Optimization of Particle Size for PLGA Nanoparticles Prepared by the Ouzo Effect

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Why Nanoparticles?

- Nanoparticles can be the right tool for the job
- Advantages
  - Enhanced bioavailability and controlled release
  - Penetration across biological barriers
  - Increased drug targeting efficiency

Methods for Nanoparticle Production

Materials

- Polymers
- Metals
- Ceramics
- Biological materials
  - Liposomes
  - Peptides

- Polymeric Nanoparticles
  - Nanoparticles formed using **monomers** as the starting point
  - Nanoparticles prepared using **preformed polymers** as the starting point

Methods Employing Preformed Polymers

- Emulsion Diffusion
  - Interfacial Precipitation
- Emulsion Evaporation
  - Double Emulsion Evaporation
- Salting Out
- Solvent Displacement
  - Nanoprecipitation, Solvent Diffusion, Spontaneous Precipitation, Ouzo Effect

Solvent Displacement

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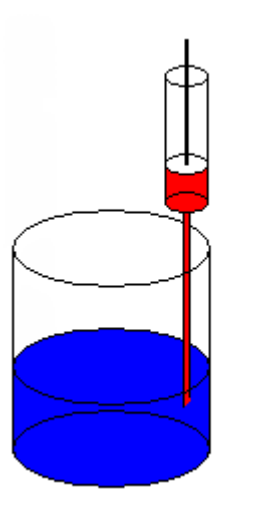
- This solution is added to an aqueous solution



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- This solution is added to an aqueous solution
- Rapid solvent diffusion leads to instantaneous nanoparticle formation
- Solvent is removed by evaporation

Solvent Displacement

- Advantages
  - Relatively simple process
  - Nontoxic solvents can be used
  - Does not require high shear stress
  - Does not require surfactants or stabilizers
- Disadvantages
  - Solvent evaporation can be time consuming
  - Poor encapsulation of hydrophilic drugs

Nanoparticle Characterization

- Size
- Surface Characteristics
- Encapsulation efficiency
- Drug Release
- Degradation
- Biocompatibility

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The Importance of Size

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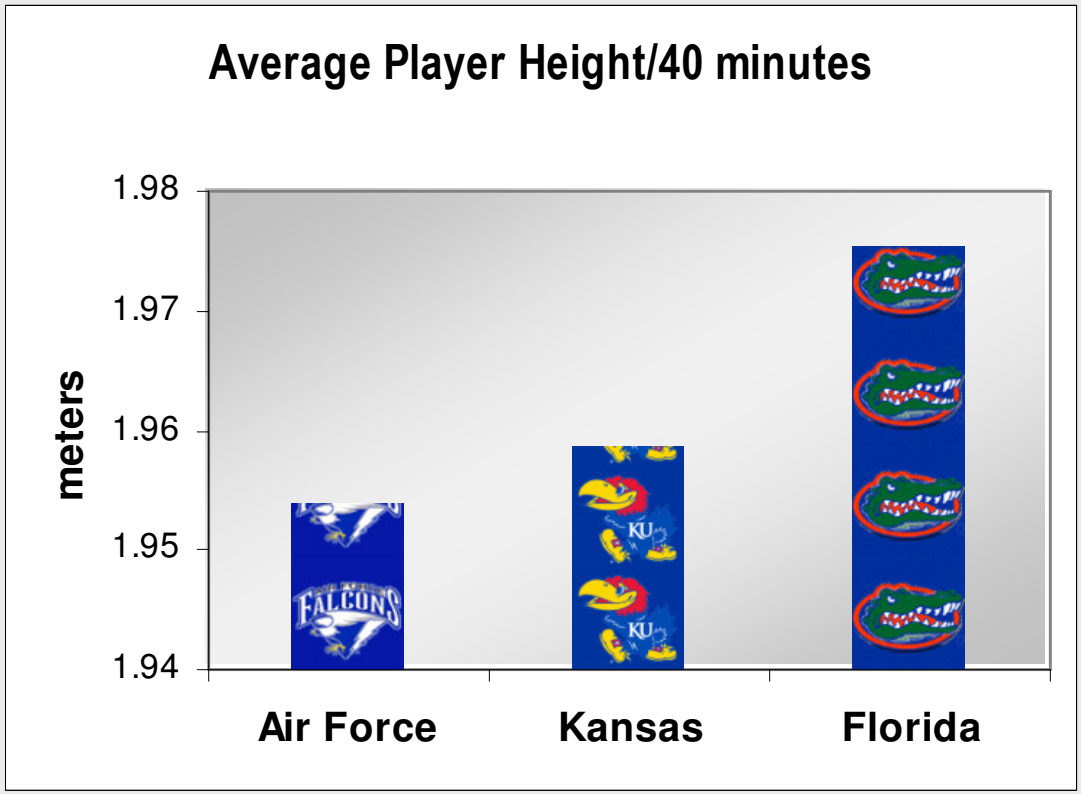
- Basketball



2005-2006 Season

The Importance of Size

NCAA Div. I Rank	Air Force	Kansas	Florida
Rebound Margin	296/326	20/326	59/326
Blocked Shots	281/326	20/326	22/326

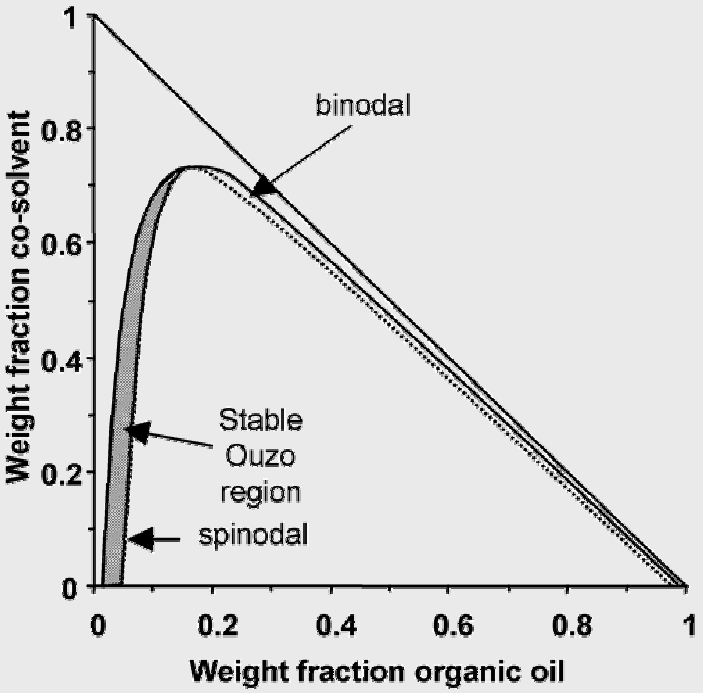
The Importance of Size

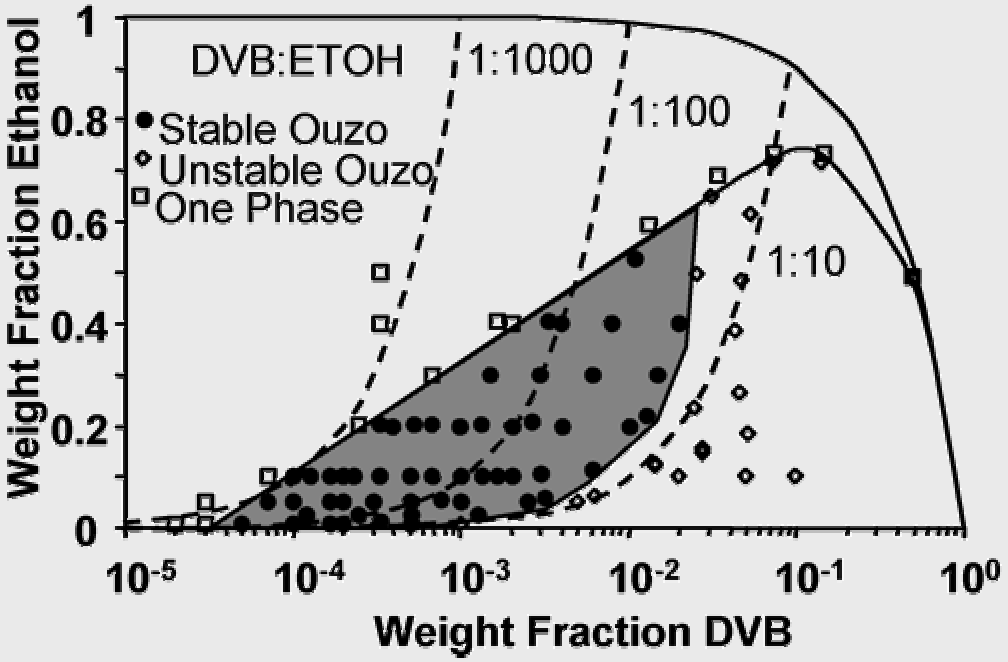
- Nanoparticle Size
  - Endothelial Permeability
    - Particle escape from vasculature
      - Liver sinus endothelium (up to 150 nm)
      - Tumor capillaries (up to 300 nm)
    - Blood-brain barrier
  - Splenic Filtration
  - Macrophage Clearance
  - Cellular Uptake
  - Particle Degradation and Drug Release Rates

