Polymer Nanotechnology: Synthesis and Novel Applications

Instructors

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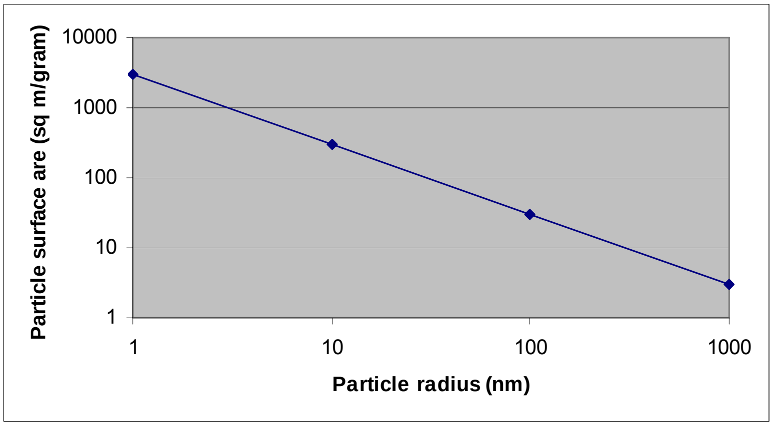
Pathways to Polymer Nanoparticles

- Nanofabrication
  - Reactive molding in nano-templates
  - Application of shear forces to spherical particles
- Dispersion Polymerization
  - Suspensions, Latices, Mini and Microemulsions
- Assembly
  - •Self and Directed
- •Application of surface and interfacial forces

The Effect of Subdividing Material



Utility of Polymer Nanoparticles Based on Size, Geometry and Chemistry

- Coatings, adhesives, impact modifiers
- Medical diagnostics
- Drug delivery
- Magnetic particles
- Conductive particles
- Stimuli responsive particles

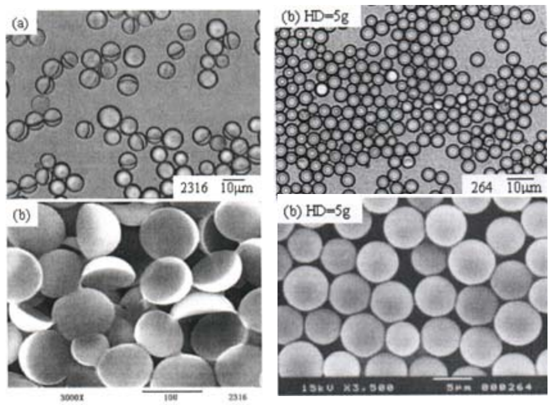
Multiple Component Polymer Microparticles

Hemisphere morphology

Core shell morphology

Unsuccessful encapsulation

Successful encapsulation



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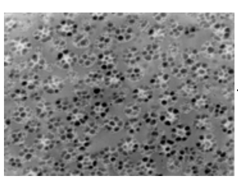
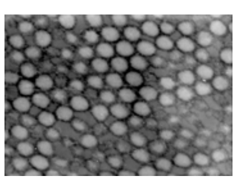
Characterization of Multiple Phase Particles

- Internal structure (morphology)

Microscopy, thermal analysis



TEM



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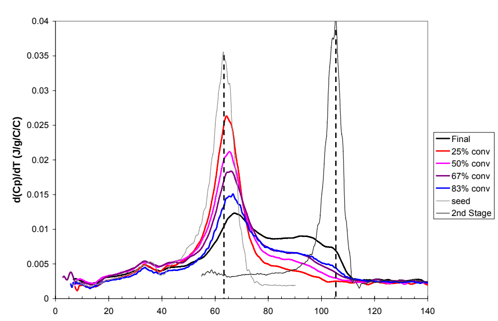


DSC

Objectives of This Workshop

- Introduce methods by which polymer nanoparticles are made
- Introduce methods by which these nanomaterials are characterized
- Discuss applications of polymer nanoparticles

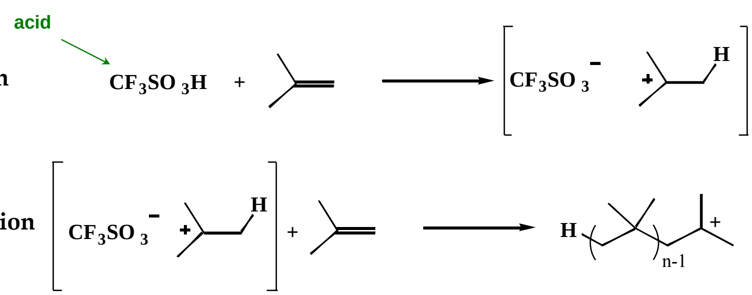
Cationic Polymerization

$$\sim\sim M_n^{+}, X^{-} \quad + \quad M \longrightarrow \sim\sim M_{n+1}^{+}, X^{-}$$

Bishop Watson *"Chemical Essays"*, **1789,** London
M. Deville *Ann. Chem.*, **1839, 75,66**
M. Berthelot *Bull. Soc. Chim. Fr.* **1866, 6, 294**

Initiation

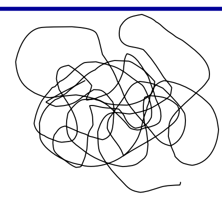
Propagation



Polymer Nanotechnology: Synthesis and Novel Applications

Polymer synthesis

Conformation



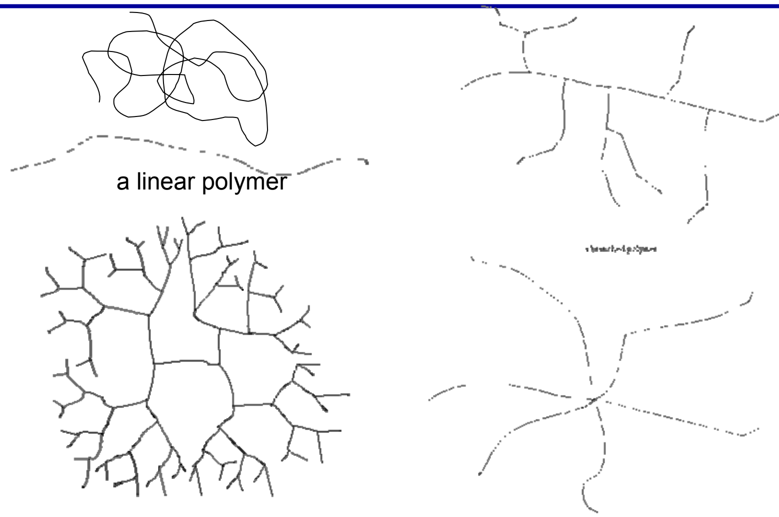
Random coil

Fiber

This is what polymer chains look like in a piece of unstretched rubber. Entropy likes this.

This is what polymer chains look like in a piece of stretched rubber. Entropy does not like this.

Architecture



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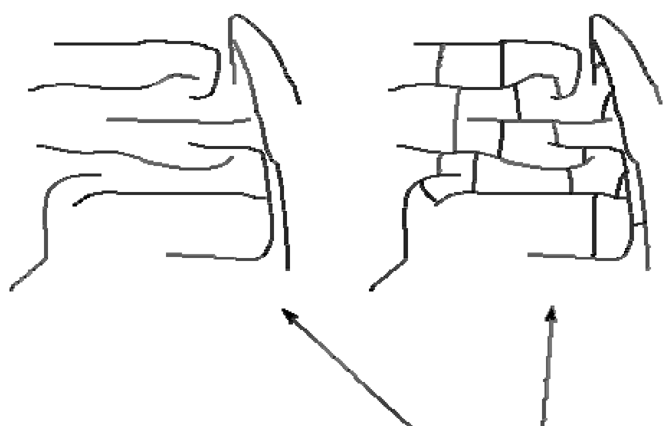
Crosslinking



Entanglement versus crosslink = physics versus chemistry

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Molecular weight

M_n - Number Average Molecular Weight

M_v - Viscosity Molecular Weight

M_w - Weight Average Molecular Weight

M_z - Z-average Molecular Weight

a=0.5 to 1
Function of solvent

$$M_n = \frac{\sum_i N_i M_i}{\sum_i N_i} = \frac{\sum_i w_i}{\sum_i \frac{w_i}{M_i}}$$

$$M_v = \left[\frac{\sum_i N_i M_i^{1+a}}{\sum_i N_i M_i}\right]^{\frac{1}{a}}$$

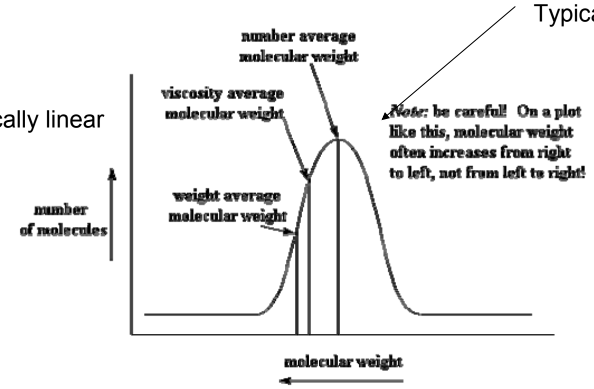
$$M_w = \frac{\sum_i N_i M_i^2}{\sum_i N_i M_i} = \frac{\sum_i w_i M_i}{\sum_i w_i}$$

$$M_z = \frac{\sum_i N_i M_i^3}{\sum_i N_i M_i^2} = \frac{\sum_i w_i M_i^2}{\sum_i w_i M_i}$$

Representation

Gaussian (bell) curve
Typically on log scale

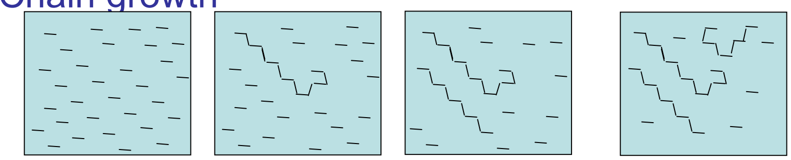
Typically linear



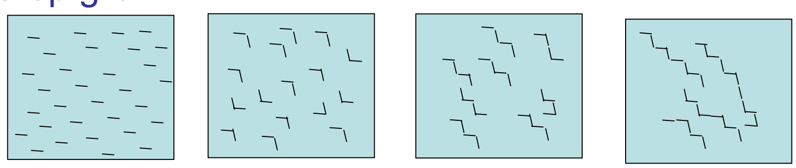
Typically a log scale

2 major categories

- Chain growth



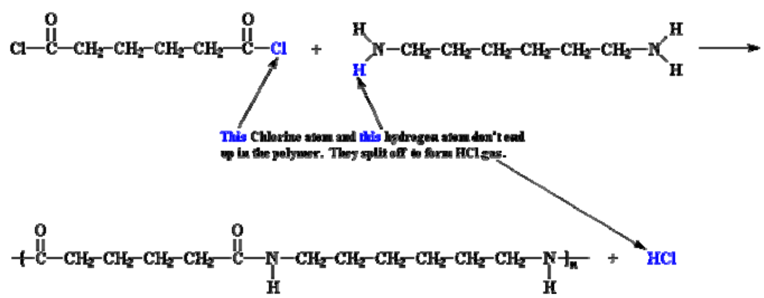
- Step growth



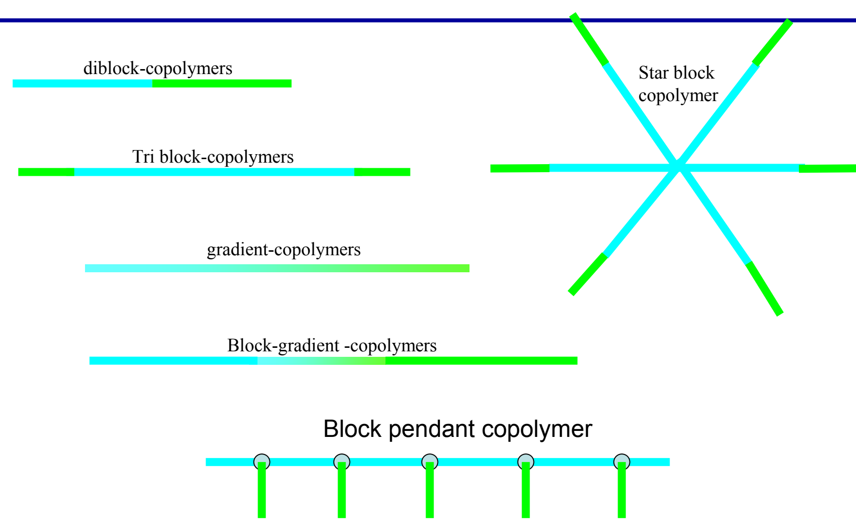
Chain growth : Active centers

- Radical polymerization
- Ionic polymerization
  - Anionic
  - Cationic
- Coordination polymerization
  - Involves a catalytic center
- Polycondensation

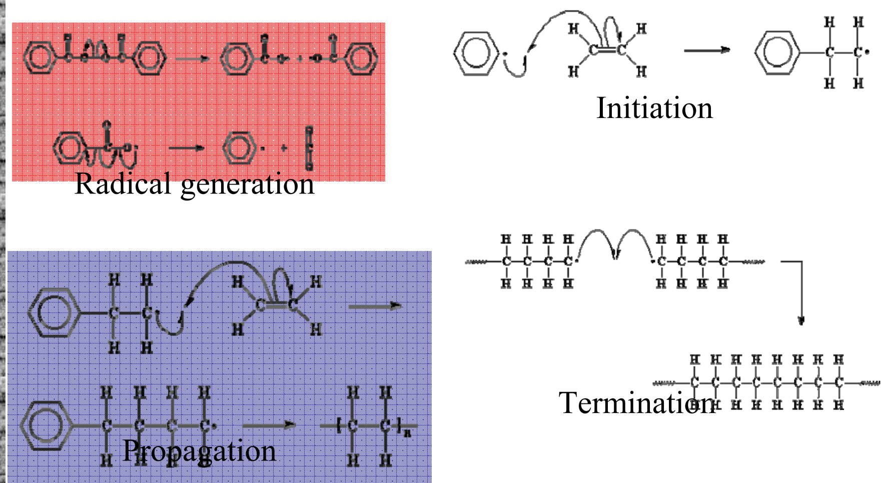
Addition / condensation



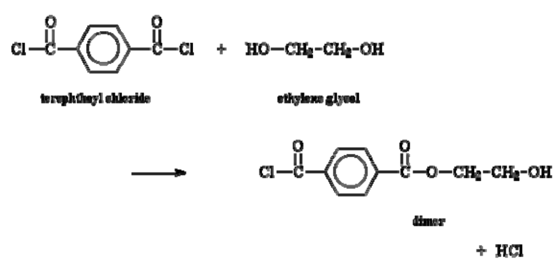
Block copolymer architecture



Radical polymerization

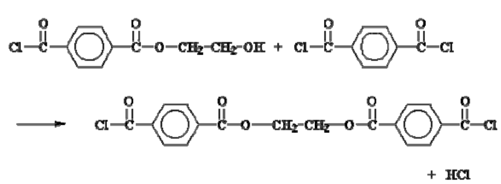


Polycondensation -1



Terephthaloyl chloride and ethylene glycol react to form an ester dimer

Our little dimer can react with a molecule of terephtoyl chloride...



