Absorbable Hydrodissection Fluid

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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.

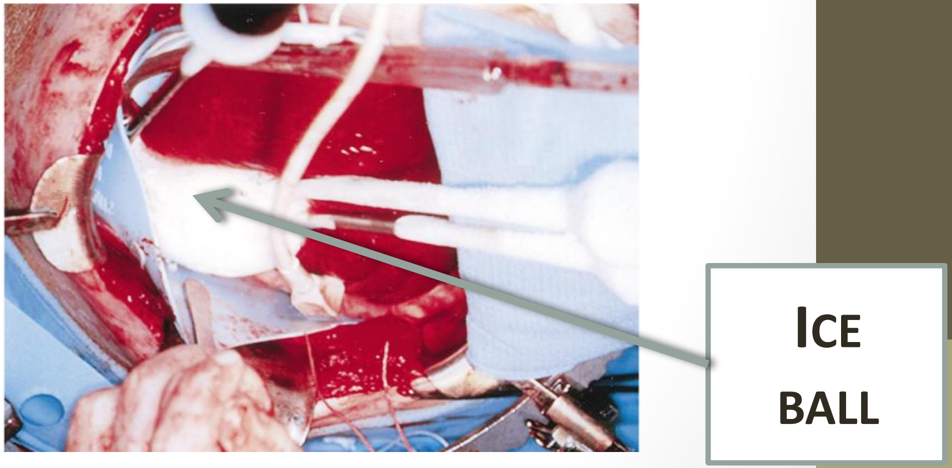
Ablation Procedures

RF Ablation (RFA)

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

Cryoablation

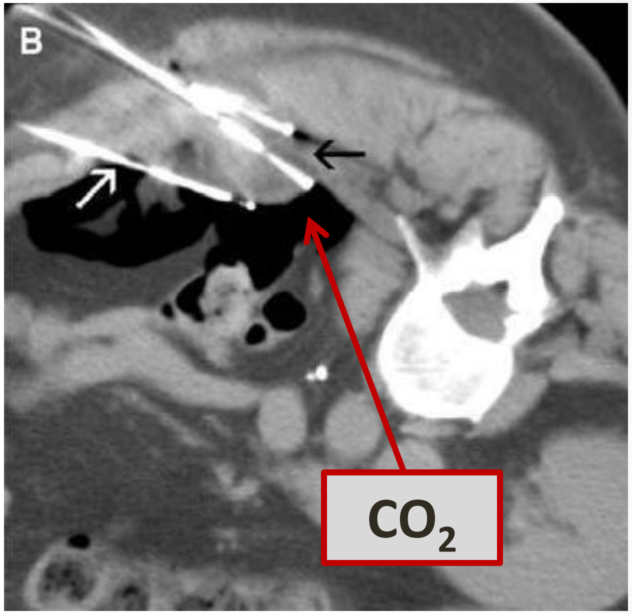
- Freezes target tissue causing necrosis
- Can treat larger tumors than RFA
- Better control than RFA



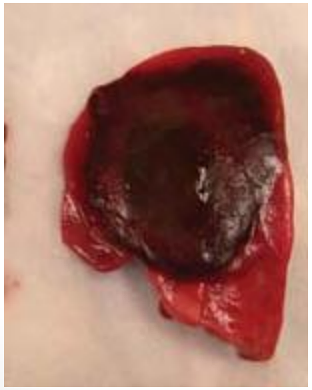
(Top) G. D. D. III, *et al.*, "Minimally Invasive Treatment of Malignant Hepatic Tumors: At the Threshold of a Major Breathrough," *RadioGraphics,* vol. 20, p. 19, 2000 and (Bottom) Adapted from G. D. D. III, *et al.*, "Minimally Invasive Treatment of Malignant Hepatic Tumors: At the Threshold of a Major Breathrough," *RadioGraphics,* vol. 20, p. 19, 2000

Current Treatments

- Hydrodissection fluids
  - 5% dextrose in water (D5W)
  - CO_2 gas bladder or insufflation
  - Saline