Ouzo Effect

- Solvent displacement is also referred to as the Ouzo effect
  - Ouzo is a mixture of anethol, ethanol, and water (from anis seeds)
  - Additional water leads to micro/nanoparticle formation
  - Solution proportions fall into a thermodynamically metastable region
    - Homogeneous nucleation occurs
    - Leads to a uniform dispersion (milliseconds) followed by Ostwald ripening (seconds)

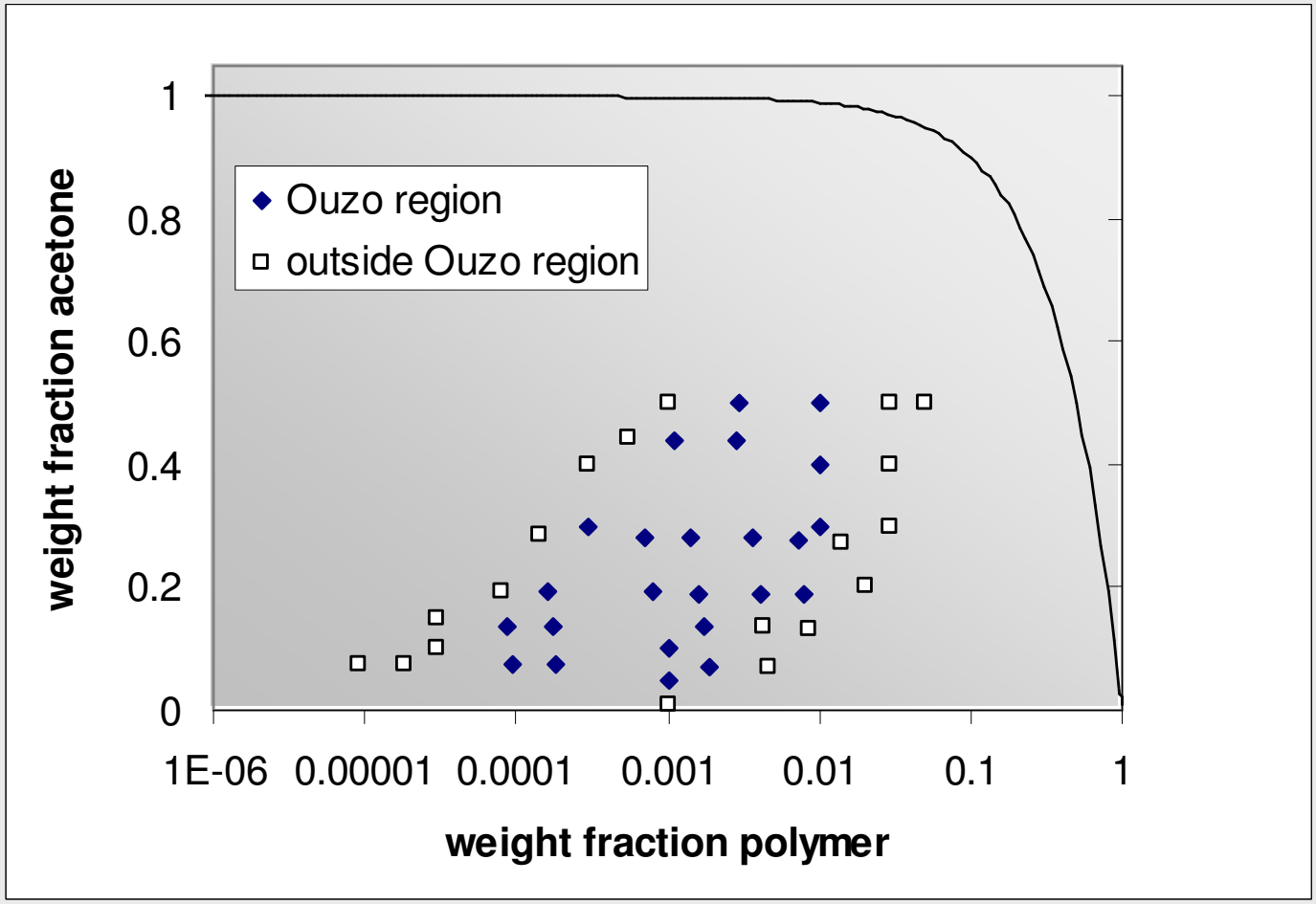
Ouzo Region





From Vitale and Katz, *Langmuir* 2003, *19*, 4105-4110.

