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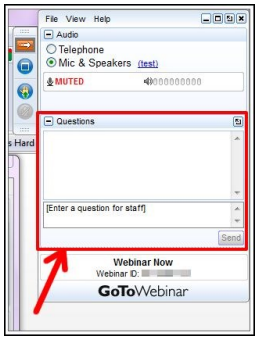

"Why am I muted?"
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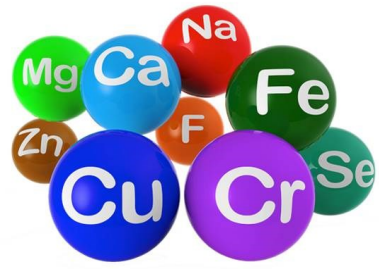

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"This particular webinar was exceptionally well presented and clear. It struck an appropriate balance for both the specialist and non-specialist alike. Kudos to the presenter."

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ACS Chemistry for Life®

Thursday, November 10, 2016

Cell Penetrating Peptides to Improve Cytosolic Drug Delivery

Session 11 of the 2016 Drug Design and Delivery Symposium

Dehua Pei, Professor, Department of Chemistry and Biochemistry, The Ohio State University

Scott Hart, Associate Director for Exploratory Pharmaceutical Sciences, Bristol-Myers Squibb

Thursday, November 17, 2016

Thanksgiving Chemistry for your Family's Feast

Guy Crosby, Science Editor, America's Test Kitchen and Adjunct Associate Professor, Harvard Chan School of Public Health

Bill Courtney, Culinary Chemist

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ACS Chemistry for Life®

2016 Material Science Series

"The Chemistry of Life: Instantly Treating Wounds with Hemostatic Gel"

Slides available now! Recordings will be available to ACS members.

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12

Technology Overview

Introduction to VETIGEL™

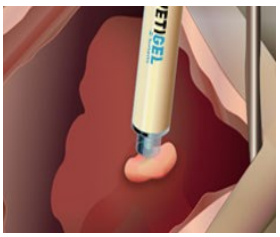
- Bringing the new technology to veterinary market under product name, VETIGEL™
- 5 mL syringe of gel comprised of two biopolymers
- When directly applied to the source of bleeding, VETIGEL™ rapidly adheres to the wound-site & stops the flow of bleeding by creating a mechanical barrier

Cresilon

Application

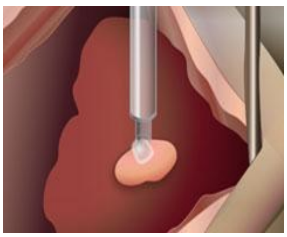
- VETIGEL™ allows the body to build a strong, natural clot without the need for applied pressure

1



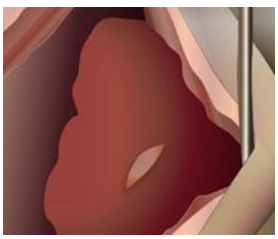
Apply VETIGEL™ directly to the wound to stop bleeding instantly.

2



Apply removal solution via a wipe for easy removal of excess VETIGEL™.

3



Remove VETIGEL™ or leave in place to be absorbed.

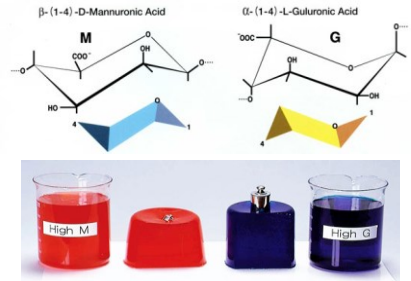
Cresilon

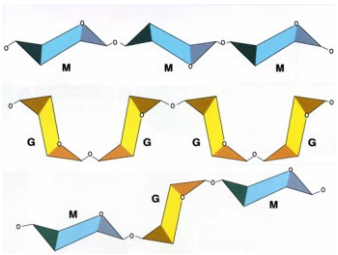
Formulation

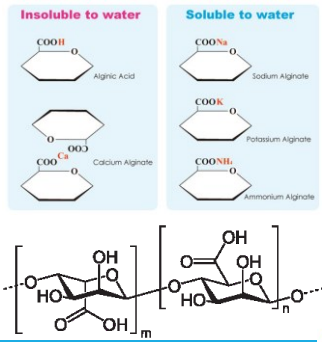
- VETIGEL™ is composed of two plant based polymer components
  - Polymer A: derived from seaweed/algae, serves as primary scaffolding component for polymer B & ECM particles
    - "Polyanionic" – has ability to be crosslinked by a positively charged divalent cation
  - Polymer B: dispersed in polymer A solution, with which it ionically interacts
    - "Polycationic" particle – present as a solid-particle in the polymer A matrix
- Both polymers are naturally derived, which gives the gel natural variability based on source material

Polymer A in Depth

- Linear copolymer with homopolymeric blocks of (1-4)-linked β-D-mannuronate (M)
- Its C-5 epimer α-L-guluronate (G) residues, respectively, covalently link together in different sequences or blocks





