Absorbable Hydrodissection Fluid

Mid-Semester Report
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ABSTRACT

Radiofrequency (RF) and cryo-ablation are two minimally invasive techniques for the treatment of malignant tumors of the liver, lungs, and kidneys. Hydrodissection is used during ablation procedures to displace surrounding tissues from the targeted ablation site. Saline and 5% dextrose in water (D5W) are commonly used for this purpose, to provide a barrier from the extreme effects of the ablation procedure. Although adequate for protection, these fluids tend to migrate throughout the peritoneal cavity. Dr. Chris Brace, Dr. James Hinshaw, and Dr. Meghan Lubner proposed the development of a more viscous hydrodissection fluid to prevent fluid migration and barrier degradation. Three design alternatives were developed; the first a viscous poly(ethylene glycol) (PEG) solution contain PEG-6000 as an additive. Two hydrogels were proposed, a calcium ion cross-linked sodium alginate hydrogel and a thermoreversible poloxamer 407 hydrogel. A design matrix was developed to determine the best of the three alternatives. The five categories of evaluation were: biocompatibility, viscosity, cost of materials, ergonomics, and temperature range. The poloxamer 407 solution was most favorable for future development and will be pursued for the remainder of the semester. Poloxamer solutions were synthesized and it was found that as concentration increases, the gelation temperature increases. Further testing is to be conducted to find the concentration of a poloxamer solution which gels at 32^{o}C.

Table of Content

PROBLEM MOTIVATION

Hepatic cancer (cancer of the liver) is one of the deadliest diseases, over 500,000 new cases are estimated annually worldwide [1]. A readily accepted method for treatment is radio-frequency ablation (RF ablation) [2]. RF ablation is a common treatment option for this, and typically yields good results. Patient complications when using RF ablation vary in severity. Damage to the diaphragm may result in slight pain while breathing, while intestinal damage can result in death [3]. Hydrodissection fluids aim to limit complications that may result from the ablation procedure.

During thermal ablation procedures, the hydrodissection fluid is injected between target ablation site and any surrounding tissues. This fluid aims to create a suitable physical, thermal, and electrical barrier to protect these vulnerable tissues. Current liquids satisfy most of these requirements and have been relatively successful; however, they lack the necessary viscosity to prevent unintended migration, quick absorption, and barrier degradation. Because of this, a large amount of liquid is typically required for adequate protection. This can lead to post-procedural complications such as bloating, which must be minimized. Therefore, our clients, Dr. Chris Brace, Dr. James Hinshaw, and Dr. Meghan Lubner have proposed that we design and fabricate a fluid that retains all the acceptable qualities of 5% dextrose with water (D5W) while alleviating its faults.

BACKGROUND

Cancer treatments for tumors of the heart, lungs, liver, and kidneys include chemotherapy, radiation therapy, and surgical removal. Aside from this, many minimally invasive procedures have become increasingly accepted over the past 15 years. Six commonly used minimally invasive surgical procedures for treating malignant tumors include: RF ablation,

microwave ablation, laser ablation, cryoablation, ethanol ablation, and chemoembolization. Results of these procedures have surpassed those of chemo- and radiation therapy [4]. For the purposes of this project, we are only concerning ourselves with the RF ablation and cryoablation procedures.

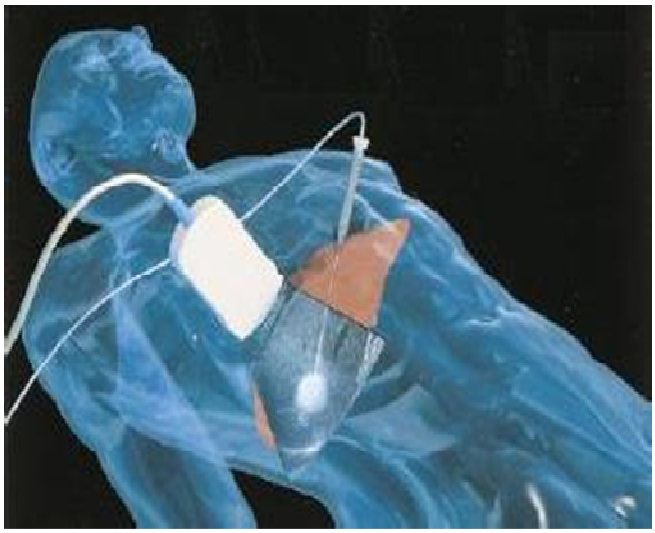

Figure 1 – RF ablation operational setup. A RF electrode is inserted into the tumor using imaging guidance. Image from [4].

Radio-frequency ablation is a relatively simple procedure. As seen in the setup shown in Figure 1, the RF ablation probe is inserted into the tumor. Radio-frequency AC electrical current is then applied through the electrode. This causes a temperature increase of the surrounding tissue which results in the ablation, or destruction, of the tumor. The three main methods of RF ablation are surgical, percutaneous, and laparoscopic. Using surgical methods is the most invasive, and involves opening up the patient for precise probe placement. General anesthesia is required for surgical RF ablation. In the laparoscopic method, an incision is made in the skin, through which a laparoscope is inserted. This device is then used to accurately place the RF electrodes.

Percutaneous RF ablation is the most common clinical method. This is similar to the laparoscopic method, except only the RF electrode is passed through the skin. A variety of different techniques may be used to accurately place the electrode, these include: ultrasound, computed tomography scan (CT scan), and magnetic resonance imaging (MRI) [5]. Only local

anesthesia is required for percutaneous and laparoscopic RF ablation; because of this, most RF ablations are outpatient procedures.