Ouzo Region for RG502H/Acetone



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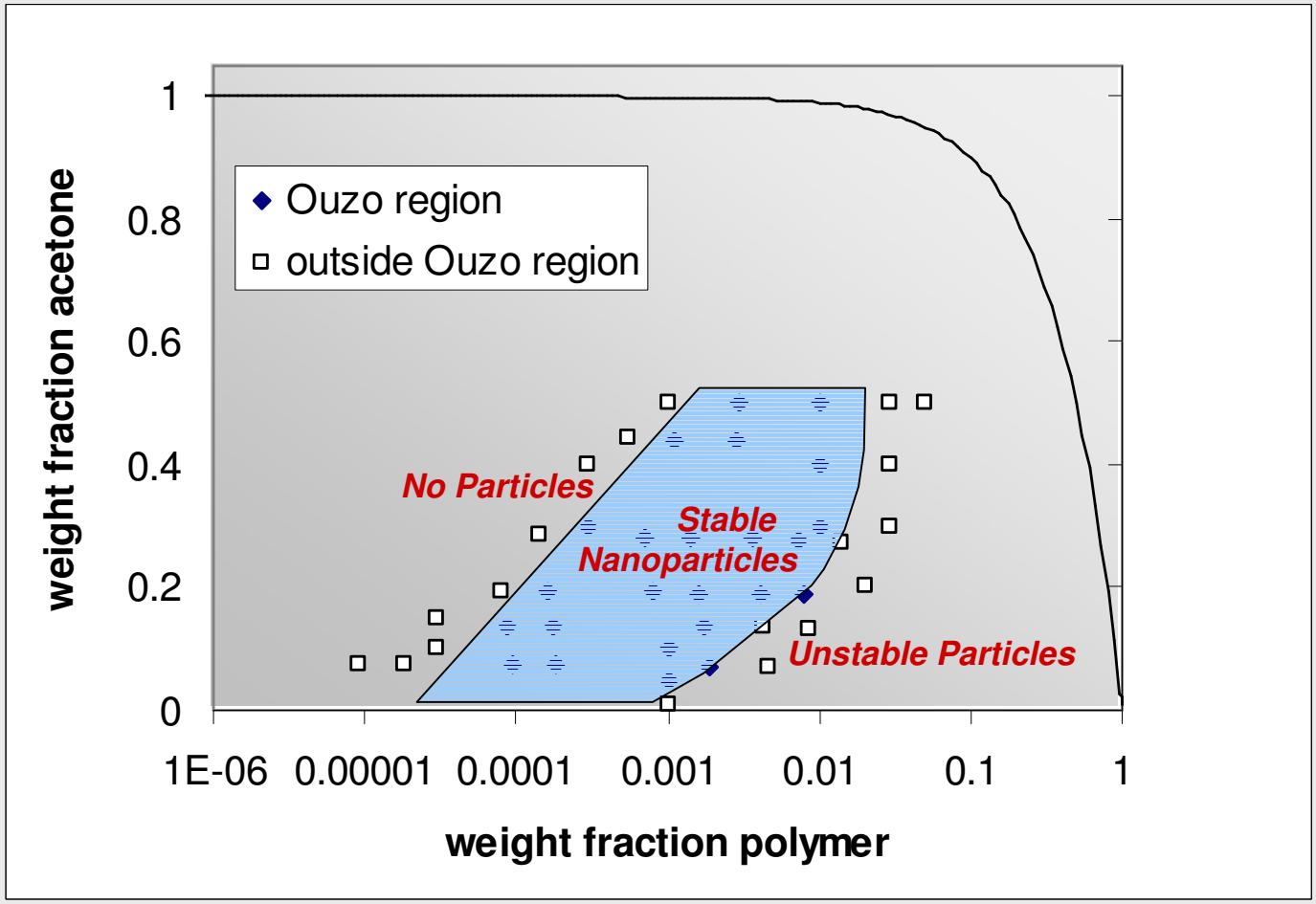
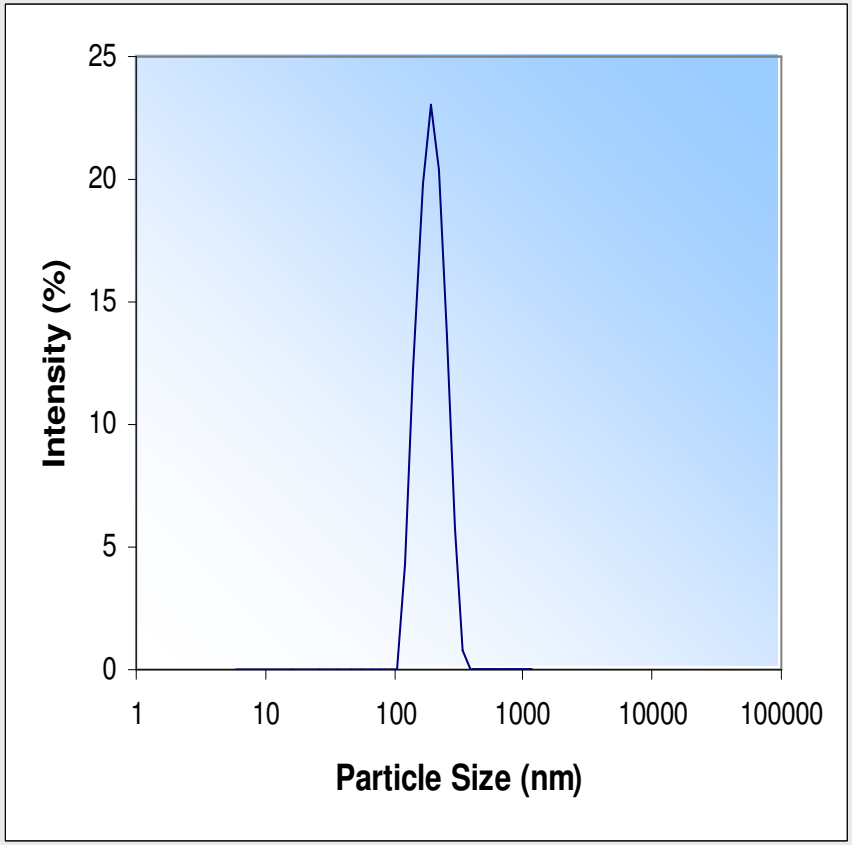
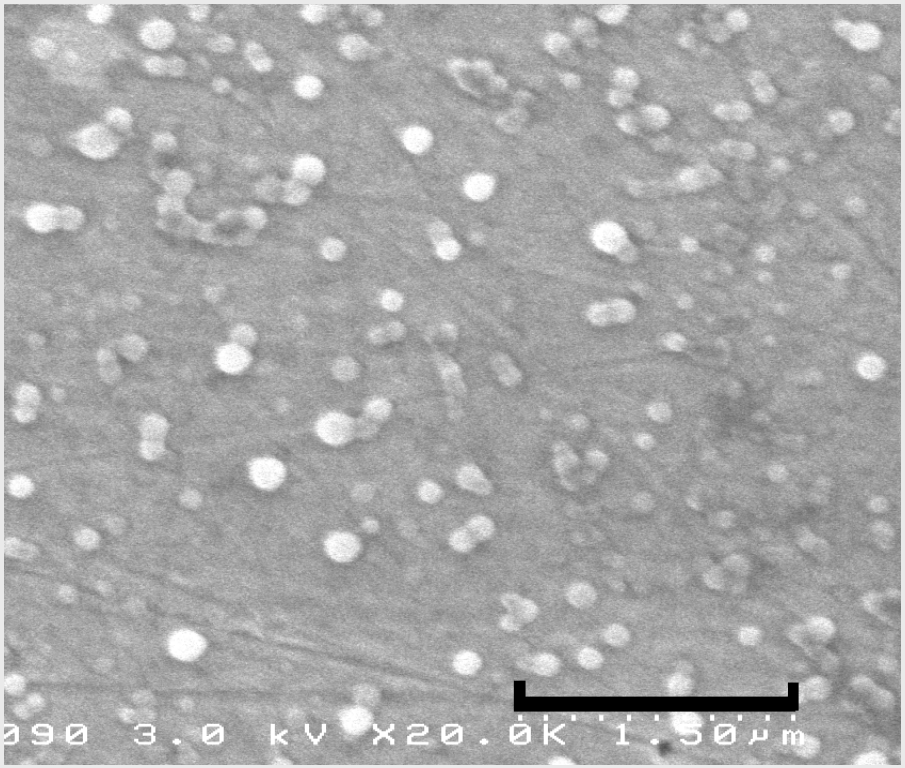
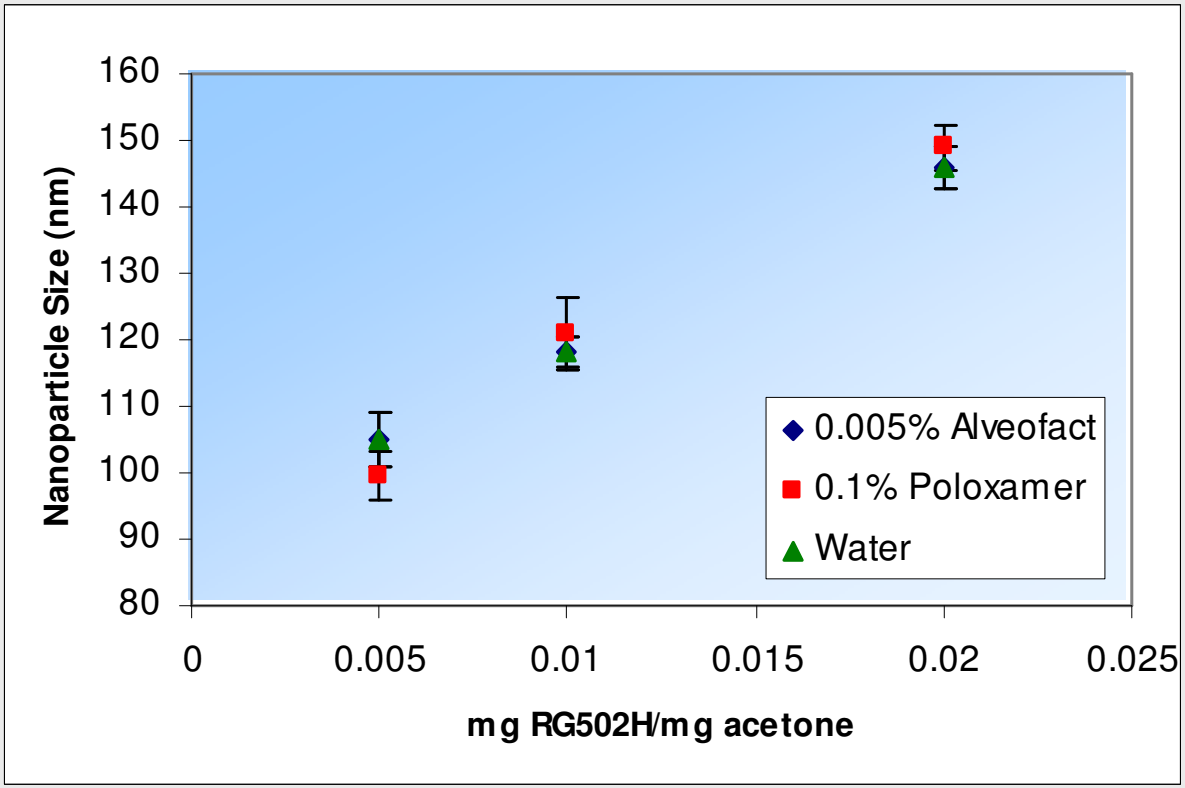