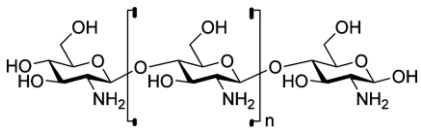


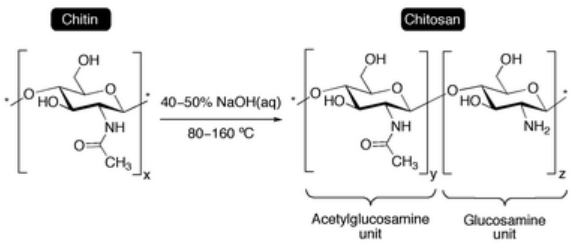
Polymer A Takeaways

- Gel's adhesive property is determined by polymer A's ratio to water
- High entanglement potential is ideal
  - Longer chains increase entanglement
  - Provide strong scaffold

Polymer B in Depth

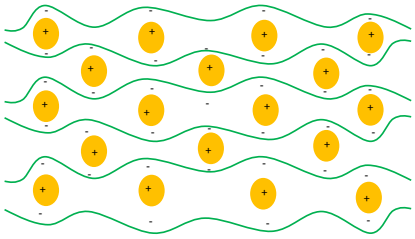
- Polymer B is cationic and soluble in low pH solvents
  - Known hemostatic agent due to deacetylated groups – higher deacetylated groups increase cellular adhesion and initiation of the wound healing cascade
  - Possesses antimicrobial properties
- Same antimicrobrial properties can induce hemolysis due to deacetylated groups
  - Need to strike a balance





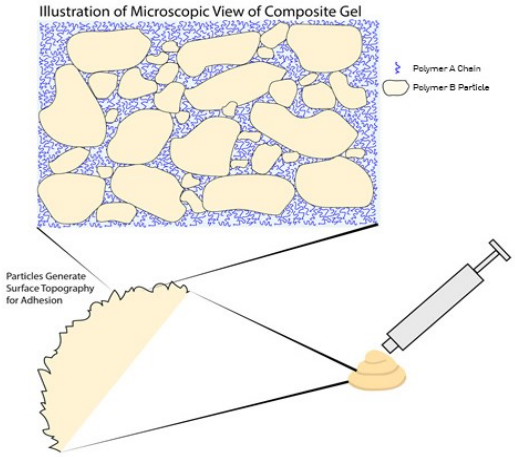
Interaction

- Polymer A chains physically entangle, but may be attracted to positively charged polymer B particles that are dispersed in solution
  - Attraction is dependent on pH of gel and protonation state of Polymer B amine groups
- Result is a very adhesive and highly viscous hemostatic product
  - Combination of strong cohesive and adhesive properties create a robust seal



How It Works

- Through the dissolution of Polymer A in water, a viscous polymer gel is formed. The addition of insoluble Polymer B particles creates a granular composite material
- The composite gel is a flowable, thick paste that adheres to tissue and forms a physical barrier to stop bleeding



Audience Trivia Question #1

Which of the following solutions will NOT solidify VETIGEL?

- ❑ $CaCl_2$ (aq)
- ❑ KCl (aq)
- ❑ $ZnSO_4$ (aq)
- ❑ $Fe(NO_3)_3$ (aq)

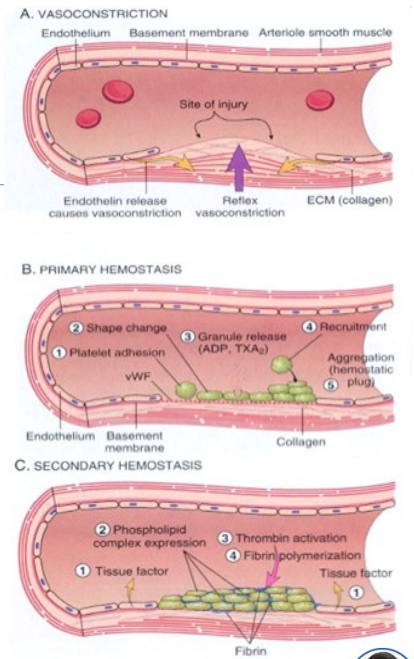
Removal

- Once the bleeding stops, 10% w/w calcium chloride solution may be applied
- Calcium ions exchange with Polymer A to crosslink the hydrogel matrix and releases saline, which disengages the product from any surface

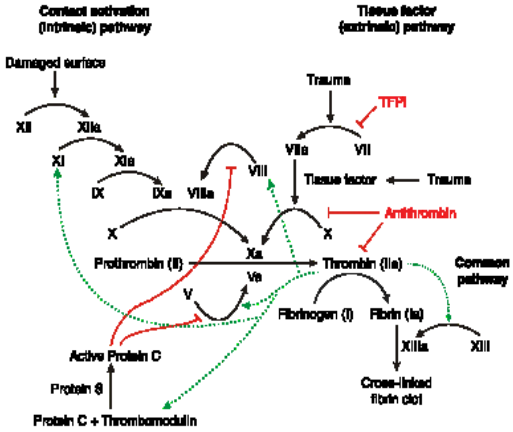
VETIGEL™ Mechanism of Action

Overview of Hemostasis

- Primary hemostasis – Injury occurs in the vessel wall
  - Injured vessel constricts to restrict blood flow
  - Presence of the sub-endothelial layer allows platelets to adhere and activate; form plug to recess the bleed
- Secondary hemostasis – Involves the coagulation cascade
  - Series of biochemical reactions that ultimately leads to the formation of fibrin polymerization
  - Further stabilizes the initial plug