Cryoablation is the oldest of the thermal ablation techniques [6]. In comparison with RF ablation, cryoablation occurs on the other end of the temperature range and uses extremely cold temperatures to kill harmful tissue. Cryoablation can also be performed surgically, percutaneously, or laparoscopically; however, the inserted probe is a cryoprobe. Instead of just being a length of metal, a cryoprobe is a hollow tube that circulates cold fluid; this can be seen in Figure 2. An advantage of cryoablation over RF ablation is that multiple cryoprobes can work simultaneously to form differently shaped ice balls. These ice balls are easier to see using imaging equipment, and can therefore treat larger tumors than RF ablation can [4].

Cryoablation and RF ablation methods have yielded good patient results. Both have successful resection more than 85% of the time with complete ablation and no reoccurrence of tumors in 52-67% of patients [4]. Cryoablation generally offers better control to the doctor during the procedure, and has better overall tumor resection. None the less, RF ablation generally has fewer patient complications. Fewer than 5% of patients are seriously injured although ablation related deaths have been reported [4-5, 7].

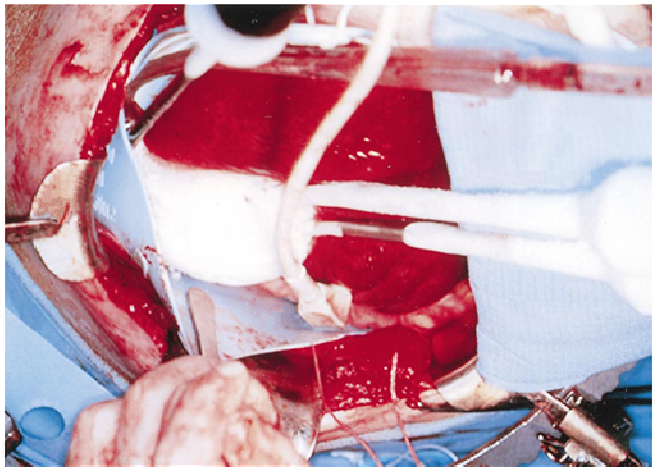

Figure 2 – An ice ball is formed during cryoablation to destroy harmful tissue. Image from [4].

CURRENT TECHNOLOGY

A crucial factor in the success of the operation and the survival of the patient is protection of the surrounding, non-cancerous tissue. Cryoablation and RF ablation do not inherently differentiate between healthy and unhealthy tissue; it is up to medical personnel to localize tissue damage to the tumors. To do this, a layer of protective fluid is injected into the patient around the target area in a process known as hydrodissection. This fluid layer dissects the target and surrounding tissue creating a barrier protecting surrounding tissue from the effects of the ablation procedure. There are three current fluids used for this: saline, D5W, and carbon dioxide (CO_2) [2].

Saline

Saline is sterilized salt water that is isotonic to body tissue (.91% NaCl) and is readily available for a variety of medical applications including: intravenous infusion, cleansing wounds, nasal irrigation, and treating dehydration. Saline is cheap and can be easily injected percutaneously to the site of ablation. Since saline is mostly water, it has a high specific heat and shields well from extreme temperature changes [8]. The intra-peritoneal pressure of the body cavity can push the non-viscous saline away from the target tissue; because of this, large amounts are often necessary to obtain adequate tissue dissection (~1cm) [9]. Lastly, saline is an ionic solution and therefore conducts electricity in RF ablation; this increases damage to surrounding tissue [2].

CO_2

CO_2 may be administered in two ways: via a gas-filled balloon, or via insufflation, injection of gas into the body cavity [10-11]. Unfortunately, both of these methods are more invasive than a saline or D5W injection. Also, CO_2 needs to be handled very carefully within the

body cavity since it could cause a fatal air embolism [10]. Gas can also be difficult to control within the peritoneal cavity. This results in the use of several gas bags or large amounts of CO_2 [2]. CO_2 is an efficient insulator; however, it blocks imaging, an effect that can be clearly seen in Figure 3.

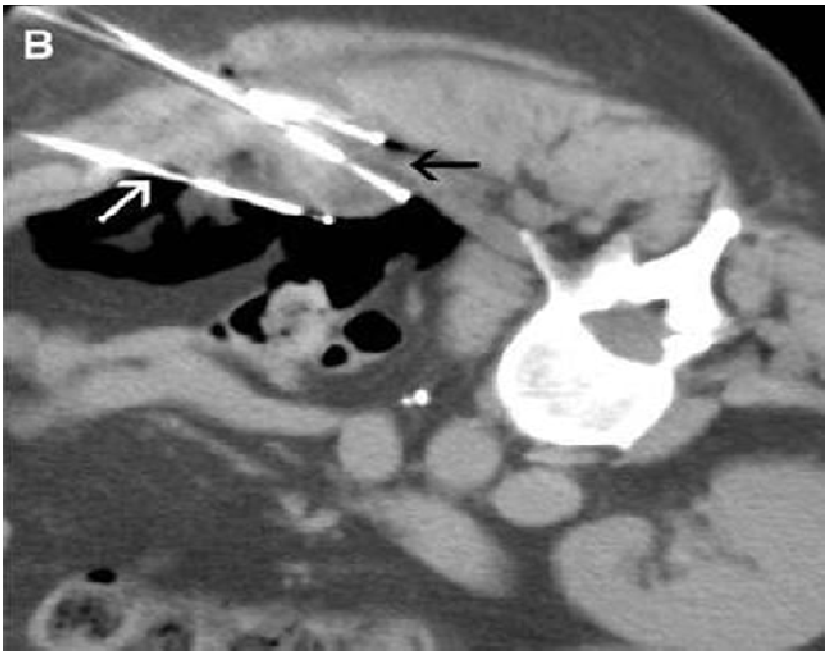

Figure 3 –The shows imaging problems of CO2 with CT scans. The white arrow points to the RF electrode and the black arrow points to a thermocouple. Image from [10].

