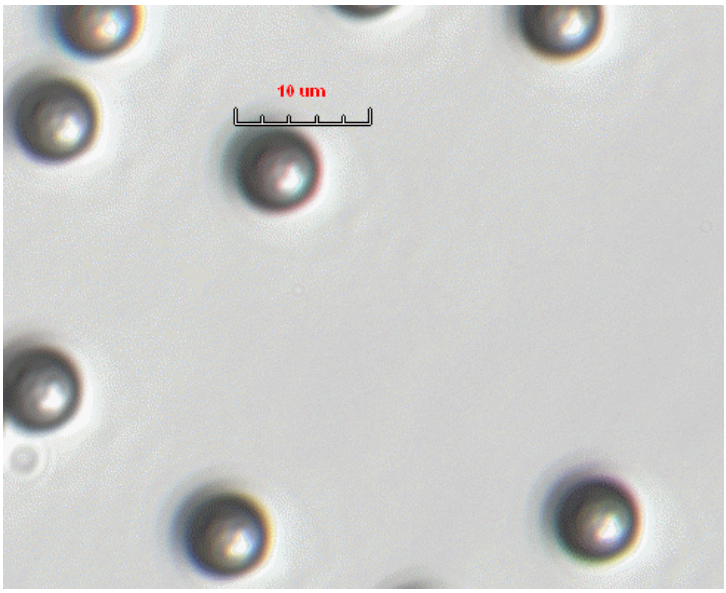

Figure 7: Image of polystyrene beads with generated scale to verify diameter of six microns.

While under magnification the gel was scraped with a tweezers to measure the adherence of the gel to the substrate. The adherence scores were administered based on this table:

- 0 = Has fallen off
- 1 = Lifts off almost intact with mild force
- 2 = Lifts off in large chunks with some force
- 3 = Lifts off in small pieces with some force
- 4 = Does not delaminate even by destroying gel with pushing force

We had the same person observe and examine the adherence each trial in order to eliminate errors in results stemming from multiple subjective opinions of the adherence

scale. Figure 8 shows the hydrogel formed around a piece of PVC. The clear structure that looks somewhat like a bubble is the PEG hydrogel.

Figure 8: Hydrogel formation around a piece of PVC.

Results and Discussion

After testing the hydrogel coated materials it was found that the hydrogel adhered poorly to all the substrates. This can be explained by the non-existent adhesion of eosin Y. It is shown in Figure 8 that the more the substrate was rinsed with distilled water after the eosin Y bath, the thinner the resulting hydrogel layer was.

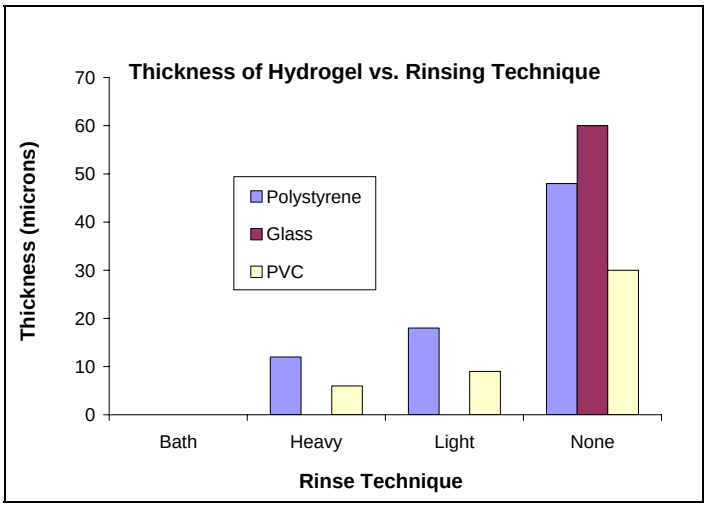

Figure 8: Thickness of Hydrogel vs. Rinsing Technique.

This result supports our conclusion that the eosin Y is not sufficiently adhering to the substrates and is easily rinsed away by water.

One of the reasons that eosin Y may not be adhering well to the PVC and polystyrene surfaces is that they are hydrophobic surfaces and hence they do not interact well with water. The eosin Y is water soluble and the solution of eosin y used in the trials was in a water solution, thus the eosin Y remained in the water and did not adhere to the substrates.

In addition to not adhering to the hydrophobic surfaces of polystyrene and PVC, Eosin Y also did not adhere to glass even though glass has a hydrophilic surface. The reason for this is that along with the hydrophilic surface of glass, glass also has a negatively charged surface. Eosin Y is an acidic molecule that has two acidic groups, a carboxylic acid group and a hydroxyl group. The pKa's of these groups respectively is 3.25 and 3.80 (11). With the eosin y solution prepared in a pH buffered solution at 7.35 to mimic homeostatic conditions, the eosin Y molecules would be deprotonated giving

the eosin Y molecules negative charges. These negative charges are repelled by the negative charges on the glass surface. The pH of the eosin Y solution could be lowered to remove the negative charge; however, doing so would remove the solution form the homeostatic range. To try to get the eosin Y to adhere to the substrates, we allowed the samples to soak in eosin Y for various amounts of time ranging from two hours to one week. As shown in Figure 9, it was found that the time in eosin y had no effect on the thickness of the hydrogel layer.