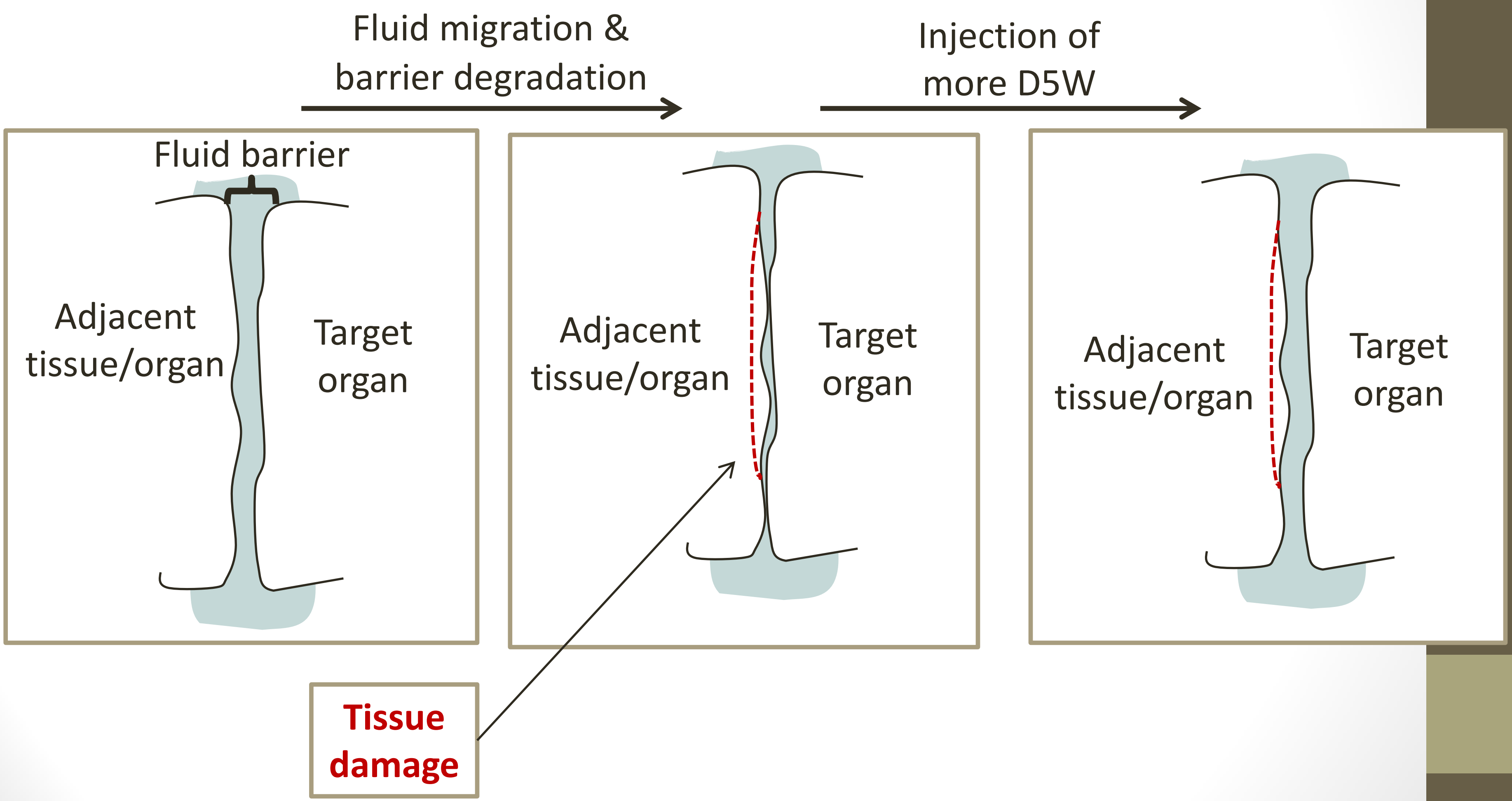


No Treatment | **Saline** | **D5W**



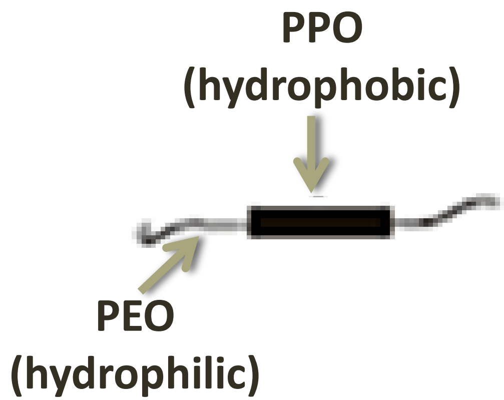
(Top Right) Adapted from Buy, X., et al., *Thermal protection during percutaneous thermal ablation procedures: interest of carbon dioxide dissection and temperature monitoring.* Cardiovascular and interventional radiology, 2009. **32**(3): p. 529-534. and (Bottom) Adapted from P. F. Laeske*, et al.*, "Unintended injuries from radiofrequency ablation: Protection with 5% dextrose in water," *Am. J. Roentgenology,* vol. 186, pp. 5249-5254, 2006.

Problem with D5W



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



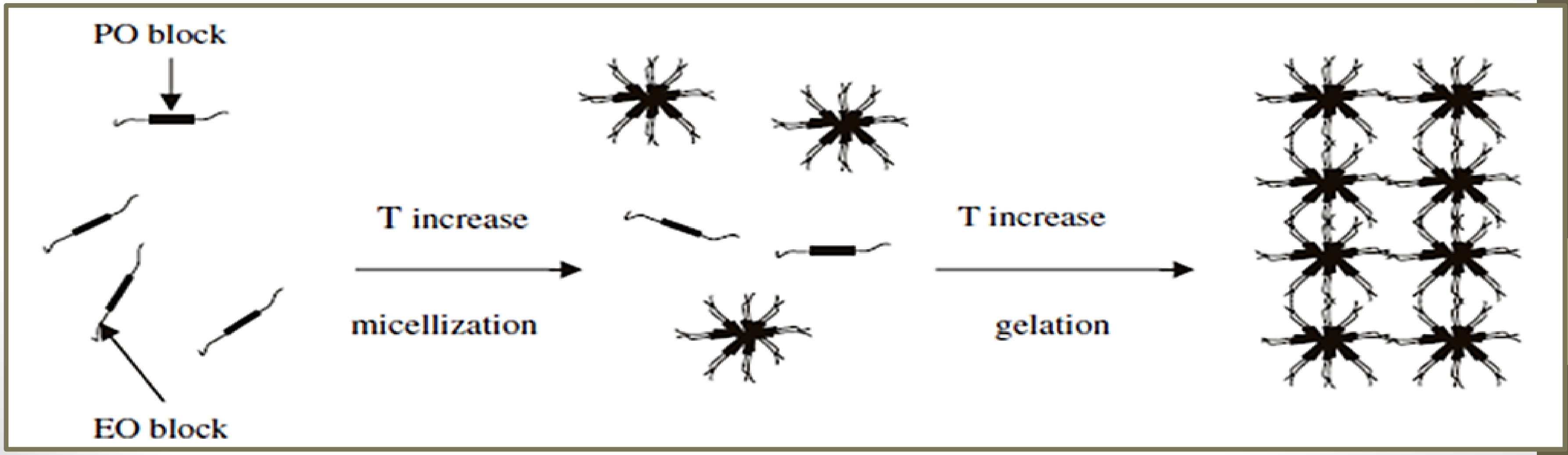


Image adapted from G. Dumortier, et al., "A review of poloxamer 407 pharmaceutical and pharmacological characteristics," Pharmaceutical research, vol. 23, pp. 2709-2728, 2006.