Coagulation Cascade



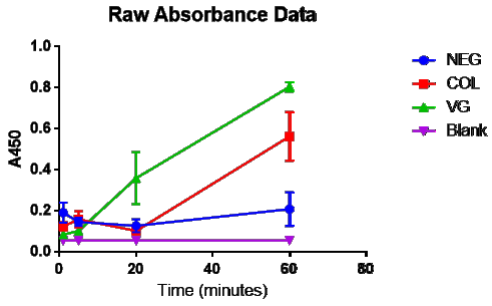
- Cascades of highly complex formations and reactions that require calcium, cofactors, and phospholipid surfaces
  - Thrombin converts fibrinogen to fibrin monomer
  - Fibrin monomer crosslinks to fibrin
  - Forms "glue" for platelet plug, strengthens the clot

Audience Trivia Question #2

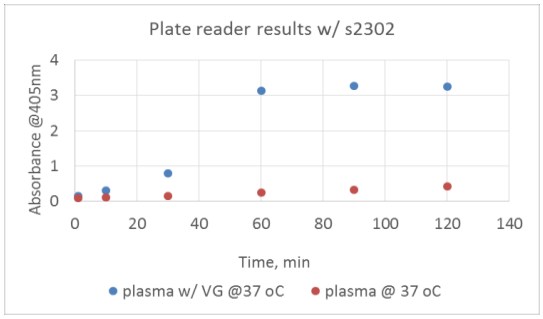
Hemophilia A is caused by a deficiency of which clotting Factor?

- ❑ Factor VII
- ❑ Fear Factor
- ❑ Factor VIII
- ❑ Factor II

Biochemical Impact



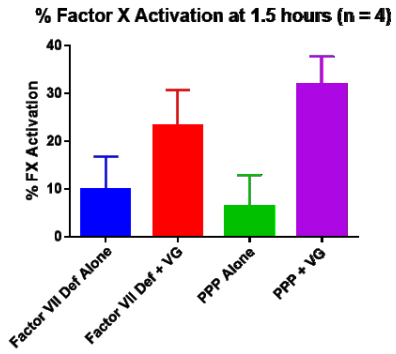
Absorbance readings directly correlating to Factor XIIa-C1 inhibitor concentration in the samples (of PPP) over a span of 1 hour



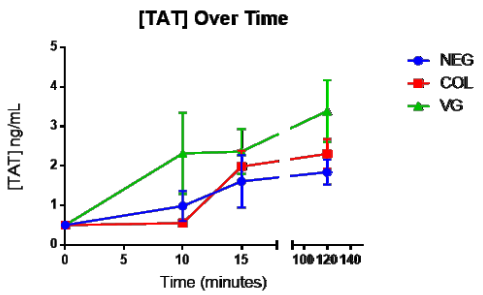
Substrate absorbance at 405 nm was monitored with and without VG in the presence of plasma at 37 deg C. Results showed that VG notably expedites the kallikrein-like behavior of plasma

VETIGEL™ increases rate of coagulation via activation of the contact pathway

Biochemical Impact



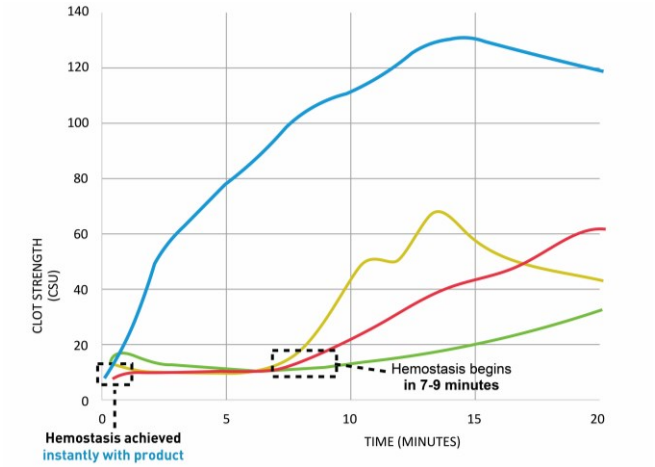
ith and without VG. Factor VII deficient plasma was used as well as PPP from a fresh donor.