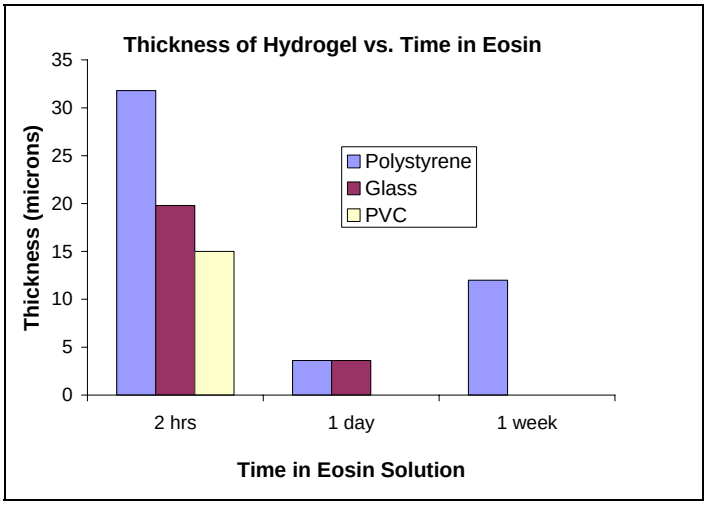

Figure 9: Thickness of Hydrogel vs. Time in Eosin Y.

Again, this supports the conclusion that the eosin does not adhere well to the substrate for reasons mentioned earlier.

The few coatings that were formed were, at best, 60 microns thick. Although this is in the range of desired thickness of 25-100 microns a handful of coatings were fewer than 25 microns making them too thin for practical use. These coatings, however, did not adhere well to the surfaces for reasons mentioned above. Also, many of these coatings turned out to be of non-uniform thickness. This can also be explained by the poor

adhesion of eosin Y to the substrates. When the eosin Y coated substrate is in the macromer solution undergoing photopolymerization, the eosin Y diffuses away from the substrate and causes a non-uniform layer of hydrogel. This diffusion of eosin Y away from the surface is due to the poor adherence of eosin Y to the substrate surfaces.

Our highest priority is to develop techniques to get the eosin Y to adhere to the substrate surfaces.

Ethical Considerations

When designing any implantable device certain ethical considerations must be taken into account. Because the device could be in direct contact with human blood and fluids, the final product must be tested and re-tested multiple times to ensure that the product is safe for use in vivo. Ultimately, for this product to be considered safe it must not break or degrade when implanted, as this could cause adverse reactions in the patient. Rigorous testing of protein interaction in solutions and in blood must be administered, along with testing of the adherence and breakdown of the gel. Here we can see the importance of thorough testing before clinical trials even begins so that we can ensure patient safety.

Even if the final product passes all testing and moves on to be implanted in human subjects, it cannot be ignored and neglected. No material implanted in the human body can be considered 100% safe, and our final product should be examined and documented while in use to ensure that any malfunction is properly noted. Efficient and well designed reporting mechanisms will help to track the product while helping to avoid any unwanted misfortune and will ultimately lead to a better and safer product.

Furthermore, as with any product that holds the potential to alleviate a patient's suffering, it is important to understand the balance between ensuring timely development while guaranteeing safety. For our team it will be necessary to identify and take into account any added risk that can result from introducing a hydrogel coated urinary catheter in vivo.

Future Work

As a result of our work this semester we have gained new insight into and knowledge about forming a PEG Hydrogel microlayer to coat a urinary catheter. After working with the flat substrates of PVC, polystyrene, and glass it became apparent that we needed to modify the staining procedure. Eosin stains are successfully used for staining biologic materials such as red blood cells but we will continue to use them with the goal of staining latex and PVC. We will focus on latex and PVC as substrates because they are directly applicable to our ultimate motivation of coating urinary catheters.

Currently, after attempting to stain the substrate surface, the eosin Y molecules are both washing off of the substrate and diffusing into solution. After examining the experimental results we conclude that our first approach to ensure sufficient staining of the substrate surface will be to increase the concentration of eosin Y in the eosin Y solution. After contacting our client with the staining issue, we decided to begin by increasing the concentration of eosin Y in solution by a factor of four to 200ppm. We make this modification with the goal of getting at least some eosin molecules to bond to the surface. This, however, does not change the fact that eosin Y is a hydrophilic

substance (14) and thus diffuses into solution when added to the macromer. To prevent diffusion of the stain molecules from the substrate surface into solution we will pursue the use of ethyl eosin as a stain (15). Ethyl eosin is more hydrophobic than the eosin Y stain we are currently using. We expect a more hydrophobic stain to be an improvement from eosin Y. A more hydrophobic stain will have less affinity to diffuse into solution and we expect it to stain the surface to a greater extent than the eosin Y solution. By having a greater amount of eosin bonded to the surface of the substrate and less eosin diffusing into solution we are closer to our goal of forming a hydrogel that better adheres to the surface of the substrate.