Particle Size Distribution

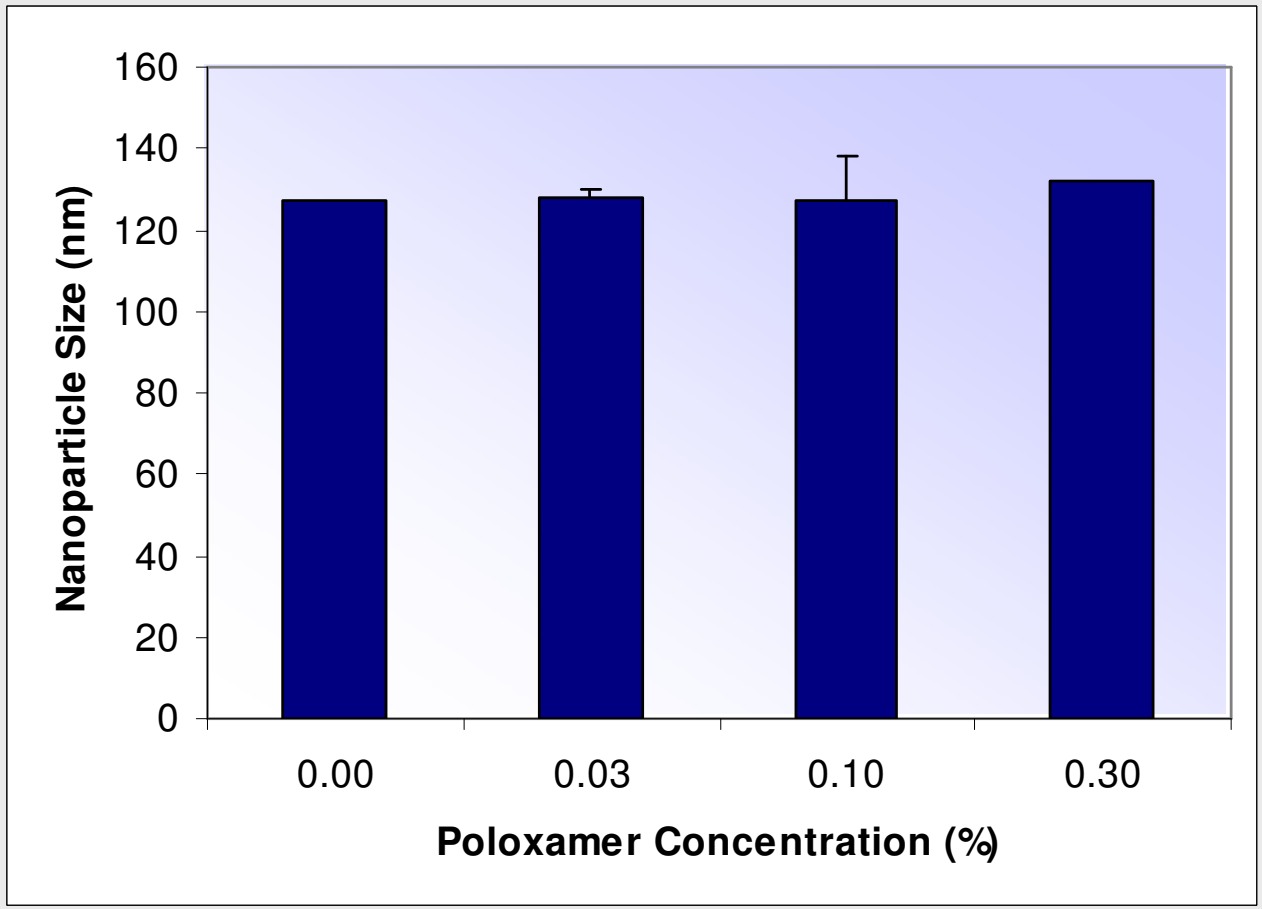




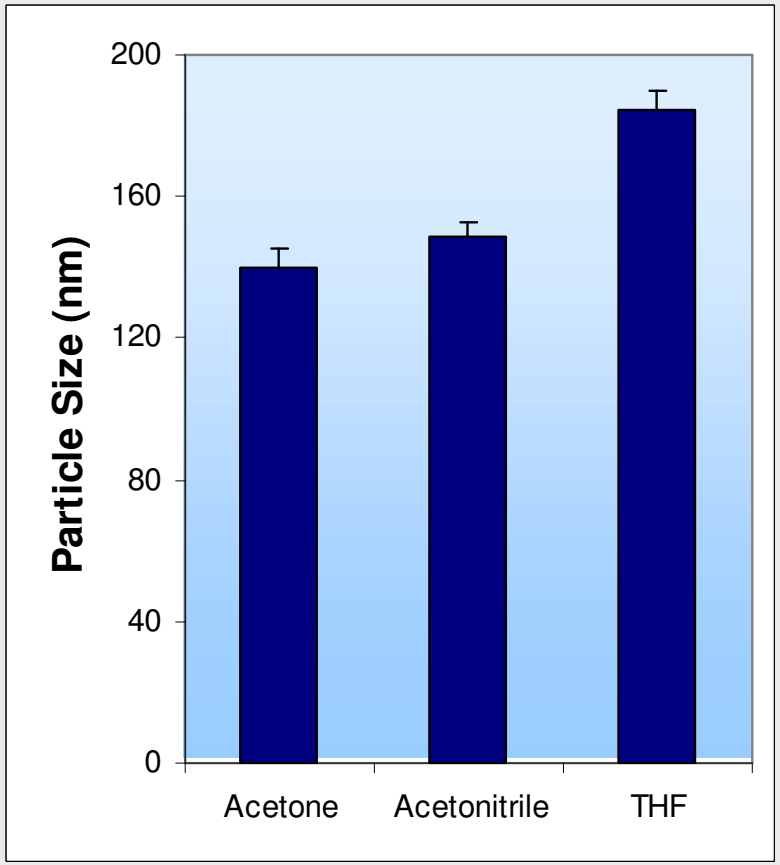
Surfactants & Polymer Concentration



Surfactant Concentrations



Different Solvents



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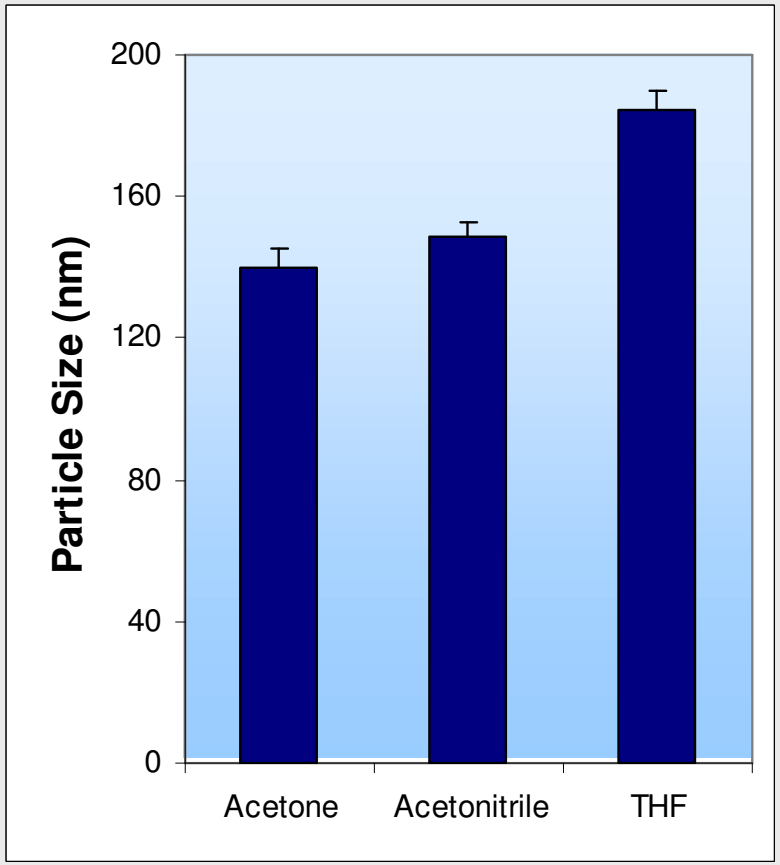
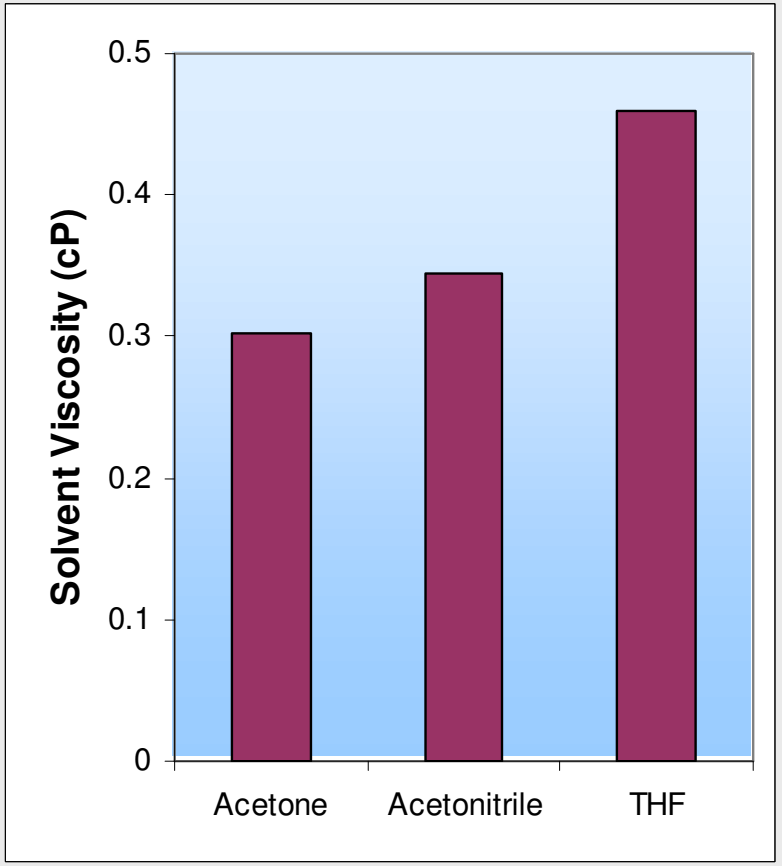
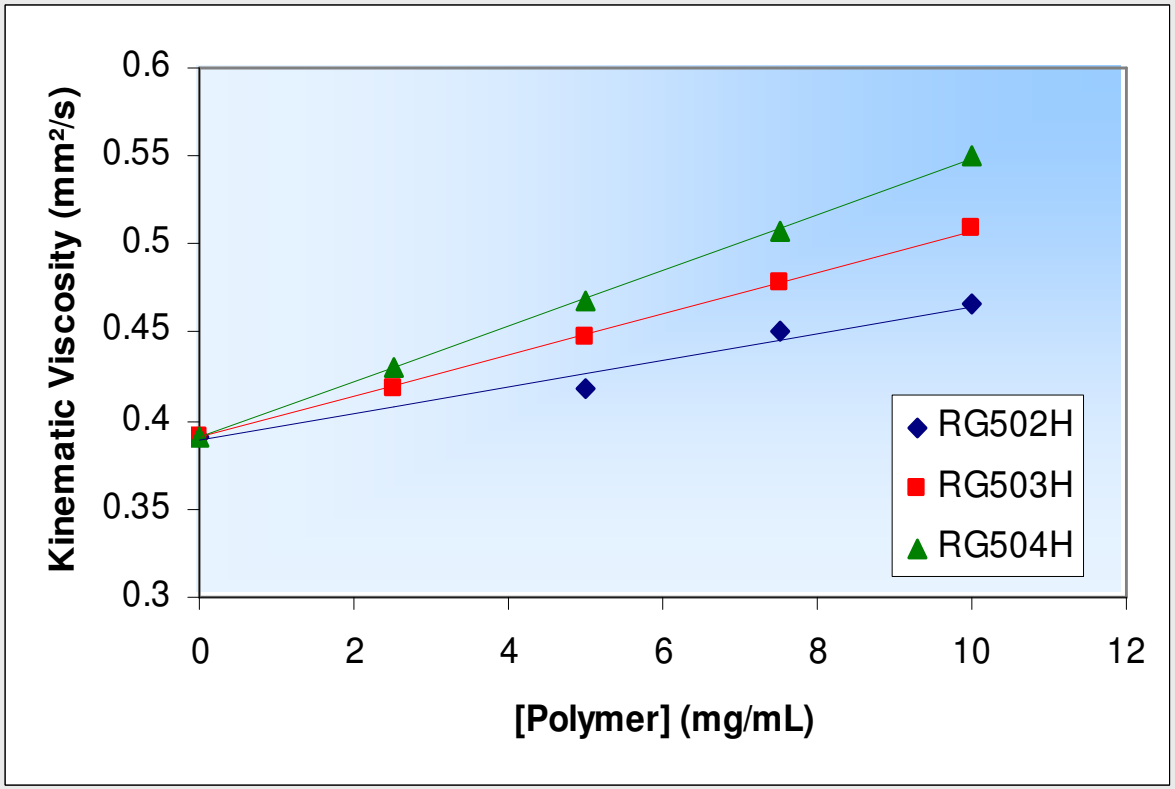


