Absorbable Hydrodissection Fluid

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Client:
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Problem Background

• Hepatocellus carcinoma is the most common human solid malignancy worldwide.
  • 1 million new incidences annually.
• 70 - 90 % of hepatic malignancies are not candidates for surgical resection.
• Ablation is used to destroy tumor tissue.
  • Often unwanted tissue damage occurs.
Ablation Procedures

RF Ablation (RFA)

- RF AC current generates heat to ‘burn out’ tumors
- Few patient complications
- 85% success in eliminating tumors

Cryoablation

- Freezes target tissue causing necrosis
- Can treat larger tumors than RFA
- Better control than RFA

Current Treatments

- Hydrodissection fluids
  - 5% dextrose in water (D5W)
  - CO₂ gas bladder or insufflation
  - Saline

Problem with D5W

Fluid migration & barrier degradation

Injection of more D5W

Fluid barrier

Adjacent tissue/organ

Target organ

Adjacent tissue/organ

Target organ

Adjacent tissue/organ

Target organ

Tissue damage
Current Design – Poloxamer 407

- Polyethylene oxide-polypropylene oxide-polyethylene oxide
  - Triblock copolymer
  - PEO-PPO-PEO
- Thermoreversible
- Bioabsorbable (MW < 13 kDa)
- Non-ionic
- Low mechanical strength

Design Specifications

• Current Design – 19.0 %w/w Poloxamer 407
  • Gels at 32ºC
  • Visible with imaging techniques (CT scan and ultrasound)
  • Biocompatible
  • Thermal/electrical insulator
  • Less than $200
  • Prevents fluid migration and barrier degradation

• Updated Requirements
  • Easy to inject through a 20 gauge needle (0.0603mm diameter)
  • Increased bioadhesion
Benzoic Acid

- Inexpensive
- Generally recognized as safe by the FDA
- Reduces gelation temperature of poloxamer solutions

Polyethylene Glycol (PEG) 400

- Hydrophilic
- Low molecular weight
- Decreases gelation temperature
- Increases gel melting temperature
- Increases elastic modulus

E. Ricci, et al., "Rheological characterization of Poloxamer 407 lidocaine hydrochloride gels"
Methylcellulose

- Nontoxic, not allergenic
- Difficult to breakdown
- Increases mucoadhesion
- 1 - 2 %w/w concentrations are effective
- Increases poloxamer gel strength

Gel Strength (g/cm²) vs. Molecular Wt. (x10⁻³ g mol⁻¹) of Methocel®

Sarkar et al. “Thermal gelation properties of Methyl and Hydroxypropyl methylcellulose”
Poloxamer 188

- Biocompatible
- Non-ionic
- Increases bioadhesion
- Changes gelation temperature

## Design Matrix

<table>
<thead>
<tr>
<th></th>
<th>Benzoic Acid</th>
<th>Polyethylene Glycol 400</th>
<th>Poloxamer 188</th>
<th>Methylcellulose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces Fluid Viscosity (40 pts)</td>
<td>40</td>
<td>40</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Biocompatibility (30 pts)</td>
<td>15</td>
<td>30</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Bioadhesion (25 pts)</td>
<td>0</td>
<td>0</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Cost of Materials (5 pts)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>75</td>
<td>55</td>
<td>84</td>
</tr>
</tbody>
</table>
Future Work

• Testing
  • Gelation temperature
  • Viscosity
  • Impedance & Imaging
  • Bioadhesion
  • Animal testing

• Cost
  • Lab supplies: $50
  • Estimated cost of product: ~$10/unit
Acknowledgements

- Dr. John Puccinelli
- Dr. Chris Brace
- Dr. J. Louis Hinshaw
- Dr. Meghan Lubner
References