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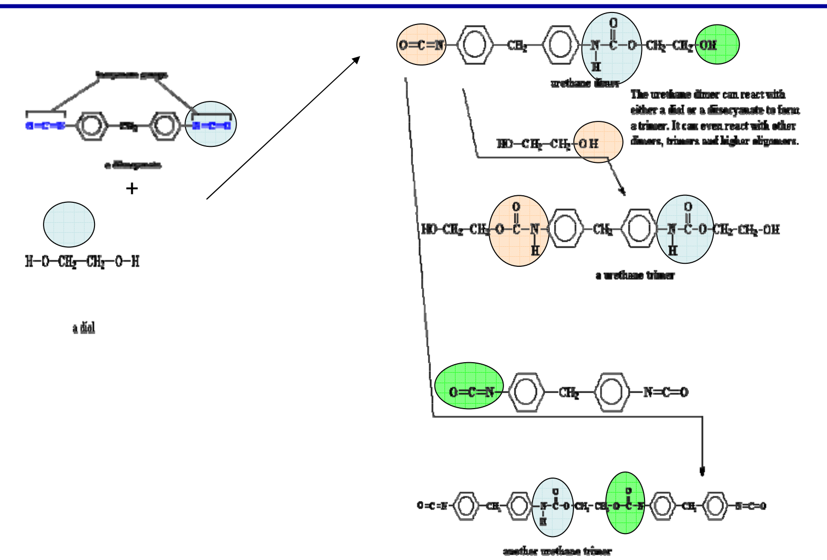
Polycondensation - 2



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Living Polymerizations

Anionic

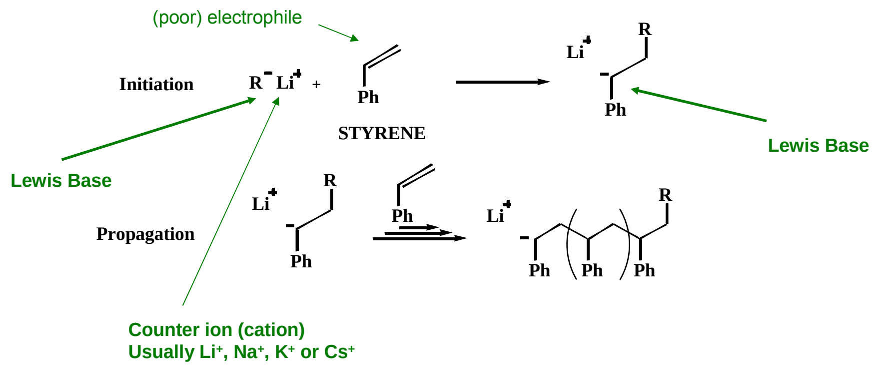
Cationic

Ring Opening

Ring opening metathesis

Anionic Polymerization

$$\sim\sim M_n^-, Mt^+ \quad + \quad M \longrightarrow \sim\sim M_{n+1}^-, Mt^+$$



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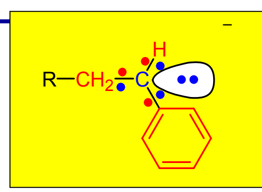
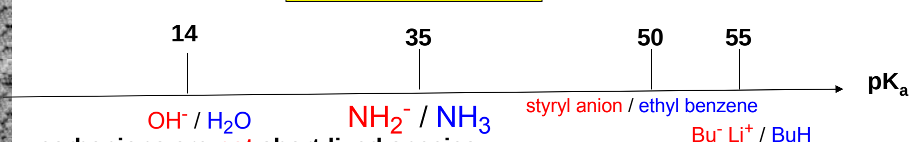
Anionic Polymerization





- carbanions are **not** short-lived species
- carbanions are terminated by oxygen, water and many polar functionalities
- carbanions are negatively charged
- carbanions can be pyrophoric (beware!)
- carbanions are tetrahedral (*sp*³ hybridized)
- carbanions are very basic (conjugated acid : alkane). They can only be formed by reacting with a stronger base.

Cationic Polymerization

$$\sim\sim M_n^{+} , X^{-} \quad + \quad M \longrightarrow \sim\sim M_{n+1}^{+} , X^{-}$$

Bishop Watson *"Chemical Essays"*, **1789,** London
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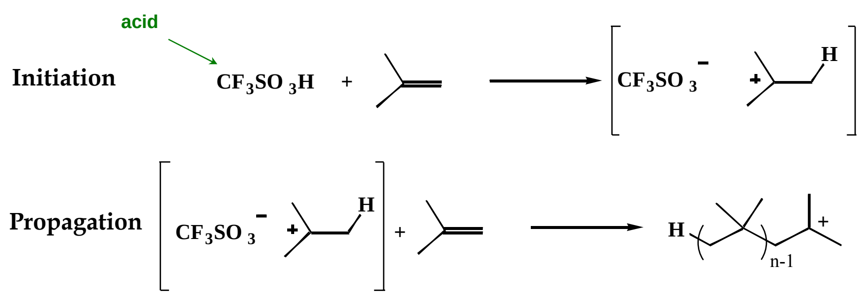
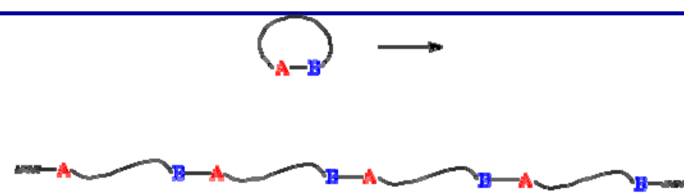
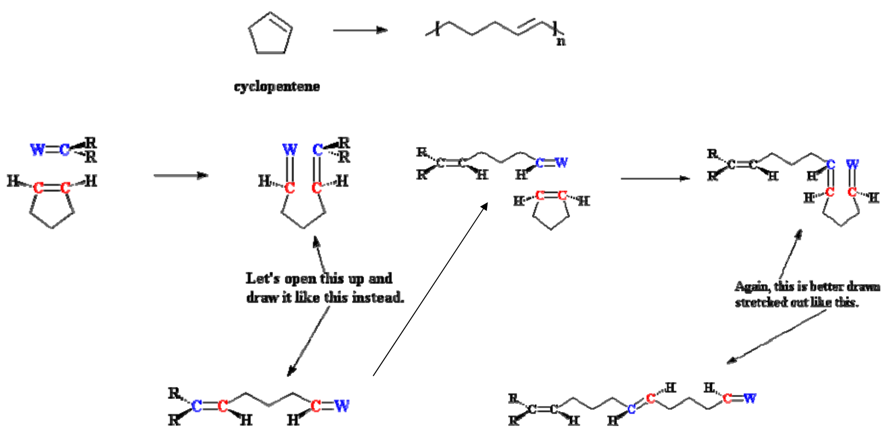


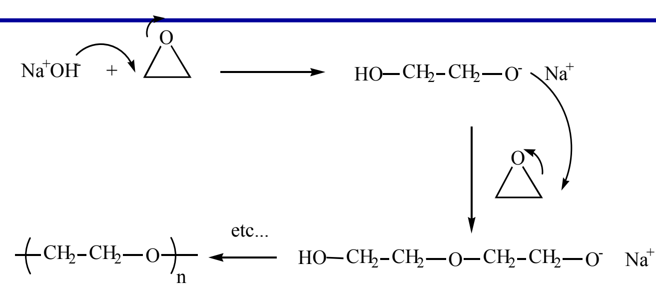
Ring Opening polymerization



Ring Opening Metathesis Polymerization



Ring-Opening Polymerization



Wurtz 1879

- Ring Strain Controls the Polymerization (C2O best)

n	ΔH(kJ/mol)	ΔS (J/K/mol)	ΔG (kJ/mol)
3	-113	-69	-92.5
4	-105	-55	-90
5	-21	-43	-9
6	2	-10	+6
7	-22	-16	-16
8	-34	-3	-34

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~~Living~~ *Controlled* Radical Polymerization

SFRP

ATRP

RAFT

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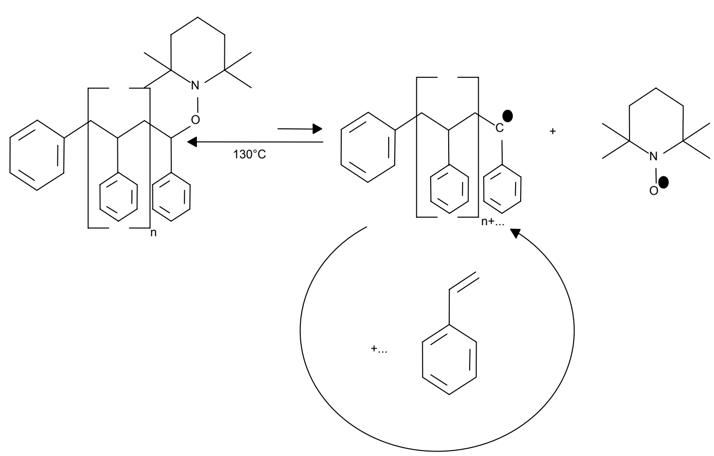
Pseudo living SFRP



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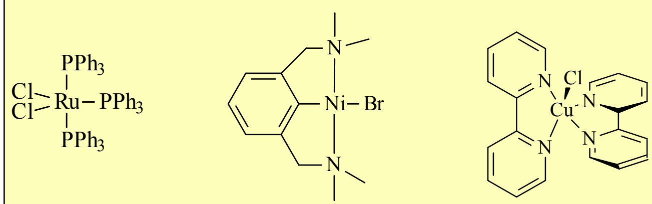
NPRC Nanostructured Polymers Research Center

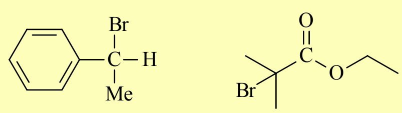
Atom Transfer Radical Polymerization

$$IM_n^\circ + MeX \rightleftharpoons IM_nX + Me$$



Sawamoto, 1995 MMA	Teyssie, 1997 MMA	Matyjaszewski, 1995 MMA, S

CATALYSTS



CCl_4 CBr_4

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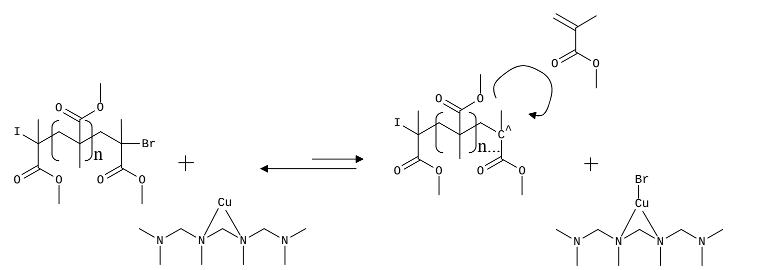
NPRC Nanostructured Polymers Research Center

The Preparation of Well-Defined Water Soluble/Swellable (Co)Polymers by ATRP - K. Matyjaszewski

- Atom Transfer Radical Polymerization is one form of Controlled Radical Polymerization (CRP)



- With ATRP one can control the architecture (blocks, stars, gradients, graft, dendrimers….)
- Fundamental mechanism : depletes termination

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ATRP - Recent improvements

- Mw/Mn=1.1
- styrene, acrylates, methacrylates, acrylonitrile
- 2-HEA, 2-HEMA, 2-(dimethylamino) ethyl methacrylate, N-(2-hydroxypropyl)methacrylamide, methacrylic acid (from tBMA).

- Works in water
- Works at 60 to 80°C
- Suspension and emulsion (use PEO/PE-PEO as stabilizers)

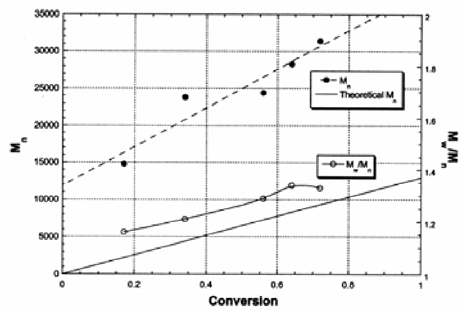

Figure 1. Dependence of molecular weight with conversion for the ATRP of HEMA.

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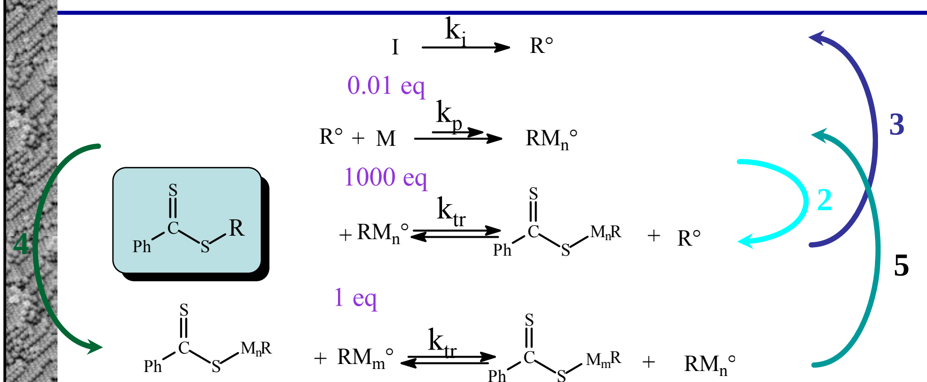
Reversible Addition Fragmentation Chain Transfer (RAFT)



Rizzardo, 1998

$C_{tr} = k_{tr}/k_p \sim 500$

Not based on a persistent radical effect

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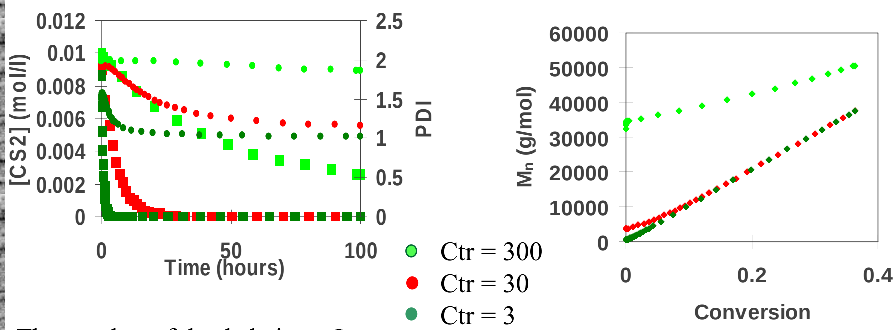
Reversible Addition Fragmentation Chain Transfer (RAFT)



The number of dead chains = I

The number of dormant chains = CS_2

Initial MW = $MW_0 \, C_{tr}^{-1} \dfrac{[MON]}{[CTA]}$

Kinetics = Kinetics of conventionnal radical polymerization

Styrene/CS_2 = 1000
CS_2/AIBN = 20

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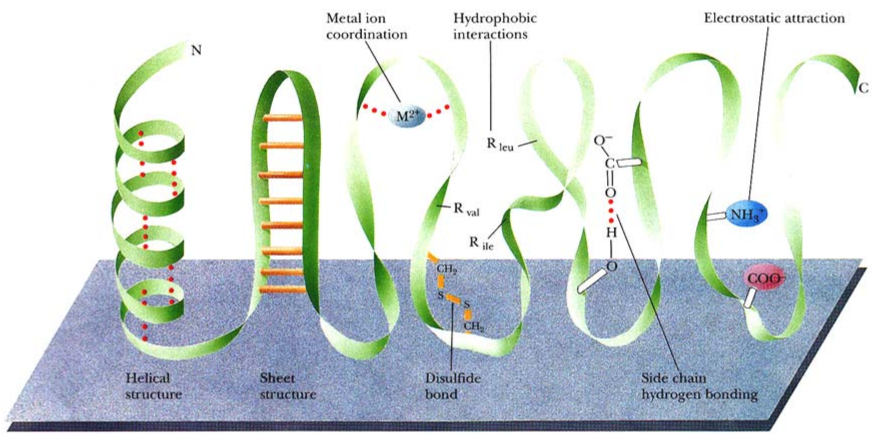
Classes of biopolymers

- Nucleic acids
  - DNA/RNA
- Proteins
  - Fibrous
    - Major structural material for animals
  - Globular
- Polysaccharides
  - Unbranched
    - Major structural material for plants, insects and others
  - Branched
- Lipids

Non-covalent forces dictate tertiary structure



Dispersion Polymerization Methods to Create Polymer Nanoparticles

Single Component Polymer Particles

- Disperse polymer solution in water/surfactant
- Shear to create dispersed particles

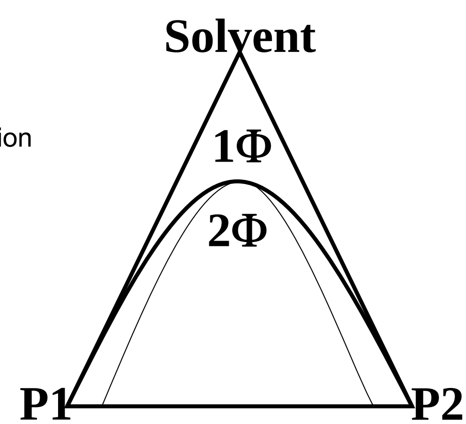
  Concern with particle size distribution
- Remove solvent while stabilizing particles

  Concern with very viscous particles
- Internal particle uniformity depends on rate of

  solvent removal

Two Component Polymer Particles

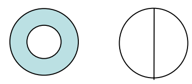
Phase separation during solvent removal



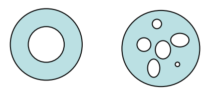
Two Component Polymer Particles

Internal particle structure depends upon

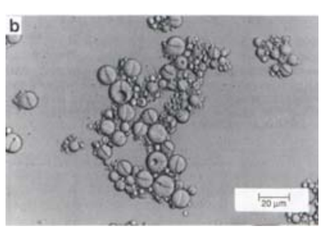
1. Interfacial energies (3 interfaces)

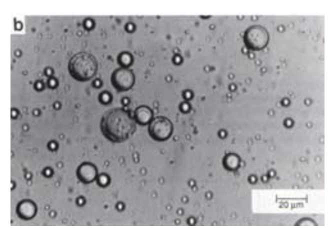


2. Rate of solvent removal



Examples of Two Component Polymer Particles via Artificial Latex Process





Artificial latex particles of two immiscible polymers exhibit distinct morphologies and can provide a convenient model system to study some aspects of particle morphology control.