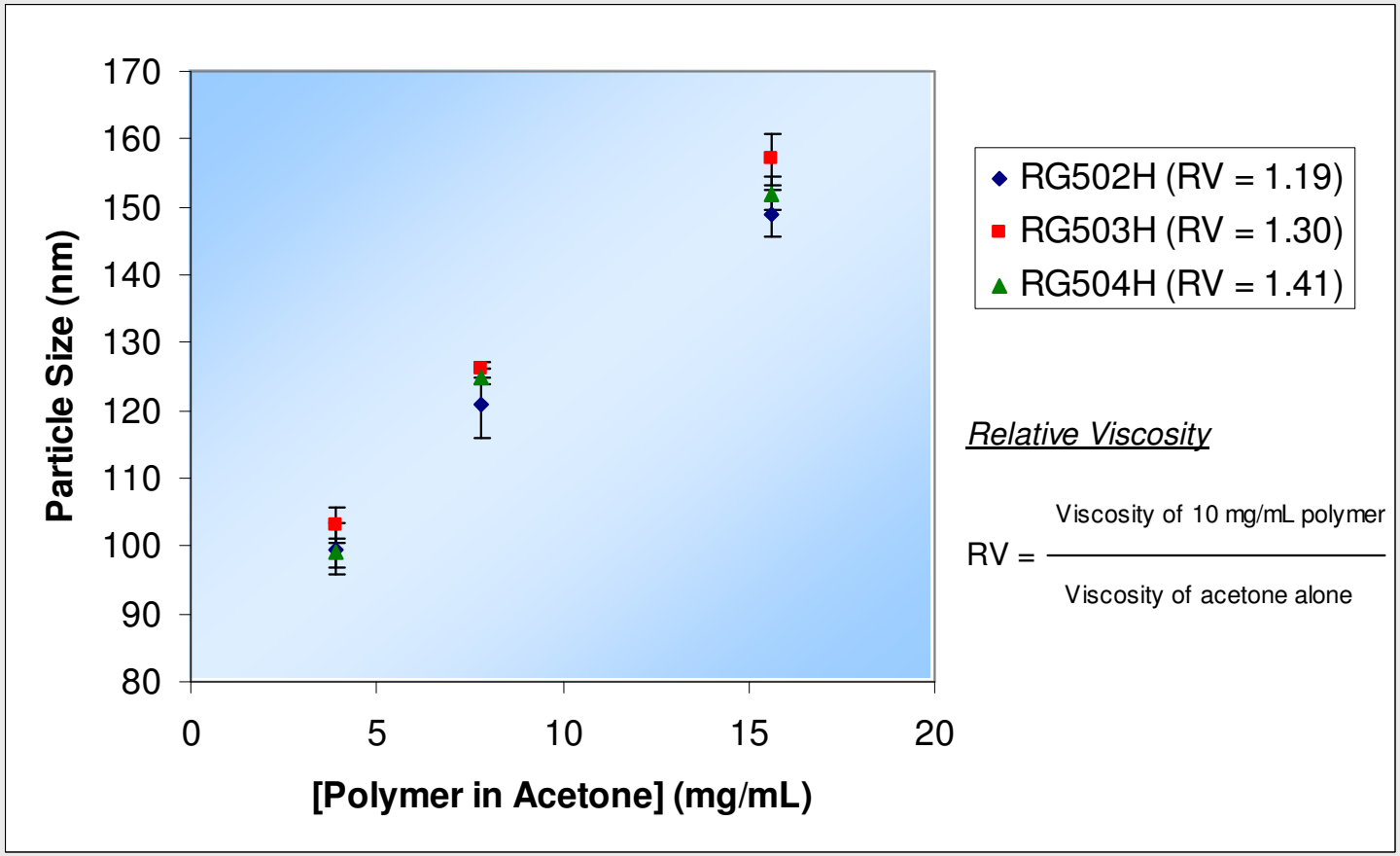


PLGAs of Increasing MW

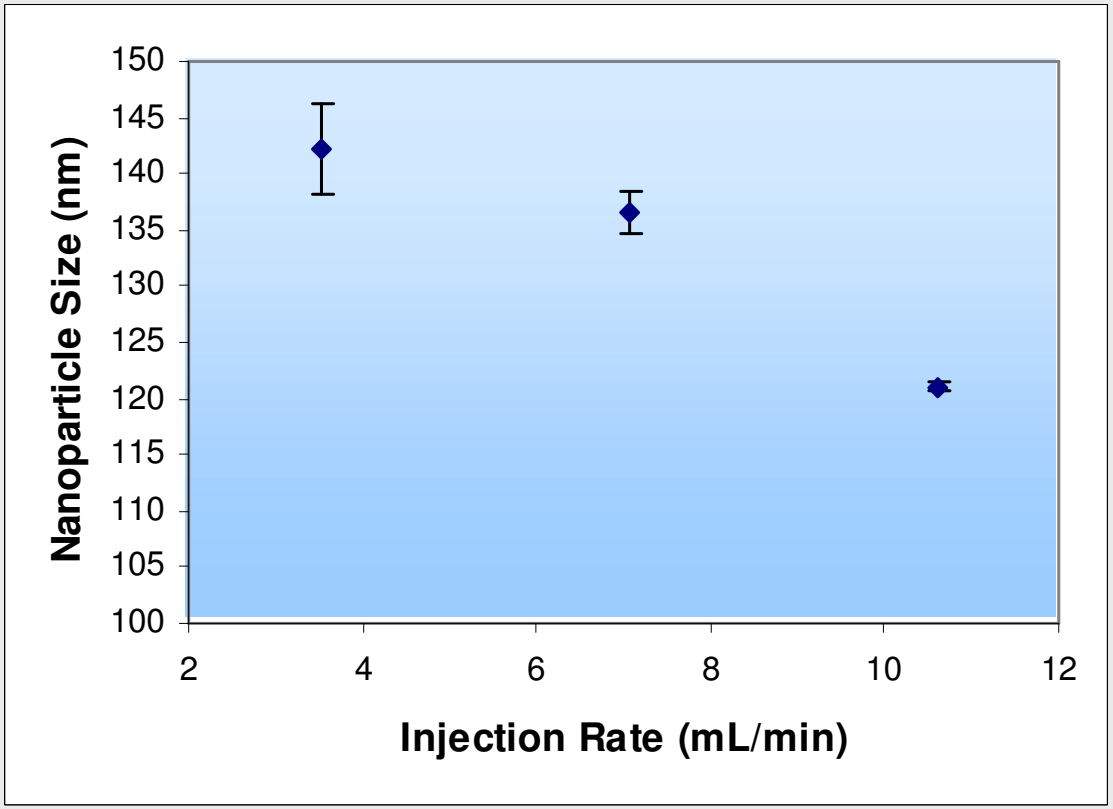
Polymer	M_n (kDa)
RG502H	12
RG503H	23
RG504H	48