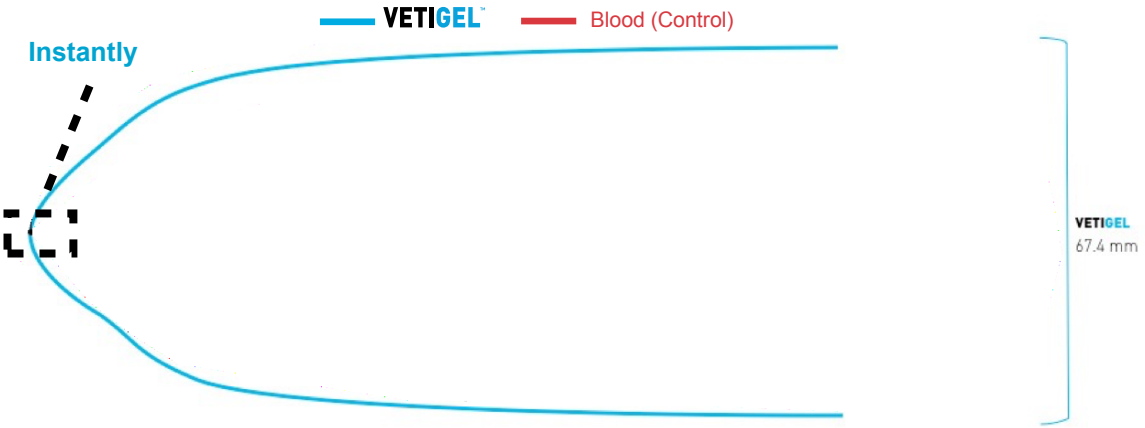
Concentrations of thrombin-antithrombin in PRP incubated with VG, collagen and just the polystyrene plastic alone over a course of 2 hours.

VETIGEL™ promotes coagulation factor activation but does not generate non-physiological levels of thrombin

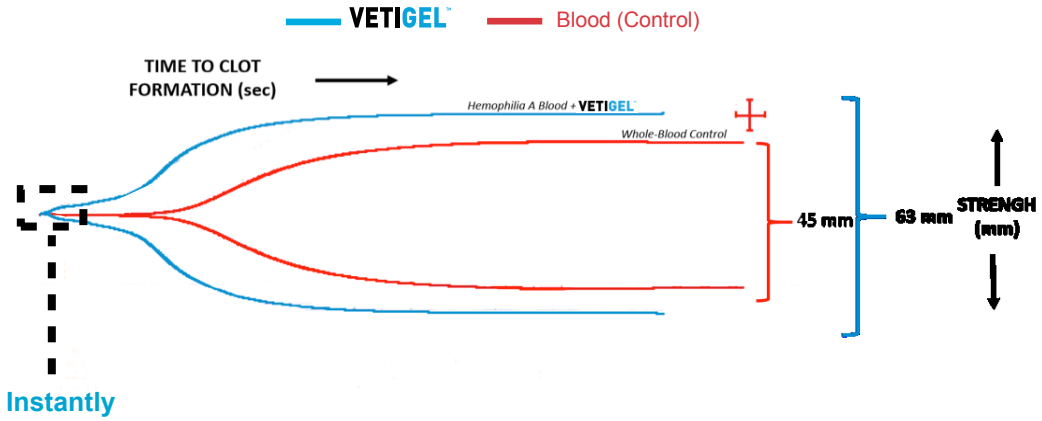
Sonoclot®



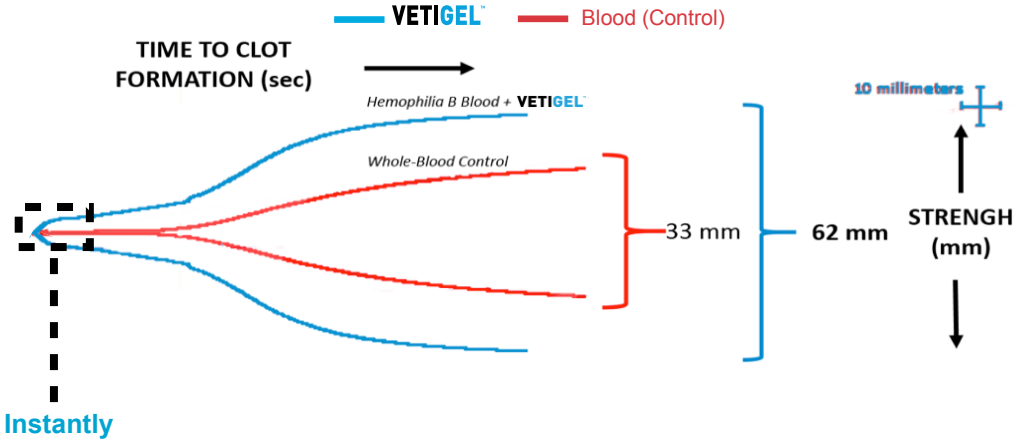
Standard Blood TEG



TEG Hemophilia A



TEG Hemophilia B



Impact on Coagulation

- Increases rate of coagulation in vitro via activation of the contact pathway
- Promotes coagulation factor activation but does not generate non-physiological levels of thrombin
- As a viscous yet granular material, the gel also provides a surface for non-specific attachment of the body's blood cells via the gel's surface topography – this enables rapid clot formation that can achieve hemostasis

