Lipid-Coated Alginate Gels as a Drug Eluting Vessel

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Motivation

- Controlled release allows for conditional drug release for example:
  - Zero order (constant release rate), temperature controlled, pH dependent, mechanically induced release
- Our focus: **Drug release triggered by cell binding** (cell-binding induced drug release)
  - Cell binding disrupts lipid bilayer structure creating microgel-environment interface for drug to diffuse outward
- Why cell-binding induced drug release? **(Fig 1)**
  - To release drug upon cell activation in response to physiological process such as platelet activation during wound healing

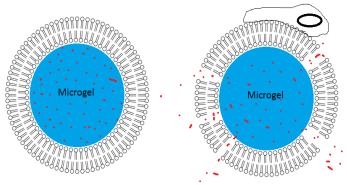

Figure1. Illustration of cell-binding induced drug release. Upon cell binding, traction forces from the cell disrupt the lipid bilayer structure exposing the microgel surface to the environment. The drug is then able to diffuse out of the gel.

Specific Aim

- Create monodisperse spherical microgels with 100µm diameter using microfluidics and inverse emulsion
  - Microfluidics offers
    - Automated process
    - Creates high output of gels with the same morphology
  - Monodispersity allows for consistent strain applied to the gel upon cell binding across different gels
    - Factor for release rate
  - Spherical shape required

Materials & Methods

- Microfluidic Device **(Fig 2)**
  - Polydimethylsiloxane channels created via soft lithography
  - PDMS chip with embedded channels sealed to glass microscope slide using oxygen plasma
  - Channels coated with Novec 1720 (0.1% fluorosilane in fluoroether solvent) to ensure channel hydrophobicity
- Inverse Emulsion and other Solutions
  - Continuous phase: mineral oil and 1.5% Span 80
  - Disperse phase: 1.25% alginic acid in 150mM NaCl
  - Polymerization bath: 102mM CaCl2 with layer of mineral oil on top (to buffer impact into stagnant bath)

Materials & Methods

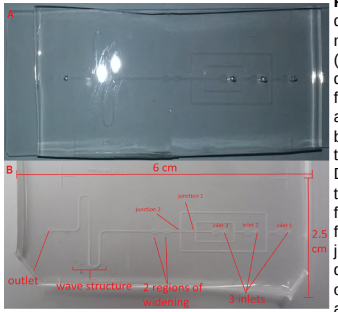

Figure 2. (a) Fully fabricated device sealed against glass microscope slide.
(b) Channel structure and dimensions. Device design is for double emulsion, but only a single emulsion was applied by flowing continuous phase through both inlets 1 and 2. Disperse phase was flowed through inlet 3. Droplets were formed at junction 1, and the flow rate was increased at junction 2. Droplets decreased velocity at regions of widening and were mixed at the wave structure.

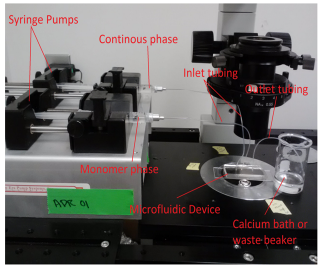

Figure 3. Complete set up. Calcium bath consisted of polymerization solution plus mineral oil which was mixed at 155 RPM with a magnetic stir bar.

Results

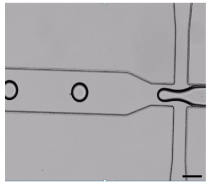

Figure 4. Droplets form through dripping (as opposed to jetting) at junction 1 as the two immiscible phases collide. Flow rates of each solution, viscosity, surface tension, and other factors impact the size of the droplets. Scale bar is 150 µm.

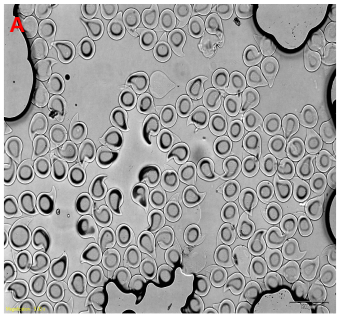

Figure 5. (A) Confocal image of gels collected after polymerization in calcium bath. All have a characteristic tear-drop shape. Scale bar is 200 µm as indicated.
(B) Image derived from Capretto et al. Illustration exhibits origin of tear-drop shape. Slow transition of the droplet from mineral oil phase to the calcium bath causes tail formation.

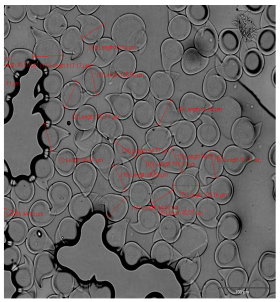

Figure 6. Gels were not radially symmetrical; a characteristic length was determined. This was the widest length within the most spherical or ellipsoidal region of the gel. Values were collected using a line measurement tool from the software cellSans.

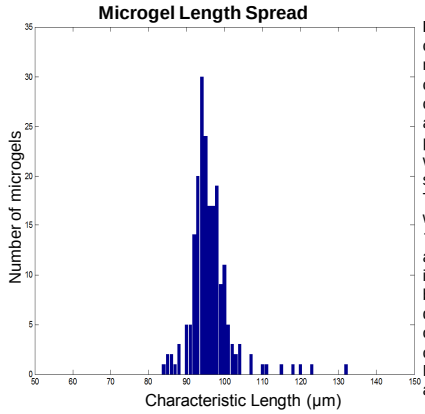

Figure 7. Histogram of the characteristic length of the microgels directly collected from the cellSans software. The average gel length was 96 µm, the standard deviation was 5.8 µm, and the sample size was 202 gels. There exists some outliers with a size greater than 100 µm. This may be attributed to droplet fusing in the polymerization bath, but since the standard deviation is less than 10% of the average, the spread can be considered narrow. Monodisperse gels were achieved.

Summary

) Specific Aim: Gel Production

- Alginate gels of characteristic length of approximately 100µm could be created using the chosen device
- Gels are monodisperse with a standard deviation less than 10% of the average length
- All gels exhibited a tear-drop shape due to a slow transition from the oil phase (mineral oil) into the polymerization solution (calcium bath

Future Work

- Eliminate tear-drop morphology
  - Experiment with increasing density of droplets to encourage faster transition from oil phase to polymerization bath
  - Apply partial polymerization by adding low concentrations of calcium to disperse phase to increase viscosity to stabilize shape
- Conduct pilot study observing cell binding
  - Optimize coating method for binding substrate such as polylysine
  - Create soft gels such that upon binding in 3D culture gels collapse
- Determine lipid type for coating
- Characterize cell traction forces
- Examine and quantify drug release in 3D culture

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References

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