Furthermore, we will have to increase our light application time to at least 160 seconds. Our client suggested using four consecutive forty second light treatments and we will use this suggestion as a baseline when we begin using the ethyl eosin staining solution. While working in the laboratory we can experimentally vary the length of light treatment to better determine the optimal light application time.

At this time we will continue to test adhesion of the hydrogel, as well as, the thickness of the microlayer. In the event that we do not have acceptable experimental results for the adhesion of the hydrogel we will then have to continue to modify the staining procedure and possibly our macromer solution. Once we achieve acceptable adhesion testing results we can then begin to test the biocompatibility of the hydrogel.

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Product Design Specification

Hydrogels for Coating Medical Devices

October 5, 2006

Team Members:

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Patrick Schenk	Communications
Darshin Patel	BWIG
Brett Mulawka	BSAC

Purpose:

To form PEG macromer-based hydrogels on biomaterial surfaces in an interfacial photopolymerization process and to screen the coatings for interactions with cells and media that mimic physiologic fluids. It is hypothesized that these coatings will resist fouling and may be useful for implantable devices.

Approach:

The biomaterial specimen is stained with an Eosin solution, which is the first component of a 2-part photoinitiator system. The stained specimen is immersed in a macromer solution containing component 2 (triethanolamine) of the photoinitiator system and ferrous and vinyl caprolactam promoters. Visible light energy is applied to the aqueous solution. At the intersection of the stain, the macromer and the light on the surface, an adherent, thin, self-limiting hydrogel forms by polymerization of the macromer. The coated specimen is exposed to cells in culture and ionic (calcium-rich) media to

determine if the cells attach to the coating, and spread relative to controls. Resistance to such fouling is indicative of utility in applications such as catheters, sensors, etc.

Client Requirements:

- Detailed process for applying a hydrogel to surfaces.
- Testing of thickness of hydrogel coatings using a subjective adherence rating system.
- Testing of fouling resistance of hydrogels in various physiologically imitated environments.
- Testing adherence of hydrogels to different materials.
- Resolve logistics of performing experiments.

Design Requirements:

1) Physical and Operational Characteristics

    a. *Performance Requirements:* Testing processes must have universal applications, standardized procedures, and consistent data collection.
    b. *Safety:* The PEG being tested must be non fouling and not negatively affect a physiological environment in any other way. Also, during the creation and application of the hydrogels the team needs to be conscious of the chemicals they are working with and take necessary precautions.

c. *Accuracy and Reliability:* Although some data will be subjectively collected, the same team member will be judging results to ensure consistency.
d. *Life in Service:* Unresolved. The hydrogels will need varying service lives based on where and how they are used.
e. *Shelf Life:* All hydrogel reagents have specific needs as far as temperature during storage. The hydrogel will not be stored once the desired testing of it is complete.
f. *Operating Environment:* The hydrogel could potentially operate in urine in the case of catheters. Possibly blood, or interstitial fluid as well.
g. *Ergonomics:* Not Applicable.
h. *Size:* The testing samples will either be one by one square centimeters or one by two square centimeters and between 25 and 100 microns in thickness.
i. *Weight:* Will be determined once the hydrogel tests samples have been produced.
j. *Materials:*
    i. Eosin Y
    ii. Phosphate Buffered Saline (PBS)
        1. NaCl
        2. Na2HPO4 Anydrous
        3. KH2PO4

4. Distilled Water

iii. Macromer Solution

1. Macromer – 3.35KA2 or 20KA2
2. 10X Buffer
    a. Triehanolamine (TEOA)
    b. Potassium Phosphate, Monobasic (K-Phos)
    c. Water for Injection (WFI)
    d. 2 N Hydrochloric Acid (HCl)
3. N-Vinylcaprolactam (VC)
4. WFI
5. Ferrous Sulfate Heptahydrate
6. D-Fructose

k. *Aesthetics, Appearance, and Finish:* No appearance requirements.

2) Production Characteristics

a. *Quantity*: One application process and multiple experiments with different materials.

b. *Target Product Cost:* No cost restrictions for testing.

3) Miscellaneous

a. *Standards and Specifications:* None

b. Customer: Genzyme Corporation

i. Arthur J. Coury, Ph.D. – Vice President, Biomaterials Research

c. Patient-related concerns: None at this point.

d.*Competition:* Abbott Labs, Amgen, Johnson & Johnson.