Characterizing Materials

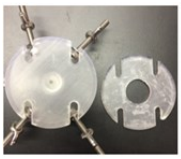
- Raw Materials
  - Molecular weight (PolyA and PolyB)
  - Degree of Deacetylation (PolyB): influence on the gel, packing
  - Particle size distribution, packing fraction, shape/morphology (Poly B)
  - M to G block ratio (PolyA)
  - Other QC Assays – determination of impurities, heavy metals, bioburden, sterility, etc.
- Final Product (current focus)
  - Rheology/viscoelastic properties
  - Burst Assay

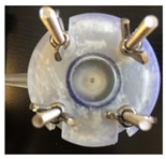
Burst Assay Overview

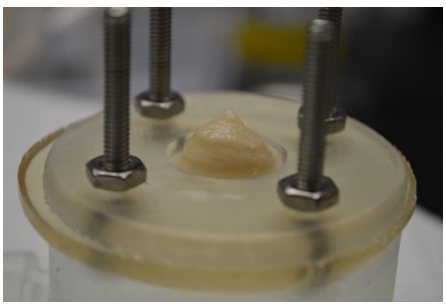
- Based off of ASTM F2392-04: Burst Strength of Surgical Sealants
- Observe gel's burst performance by applying a constant flow rate to increase fluidic pressure
  - Similar to a bleeding biopsy
- Test is completed once fluid is observed flowing out of the stage
- Data collected
  - Final burst pressure
  - Failure mode

Burst Assay Brief Procedure

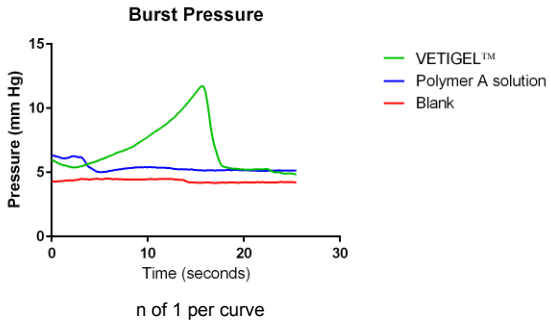
- Dry collagen casings rehydrated with salt solution
  - NaCl and CaCl2 are at physiological concentrations with respect to blood
- 3 mm hole induced in rehydrated casings
  - 2 ml of gel applied over the biopsy hole and placed on stage
  - 2ml/min flow rate is applied until the gel fails
- Pressure readings captured by a differential pressure transducer
  - Each group requires 10 replicates







Burst Assay Data Examples



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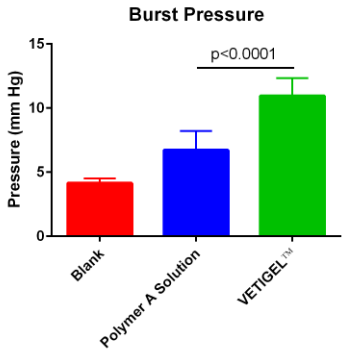


Impact of Component Formulation on Material Properties

How does varying the ratios of the components impact the viscoelastic signature of the final product?

Audience Trivia Question #3

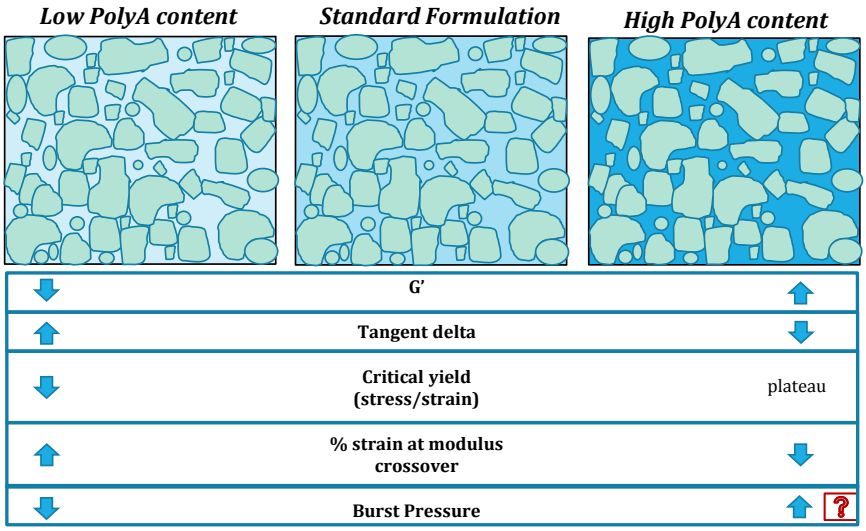
A gel made with too much Poly A will exhibit which of the following characteristics?