Reactive Processes

<u>General Mechanisms for Particle Formation</u>

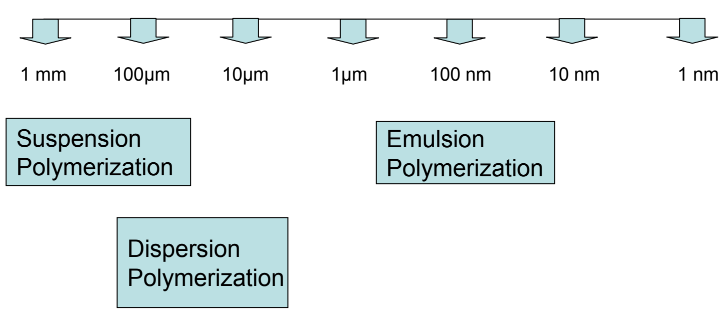
- Nucleation within pre-formed dispersed phase

  Suspension and emulsion (micelle) polymerizations

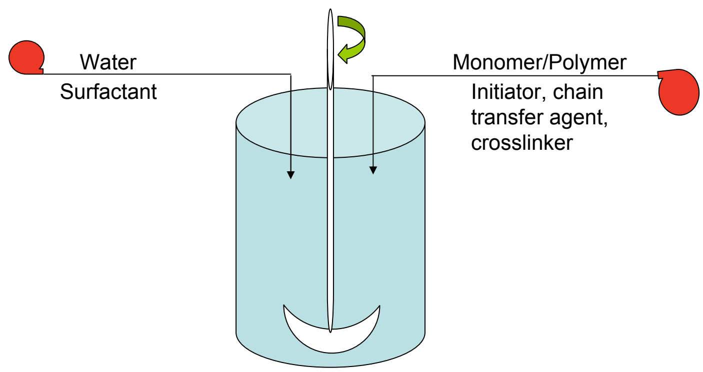
- Polymer precipitation from solution

  Dispersion and emulsion (homogeneous nucleation) polymerizations

Particle Size Ranges Achievable via Reactive Processing



Suspension Polymerization



Suspension Polymerization

- Stabilizers (surfactants) – often are water soluble polymers, e.g. PVOH, PVP. Added at ~0.1% of aqueous phase.
- Initiators (oil soluble), peroxides, azo compounds.
- High stirring rates required to create particles and to keep them suspended (Brownian motion insufficient).
- All organic phase ingredients must be added to monomer stream as there is no effective transport through aqueous phase.

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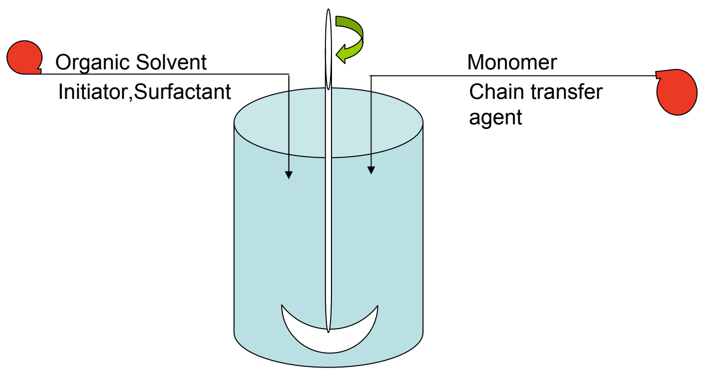
Dispersion/Precipitation Polymerization



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Dispersion/Precipitation Polymerization

Mechanism

- Early stage polymerization in solution to form low MW polymer chains
- Precipitation of polymer from solution to form particles
- Partition of monomer(s), initiator, CTA between solution and particle phases
- Adsorption of surfactant on particle surface
- Continued polymerization, occurring more and more in the particle phase

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Dispersion/Precipitation Polymerization

- Broad range of copolymers can be produced
- Choice of solvents (often mixtures with alcohols) is critical
- Use of continuous phase to transport reactants to particle phase
- Can do "second stage" processing to add second type of comonomer to create composite particles
- Decent particle size distribution control

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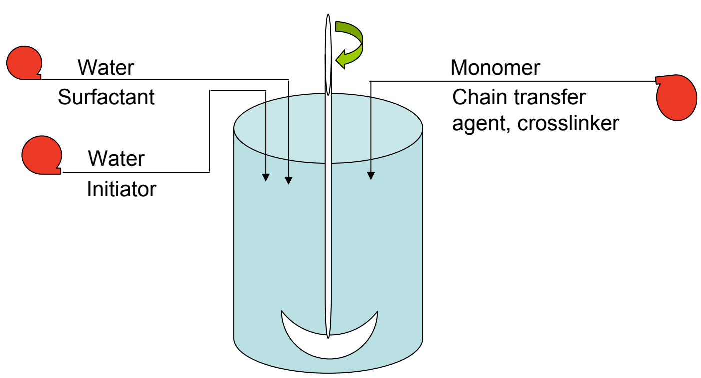
Emulsion Polymerization



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Emulsion Polymerization

- Limited to free radical chemistry, but a wide range of monomers can be used
- Water phase provides for low viscosity and very good heat removal – environmentally positive
- Latex particles are small enough to be effected by Brownian motion and thus stirring speeds can be low
- Mechanical stability is much better than than in other dispersion polymerization methods, but can be an issue
- Process is easily adapted to multi-stages to build composite particles with many morphologies
- Particle surfaces can be easily modified with reactive end groups

Emulsion Polymerization

Mechanism

- Add water and surfactant to reactor
- Add water insoluble monomer, CTA, crosslinker, etc. to form emulsified droplets (10-50 micron)
- Add water soluble initiator to start reaction
- Micellar or or precipitation (called homogeneous) polymerization to nucleate particles
- Particles grow by continued adsorption of monomers and conversion into polymer

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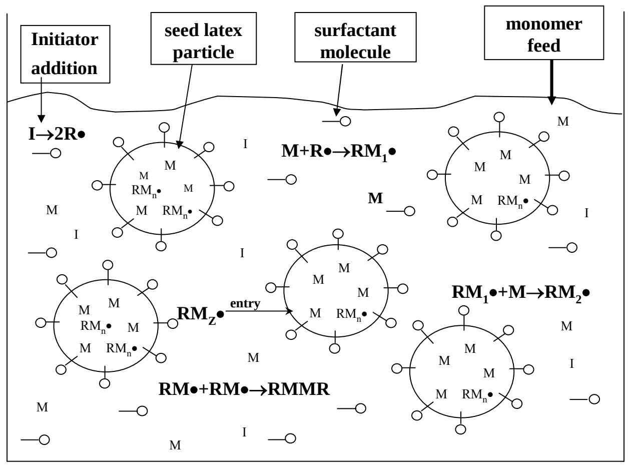
Second Stage Emulsion Polymerization



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Emulsion Polymerization

<u>Characteristic features of latex particles</u>

- Single component particles are spherical when made in a one step process
- Small enough to generally avoid settling/creaming because of Brownian motion
- Small size leads to potentially high latex viscosity at solids contents exceeding 40-50%
- Functional polymers can be located at particle surface

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Emulsion Polymerization

Micellar Mechanism

- Surfactant in excess of CMC forms aggregates of molecules with oily ends in center and hydrophilic ends towards water
- Monomer diffuses to micelles to concentrate in the center
- Free radicals diffuse through the water and penetrate the micelles to create a latex particle
- These new particles grow in size by absorbing monomer transported through the water. Surfactant adsorbs on growing surfaces to stabilize the particles
- Particle size and number dependent on surfactant level, initiator level and temperature

Emulsion Polymerization

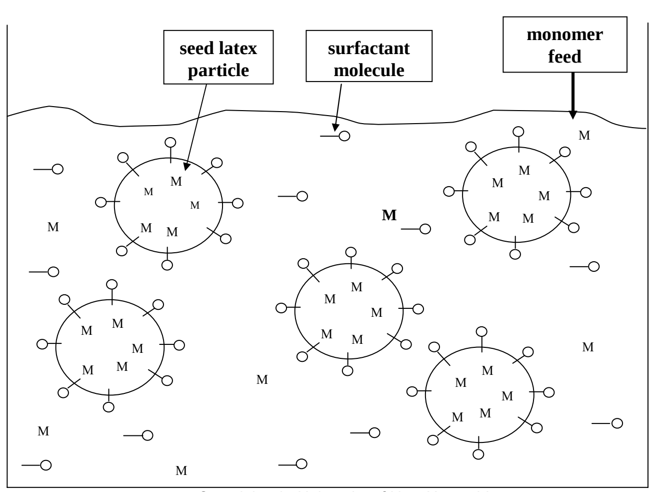
Homogeneous Nucleation Mechanism

- Oligomeric radicals form in the aqueous phase and grow until they precipitate to form a new particle
- New particles absorb monomers, adsorb surfactant, and are penetrated by initiator radicals
- New oligomer radicals produced in water phase either adsorb onto existing particles or precipitate to form new particles
- New particle formation continues until all new oligomer radicals adsorb onto existing particles

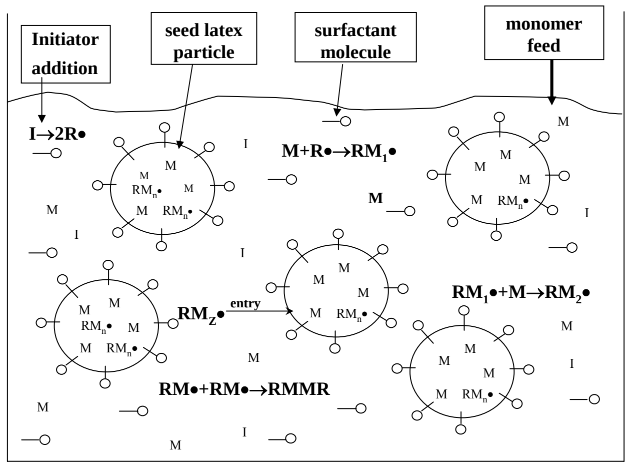
Multiple Stage Processing via Polymerization

- Build upon the structure of the precursor particle by adding another polymer to it
- Polymerize the two (or more) polymers in separate processes and locations. Blend the two, effecting particle interactions leading to a single, more complicated particle. Particle "engulfment" technology has been demonstrated
- Alternatively, can add the "second stage" as a monomer and create the composite particle by in-situ polymerization
- Second stage polymerization is commonly practiced and requires phase separation to occur within the primary (seed) particles

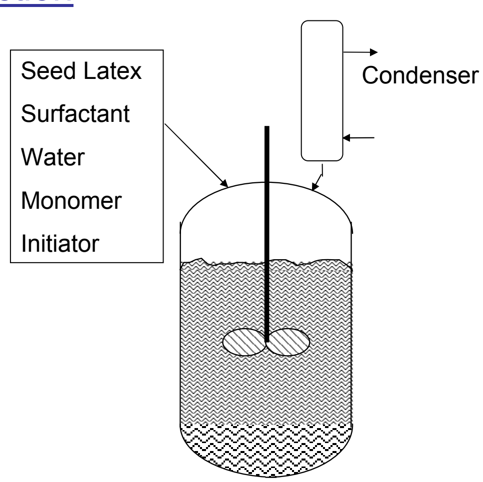
Second Stage Emulsion Polymerization



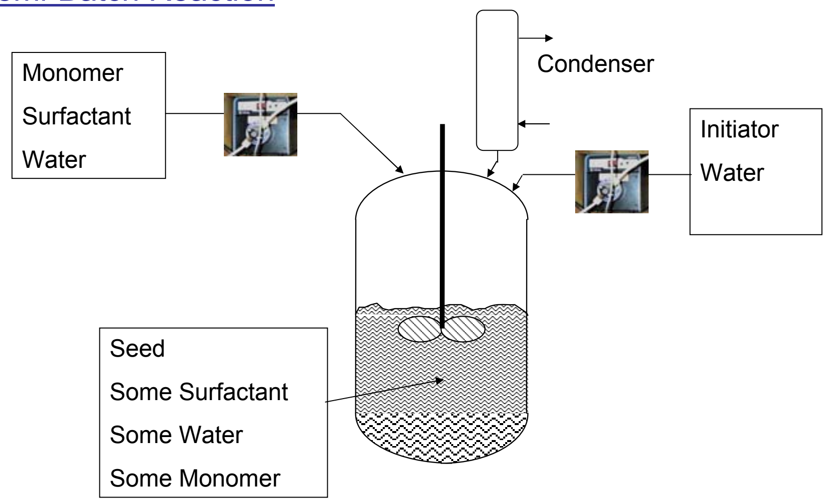
Second Stage Emulsion Polymerization



Batch Reaction



Semi-Batch Reaction



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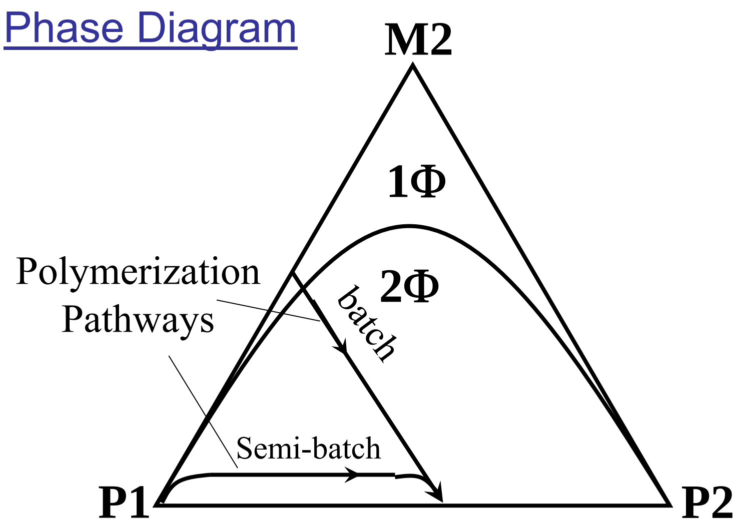
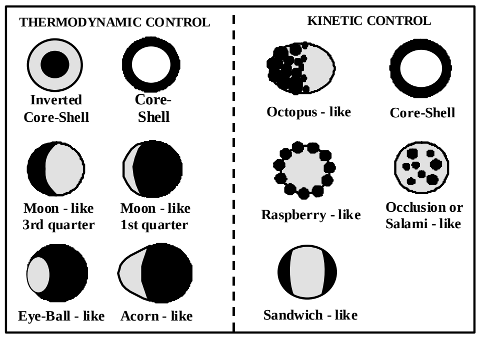
Phase Diagram

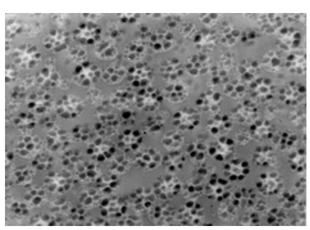


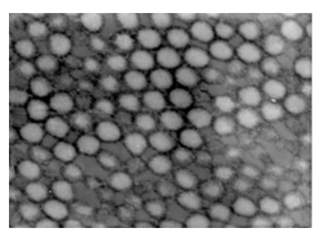
Multiple Component Polymer Nanoparticles

Two Component Particles – Morphological Options



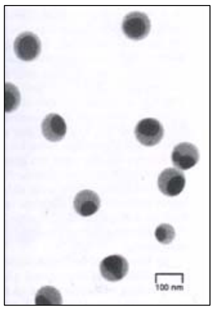
Sensitivity of Particle Morphology Control

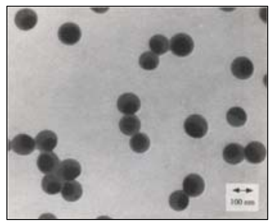

Batch reaction

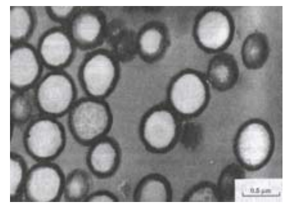

Semibatch reaction

System: P(MA-co-MMA) seed, PS second stage. All conditions are identical except mode of addition of monomer, batch vs. semibatch.