Viscosity

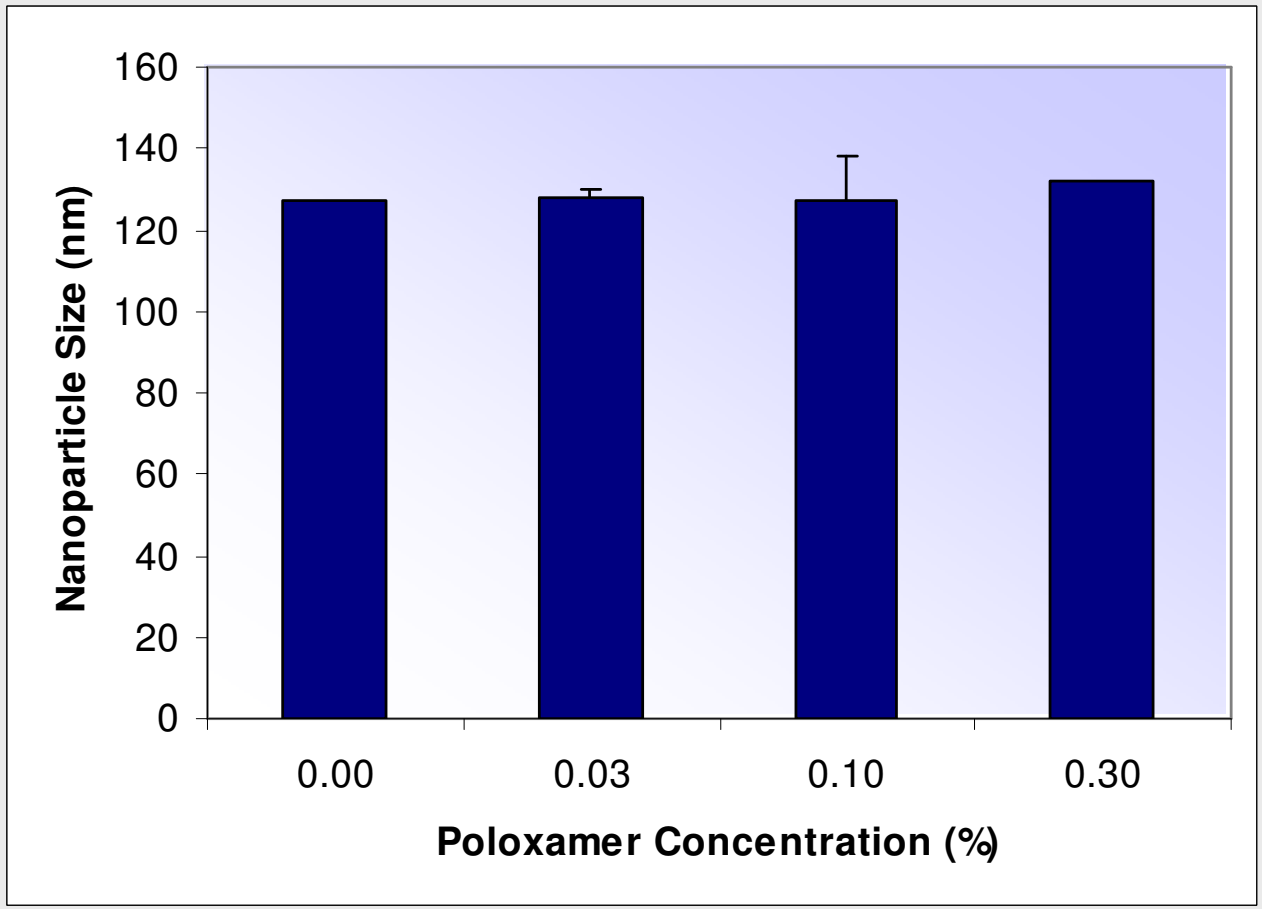

170
160
150
140
130
120
110
100
90
80
Particle Size (nm)
0
5
10
15
20
[Polymer in Acetone] (mg/mL)
RG502H (RV = 1.19)
RG503H (RV = 1.30)
RG504H (RV = 1.41)
Relative Viscosity
RV = Viscosity of 10 mg/mL polymer / Viscosity of acetone alone

Injection Rate

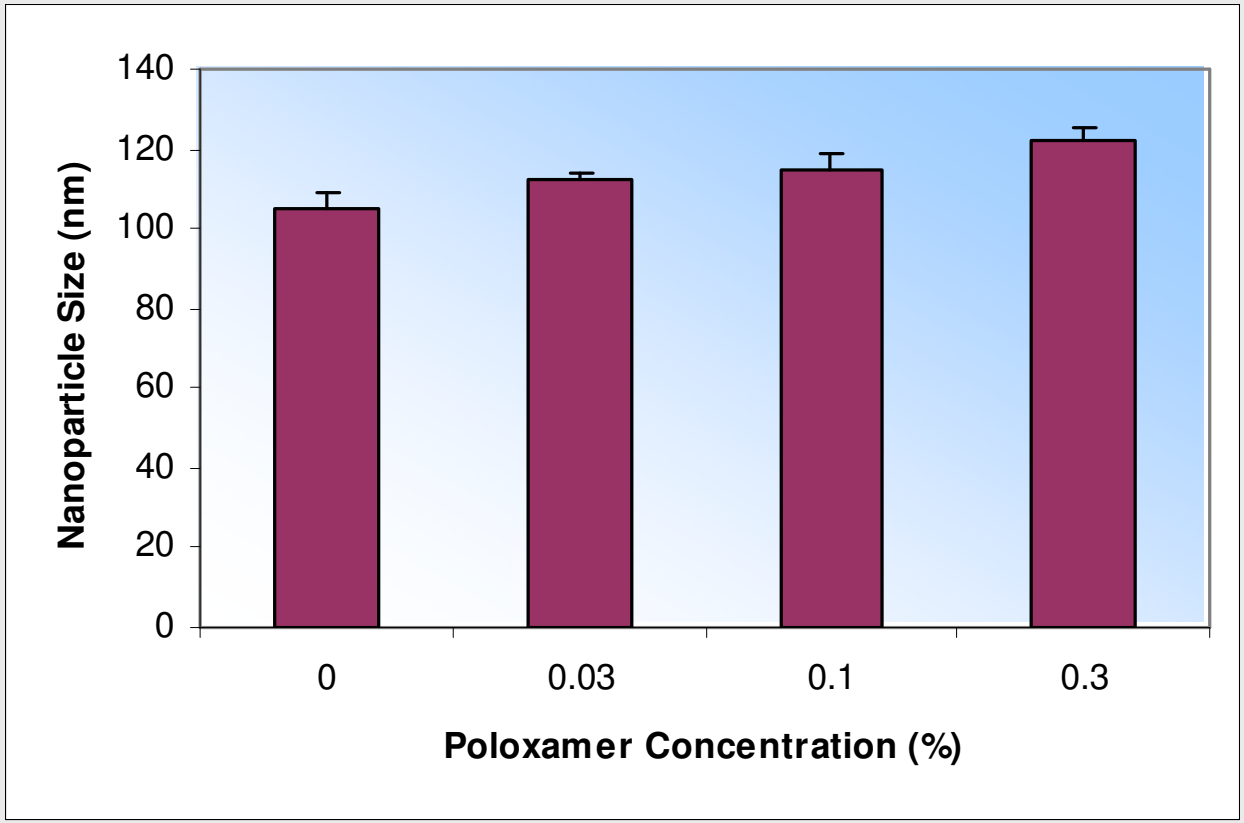


4.0 mg/mL RG 502 H in acetone added to 0.1% Poloxamer.