5% Dextrose in Water (D5W)

The most commonly used hydrodissection fluid, D5W, is a sterilized isotonic solution of dextrose sugar water that is commonly used as IV fluid. It is both cheap and plentiful in the hospital environment and can be easily introduced to the target area by percutaneous injection. D5W is relatively non-invasive, though it suffers from many of the same setbacks as saline. Again, large volumes may be required to adequately protect tissue due to the low viscosity of the solution and the pressure of the body cavity. A 1 cm layer of D5W provides adequate protection for surrounding tissue [2]. The main advantage of D5W over saline is that it is not electrically

conductive. This reduces unwanted tissue damage by as much as 35% compared to saline. The effectiveness of D5W can be seen in Figure 4 [9].

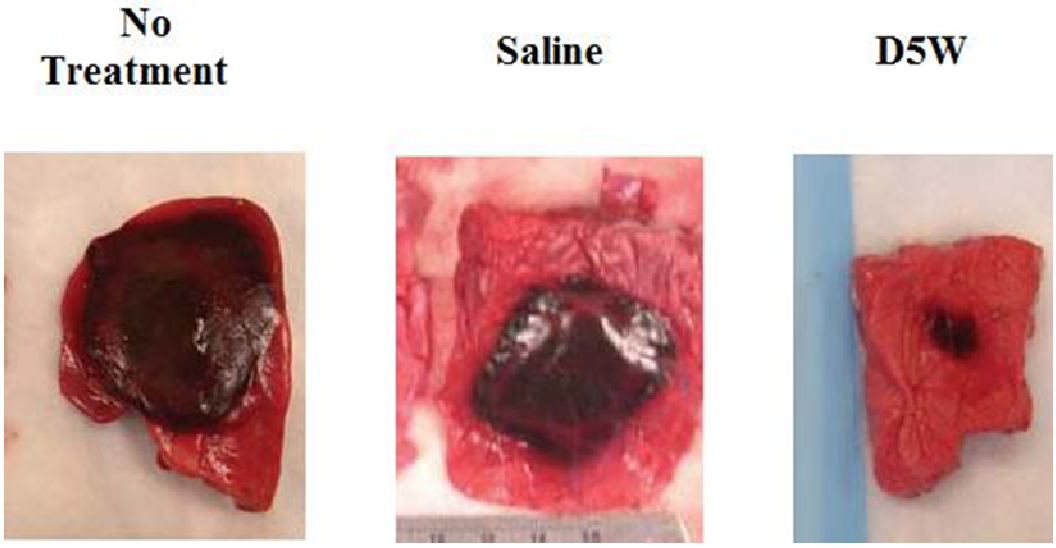

Figure 4 – Swine lung lesions resulting from RF ablation treatment. D5W localizes tissue damage most efficiently. Image from [9].

DESIGN REQUIREMENTS

The clients require that the new product be equal in favorable characteristics of D5W and saline, the two most commonly used hydrodissection fluids, while incorporating additional characteristics that are ideal for hydrodissection. This is also necessary for the product to be competitive on the market.

Since patient safety is of the utmost importance, the first necessary requirement is biocompatibility. The design is intended for use on human subjects and must meet the requirements of the FDA (Food and Drug Administration). The product is to be injected into the body cavity and should accurately function within the body's environmental thresholds. The fluid must be completely biodegradable or bioabsorbable and cause no immune response. During breakdown and absorption the product should be easily excreted from the human body. The final

design should optimize physician ease of use as well as patient safety and comfort both during and post treatment.

To effectively protect tissues adjacent to the target organ the product must be both a thermal and electrical insulator. During RF ablation, a current is applied directly to the target site, heating tissue to temperatures exceeding 60^{o}C. Because of the extreme temperatures involved, ineffective insulation surrounding the target organ could result in patient complications and tissue death. Because of this the product must be completely reliable and accurate.

The design must be ergonomically efficient for effective procedural use. To maintain a minimally invasive treatment, the product must be easily injectable through a 20 gauge needle for initial placement. Guidance of the ablation applicator is done through ultrasound imaging, CT scans, or MRIs. For this reason the product must be ultrasound transparent and easily distinguishable from surrounding tissue; the product should not inhibit imaging during the ablation procedure.

To outperform current methods of hydrodissection, the product must not migrate through the peritoneal cavity. Current methods sometimes require over a liter of fluid to achieve adequate tissue displacement. Once product placement has occurred the fluid should remain there until degradation or absorption is complete. The product must maintain at least a 1cm displacement of tissue throughout the ablation procedure.

The product is to be sterilized and packaged in single use, 250ml IV bags. The target cost of the product is less than 200 dollars. Saline and D5W are significantly cheaper than this; however, with less fluid volume needed for adequate protection, the product's benefits will outweigh the large cost increase. A complete list of product design specifications can be found in Appendix A.

Poly(ethylene glycol)

Poly(ethylene glycol) (PEG) consists of a long polymer chain made of repeated $–CH_2-CH_2O-$ units, see Figure 5 [12]. Polymers with different numbers of these repeated units have different molecular weights. High molecular weight polymers tend to be solid at room temperature while low molecular weight polymers tend to be liquid. PEG is FDA approved and it is considered a biologically inert substance [13].

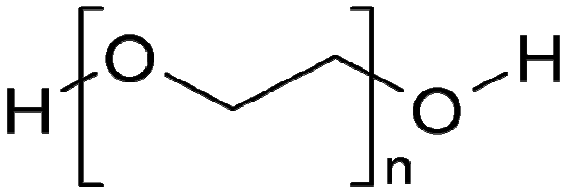

Figure 5 - PEG polymer structure, higher number of repeating *n* units results in a higher molecular weight. Image adapted from [12].