Design Specifications

- Current Design – 19.0 %w/w Poloxamer 407
  - Gels at 32^{o}C
  - 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

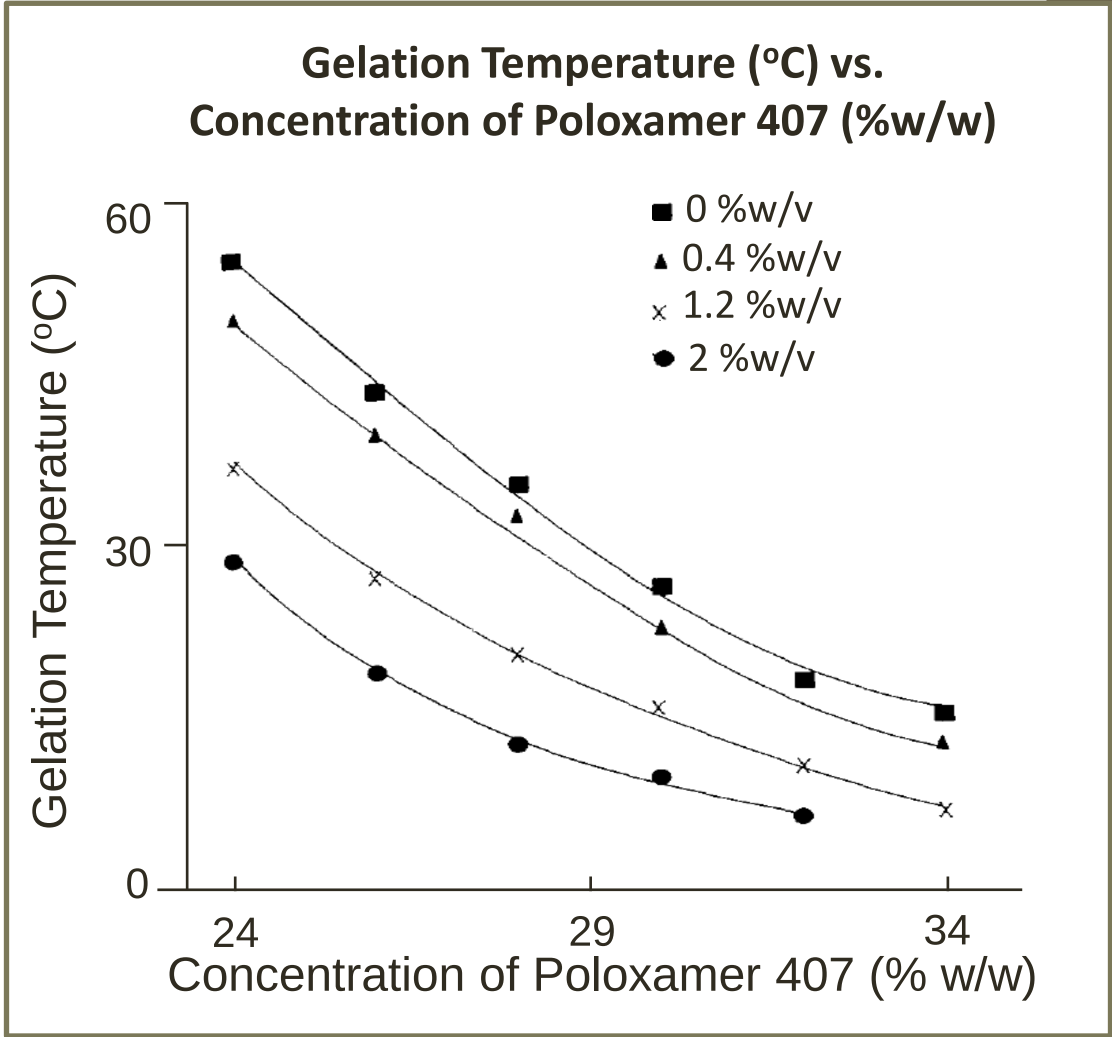
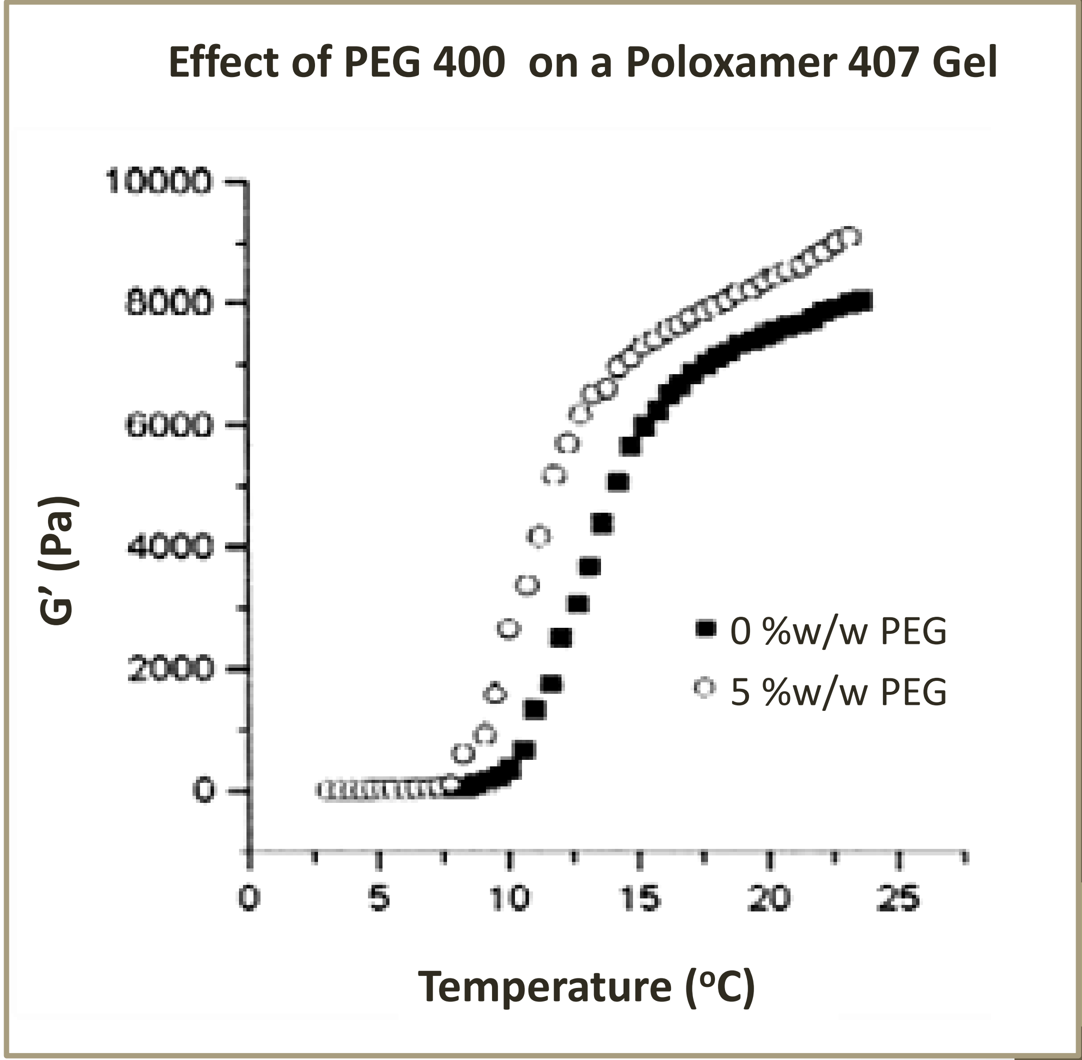