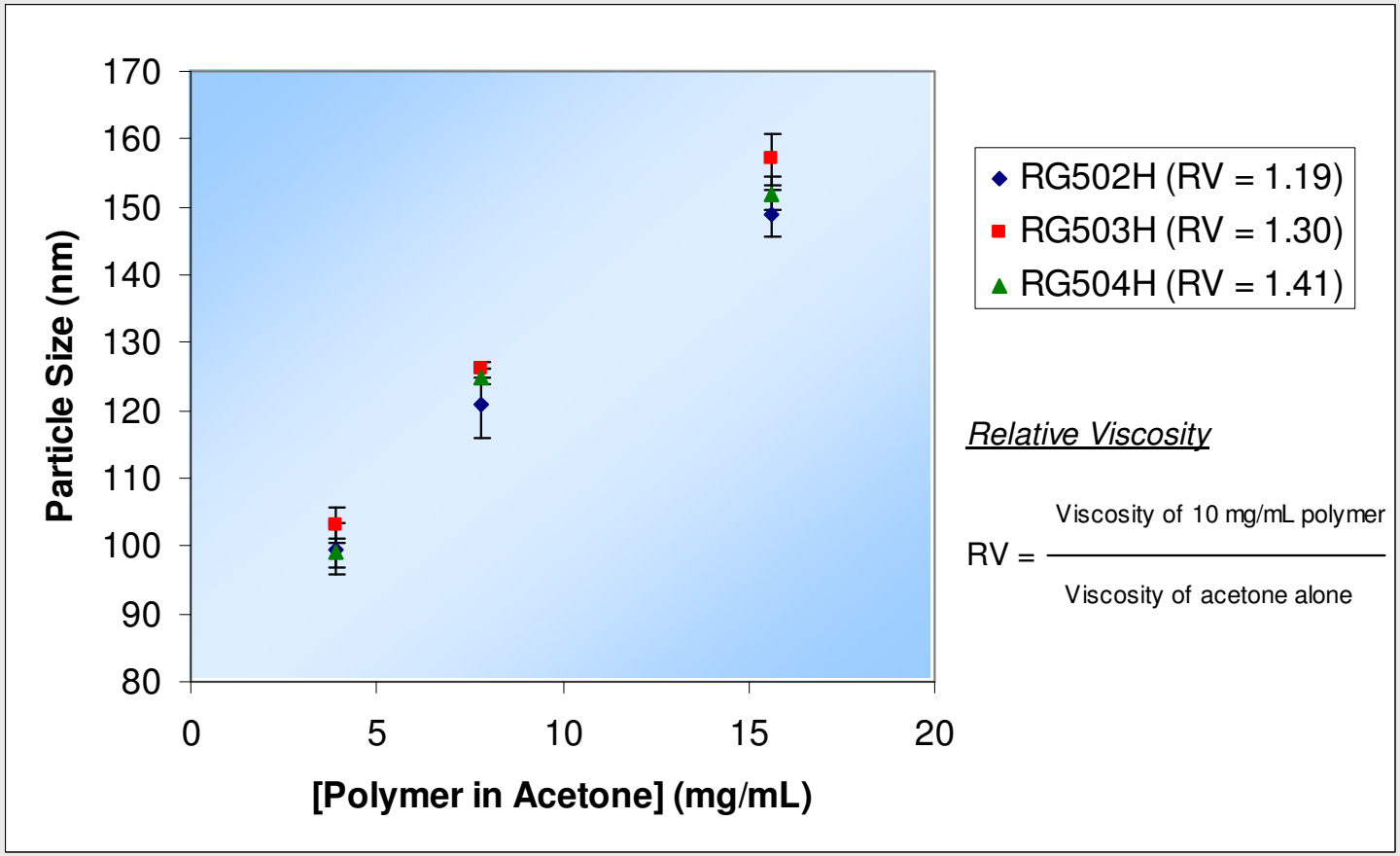
Surfactants – Fast Injection



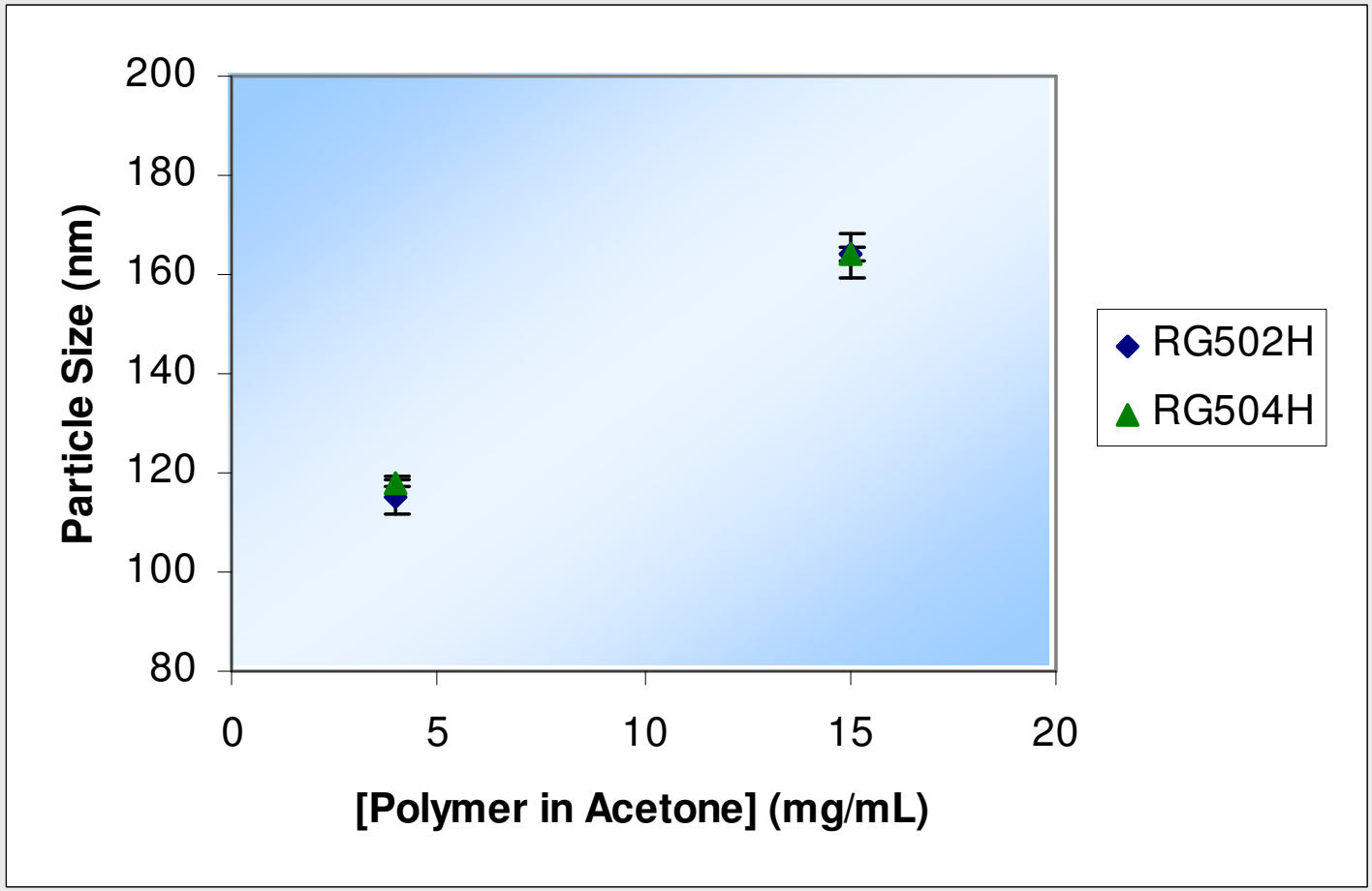
Surfactants – Slow Injection



Viscosity – Fast Injection



Viscosity – Slow Injection



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	Air Force	Kansas	Florida
Win-Loss Record	24-7	25-8	33-6

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Scoring Defense	1/326	33/326	50/326
Field Goal % Defense	132/326	1/326	21/326
Scoring Offense	267/326	42/326	22/326

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Scoring Offense	267/326	42/326	22/326
Personal Fouls/Game	13/326	140/326	29/326
3-Pointers Made/Game	12/326	173/326	70/326
3-Point Shooting %	4/326	44/326	15/326
Free Throw Shooting %	29/326	226/326	34/326

Improved Drug Delivery

- Nanoparticle Size

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- Precision/Accuracy

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- Precision/Accuracy/Targeting

Improved Drug Delivery

- Nanoparticle Size
- Precision/Accuracy/Targeting
- Other Strategies

Summary

Summary

- How can one control Basketball player size?
  - Nutrition
  - Exercise
  - Genetics