- ❑ % strain at modulus crossover will increase
- ❑ G' will increase
- ❑ Max pressure on burst assay will decrease
- ❑ Efficacy will increase

Defining Release Criteria

- To fully understand product tolerances and define release criteria, several libraries were constructed to determine the impact of the individual components on the composite gel:
  - Poly A Library (changing poly A concentration)
  - Poly B Library (changing poly B concentration)
  - Particles size library (changing average particle size/diameter)
  - Water Content Library (changing volume of water - thus simultaneously changing poly A and poly B concentration)

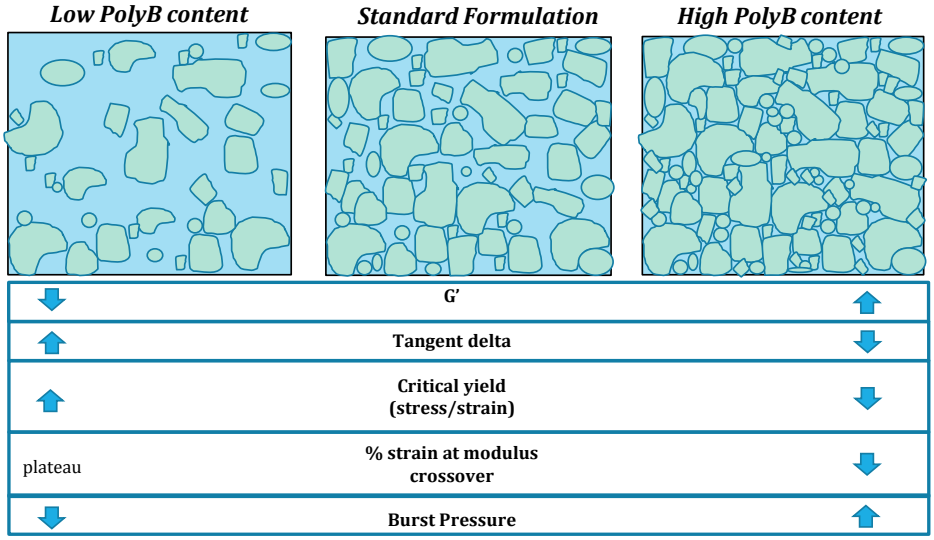
Understanding the contribution of Polymer A to the viscoelastic properties of the final product



Polymer A – Structure Stabilization

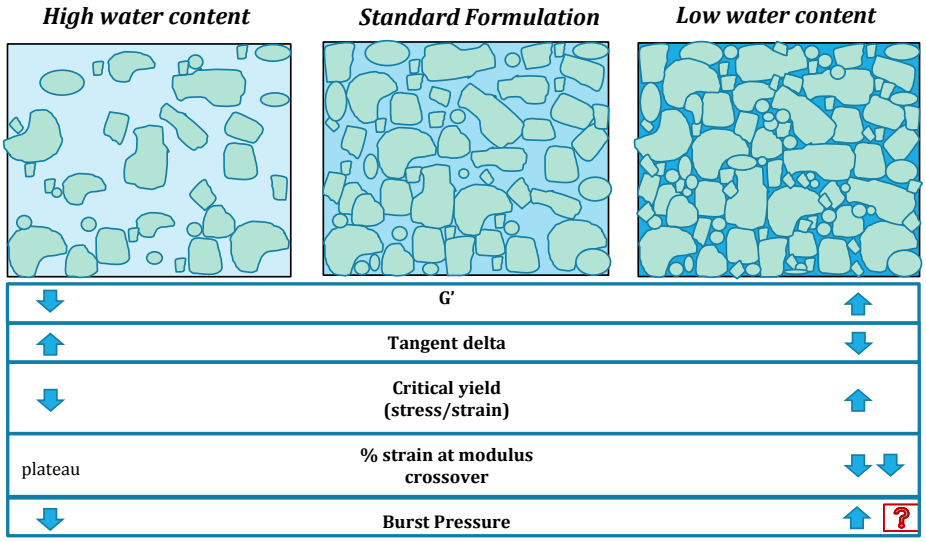
[redacted]

Understanding the contribution of Polymer B to the viscoelastic properties of the final product



Polymer B – Structure Reinforcement

Understanding the contribution of water/hydration to the viscoelastic properties of the final product



Water Library

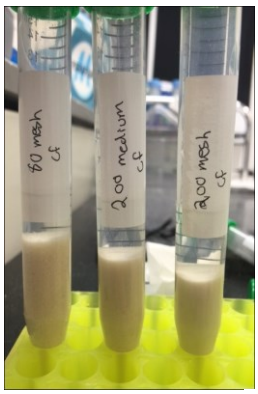
[redacted]