Image adapted from Gilbert, J.C., et al., The effect of solutes and polymers on the gelation properties of Pluronic F-127 solutions for controlled drug delivery. Journal of Controlled Release, 1987. ***5****(2): p. 113-118.*

Polyethylene Glycol (PEG) 400

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

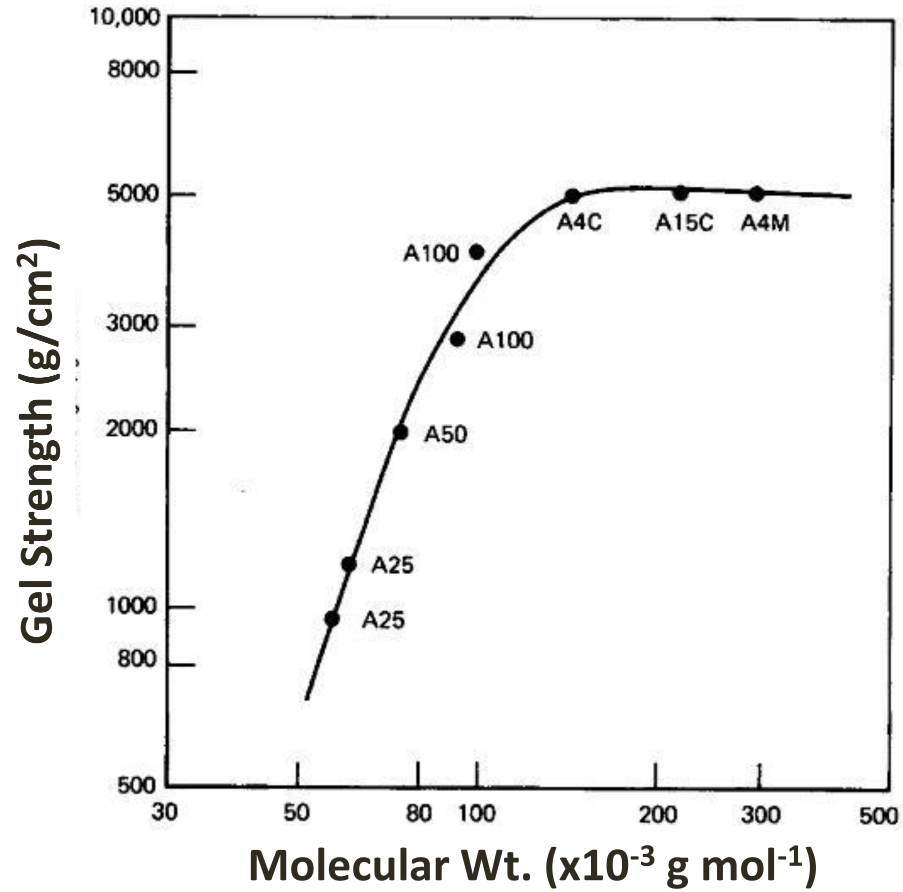


E. Ricci, *et al.*, "Rheological characterization of Poloxamer 407 lidocaine hydrochloride gels

Methylcellulose

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

Gel Strength (g/cm^2) 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

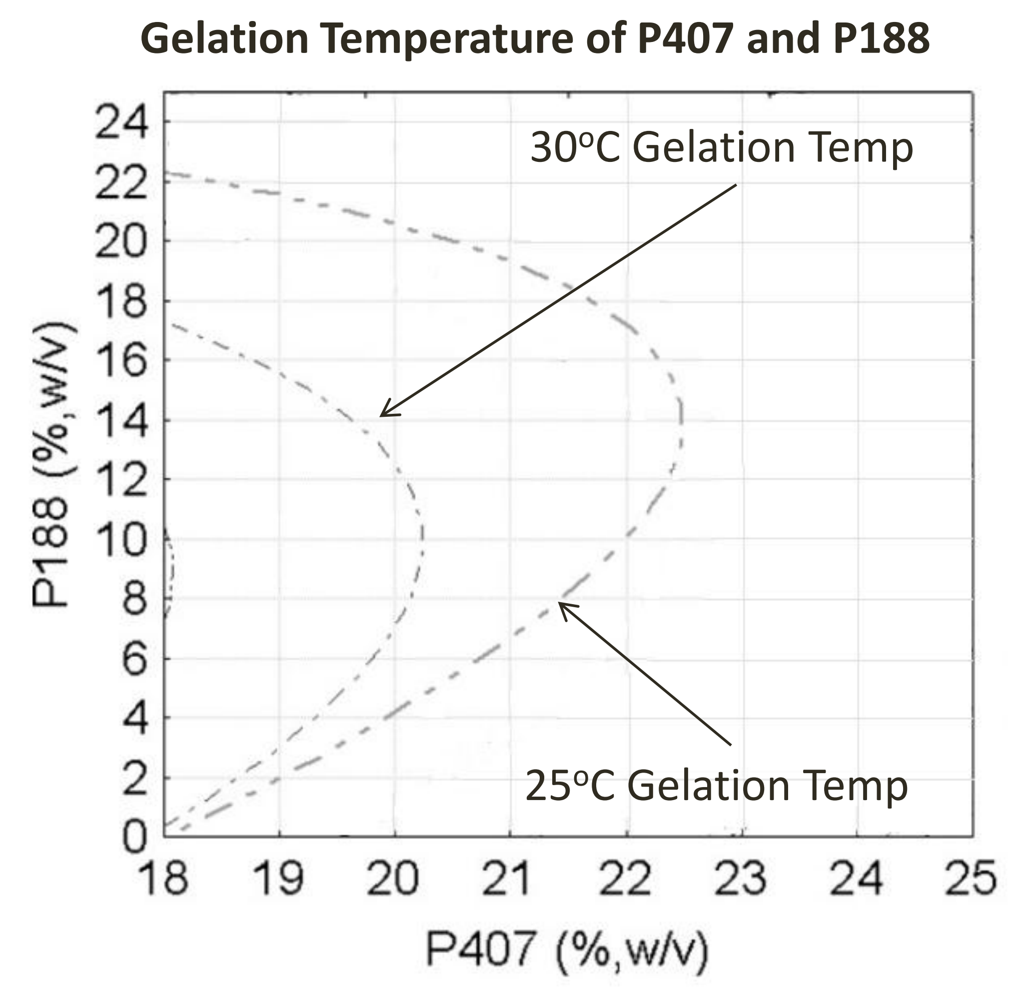