Summary

- How can one control Nanoparticle size?
  - Solvent viscosity
  - Injection speed
  - Polymer concentration

Acknowledgments

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- Others
  - Claudia Packhäuser
  - Theresa Haas
  - Ulrike Nierste

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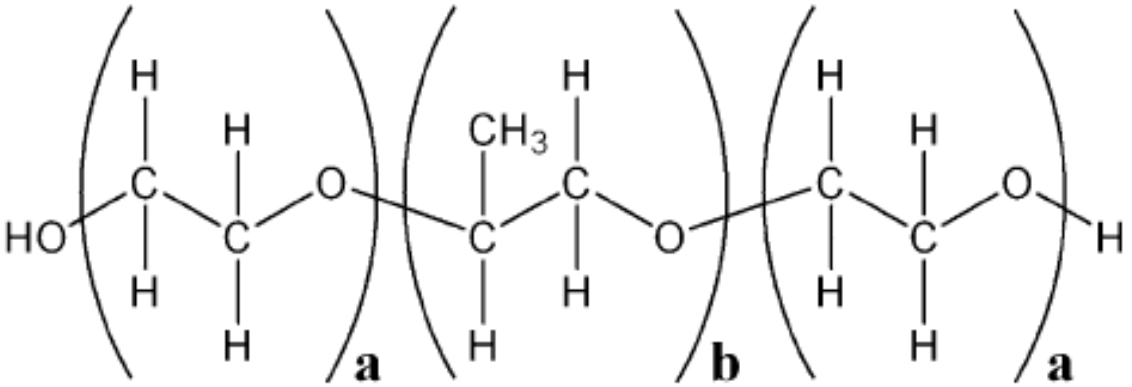
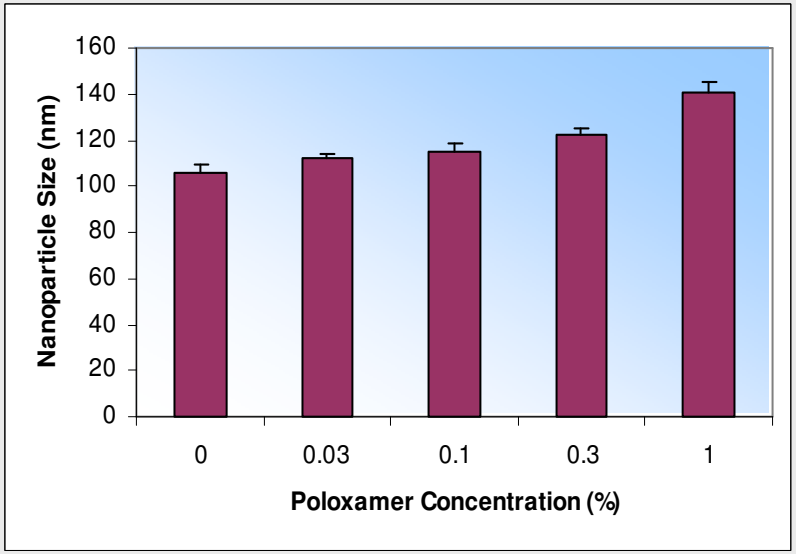
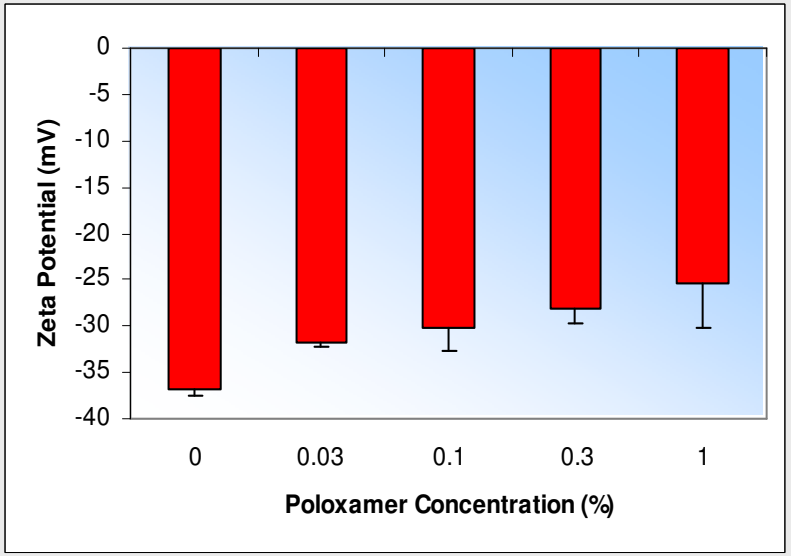
Poloxamer 188 NF (Pluronic F68)



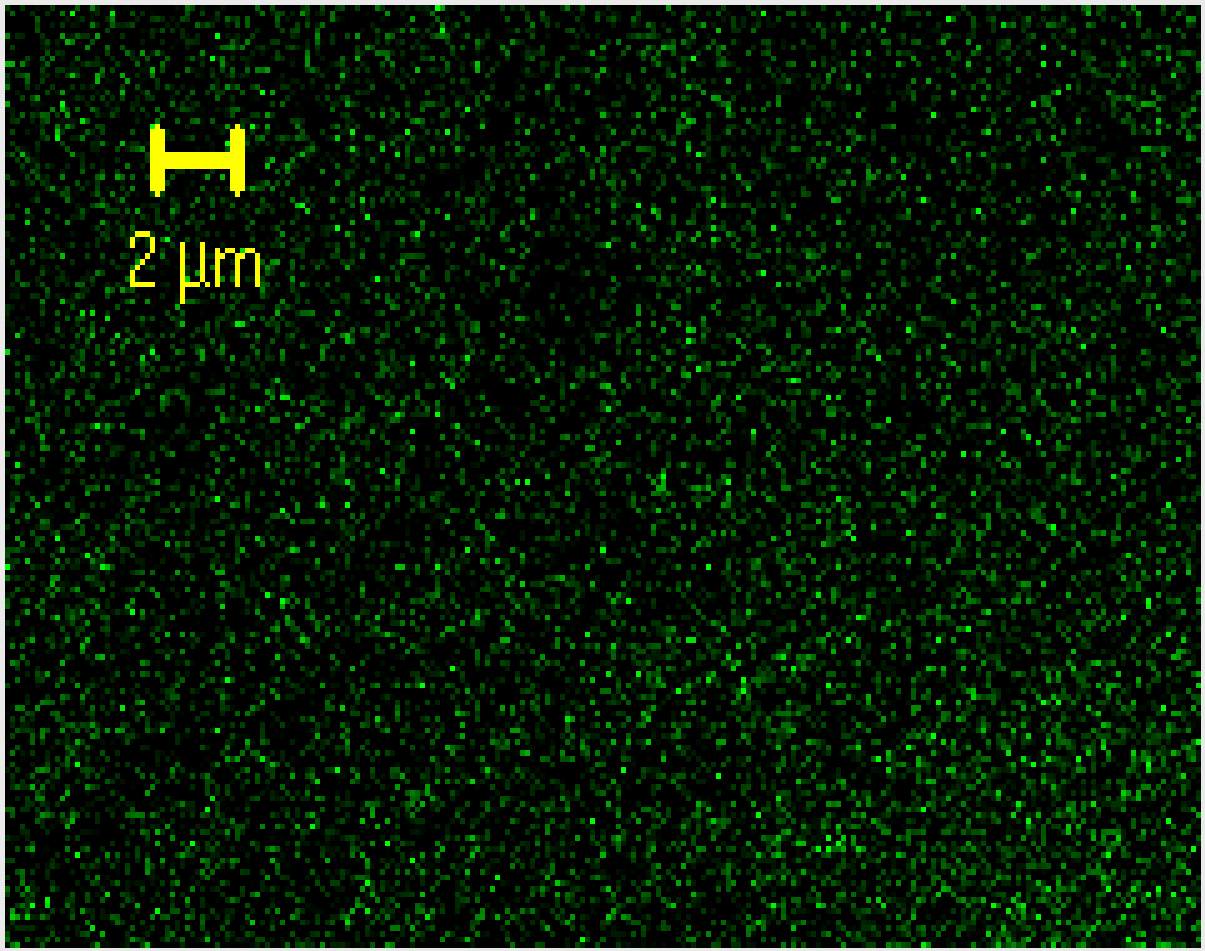
From Walsh et al., *Ann. N.Y. Acad. Sci.* 1066: 321–327 (2005).

Surface Charge





Fluorescent Nanoparticles



Nanoparticles prepared with 10 µg Coumarin-6 per 10 mg RG502H in 1 mL acetone, Z_{ave} = 117 ± 3 nm. Fluorescence Microscopy settings: λ_{ex} = 488 nm, λ_{em} = 515 nm. Suspension of particles in water after washing in a Sephadex G-50 column.