- Brace, C., et al. Electrical isolation during radiofrequency ablation: 5% dextrose in water provides better protection than saline. 2008: IEEE.
- BASF, "Lutrol L and Lutrol F-Grades.“
Questions?
The triblock structure of poloxamer. The number of units in a poloxamer gives the poloxamer its name and special characteristics. The center, PPO block is hydrophobic and flanked by two hydrophilic PEO blocks.
A schematic of the adhesion test reported by Barakat et al. Modifications may be made to this design. A piece of tissue is secured on top of a glass vial; two of these are formed, one is secured to an adjustable plate (B) and one to the balance. A gel (A) is placed between the two pieces of tissue. The diameter of the tissue/gel must be recorded for calculations. A mass (C) is placed on the other side of the balance; additional weight is added until the gel and tissue separate. From this a stress can be determined as \( \text{Force/Area} = \frac{4mg}{\pi d^2} \). Where \( m \) is the mass, \( g \) is the gravitational force, and \( d \) is the diameter.
Impedance Testing

A schematic showing experimental set-up for impedance testing of the poloxamer solution and gel. A RF generator used for ablation procedure has the capability of measuring the impedance. Approximately 40 ml of solution will be placed in 100 ml beaker; two electrodes will be placed on opposite sides of the beaker attached to aluminum tape. The impedance between electrodes, the impedance of the solution or gel, will be tested by the RF signal generator.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Impedance (Ω)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank</td>
<td>40</td>
</tr>
<tr>
<td>Saline</td>
<td>88</td>
</tr>
<tr>
<td>D5W</td>
<td>High (&gt;1000)</td>
</tr>
<tr>
<td>19.0% Poloxamer (solution)</td>
<td>High (&gt;1000)</td>
</tr>
<tr>
<td>19.0% Poloxamer (gelled)</td>
<td>High (&gt;1000)</td>
</tr>
</tbody>
</table>
A Cannon-Fenske, size 200, viscometer was used to measure kinematic viscosity in previous viscosity tests. An analytical pipet is used to transfer 6 mL of solution into the viscometer. A bulb is used to force fluid ~1 cm past point A; when released the time taken for the fluid meniscus to travel from point A to B is directly proportional to the viscosity of the fluid. The viscosity of the poloxamer solution changes with temperature; because of this, the test must be conducted in a temperature controlled environment.
## Cost

<table>
<thead>
<tr>
<th>Material</th>
<th>Estimated Max Quantity</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poloxamer 407 ($120 for 1kg; Sigma Aldrich)</td>
<td>47.5 grams, 19.0 %w/w</td>
<td>$5.70</td>
</tr>
<tr>
<td>Poloxamer 188</td>
<td>12.5 grams, 5.0%w/w</td>
<td>$0.88</td>
</tr>
<tr>
<td>PEG 400</td>
<td>12.5 grams, 5.0%w/w</td>
<td>$0.38</td>
</tr>
<tr>
<td>Methylcellulose</td>
<td>5.0 grams, 2.0 %w/w</td>
<td>$1.50</td>
</tr>
<tr>
<td><strong>Projected Product Cost</strong></td>
<td></td>
<td><strong>$8.46</strong></td>
</tr>
</tbody>
</table>
Effects of an additive on viscosisty

Gelation temperature reducing additive is added to the poloxamer solution.

The gelation temperature is decreased.

Less poloxamer 407 is necessary for the 32°C sol-gel transition temperature.

Viscosity decreases and the poloxamer solution is able to be injected within the peritoneal cavity through a 20 gauge needle.
Gelation Temperature vs. Concentration for Poloxamer 407

\[ y = -2.04x + 70.76 \]

\[ R^2 = 0.97 \]
Imaging

Ultrasound

Ultrasound images showing the transparency of (a) poloxamer solution, (b) D5W, and (c) poloxamer gel on an ultrasound.

CT Scan

<table>
<thead>
<tr>
<th></th>
<th>D5W</th>
<th>19.0% Poloxamer</th>
<th>Gel – 19.0% Poloxamer</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI</td>
<td>8.9 ± 2.9</td>
<td>14.1 ± 2.5</td>
<td>14.7 ± 2.2</td>
</tr>
<tr>
<td>ROI w/ Iohexal</td>
<td>220.6 ± 4.3</td>
<td>106.4 ± 2.3</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Syringe guns


http://www.cammda.com/products/guns/the_gunn.html
In vivo