The higher molecular weight PEGs are used commercially and industrially as thickening agents in skin creams, lubricants, laxatives and toothpaste. A study was done at the University of Georgia in the 1970's to demonstrate the effectiveness of PEG as a thickening agent, see Figure 6 [14]. This study added PEG-6000 to water and the results showed a substantial increase in viscosity. In all temperature scenarios the increase in viscosity was directly attributed to an increase in the mass to volume ratio of PEG-6000 and water. So the incorporation of this polymer into a D5W solution would fix the migration and viscosity problems associated with D5W, while retaining all

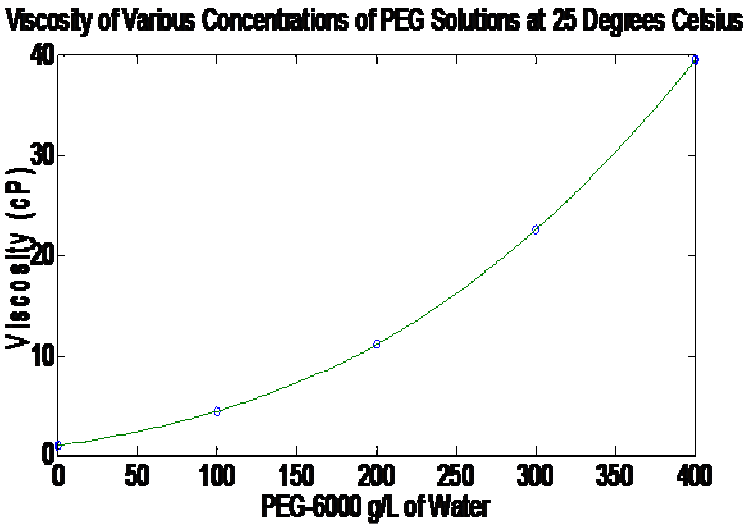

Figure 6 - Viscosity of various PEG-6000 solutions at 25°C. An increase in PEG resulted in a much higher viscosity. Image adapted from [14].

of its superior characteristics. This approach would also provide a substantially more stable barrier for protection while using less volume.

Sodium Alginate

Sodium alginate is a natural polymer that comes from seaweed. It is inert in the human body, and allows for natural degradation. Alginate hydrogel is commonly used as a scaffold for tissue growth, drug delivery vehicles, and wound dressings [15].

Sodium alginate solution forms a hydrogel when mixed with divalent cations. During gelation Ca^{2+} ionically cross-links the carboxylate groups of alginate. The gelation is instantaneous upon contact with a solution sufficient in calcium ions. A solution of 1% alginate can be gelled with a 0.1M solution of $CaCl_2$ [16]. After forming a gel, the hydrogel is sufficiently viscous to deter migration into the body cavity. After an ablation procedure, the hydrogel will degrade naturally over time. Degradation rates for sodium alginate hydrogels vary based on the concentration of sodium alginate. Typical alginate hydrogels degrade uncontrollably, leaving many large strands which are hard for the body to breakdown. To counter this uncontrollable degradation, partially oxidized alginate can be used. Partially oxidized alginate is made when a solution of alginate is mixed with sodium periodate and is then precipitated using ethyl alcohol [16]. As seen in figure 7, partially oxidized alginate hydrogel degrades in approximately a week, whereas the typical alginate hydrogel takes over a

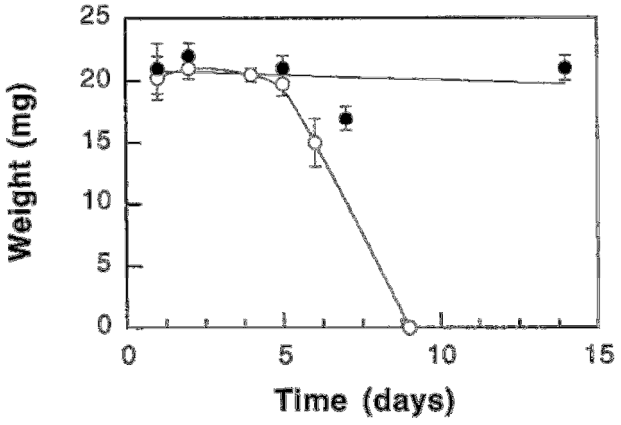

Figure 7 - Change of dry weight of partially oxidized (white dots) and alginate (black dots) as a function of degradation time. Image from [15].

month to fully degrade. Also influencing this rate is the molecular weight of the hydrogel; larger weights take longer to degrade [16].

Despite the definite benefits of alginate hydrogels, there are a few potential problems with its widespread use. Due to the ionic nature of the cross-linking, the gel may create an electric current in the body during RF ablation. Additionally, injecting the alginate could be problematic. Either the alginate gel will require two injections, one for each the alginate and calcium ion solution, or a slow gelling process will need to be attempted. One such process involves $CaSO_4$ powder mixed into the alginate solution. The powder slowly releases Ca ions to form the gel [15]. A third possibility is having one needle but three syringes as seen in Figure 8. The first injection is $CaCl_2$, followed by an injection of D5W to clear calcium ions out of the needle. Finally, the injection of sodium alginate will cause the gel to form in the body.