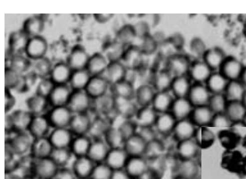
Latex Particle Morphologies: Fully Consolidated Particles

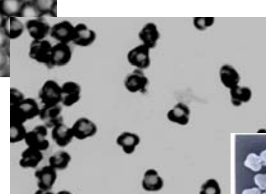


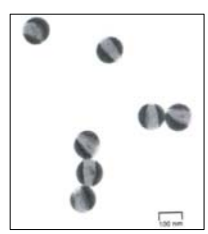




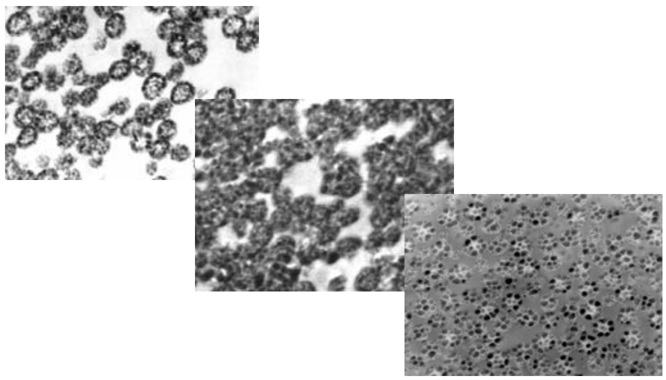
Latex Particle Morphologies: Partially consolidated



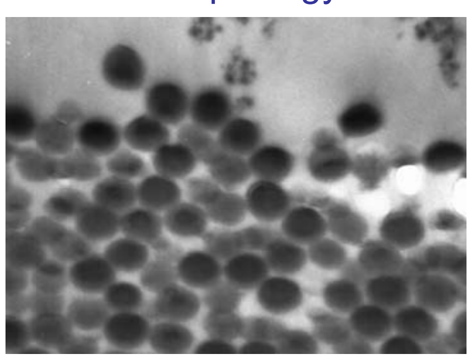




Latex Particle Morphologies: Occluded morphologies (not consolidated)



Latex Particle Morphologies: No apparent morphology??



This represents a composite particle in which contrast between the phases should be apparent in TEM (by selectively staining one phase with Ruthenium). No obvious morphology is observed!?

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Polymer Nanotechnology:
Synthesis and Novel Applications

Polymer Synthesis III

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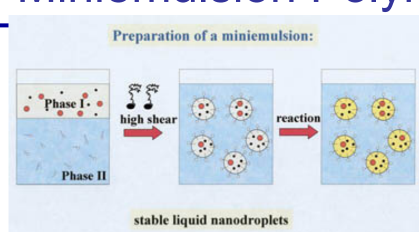
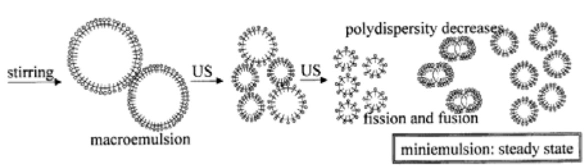
Miniemulsion Polymerization



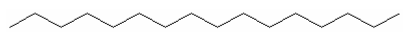
http://www.mpikg-golm.mpg.de/kc/landfester/



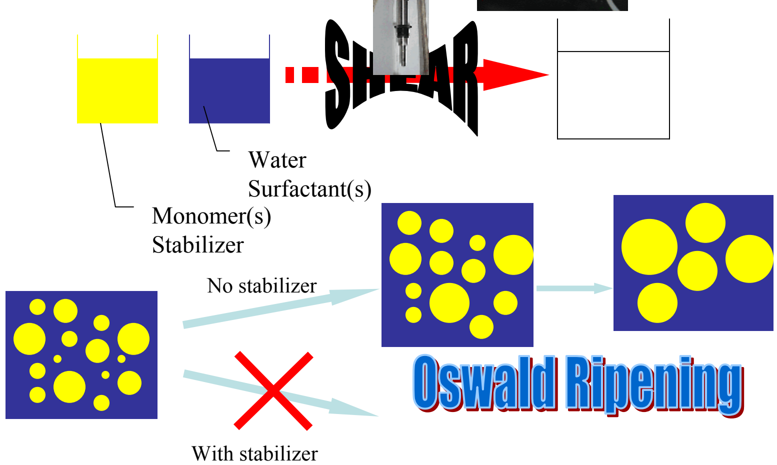
Macromol. Rapid Commun. **2001**, 22, 896–936

Miniemulsion Polymerization

- Create a meta-stable emulsion of the monomer(s).
- Use 2 key elements :
  - High shear source to break large droplets
    - Sonicator
    - Microfluidizer
    - Homogeneizer
  - Use a water insoluble molecule to stabilize the particle
    - Sometimes called cosurfactant (missleading)
    - Hexadecane, Eicosane, polymer, macromonomer, macroinitiator, CTA, ...



Miniemulsion stability



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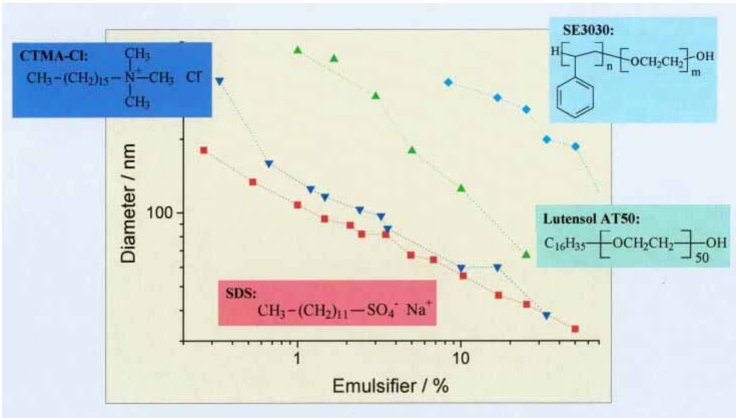
Particle size control



K. Landfester, N. Bechthold, F. Tiarks, and M. Antonietti, *Miniemulsion Polymerization with Cationic and Nonionic Surfactants: A Very Efficient Use of Surfactants for Heterophase Polymerization*. Macromolecules **1999**, *32*, 2679.

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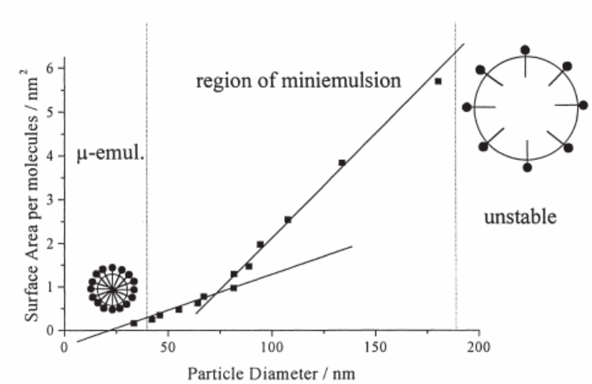
Mini to micro emulsion



K. Landfester, *Recent Developments in Miniemulsions - Formation and Stability Mechanisms.* Macromol. Symp. **2000**, *150*, 171.

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Microemulsion

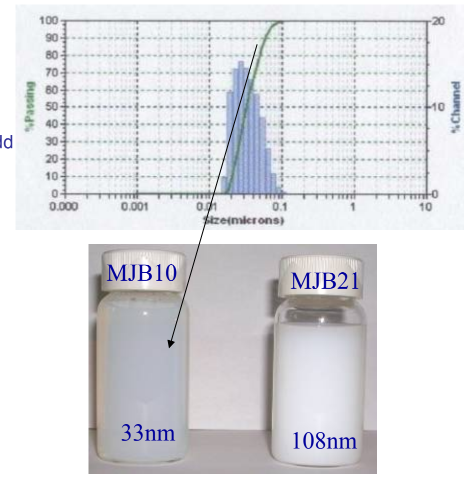
Recipe MJB-10: microemulsion (seed)

Water 82.84%
NaHCO3 0.043%
Na2O5S2 0.011%
SDS 8.27%
KPS 0.17%
Styrene 8.67%

Water, Salts, SDS, stirred, degassed. Add 20% of styrene. Heat. When at 80C, add KPS. Let react for 20 minutes. Start feeding with styrene, over 2 hours. 30 minutes of Post polymerization.

SCexp = 15.1% Conversion = 77.47%

Size = CHDF:
Dv = 35.5 nm, Dn = 33.2 nm
Nanotrac:
Dv = 36.8 nm, Dn = 25.13 nm



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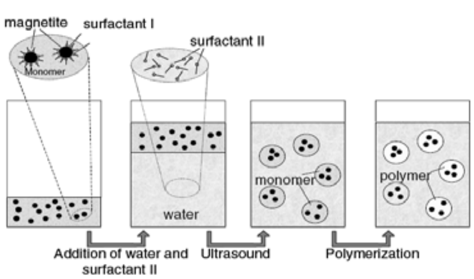
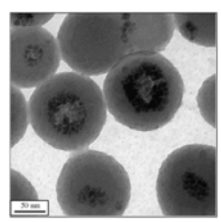
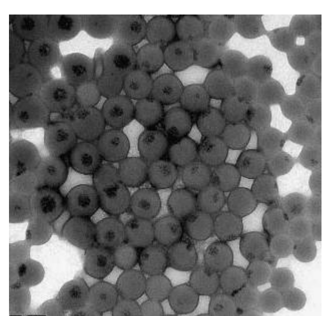
Encapsulation of magnetite in polymer particles by miniemulsion



J. Phys.: Condens. Matter 15 (2003) S1345–S1361





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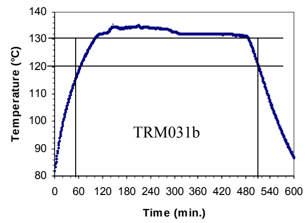
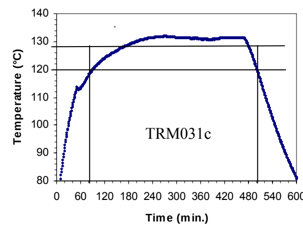
Block copolymer direct from miniemulsion

Comp.	
Potassium Myricyl Sulfate (pphm	2
di-octyl sulfosuccinate (pphm)	2
Eciosane (pphm)	3
OH-TEMPO/tBHP (mole/mole)	1.30

	TRM-031b	TRM-031c
Mn (g/mole)	21312	34987
Mw (g/mole)	32815	56720
Mw/Mn	1.54	1.62
Conversion	0.845	0.71
Mn (g/mole) (theoretical f=1.3)	33540	52227.6
Polymerization time (h:min)	7:26	6:52
Polymerization Temperature (°C)	132	129
Polymerization Pressure (Atm)	3	3
PD (nm) before polymerization	208	423
PD (nm) after polymerization	287	526
Coagulum	none	high
Initial monomer content (%)	31	22.2
Final Solid Content (%)	26.4	19.4
Tg (°C) (DSC)		43.7
Tg (°C) (calculated for blend)		43.7
Sty/BA		49-51
Block ratio (block/precursor)		1.84





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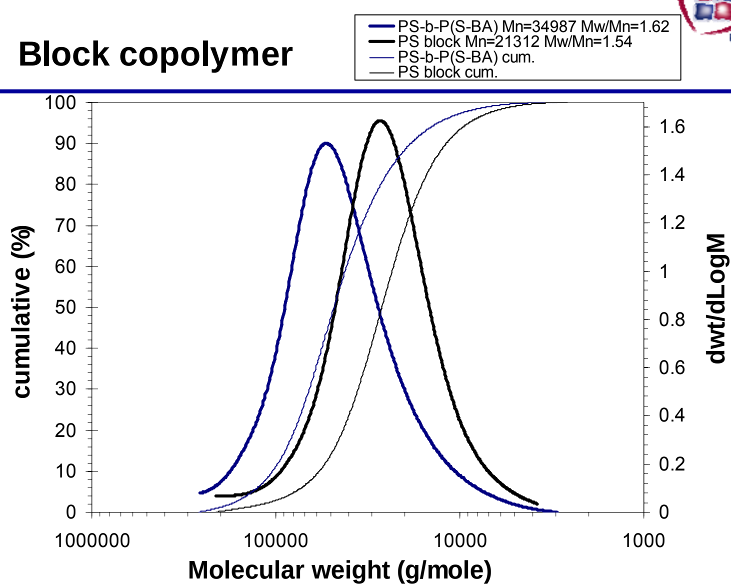
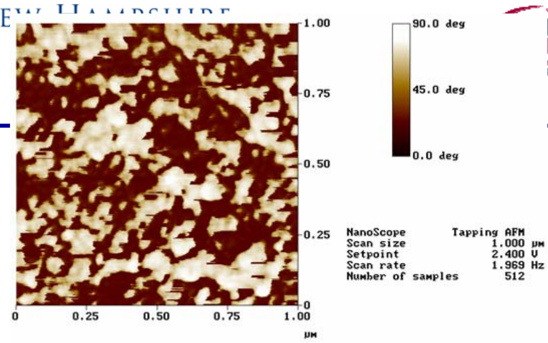
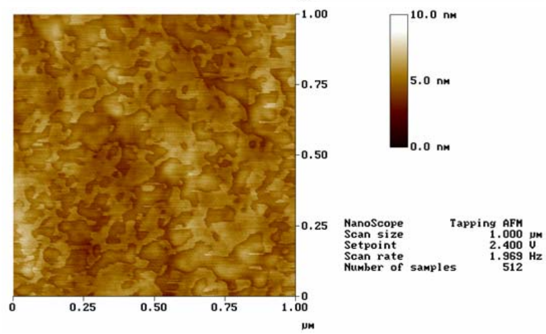
Block copolymer



TRM031

AFM





Block copolymer spin cast from THF, 8000rpm, 20 sec

Self Assembly

- Lipids
- PGlu – PLeu
- UNH tri-block

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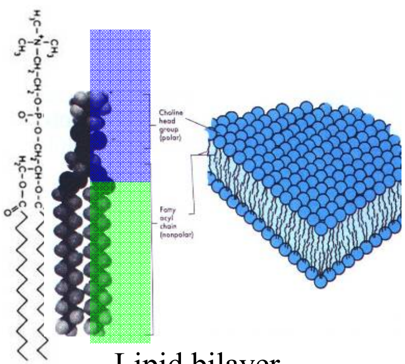
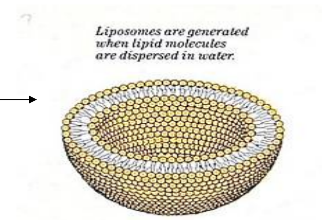
Liposomes



Lipid bilayer



Liposome

http://www.avantilipids.com/PreparationOfLiposomes.html

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Self assembly of Liposome

Multi Lamellar Vesicles

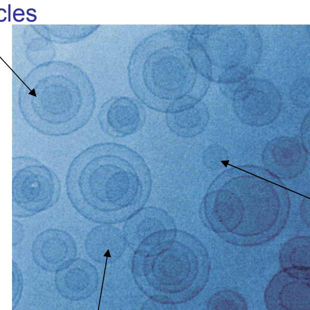


Photo courtesy of FEI Company Japan Ltd.)