Impact of Process Development on Material Properties

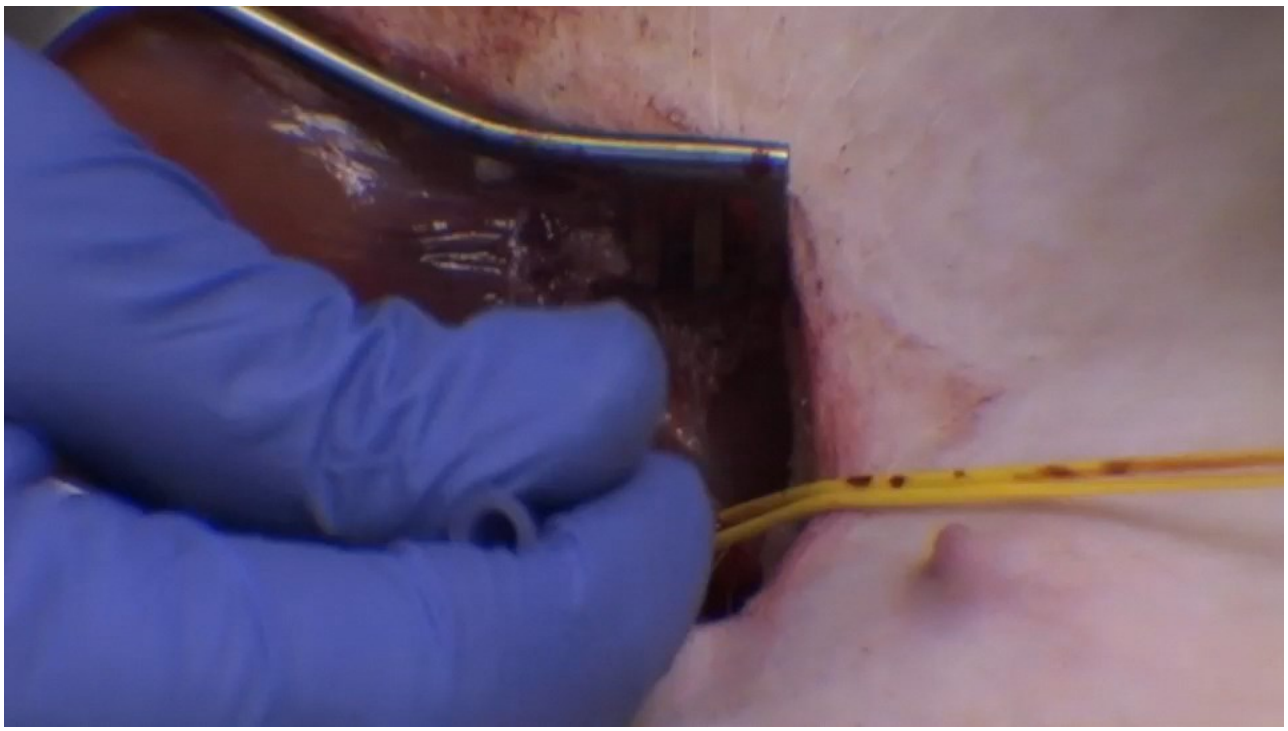
How does scaling the process from the bench to a manufacturing scale mixer affect final product viscoelasticity/function?