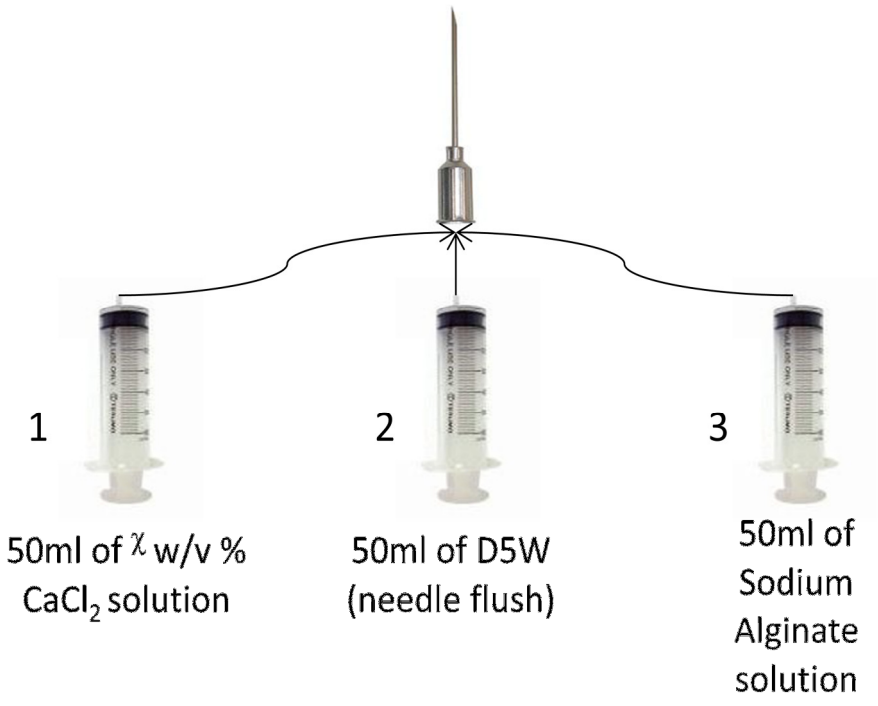

Figure 8 - A possible injection method accomplished using one needle and three different syringes. Images adapted from [23, 24].

Poloxamer

A poloxamer is a polymer containing both hydrophobic and hydrophilic groups [17]. The triblock copolymer consists of a number of poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide) or PEO-PPO-PEO blocks; a figure of the polymer block can be viewed in Figure 9 [15, 18]. The number of blocks in each poloxamer gives it unique characteristics. Poloxamers are non-ionic and are considered bioabsorbable when the polymer has a molecular weight less than 13 kDa [15].

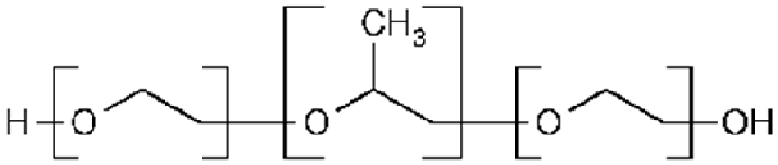

Figure 9 – The triblock structure of poloxamer. The number of units in a poloxamer gives the poloxamer its name and special characteristics. Image adapted from [18].

Poloxamer 407 (Lutrol F 127; BASF) has the unique property of thermoreversibility when mixed with deionized water, and will be used in this product design. This thermoreversible solution to gel phase change occurs as micelles form amongst hydrophobic (PPO) and hydrophilic (PPE) groups; micelles form as temperature increases. These micelles become organized and form structure [15, 19].

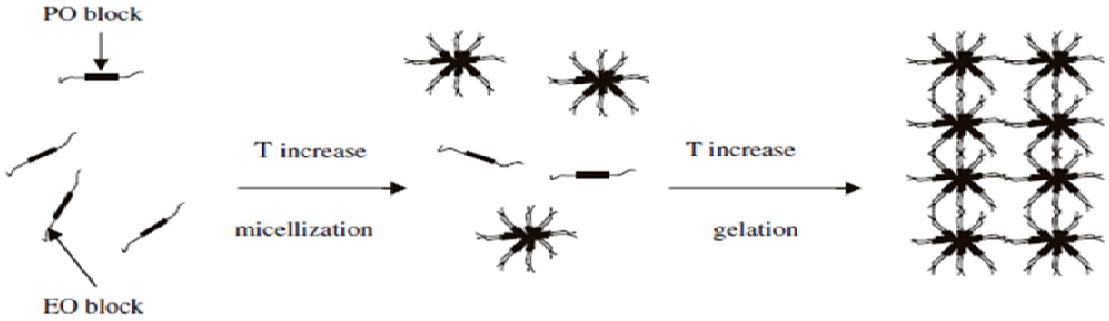

Figure 10 – Micellization process for poloxamer units. As temperature increases the units in solution begin to form micelles which then produce an organized structure. Image adapted from [19].

This micellization process can be viewed in Figure 10. The temperature at which this takes place is named the gelation temperature. This gelation temperature must be experimentally determined and varies depending on the concentration of poloxamer (w/v %) in solution [15, 17, 19]. The

gelation temperature would be altered to 32°C and further optimized to increase viscosity once injected.

The poloxamer gel is often unattractive as a biomaterial because of its rapid erosion and low mechanical strength; however, this could work well for this design [15]. Rapid erosion of the gel would expedite the excretion of the fluid and lessen the likelihood of residue deposits. The low mechanical strength is not of concern since the patient is relatively still throughout the procedure. Poloxamer solutions are non-ionic and it is expected to work well as both a thermal and electrical conductor.