Image adapted from H. Qi, et al., "Optimization and Physicochemical Characterization of Thermosensitive Poloxamer Gel Containing Puerarin for Ophthalmic Use," Chemical & Pharmaceutical Bulletin, vol. 54, pp. 1500-1507, 2006.

Design Matrix

	Benzoic Acid	Polyethylene Glycol 400	Poloxamer 188	Methyl-cellulose
Reduces Fluid Viscosity (40 pts)	40	40	0	40
Biocompatibility (30 pts)	15	30	25	15
Bioadhesion (25 pts)	0	0	25	25
Cost of Materials (5 pts)	5	5	5	4
Total	60	75	55	**84**

Future Work

- Testing
  - Gelation temperature
  - Viscosity
  - Impedance & Imaging
  - Bioadhesion
  - Animal testing
- Cost
  - Lab supplies: $50
  - Estimated cost of product: ~$10/unit

Acknowledgements

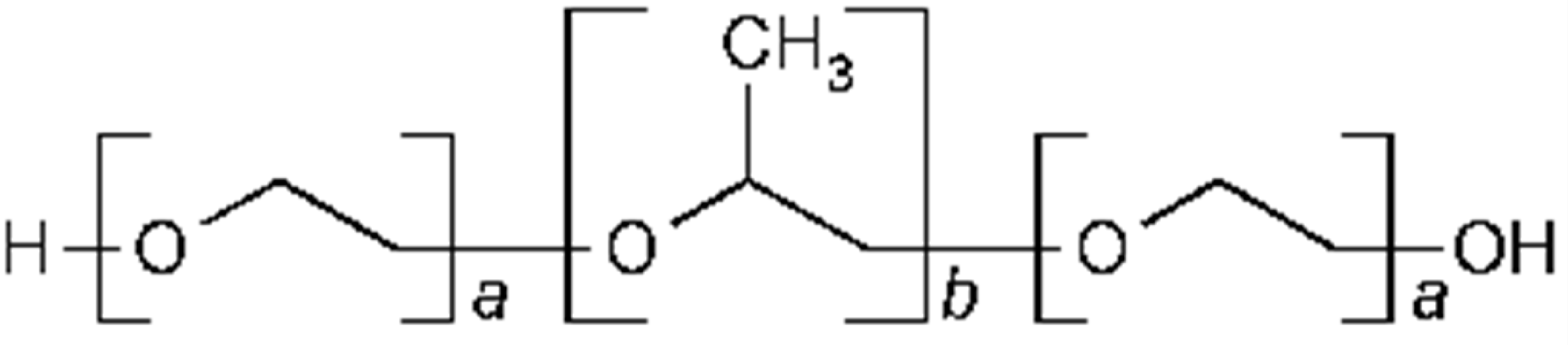
- Dr. John Puccinelli
- Dr. Chris Brace
- Dr. J. Louis Hinshaw
- Dr. Meghan Lubner