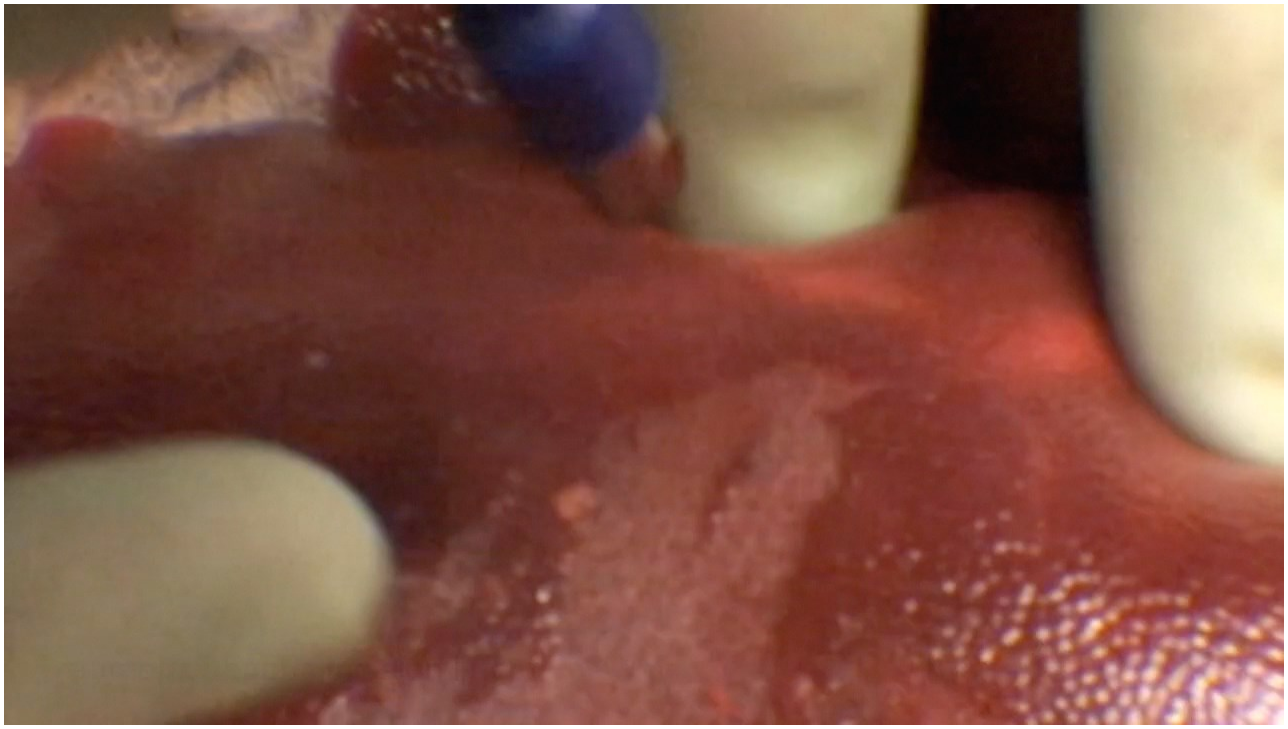
Protocols

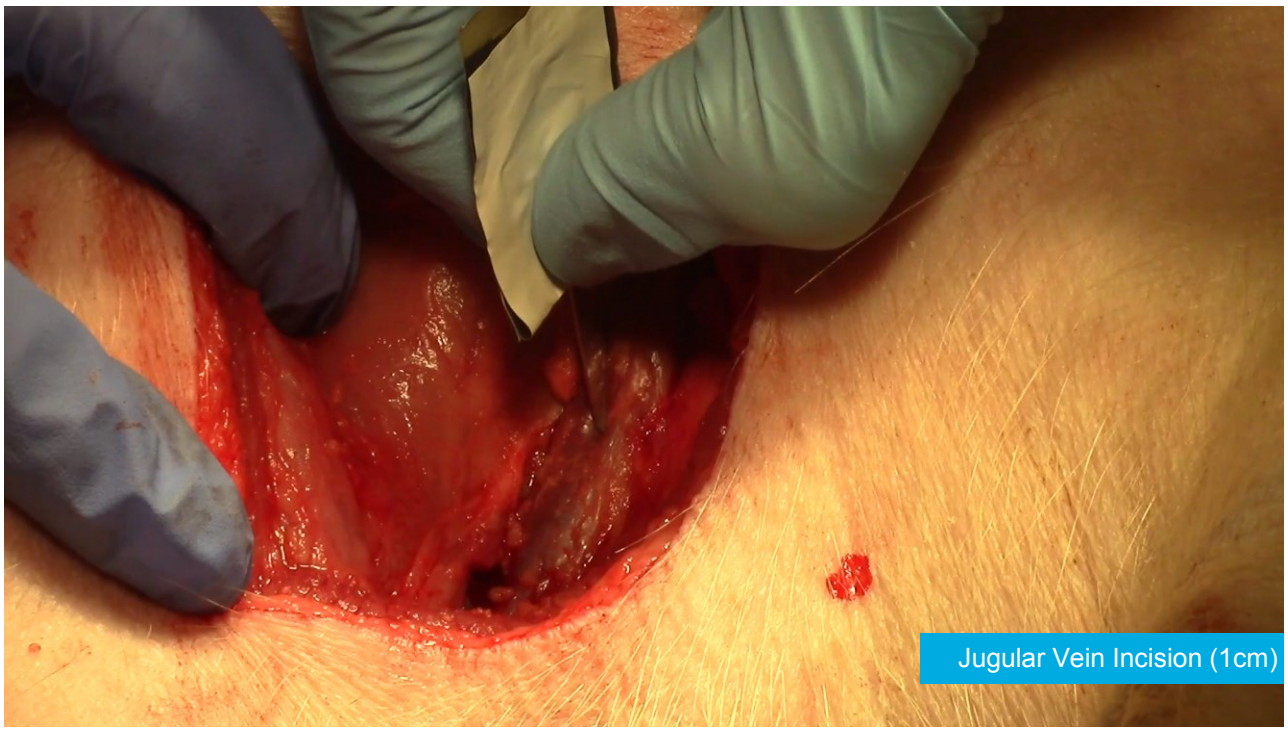
- Protocol was developed based on ASTM C 1252 and C 128 for the concrete industry
- Questions however remain as to:
  - High variability in specific gravity calculations
  - Impact of degree of deacetylation



In Vivo Efficacy of VETIGEL™






Jugular Vein Incision (1cm)

Path Forward

New Facility

TRAUMAGEL™ & Beyond

- Cresilon will file a *de novo* 510(k) pre-submission packet in Q4 2016

Questions?

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Thursday, November 10, 2016

Cell Penetrating Peptides to Improve Cytosolic Drug Delivery

Session 11 of the 2016 Drug Design and Delivery Symposium

Dehua Pei, Professor, Department of Chemistry and Biochemistry, The Ohio State University

Scott Hart, Associate Director for Exploratory Pharmaceutical Sciences, Bristol-Myers Squibb

Thursday, November 17, 2016

Thanksgiving Chemistry for your Family's Feast

Guy Crosby, Science Editor, America's Test Kitchen and Adjunct Associate Professor, Harvard Chan School of Public Health

Bill Courtney, Culinary Chemist

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62

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65

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Scott Hart, Associate Director for Exploratory Pharmaceutical Sciences, Bristol-Myers Squibb

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66