The key characteristic, thermoreversibility, would allow the product to be injected into the patient as a solution which would then gel at body temperature. A visual representation of the phase change from solution to gel can be seen in Figure 11. Due to the solution to gel transition of poloxamer, the viscosity of the product would greatly increase once injected into the peritoneal cavity. This would be ideal for a hydrodissection fluid because the product could be injected as a solution through a 20 gauge needle and would create a gel at approximately 32°C. The viscosity of the poloxamer solution increases with an increase in temperature or concentration until a temperature is reached where the poloxamer begins to precipitate out of solution [15]. With the viscosity increase, it

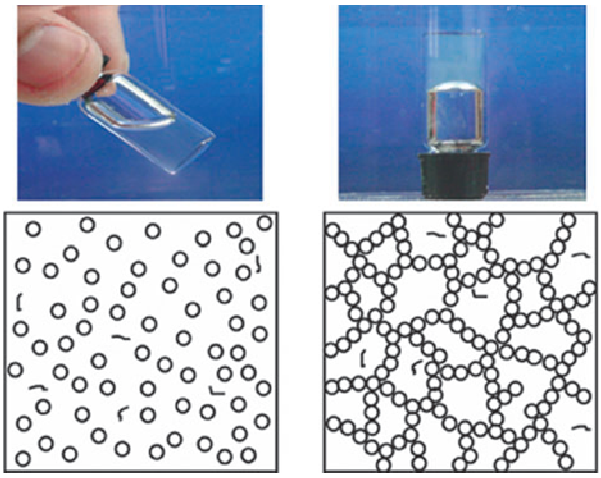

Figure 11 – A noticeable phase change occurs as micelles become organized and the solution becomes a gel. Adapted from [15]

is expected that the migration of fluid within the body cavity would be greatly reduced during the ablation procedure. With a gel formation at the site of ablation, it is hypothesized that a fluid volume of less than 250ml would be required for effective tissue displacement.

DESIGN MATRIX

	Poly(ethylene glycol)	Poloxamer 407	Sodium Alginate
Biocompatibility (30 pts)	30	25	20
Viscosity (20 pts)	15	20	20
Cost of Materials (10 pts)	8	10	5
Ergonomics (15 pts)	10	15	5
Temperature Range (25 pts)	25	20	25
Total	88	**90**	75

Table 1 – Design Matrix – Five categories were chosen based on client preference to evaluate each design alternatives.

A design matrix was used to assess which design option would be best to pursue for the remainder of the project. The five categories chosen were biocompatibility, viscosity, cost of materials, ergonomics, and temperature range. These were based on the design specifications desired by the client. The client ranked each attribute according to importance, and from this, point values were assigned. Thermal and electrical resistance was not included in the design matrix, as it is an inherent property of each design option we are investigating. If any option did not have this property, it would not be valid. We have chosen to pursue Poloxamer 407 based on the results of our design matrix.

Biocompatibility

Biocompatibility is the ability for a material that is introduced into a biological environment to perform its intended function without eliciting any undesirable effects [20]. This category was allocated thirty points in the design matrix because having a product that works effectively but causes harm to the user would be futile.

Poly(ethylene glycol) is an FDA approved material [21]. It is biologically inert and passes through the body mostly unaffected [13]. Because of this unique property, it has been used in many medical products, the most common being laxatives. It has also been added in skin creams and lubricants because of its thickening ability. PEG was given full points in this category because of its use in everyday materials and the fact that it is FDA approved.

While alginate is extremely biocompatible in the human body, it is flawed. Due to the gel being formed by an ionic solution, there will be ions left over after gelation. These ions may cause electrical conductivity to increase which can damage other organs in the body. Because of this, sodium alginate was given a 20 out of 30 points.

Poloxamer was giving a value of 25 out of 30. It was graded less than PEG for biocompatibility because the poloxamer gel is bioabsorbable, not biodegradable. The gel would be broken down, processed through the kidneys, and excreted in the urine. Poloxamer was given a higher value than alginate because it is non-ionic.

Viscosity

The major problem with current methods is their lack of viscosity which results in unintended migration. Designing a product to minimize migration would infer a viscous material so viscosity was given one fifth of the total points.

One of PEG's commercially and industrially favorable properties is its ability to act as a thickening agent. This is evident in its addition to some skin creams, lubricants and toothpaste. PEG was given a relatively high value of fifteen; however, poloxamer and sodium alginate received the highest possible point value because of their ability to form a viscous gel in vivo.

Ergonomics

In order to be used during the ablation procedure the product must be ergonomically efficient for medical personnel. This category was given a max point value of fifteen. The use of the poloxamer solution would make no change in the current hydrodissection procedure, and less total fluid volume would be required for effective hydrodissection. Therefore, the poloxamer solution was given the maximum point value for this category. Unlike poloxamer, PEG would have to be injected as a viscous solution. This may be difficult to push through a 20 gauge needle and accurately place on the ablation site which is why PEG was given ten out of fifteen possible points. Sodium alginate lost points here due to the difficulties involved in injecting the solution. The multiple injections or multiple syringes make the gel more cumbersome to use efficiently.

Temperature Range

The operating temperature range of the gel was very important to our clients, which warranted the heavy weight of the category. Sodium alginate got full points in this category because the gelation is not based on temperature. The gel is cross-linked by ionic calcium and will hold together regardless of temperature in the body. PEG is commercially used as a thickening agent and this property will allow it to retain its viscosity at temperatures typically associated with RF ablation. For this reason it was given full points in this category. Because the viscosity of the gel varies with temperature, poloxamer was given the least point value out of the

three alternatives. This temperature dependent characteristic gives medical personnel little control over gel function once injected into the peritoneal cavity.

Cost

In order for our fluid to be competitive in the current market, it must be relatively inexpensive. Our clients reported that a product with favorable properties would receive widespread use if it cost less than $200. Production of such a fluid using PEG would result in a product that exceeds the cost of poloxamer; this is why PEG lost points. Due to the high cost of pharmaceutical grade alginate, which is necessary for use in the body, sodium alginate lost points in this category. However, the cost of poloxamer is relatively cheap compared to PEG and is well within the limits of the client for the target product cost.