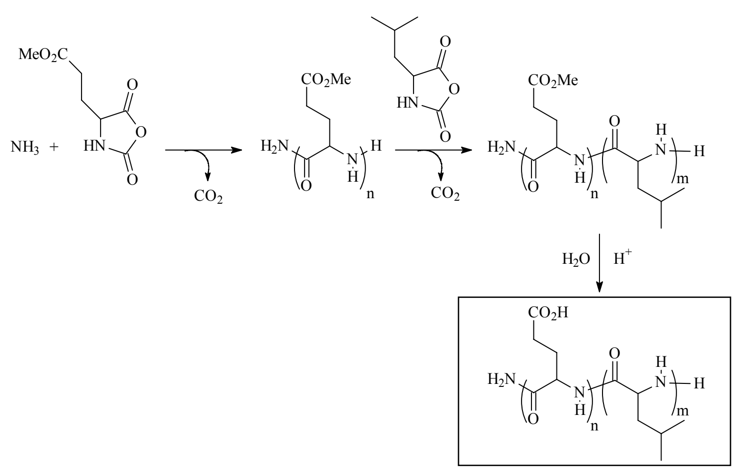
Small Unilamellar Vesicles

Large Unilamellar Vesicles : LUV

Self Assembly

- PGlu - PLeu

Synthetic Scheme



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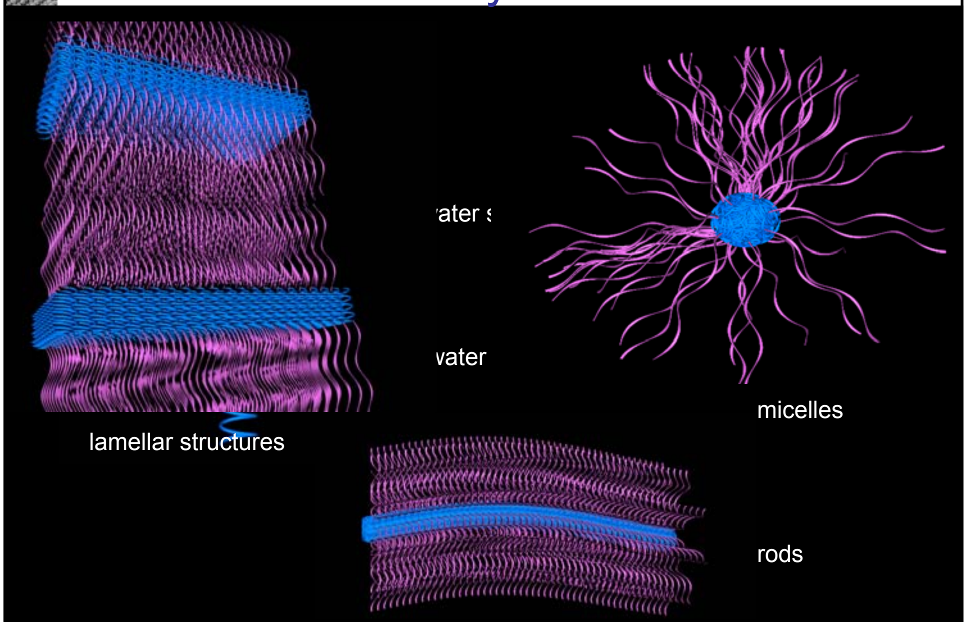
Self-assembly in water



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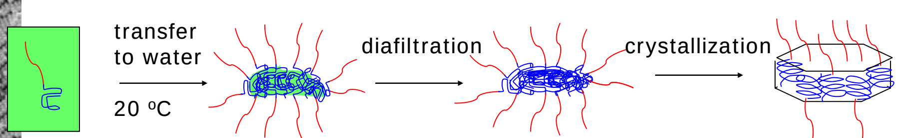
Self Assembly Process (L = 12, G = 35)



NMP

Dh (nm)	28	18	18
2*Rg (nm)	-	9	9
M_w (g/mol)	620 000	320 000	320 000
%α-helix	< 5	< 5	85
Crystallinity	No	No	Yes

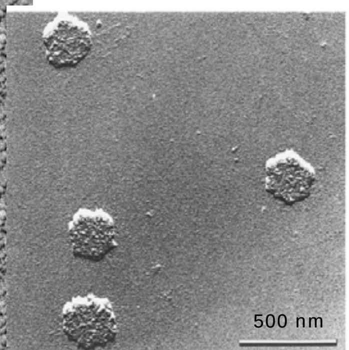
Rh : QELS, Rg : Zimm plot, Mw : FFF-LS, %α-helix CD at pH = 8

Crystallinity : RX

University of New Hampshire

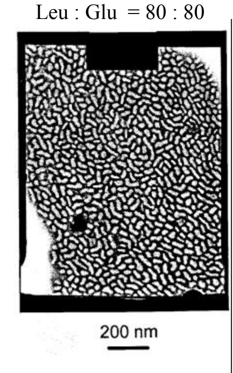
Nanoparticles

Leu : Glu = 300 :100



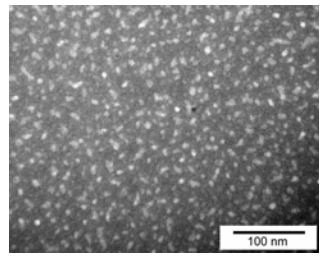
N_{agg} = 80 000
d_h = 310 nm

Leu : Glu = 80 : 80



N_{agg} = 1000
d_h = 45 nm

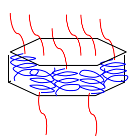
Leu :Glu = 12 : 35



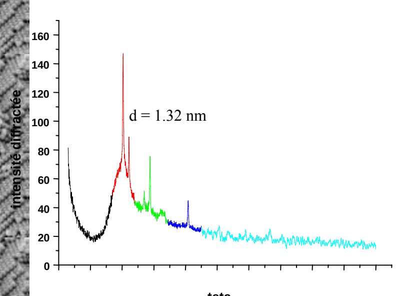
N_{agg} = 50
d_h = 19 nm

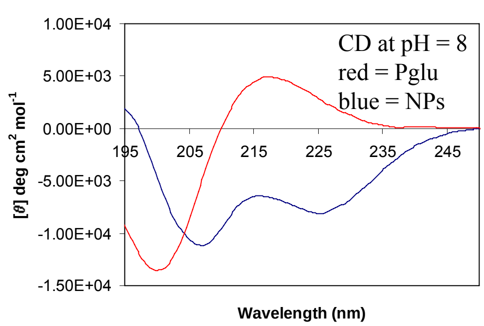
University of New Hampshire

Morphology of the Nanoparticle



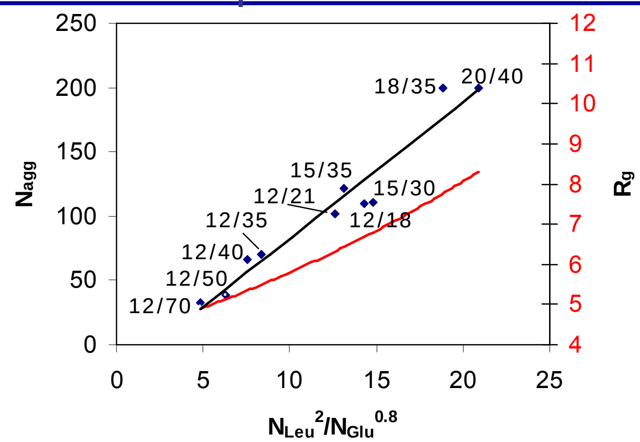
T_2 Leu = 15 µs
T_2 Glu = 8 ms
T_2 HS PGlu = 150 ms





⇨ *Hexagonal platelets containing a central core of crystallized PLeu and layers of PGlu on top and bottom*

Aggregation Number versus L/G composition

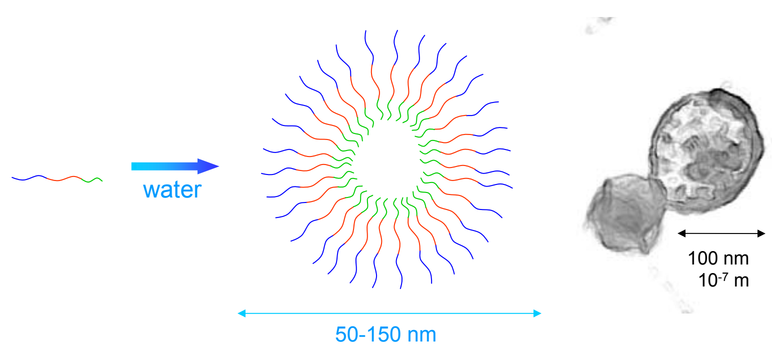


Zhulina et al $N_{agg} \propto N_{Leu}^2/N_{Glu}^{0.8}$

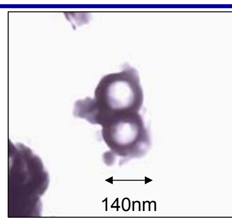
Forster et al $N_{agg} \propto N_{Leu}^2/N_{Glu}$

UNH polymer self assembly

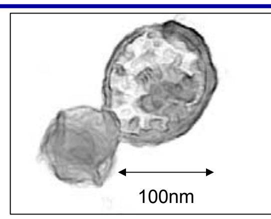
1. Self Assembly



Electronic Microscopy

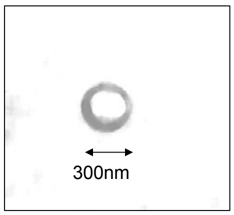


FMC x

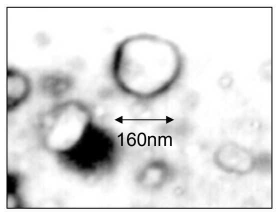


FMC xx

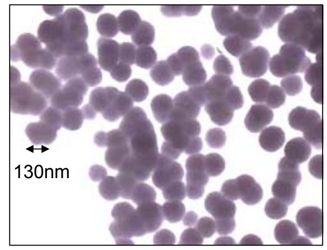
Branched Triblock



FMC xxx



FMC xxxx



Linear Triblock

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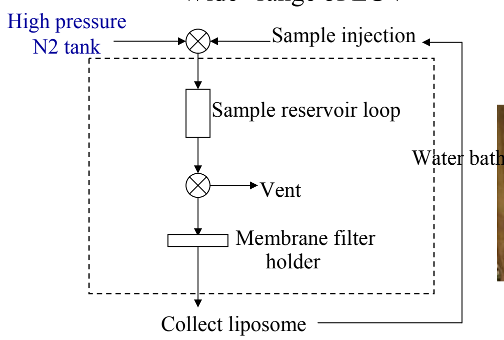
Directed Assembly

- Lipids
- Branched tri-block

Directed assembly : extrusion

- •Operates above Tc
- •Membrane pore size control vesicle size
- •Multiple extrusion (typically 5 passes)
- •Good reproducibility
- •Can operate at up to 10 bar (typically 4)
- •“Wide” range of LUV



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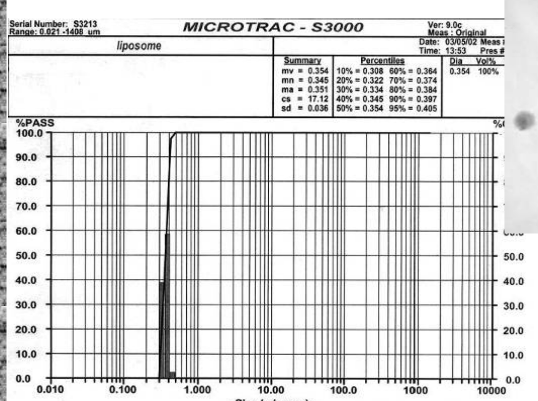
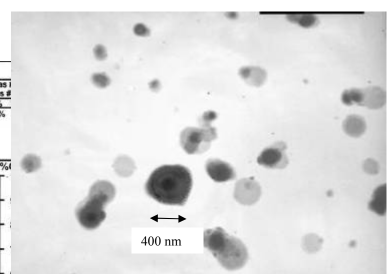
DPPC liposome size distribution after extrusion through a 400 nm polycarbonate membrane filter.

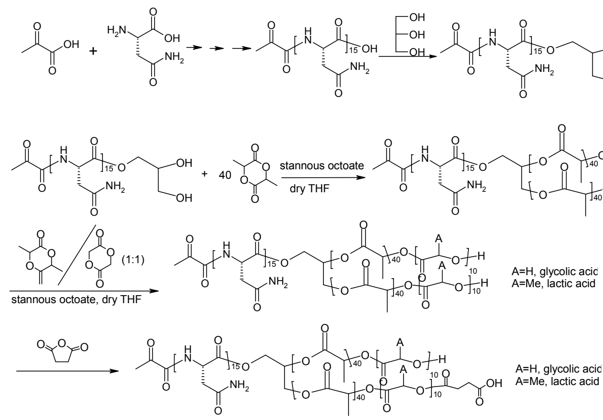




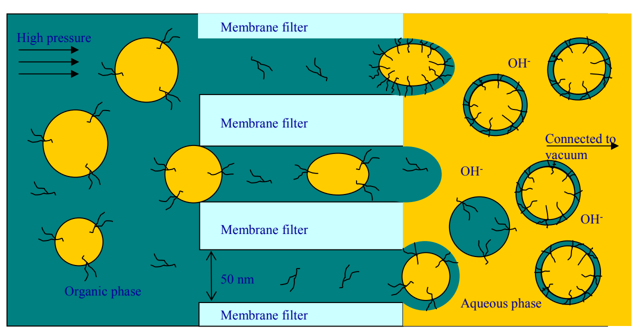
Negatively-stained TEM

Can be VERY monodispersed

Branched-tri-block copolymer



Directed assembly



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Characterization of Particle Size and Distribution of Polymer Micro- and Nanoparticles

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The Challenge – How to Obtain Reliable Data?