References

- Brace, C., et al. Electrical isolation during radiofrequency ablation: 5% dextrose in water provides better protection than saline. 2008: IEEE.
- Dodd, G., et al., Minimally Invasive Treatment of Malignant Hepatic Tumors: At the Threshold of a Major Breakthrough1. RadioGraphics, 2000. 20(1): p. 9.
- Buy, X., et al., Thermal protection during percutaneous thermal ablation procedures: interest of carbon dioxide dissection and temperature monitoring. Cardiovascular and interventional radiology, 2009. 32(3): p. 529-534.
- C. Sheeham. October 9). Poloxamer. Available: http://www.uspbpep.com/usp28/v28230/usp28nf23s0_m66210.htm
- G. Dumortier, et al., "A review of poloxamer 407 pharmaceutical and pharmacological characteristics," Pharmaceutical research, vol. 23, pp. 2709-2728, 2006.
- S. Singh-Joy and V. McLain, "Safety assessment of poloxamers 101, 105, 108, 122, 123, 124, 181, 182, 183, 184, 185, 188, 212, 215, 217, 231, 234, 235, 237, 238, 282, 284, 288, 331, 333, 334, 335, 338, 401, 402, 403, and 407, poloxamer 105 benzoate, and poloxamer 182 dibenzoate as used in cosmetics," International journal of toxicology, vol. 27, p. 93, 2008.
- B. Fussnegger. (2000, October 8). Poloxamers (2). Available: http://worldaccount.basf.com/wa/NAFTA/Catalog/Pharma/doc4/BASF/exact/lutrol_f_127/.pdf?title=Poloxamers%20%282%29%20Lutrol%20F%20127%20%28Poloxamer%20407%29.&asset_type=pi/pdf&language=EN&urn=urn:documentum:eCommerce_sol_EU:09007bb28001ac1d.pdf
- N. K. Pandit and H. J. McIntyre, "Cosolvent Effects on the Gel Formation and Gel Melting Transitions of Pluronic® F127 Gels," *Pharmaceutical Development and Technology,* vol. 2, pp. 181-184, 1997.
- T. Ma*, et al.*, "PEG 400, a hydrophilic molecular probe for measuring intestinal permeability," *Gastroenterology,* vol. 98, p. 39, 1990.
- E. Ricci*, et al.*, "Rheological characterization of Poloxamer 407 lidocaine hydrochloride gels," *European Journal of Pharmaceutical Sciences,* vol. 17, pp. 161-167, 2002.
- E. Ricci*, et al.*, "Sustained release of lidocaine from Poloxamer 407 gels," *International journal of pharmaceutics,* vol. 288, pp. 235-244, 2005.
- from P. F. Laeske*, et al.*, "Unintended injuries from radiofrequency ablation: Protection with 5% dextrose in water," *Am. J. Roentgenology,* vol. 186, pp. 5249-5254, 2006
- H. Qi*, et al.*, "Optimization and Physicochemical Characterization of Thermosensitive Poloxamer Gel Containing Puerarin for Ophthalmic Use," *Chemical & Pharmaceutical Bulletin,* vol. 54, pp. 1500-1507, 2006.
- BASF, "Lutrol L and Lutrol F-Grades.“
- EPA. *Benzoic acid (CASRN 65-85-0)* 2011 [cited 2011 Jan 26]; Available from: http://www.epa.gov/iris/subst/0355.htm.
- FDA. *Benzoic Acid; Inactive Ingredient*. 2011 [cited 2011 Jan 30]; Available from: http://www.accessdata.fda.gov/scripts/cder/iig/getiigWEB.cfm.
- Gilbert, J.C., et al., *The effect of solutes and polymers on the gelation properties of Pluronic F-127 solutions for controlled drug delivery.* Journal of Controlled Release, 1987. **5**(2): p. 113-118.
- Yu, L. and J. Ding, *Injectable hydrogels as unique biomedical materials.* Chemical Society Reviews, 2008. **37**(8): p. 1473-1481.
- Barakat, N.S., *In Vitro and In Vivo Characteristics of a Thermogelling Rectal Delivery System of Etodolac.* AAPS PharmSciTech, 2009. **10**(3): p. 724-731.

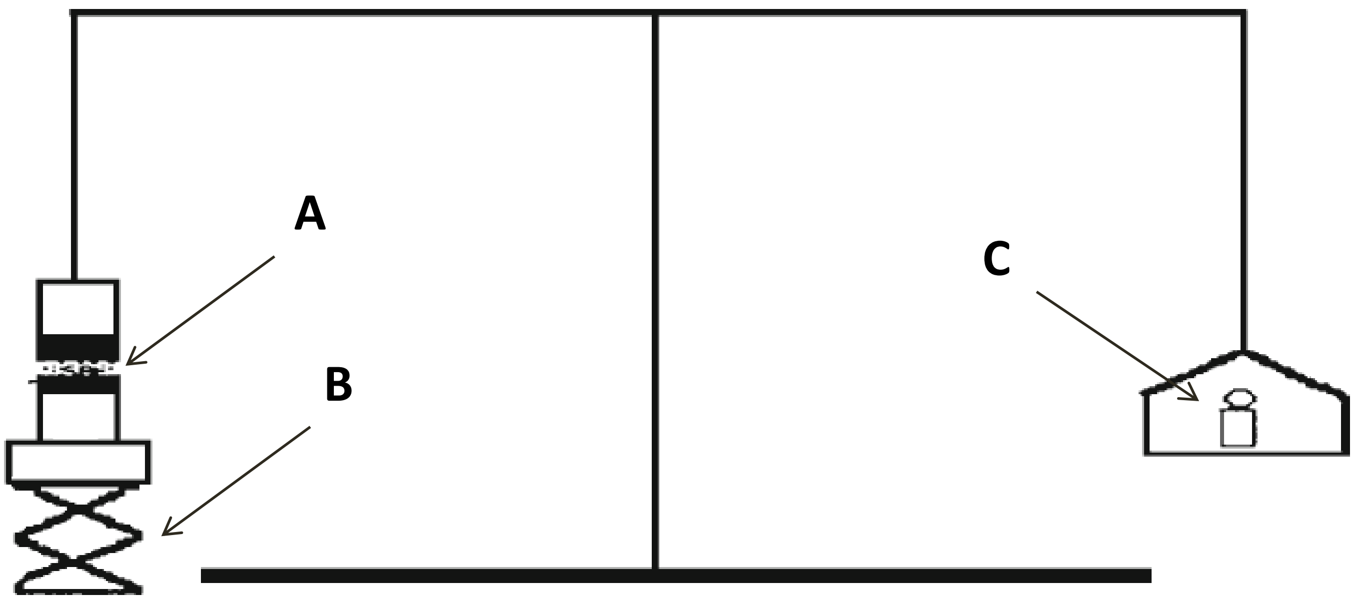
Questions?

Poloxamer unit structure



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.