POLOXAMER TESTING

Testing of Poloxamer 407 was done in order to determine the relationship between gelation temperature and concentrations of poloxamer 407 (w/v %). Lutrol F 127 (Poloxamer 407) was received from BASF as a testing sample for the design alternative.

The poloxamer solutions were prepared in filtered deionized water. The water was stored at 4^{o}C prior to solution synthesis and placed on ice during formulation. The appropriate amount of Poloxamer 407 for 120 mL of water was measured on an analytical balance. The poloxamer was slowly added to the 500 mL beaker containing 120 ml of water while being stirred on a hot plate at a rate varying from 500-1000 rpm. At higher concentrations (20, 22.5 w/v %) the solution began to gel prior to full incorporation of poloxamer. In this case a 1 liter beaker with ice was used to cool the smaller beaker while stirring continued; this reduced the temperature of the solution, thereby lowering the viscosity. The protocol for poloxamer fluid synthesis can be found in Appendix B.

Concentration (w/v %)	Gelation Temp (^{o}C)
15	N/A
17.5	N/A
18.75	N/A
20	25.7 ± 1.5
22.5	23.1 ± 0.3

Table 2 – Gelation temperatures were determined for 20 and 22.5 w/v % poloxamer solution. Further experimentation is necessary for testing of solution with concentration less than 20 w/v % poloxamer.

The solution to gel phase change was considered the time point when the stir bar could no longer freely move in solution. At this time the temperature was recorded, triplicates were preformed for each condition and the average gelation temperatures are reported in Table 2. The gelation temperatures of the 15, 17.5, and 18.75 w/v % solutions were indeterminate. It was expected that the solution was heated unevenly. This uneven heating resulted in a gel at the top of the beaker and solution at the bottom which infers a difference in concentration throughout the solution. This did not occur for the 20 and 22.5 w/v % solutions. It was found that the 20 w/v % solution gelled at 25.7 ± 1.5 ^{o}C and the 22.5 w/v % gelled at 23.1 ± 0.3 ^{o}C. A visual representation of the solution when gelled can be seen in Figure 12. It should be noted that the values corresponding to our gelation temperatures are below those required for the product.

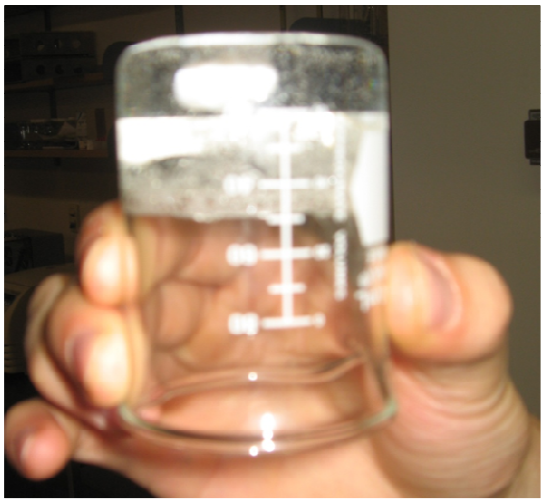

Figure 12 – A 20.0 w/v % poloxamer gel past gelation temperature produces in the Tissue Engineering Lab at the University of Wisconsin-Madison.

Further experimental methods and concentrations will be tested to determine the concentration necessary for product success.

FUTURE WORKS

General

In the future, optimizing the viscosity in vivo will be addressed in order to increase the poloxamer gel's effectiveness. In addition to the viscosity, our gel will be optimized to provide the best medical imaging possible. To further increase visibility on MRI or CT scans, an iodinated medium may be added to the solution prior to gelation [22].

The expected cost of the project is minimal. Thus far, lab supplies are expected to cost $30 for the semester. All chemical supplies for the project have been provided by BASF as samples. For the final design prototype it is expected that approximately 50 grams of poloxamer 407 will be necessary ($120 for 1kg of Poloxamer 407; Sigma Aldrich); this would result in a final product costing less than $10/unit.

Testing

Multiple factors of the gel still need to be tested including: conductivity, gelation temperatures, viscosity, mechanical strength, and image contrast optimization. Immediate testing of the poloxamer solution at varying concentrations will be conducted to determine the concentration that best meets the design specifications. Properties such as viscosity and temperature of gelation will first be compared between differing concentrations. Due to problems encountered in our earlier testing, a water bath will be used to evenly heat the poloxamer solution. This is expected to prevent the development of a heterogeneous solution.
The poloxamer solution with ideal gelation temperature will then be further tested with electrical and thermal conductivity using an RF ablation probe. Tests in an agar medium will provide data

that will be comparable to in vivo conditions; methods reported by Brace et al. will be used [2]. To satisfy the design requirements, ultrasound must pass through the gel and the gel must be distinguishable on a MRI. The obvious way to test these is to image the gel with known substances around it. Future testing on this design would also consist of animal testing on swine. A comparison test with poloxamer, D5W, and saline would be conducted in similar fashion to methods previously reported by P. Laeseke, et al. [9].

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APPENDIX A

ABSORBABLE HYDRODISSECTION FLUID

PRODUCT DESIGN SPECIFICATIONS

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Hydrodissection is used to protect adjacent organs during percutaneous thermal ablation. Current techniques involve the injection of 5% dextrose with water (D5W) or saline. Although effective in protecting surrounding tissue, these solutions tend to migrate into the body cavity. To remain effective, large amounts of fluid are necessary (approximately one liter). The goal of this project is to develop a solution/gel that encompasses favorable aspects of the current solutions: easy to introduce, ultrasound transparent, visible on CT/MRI, biocompatible, absorbable, thermally and electrically insulating, and relatively low cost; but also puts a stop to solution migration into the body cavity.