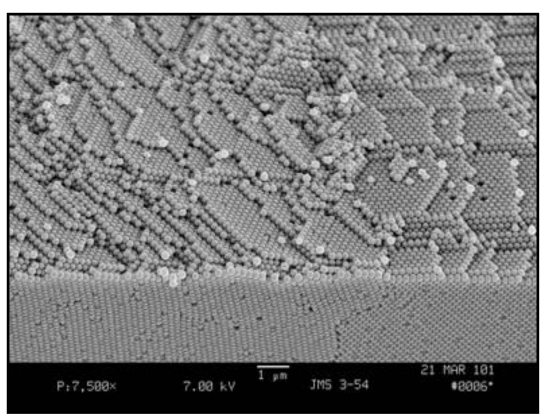
Particle Concentration in Dispersion:

1,000,000,000

000,000

Particles Per

Liter



SEM of Dried Polystyrene Latex Particles

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Basic Considerations

- Obtaining a "representative" sample
  - Settling, contamination, coagulum
- Individual vs "agglomerate" size
  - Colloidal stability
- Particle shape
  - Microscopy needed to determine non-spherical shapes

Particle Diameter Averages

$$d_n = \sum n_i d_i \;/\; \sum n_i$$

$$d_w = \sum n_i d_i^4 \;/\; \sum n_i d_i^3$$

$$= \sum w_i d_i \;/\; \sum w_i$$

Dispersion Index = Weight Average/Number Average

Example Distributions

System	di(nm)	ni	dn(nm)	dw(nm)	DI
A	400	100	470	1890	2.7
	1000	10			
	2000	1			
B	100	10	550	999	1.8
	1000	10			
C	100	100	100	100	1.0

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Basic Methods and Size Ranges

Methods

- Microscopy (light, electron [SEM, TEM])
- Light scattering
- Particle movement (e.g. sedimentation)

Size ranges

Diameter > ~ 1 micron

100 nm < Diameter < 1 micron

Diameter < 100 nm

Useful Methods – Practical Size Ranges

Table 12.3 Particle size methods and size ranges

Method/instrument	Size range/μm
1. Sieves	5.0–5000
2. Optical microscopy	0.5–500
3. Micromerigraph	1.0–400
4. Electrozone sensing	
• Coulter Multisizer IIe	0.4–1200
• Particle Data 282PC	0.4–1200
5. Soap titration	0.05–0.5
6. Light scattering	0.05–60
7. Electron microscope	0.001–10
8. Ultracentrifuge	0.01–30
9. Millipore filters	0.01–100
10. Sedigraph (5100)[a] (Micromeritics)	0.1–300
5500L	0.1–100
11. Fractional creaming	0.05–1.0
12. Joyce Loebl Disc Centrifuge DCF-4	0.01–60
13. Flow ultramicroscope	0.05–1.0
14. Dark field microscopy[a]	0.05–0.8
15. Hydrodynamic chromatography	
Flow Sizer 5600	0.03–1.5
CHDF (1100)(Matec)	0.015–1.1
16. HIAC PA 520 and 720	1.0–9000
4300	0.25–9000

Credit: E.A. Collins in "Emulsion Polymerization and Emulsion Polymers"

Useful Methods – Practical Size Ranges

Method/instrument	Size range/μm
17. Microtrac Series 9200	
FRA[a]	0.1–700
SRA	0.2–700
UPA	0.003–6.0
18. Microtrac X100	0.1–700
19. Prototron Laser L. S.	1.0–100
20. Seishin Micron Photosizer (MPS 2000)	0.1–500
21. API Aerosizer	0.2–700
22. HORIBA CAPA 700	0.01–300
Centrifugation	0.01–30
Gravitational	10.0–300
CAPA 500	0.04–300
LA 500[a] (laser diffraction)	0.1–200
LA 700[a]	0.04–262
LA 900[a]	0.04–1000
LA 910[a]	0.02–1000
23. APS 33 Aerodynamic	0.3–15
24. DMPS (TSI (aerosol)	0.01–1.0
25. Coulter N-4 Plus (N4MD) Multiangle	0.003–3.0
Coulter DELSA 440SX Multiangle	0.03–3.0
Coulter LS 200 (laser diffraction)	0.04–2000
Coulter LS 230	0.04–2000
26. Malvern Autosizer HI-C	0.003–3.0
LO-C (laser diode and fibre optics)	0.003–3.0
Zetamaster[a]	0.003–3.0
Zetasizer-3	0.001–30
Mastersizer Micro[a]	0.3–300
Mastersizer X[a]	0.1–2000
Mastersizer S[a]	0.05–3500
27. Pen Kem System 3000	0.01–50
Acoustophor 8000	0.1–10+
28. NICOMP Model 200/370	0.003–5.0
29. Shimadzu SACP4 (11000 rpm)	0.01–500
SACP3 (5000 rpm)	0.02–300
SALD[a] 1100 (laser diffraction)	0.1–500
30. Brookhaven	
BI-DCP	0.01–30
BI-XDC	0.01–100
BI-90	0.002–2.0
31. FF Fractionation, Inc.	
SFFF-S101	0.05–80
FFF-F1000	0.004–80
32. Accusizer 770 (PSS)	<0.5–2500
33. Quantochrome Microscan II	0.1–300
Cilas 715	1.0–192
Cilas 850	0.1–600
Cilas 920	0.7–400
Cilas 1064	0.1–500

[a]Suitable for quality control

Credit: E.A. Collins in "Emulsion Polymerization and Emulsion Polymers"

Microscopy Techniques

- Light and Electron Microscopy (TEM and SEM)
- Concentration effects (touching particles difficult to observe accurately
- Particle damage in beam
- Counting to obtain good size measurements

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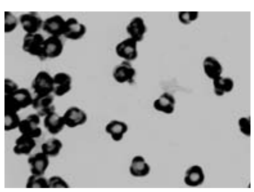
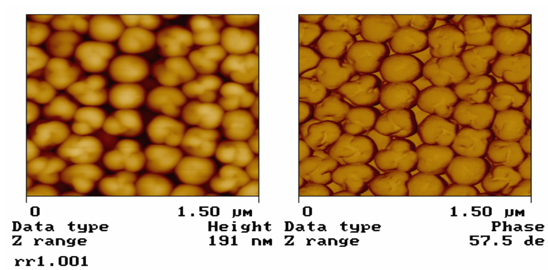
Microscopy Data



TEM

SEM



AFM

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Light Scattering Techniques

- Classical (Rayleigh) light scattering

  Static measurement of scattered light
  Makes use of Mie scattering theory

- Quasi-Elastic (or dynamic) light scattering (QELS, DLS)

  Measures time dependent fluctuations in scattered light intensity. Relates this to the diffusion coefficient of the particles

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Static Light Scattering (SLS)

Example of Turbidity

Light Scattering Behavior Non-Interacting Spherical Particles

$\alpha = \pi d / \lambda_m$
$m = n / n_0$

λ_m is wavelength of light in medium
n is refractive index of particle
n_0 is refractive index of medium

$I / I_0 = f(\theta, m, d, \lambda)$
I is the light intensity measured at angle of θ (180 degrees)

Dynamic Light Scattering

Nanotrack™ Ultrafine Particle Analyzer

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Dynamic Light Scattering

- Particle movement by Brownian motion
- Time and frequency fluctuations of scattered light
- Allows the determination of the diffusion coefficient of the particles

$$D = k\,T / (3\pi\,\eta\,d)$$

- Use of Stokes-Einstein equation to obtain particle size
- Autocorrelation function allows for size distributions

Techniques That Rely on Particle Movement

- Disk Centrifugation
- Analytical Ultracentrifugation
- Hydrodynamic Chromatography
- Field Flow Fractionation

Disk Centrifugation

Brookhaven Instruments BI-XDC

Disk Centrifugation

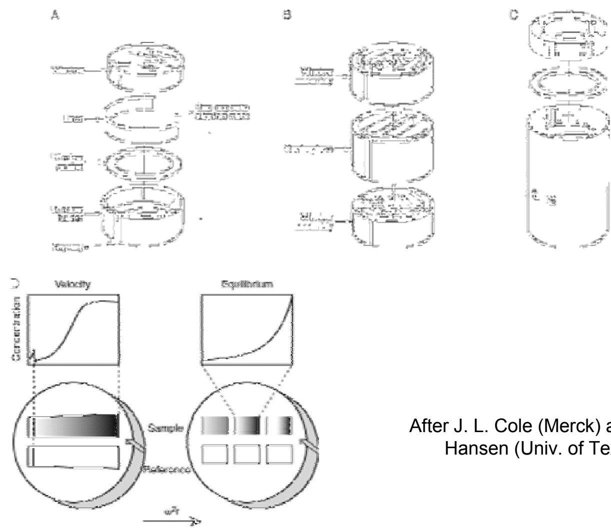
Stokes Law   t = [k η ln (rd / ri)] / {ω2 (Δρ) d2}

where ω = RPM and η = viscosity

- Measure the time for particle front to move across the spinning disk
- 10 nm < d < 10μm range
- Yields particle size distributions

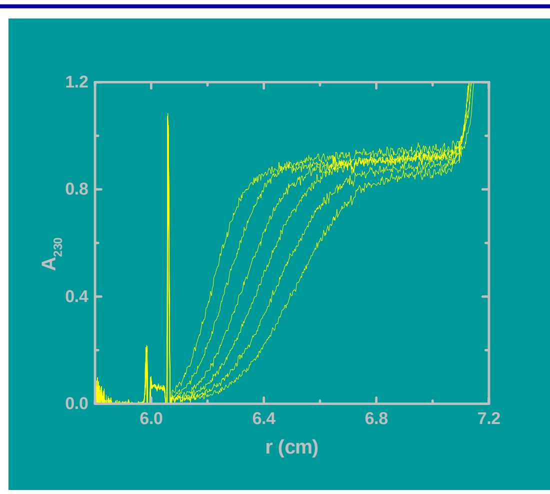
Analytical Ultracentrifugation

Analytical Ultracentrifugation



After J. L. Cole (Merck) and J. C. Hansen (Univ. of Texas)

Analytical Ultracentrifugation



Sedimentation Velocity Profile

Courtesy of Thomas Laue, Univ. of New Hampshire

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NPRC Nanostructured Polymers Research Center

Capillary Hydrodynamic Fractionation

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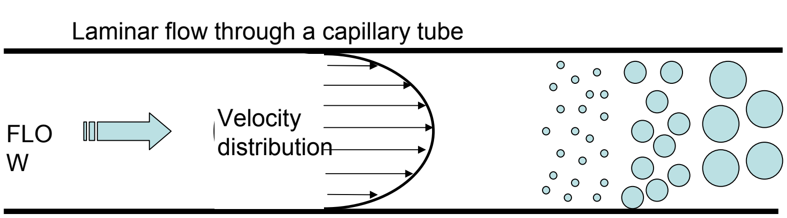
NPRC Nanostructured Polymers Research Center

Capillary Hydrodynamic Fractionation (CHDF)



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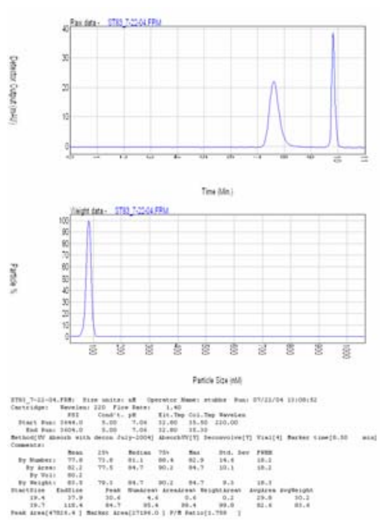
Capillary Hydrodynamic Fractionation



83 nm PS standard

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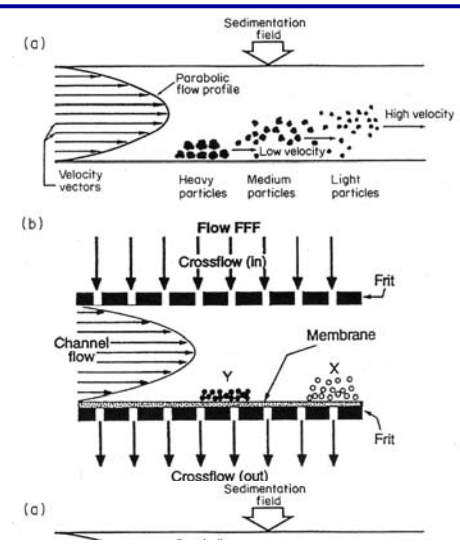
Field Flow Fractionation



Credit: E.A. Collins in "Emulsion Polymerization and Emulsion Polymers"

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Comparative Data from Different Methods

Table 12.11 Comparison of particle diameters (μm) of PMMA latexes measured by various methods

Latex	TEM		DCP		SFFF		HDC		Turbidity	QELS
No.	d_n	d_w	d_n	d_w	d_n	d_w	d_n	d_w	d_{LS}	d_{LS}
1	160	162	182	192	205	222	255	257	237	223
2	239	241	233	247	261	267	322	342	275	305
3	293	298	344	351	346	350	422	423	357	413
4	377	283	418	432	410	421	540	542	459	468
5	448	469	550	566	521	529	664	668	667	578
6	574	611	658	686	600	605	893	901	817	746

Credit: E.A. Collins in "Emulsion Polymerization and Emulsion Polymers"

Data from Koehler and Provder, ACS Symp. Ser. No.332, 1987, p 231-239

Comparative Data from Different Methods

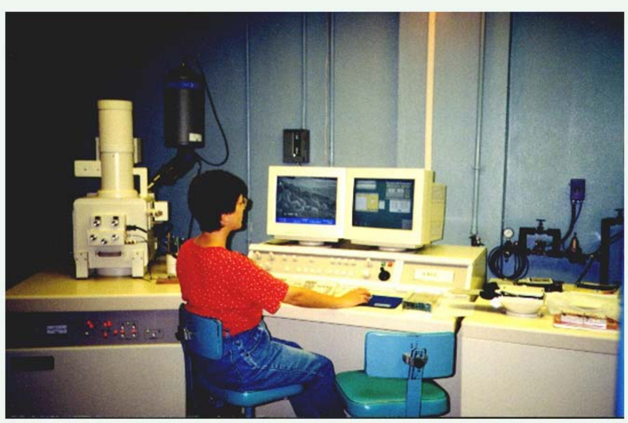
Table 12.12 Comparison of latex particle diameter (μm) measurements

Method	Latex A (PVC copolymer)	Latex B (PVC homopolymer)	Latex C (acrylic copolymer)
EM, d_n	0.292	0.096	0.273
Joyce Loebel, d_{50}	0.274	0.095	0.273
Horiba Capa 500, d_w	0.330	0.100	0.240
Coulter N-4, d_v	0.293	0.095	0.289
95% in the range	(0.285–0.301)	(0.0936–0.096)	(0.282–0.295)
NiComp 200, d_h^*	0.274	0.100	0.277
	(10%>0.064)	(50%>0.035)	(0 small)
BI-90, d_w	0.289	0.097	0.294
Polydispersity	0.06	0.078	0.005
d_{av}	0.259	0.083	0.292
HDC 5600	0.270	0.089	0.270
d_n	0.340	0.089	0.320
d_w	BiModal	Narrow	BiModal
Range	0 below 0.200	0 below 0.065	0 small
	0.112–0.420	0.065–0.110	0.110–0.400
	0.5–0.7 small peak	—	0.55–0.70
SFFF d_n	0.236	0.058	0.238
d_w	0.265	0.066	0.265
SCM DCP d_n	0.279	0.080	0.306
d_w	0.329	0.094	0.357
d_{ls}	0.351	0.125	0.381
d_{50}	0.317	0.087	0.341

Credit: E.A. Collins in "Emulsion Polymerization and Emulsion Polymers"

Characterization of Surface Composition of Polymer Micro- and Nanoparticles

Scanning Electron Microscope



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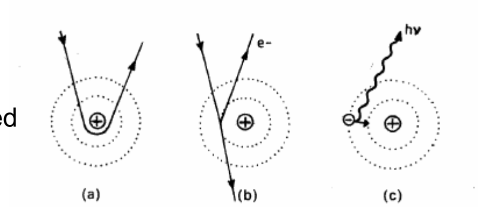
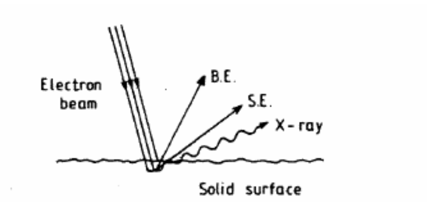
Scanning Electron Microscope

Rutherford scattering (a): ejected electron (b), emitted x-ray photon (c)