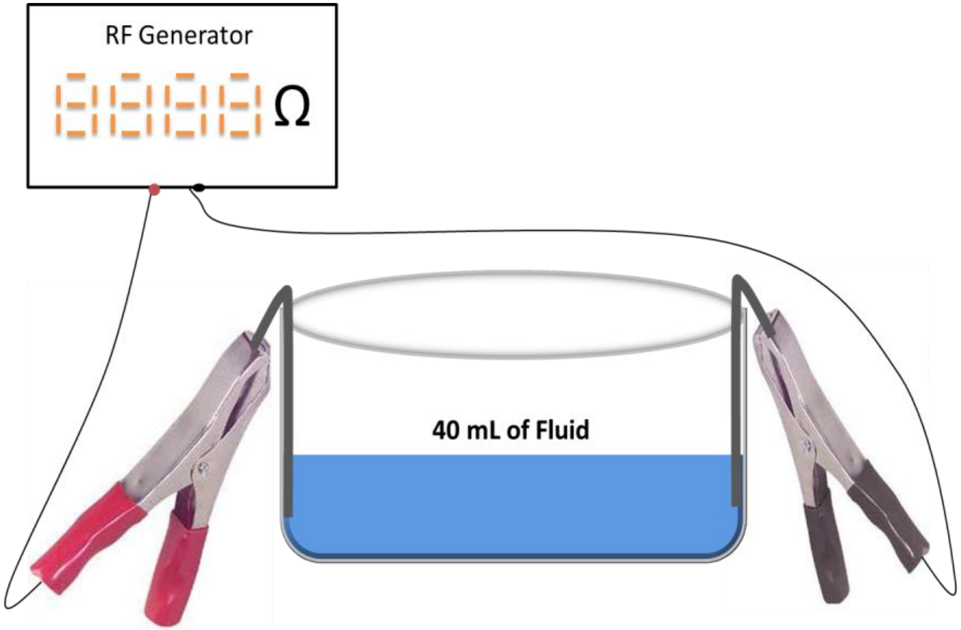
Bioadhesion Testing



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 place on the otherside of the balance; additional weight is added until the gel and tissue separate. From this a stress can be determined as Force/Area = $4mg/\pi d^2$. Where m is the mass, g is the gravitational force, and d is the diameter.

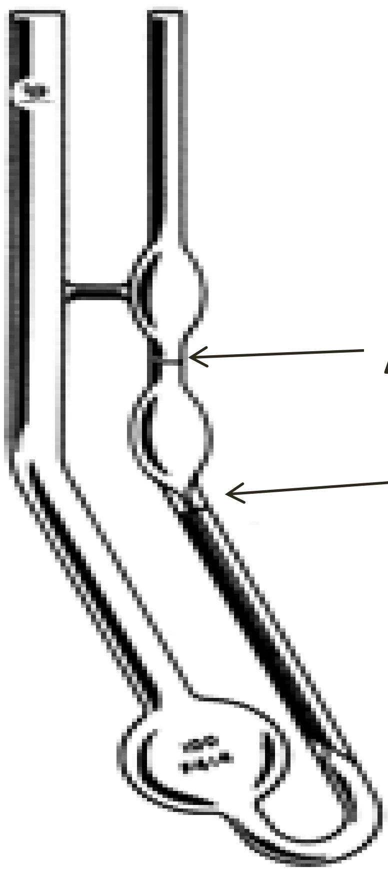
Impedance Testing

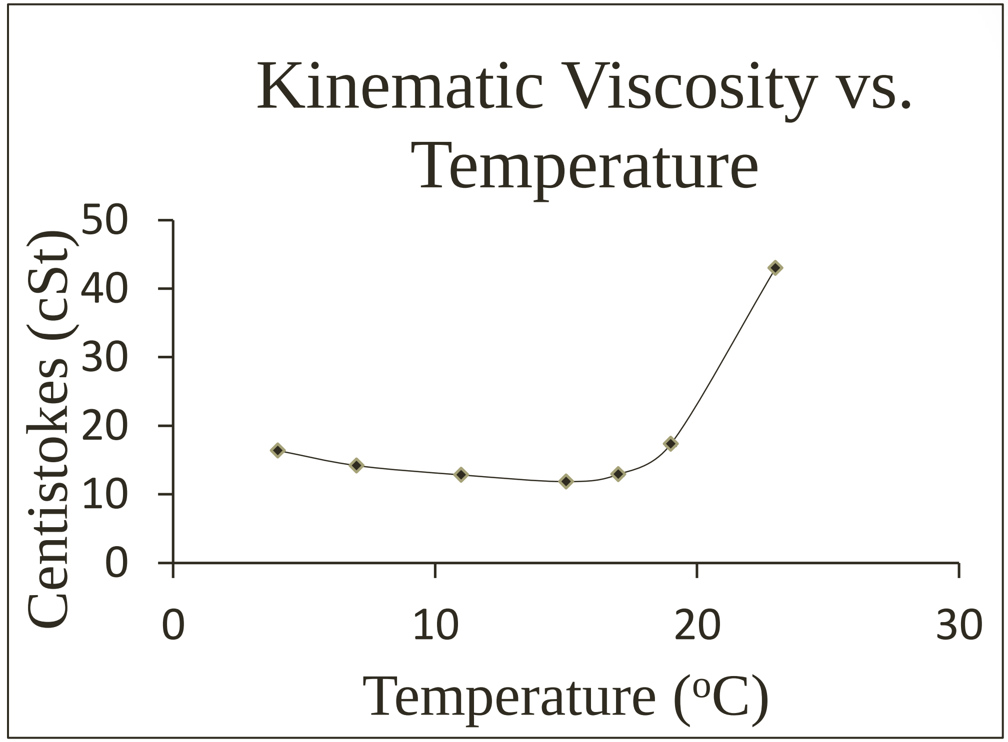
Sample	Impedance (Ω)
Blank	40
Saline	88
D5W	High (>1000)
19.0% Poloxamer (solution)	High (>1000)
19.0% Poloxamer (gelled)	High (>1000)



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.

Viscosity Testing





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 ~ 1cm 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.