Client Requirements:

- The designed fluid must prevent the migration of solution within the body cavity during hydrodissection and ablation.
- The designed fluid must be comparable with the current favorable characteristics of D5W. These include:
    - Easy to introduce/inject – The product must be able to be introduced through 20 gauge needle (0.6 mm inner diameter).
    - Ultrasound transparent and visible on CT/MRI – The product should not reduce tumor visibility or imaging capabilities.
    - Biocompatible/absorbable – The product must be well tolerated by the body cavity and leave no post treatment residue.
    - Thermal /electrical insulator – In order for the product to effectively protect adjacent tissue, it must be a thermal and electrical insulator.
    - Comparable cost – The current cost of D5W is minimal, approximately five dollars per one liter unit.

Design Requirements:

1. Physical and Operational Characteristics

A. *Performance requirements:* The product must contain all favorable characteristics of current hydrodissection methods: ease of injection, biocompatibility, thermal and electrical insulator, and reasonable cost. In addition, it must prevent the migration of fluid into the peritoneal cavity.

B. *Safety:* Since the fluid is to be introduced into the body cavity, the final design must be non-toxic, biocompatible, and hypoallergenic.

C. *Accuracy and Reliability:* Failure of the product could result in serious complications to the patient; therefore, the product must be completely reliable. The accuracy of fluid retention time is imperative to the effectiveness of the treatment. Efficient hydrodissection must persist for at least one hour.

D. Life in Service: This product is to be used for hydrodissection during radiofrequency ablation lasting approximately one hour. Prior to treatment, the fluid will be stored in a 250 ml IV bag.

E. Shelf Life: The fluid is to be packaged in 250 ml IV bags and must have at least a one year shelf life; this is necessary to be competitive with currently used products.

F. Operating Environment: The product is designed to be injected into the body cavity and should function predictably within the body's normal thresholds: approximately 7.3 pH, 35-37^{o}C, and should be isotonic to the peritoneal fluid.

G. Ergonomics: The final design must be comparable to D5W for ease of injection. The ability of the fluid to be introduced through a 20 gauge needle is necessary for patient safety.

H. Size: A single effective treatment should require less than one IV bag, 250mL of fluid.

I. Weight: Weight requirements are not applicable for this product.

J. *Materials:* All the materials used in this design must meet the standards of the Food and Drug Administration (FDA), as it is designed for use on human subjects.

K. Aesthetics, Appearance, and Finish: Requirements for the design necessitate distinction between the fluid and tumor during procedural imaging.

2. Production Characteristics

A. Quantity: A volume of 250mL or less should be sufficient for one treatment.

B. Target Product Cost: Less than $200 per unit. Minimizing the cost is essential to market success of this product. Ideally the unit price would be comparable to D5W.

3. Miscellaneous

A. *Standards and Specifications:* The final product will require the approval of the Food and Drug Administration for use in the human body.

B. Customer: Prospective customers of this product would require effective hydrodissection, ease of use, reasonable cost, and biocompatibility. The primary customers are medical personnel performing hydrodissection procedures, this product will be an alternative to current hydrodissection techniques during patient consults.

C. Patient-related concerns: Patient safety is the first concern; the prevention of non-targeted tissue damage is essential. Additionally, patient comfort should be maximized during and after treatment.

D. Competition: D5W is most commonly used in hydrodissection procedures and fulfills most requirements for an ideal hydrodissection fluid. Also, 0.9% saline is used for hydrodissection; however, because of the ionic characteristic of saline, it is less common than D5W.

APPENDIX B

POLOXAMER FLUID SYNTHESIS - PROTOCOL

Purpose:

To develop a poloxamer solution that will effectively form a gel at body temperature, approximately 37°C. Because the gel becomes more viscous as temperature increases, a solution that gels between 32-34°C would be ideal. This fluid is being synthesized for future testing. The hopes of this design are for medical application as a fluid for hydrodissection during tumor ablation procedures.

Materials:

- Beakers (100ml, 500ml, 1L)
- Pipette helper
- Pipette helper tips (25ml)
- Parafilm
- 50ml Centrifuge tubes
- Poloxamer - Lutrol F 127 (BASF)
  Article #: 51632903
- Ultra-pure deionized water
- Stir/hot plate
- Magnetic stir bars
- Analytical balance
- Weight boats
- Spatula

Procedure:

1. Obtain 1 L of deionized water and cool to 4°C.
    a. This is necessary to synthesize fluids with high concentration of poloxamer because at room temperature the fluids begin the sol-gel transition.
2. Determine the amount of poloxamer solution to be synthesized and the sought concentration.
    a. For example, we want 120ml of 20 w/v % poloxamer solution.
3. Place 120ml of deionized water in a 500ml beaker and place on a stir plate.
4. Stir the water with a magnetic stir bar at a speed with the range of 500-1000 rpm.
5. Weight out required amount of poloxamer.
    a. Ex.

$$\frac{20\ \text{w/v\%}}{100\%} * 120\text{ml} = 24\ \text{grams of Lutrol F 127}$$

6. Slowly pour the poloxamer into the deionized water.
7. Mix until all poloxamer is in solution.
8. This could take several hours.
    a. If necessary place parafilm over the top of the beaker and leave overnight.
    b. To help poloxamer uptake at high concentration, place beaker with poloxamer solution inside a larger 1L beaker and surround the 500ml beaker with ice. This will cool the poloxamer solution which will decrease the viscosity and allow for better mixing.
9. Poloxamer solution can be stored at room temperature or 4°C.