Backscattered electron, secondary electron, x-ray



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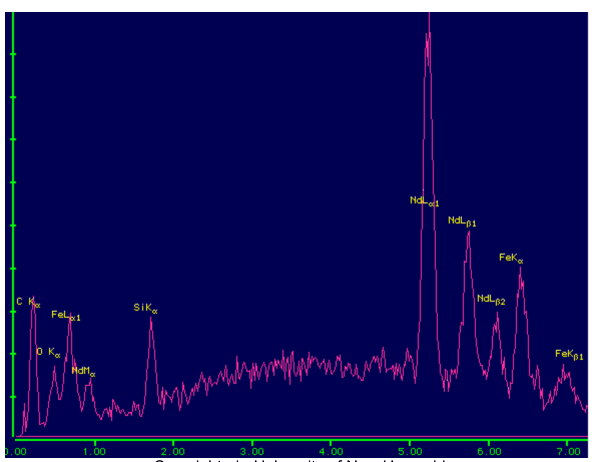
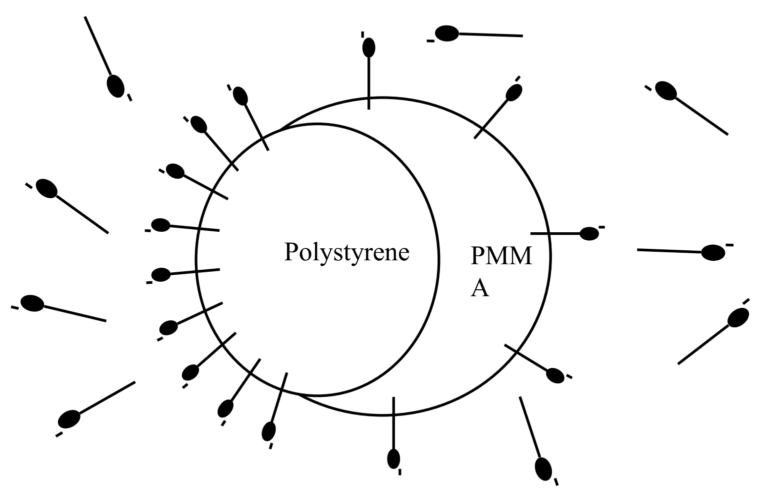
Energy Dispersive X-Ray Spectroscopy



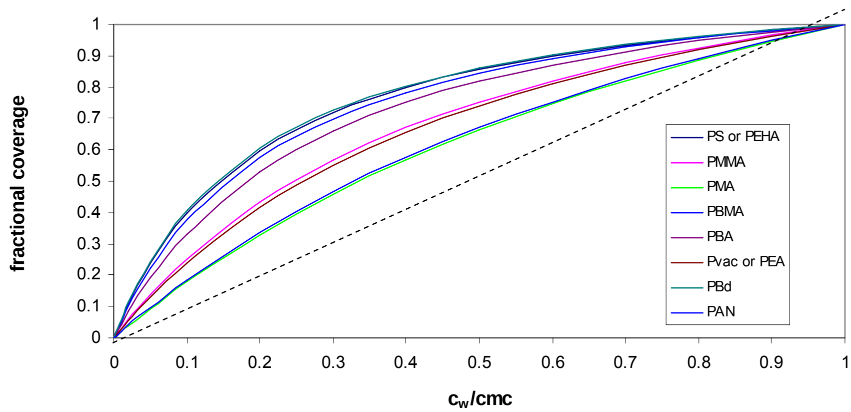
Surfactant Titration

Titration of the composite latex with a specific surfactant such as Sodium Dodecyl Sulfate (SDS) is a simple technique offering reliable information regarding the composition of the particle surface. The technique consists of measuring the specific adsorption surface area of a given surfactant on the composite particle with the Maron technique. Comparison of this specific area with the one of that surfactant onto the pure material (the one each phase is made of) will describe on much of a given phase is present at the particle surface. For example if one makes a polystyrene (PS) / polymethymethacrylate (PMMA) composite particle and finds a specific area of ~100 Å2 per molecule of SDS, then one can conclude that PMMA covers the entire particle. This implies previous knowledge that the specific area of SDS on PMMA is 100 Å2 and 45 Å2 on PS.

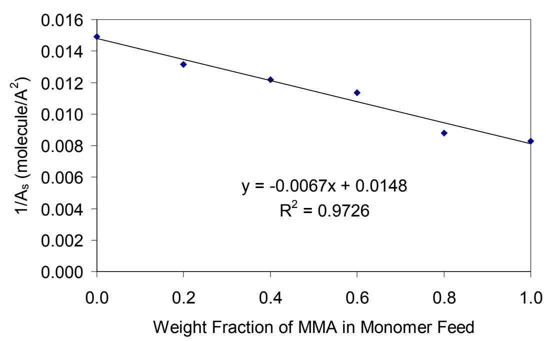
Surfactant Distribution on Composite Particle



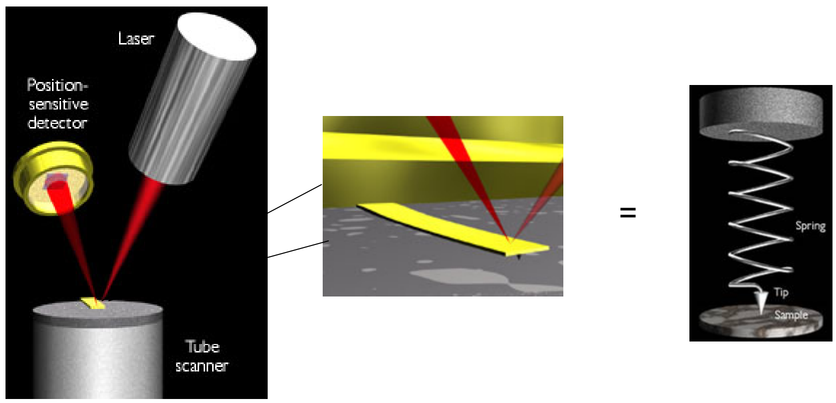
EQMORPH Adsorption Isotherms for SDS from Szyszkowski-Gibbs treatment



Surfactant Adsorption on Composite Latex Particles



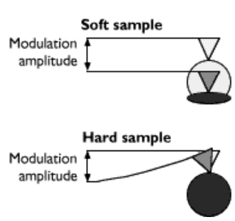
Atomic Force Microscopy (AFM)

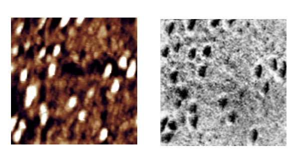


AFM Tips

$$\text{resonant frequency} = \frac{1}{2\pi}\sqrt{\frac{\text{spring constant}}{\text{mass}}}$$

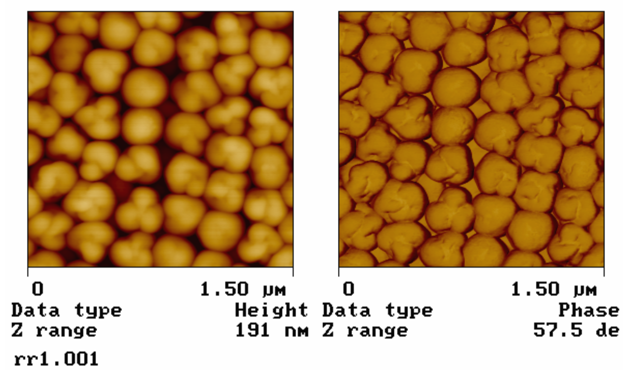
Phase contrast





1 x 1 µm simultaneous topography (left) and elasticity (right) images of bovine serum albumen on silicon

AFM Tapping Mode Analysis of Polymer Particles

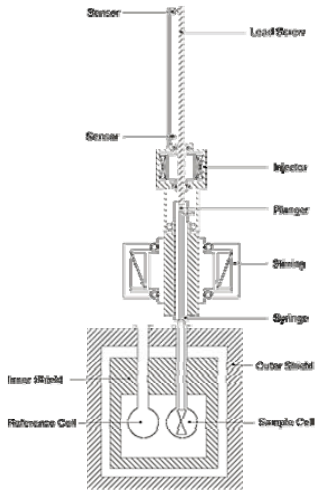


"Height" Image

"Phase Contrast" Image

Isothermal Titration Calorimetry

ITC



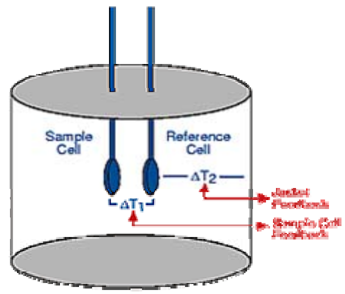


Figure 2.

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Characterization of the Internal Structure of Polymer Micro- and Nanoparticles

Useful Methods to Determine Internal Particle Morphology

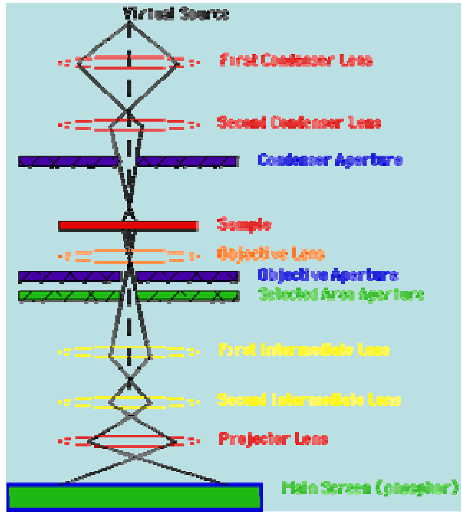
- Transmission Electron Microscopy (TEM)
- Differential Scanning Calorimetry (DSC)
- Scanning Transmission X-Ray Microscopy (STXM)

How do Electron Microscopes Work?

Electron Microscopes function exactly as their optical counterparts except that they use a focused beam of electrons instead of light to "image" the specimen and gain information as to its structure and composition.
The basic steps involved in all EMs:

- A stream of electrons is formed (by the Electron Source) and accelerated toward the specimen using a positive electrical potential
- This stream is confined and focused using metal apertures and magnetic lenses into a thin, focused, monochromatic beam.
- This beam is focused onto the sample using a magnetic lens
- Interactions occur inside the irradiated sample, affecting the electron beam
- These interactions and effects are detected and transformed into an image

Magnetic Lens Arrangement in the TEM



JEOL Current EM

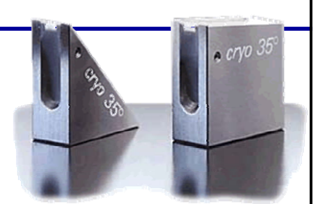
Specifications	JEM-1010	JEM-1230
Resolution	0.2nm Lattice	0.2nm Lattice
Accelerating Voltage	40 to 100kV	40 to 120KV
Magnification	50x to 1,000,000x	50x to 600,000x

Specifications	JEM-3010	JEM-3000F FasTEM™
Resolution	0.14nm Lattice	0.10nm Lattice
Accelerating Voltage	100 to 300 KV	100 to 300kV
Magnification	50x to 1,500,000x	60x to 1,500,000x

Transmission Electron Microscopy

The Jeol 2000FX TEM with an EDS microanalysis system is a research microscope equipped with a LaB6 gun to give high performance in TEM, STEM, SEM, EDS, and diffraction modes.

Sample preparation



This is the hard part…

TEM:

1. Embedding ?
   - Choice of matrix ?
   - Cure ?
   - Dry ?
2. Rough cutting
3. Microtoming
   - Microtoming
   - Cryomicrotoming
   - Freeze fracture
4. Staining, contrasting, shadowing
5. Sample transfer to Cu grid
   - Colloid membrane ?

SEM:

Stem attachment

Coating with conductor (Au, C, …) typically by electron sputtering

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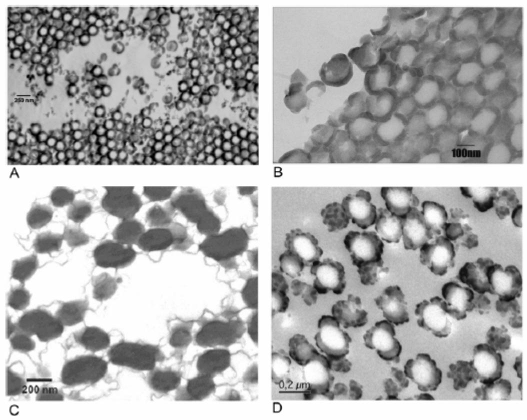
Examples of Potential Problems with Contrast Staining



Sample C was unstained. Sample D was over stained

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Thermal Analysis Techniques

- Differential Scanning Calorimetry (DSC) , especially modulated temperature - for particles and films
- Dynamic Mechanical Analysis (DMA) for films

DSC

DMA

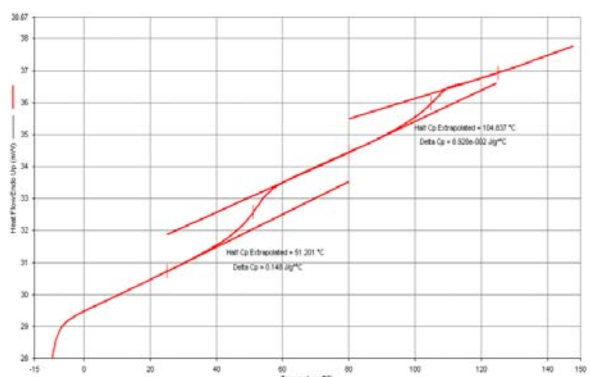

Figure 2 DSC trace for an acrylic copolymer seed and polystyrene composite latex.

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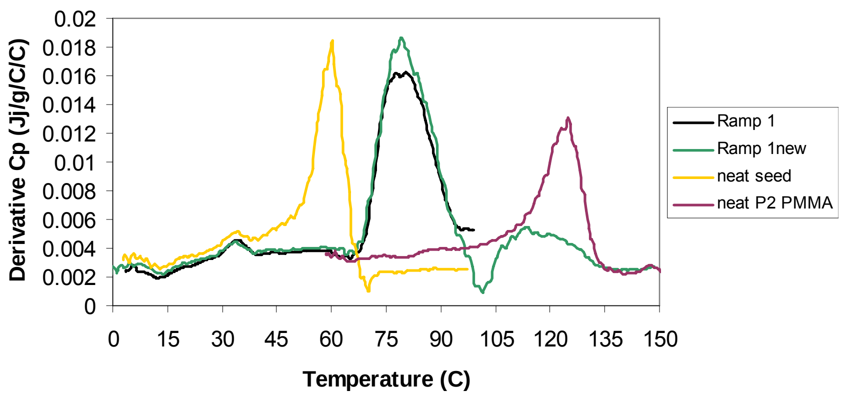
Example of DSC Data for Composite Latex Particles



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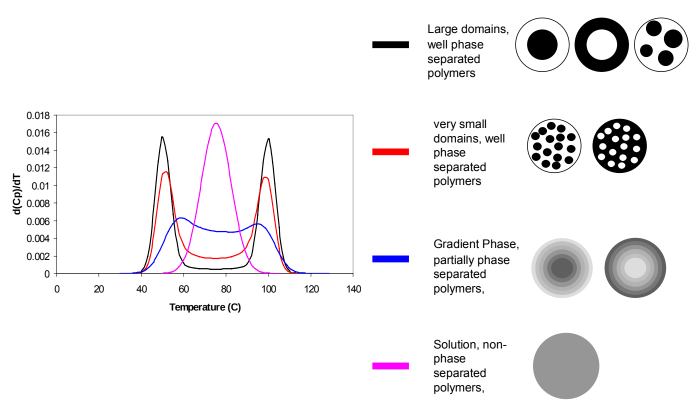
DSC results for Various Particle Morphologies



UNH Latex Morphology Industrial Consortium Advisory Board Meeting – June 3, 2004

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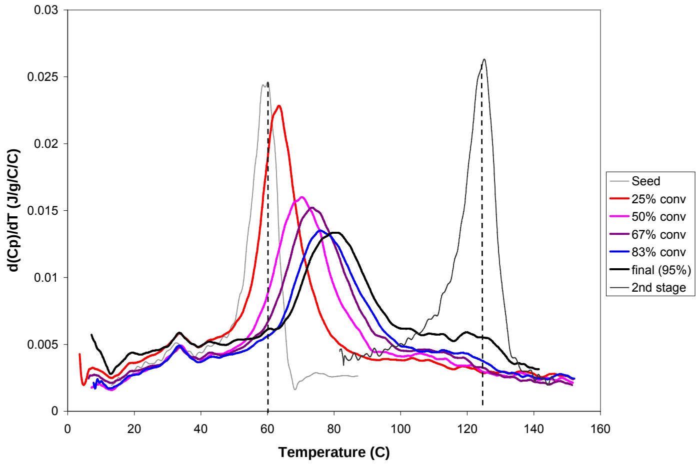
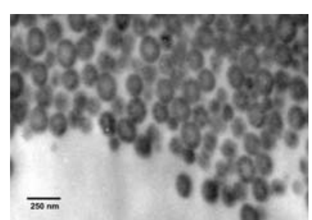
Modulated Temperature DSC Data as a Function of Extent of Reaction