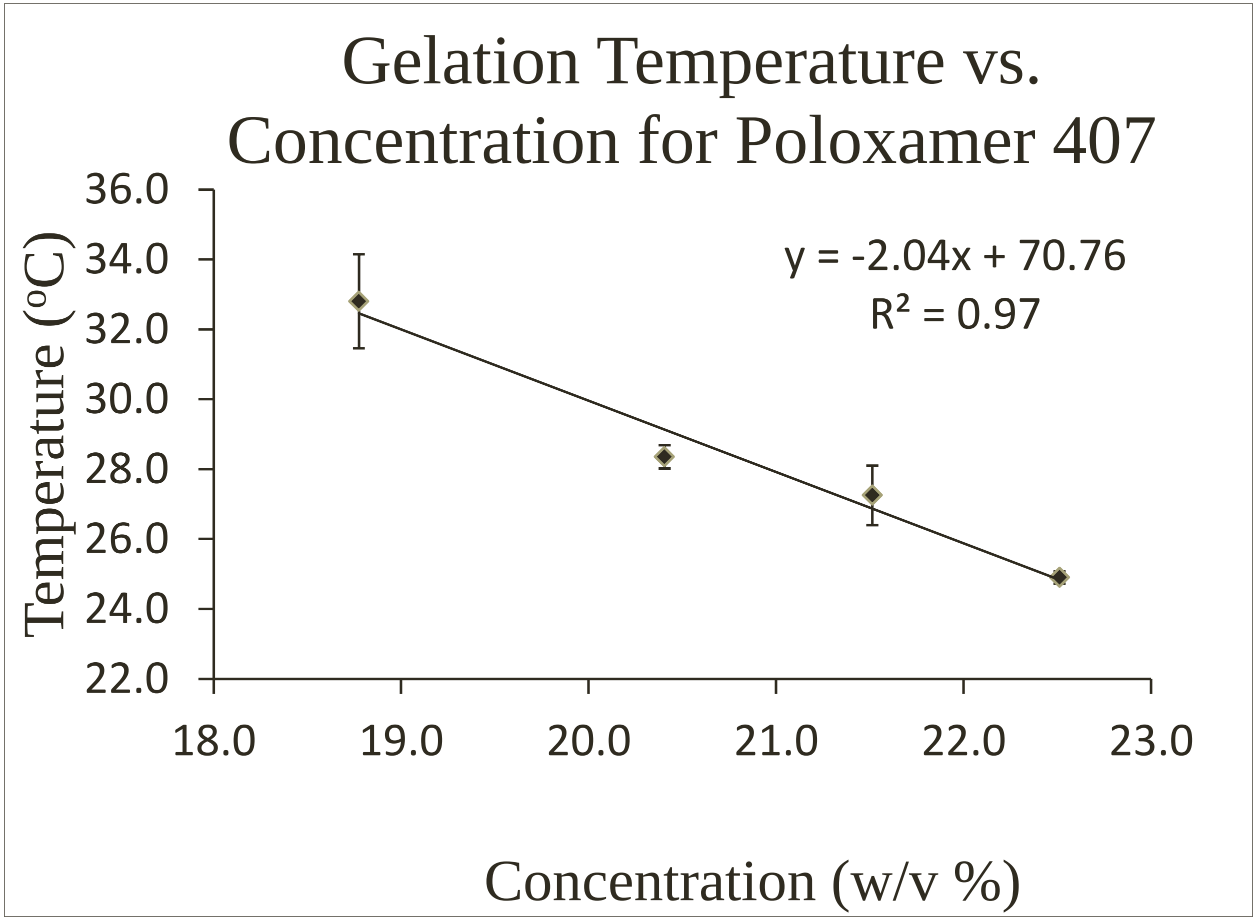
Cost

Material	Estimated Max Quantity	Cost
Poloxamer 407 ($120 for 1kg; Sigma Aldrich)	47.5 grams, 19.0 %w/w	$5.70
Poloxamer 188	12.5 grams, 5.0%w/w	$0.88
PEG 400	12.5 grams, 5.0%w/w	$0.38
Methylcellulose	5.0 grams, 2.0 %w/w	$1.50
Projected Product Cost		**$8.46**

Effects of an additive on visocisty

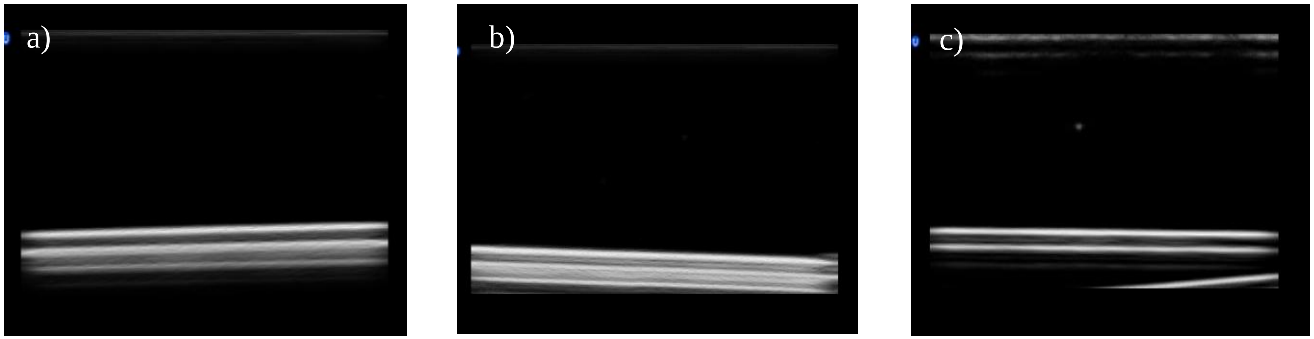
- Gelation temperature reducing additive is added to the poloxamer solution.
- The gelation temperature is decreased.
- Less poloxamer 407 is necessary for the 32^{o}C sol-gel transition temperature.
- Viscosity decreases and the poloxamer solution is able to be injected within the peritoneal cavity through a 20 gauge needle.

Gelation Temp. vs. Concentration



Imaging

Ultrasound



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

CT Scan

	D5W	19.0% Poloxamer	Gel – 19.0% Poloxamer
ROI	8.9 ± 2.9	14.1 ± 2.5	14.7 ± 2.2
ROI w/ Iohexal	220.6 ± 4.3	106.4 ± 2.3	N/A

Syringe guns

http://www.oki-usa.com/930-msg.aspx

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

In vivo