TEM Results

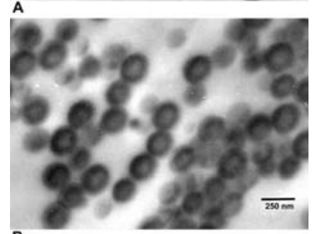
All acrylic (polar) seed latex

Second stage styrene monomer added slowly



A

After 50% mono-mer add



B

After 100% mono-mer add

Polymer Nanotechnology: Example of Applications

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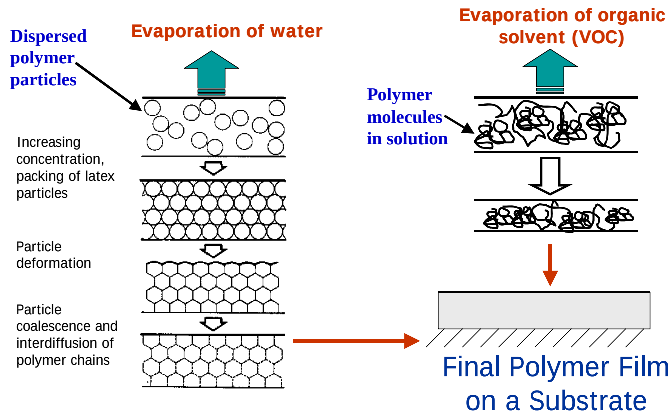
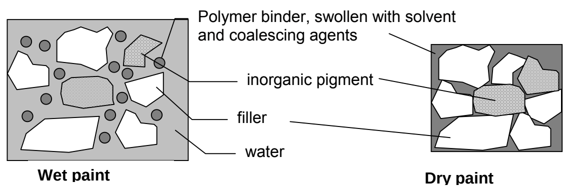
Waterborne Paints

Film Formation

Waterborne Latex Coating | Solventborne Coating



Traffic paint background



- Prior to April 1995, EPA standards – VOC<450g/l
- After VOC<150g/l.
- Current 100% acrylic WB paints have VOC's between 98 and 120 g/l.
- Fast dry contain 149 g/l Methanol
- NHDOT current requirement
  - 100% acrylic
  - No minimum binder content

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Wear resistance improvement

- Estimated service life by class (median lifetimes in days) 1990 report

	Arizona		Florida		Pennsylvania	
	OGAFC	PCC	DGAFC	OGAFC	DGAFC	PCC
Alkyd--White	163	>900	>900	101	341	390
Alkyd--Yellow	293	>900	>900	173	258	284
Chloro Rubber--White	478	>900	>900	255	444	470
Chloro Rubber--Yellow	159	>900	368	83	389	470
Water-base--White	>703	>900	>900	>900	505	823
Water-base--Yellow	>765	>900	>900	>900	474	684
Solv. Borne Epoxy--White	755	>900	>900	436	>1100	>1100
Solv. Borne Epoxy--Yellow	>900	>900	>900	400	>1100	>1100
Urethane--White	883	>900	>900	577	630	>1100
Urethane--Yellow	617	>900	>900	607	578	>1100
Thermoplastic--White	>900	>900	>900	824	>1100	413*
Thermoplastic--Yellow	>900	>900	>900	420	>1100	354*
Cold Plastic--White	>900	>900	>900	377	386	>1100
Cold Plastic--Yellow	>765	>900	>803	625	298	365
Foil Tape--White	>900	>900	>900	>900	NA	NA
Foil Tape--Yellow	>900	>900	>900	>836	NA	NA

25% increase

- NA - Not Available, OGAFC - Open-graded asphaltic concrete, * - Data may not be reliable due to snowplow damage, DGAFC - Dense-graded asphaltic concrete, PCC - Portland cement concrete

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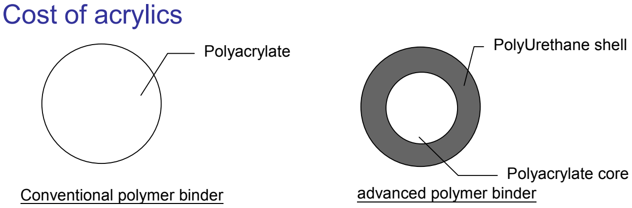
Wear resistance improvement

- Hybrid technology
- Combine properties of PU and water base acrylics
  - Wear resistance properties of urethanes
  - Cost of acrylics



- Binder can be prepared by miniemulsion polymerization

Application

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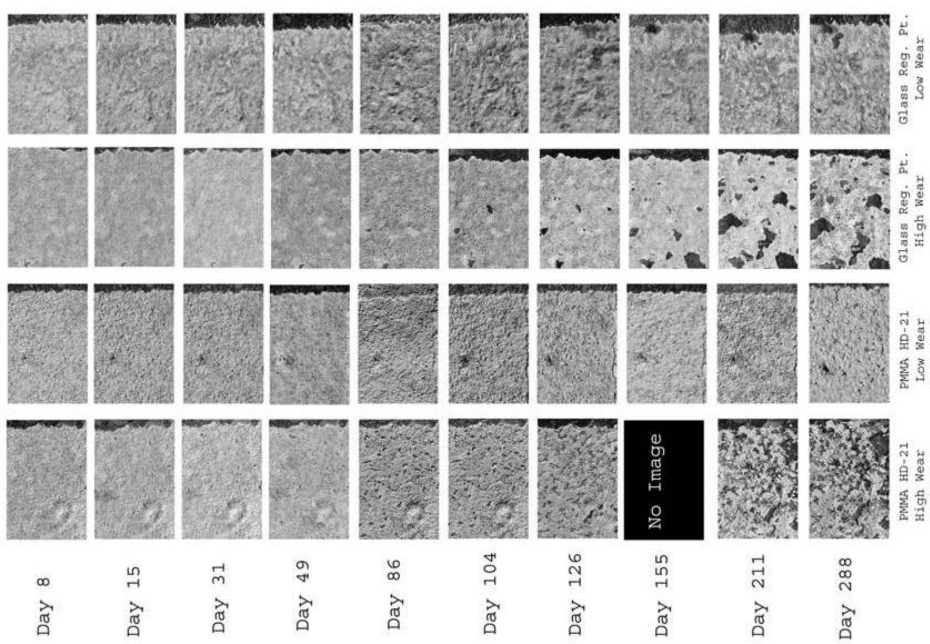

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Drug release

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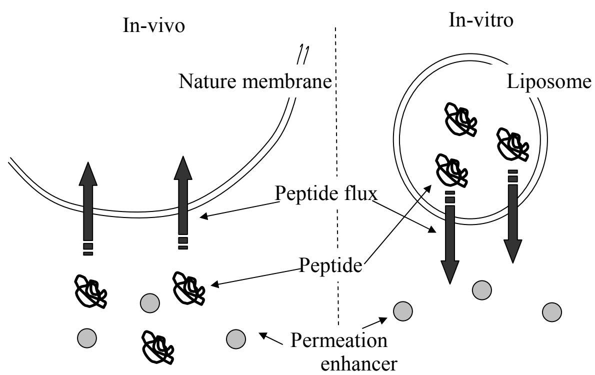
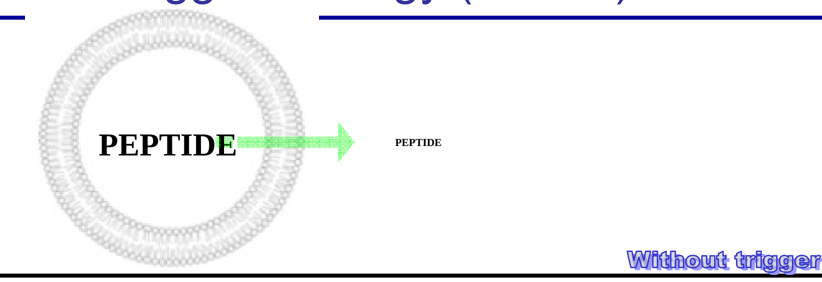
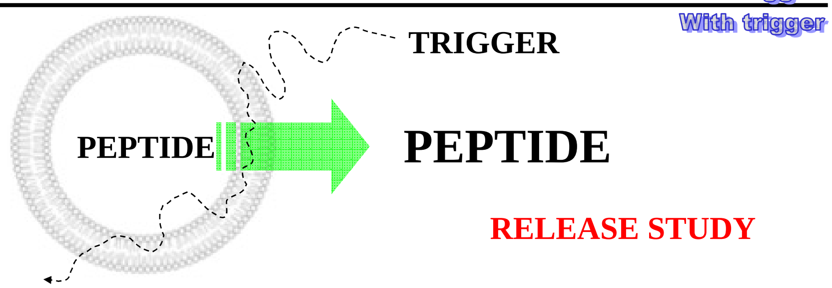
Release Concept “In Vivo” Vs. “In Vitro”



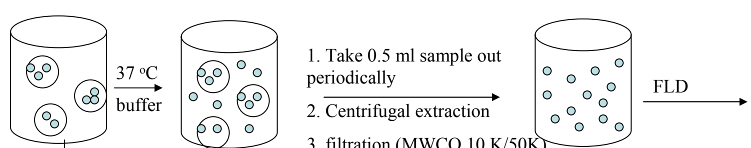
Trigger strategy (in vitro)

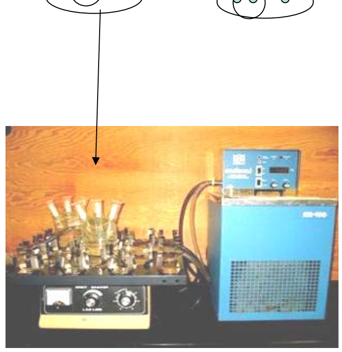


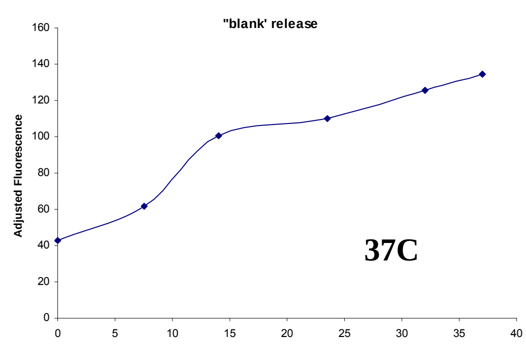


RELEASE STUDY

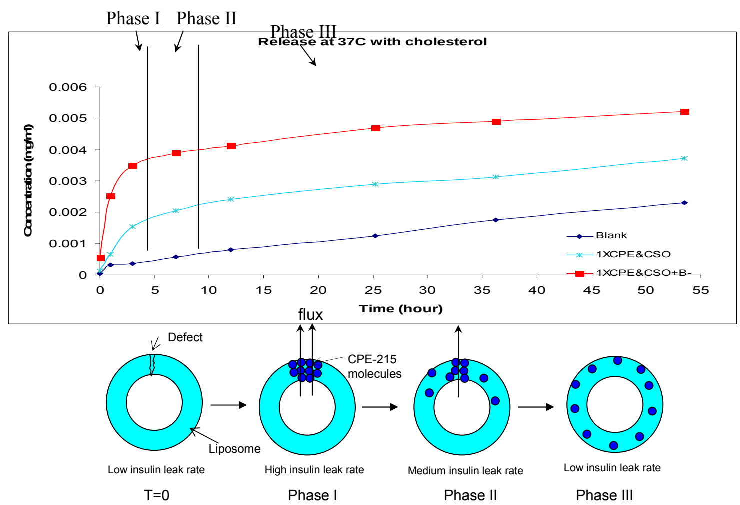
Release study strategy







Transmembrane transport mechanism of insulin with excipient triggering



Drug delivery

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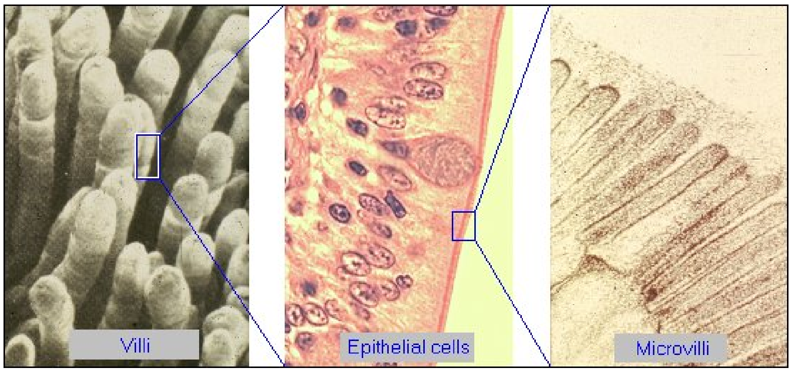
Oral Delivery of Proteins

Numerous barriers

- Stomach (pH ~ 3) => Use of an enteric coating
- Intestine (pH ~ 6.8 -7.4)



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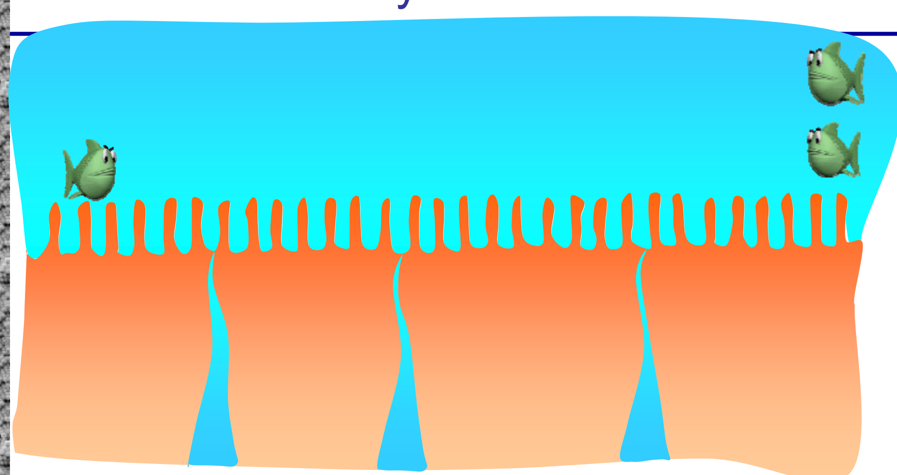
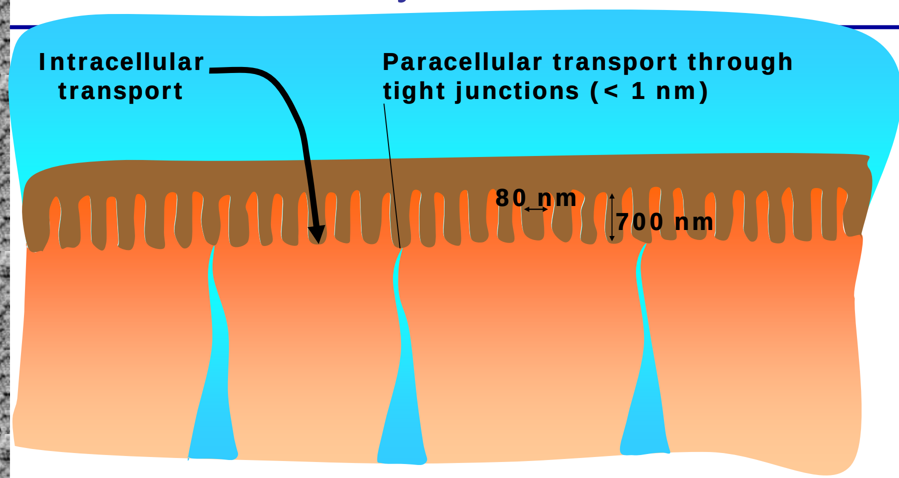
Oral Delivery of Proteins



Enzyme : trypsin, chymotrypsin, pepsin, carboxypeptidase, lipase, amylase,sucrase, maltase, lactase

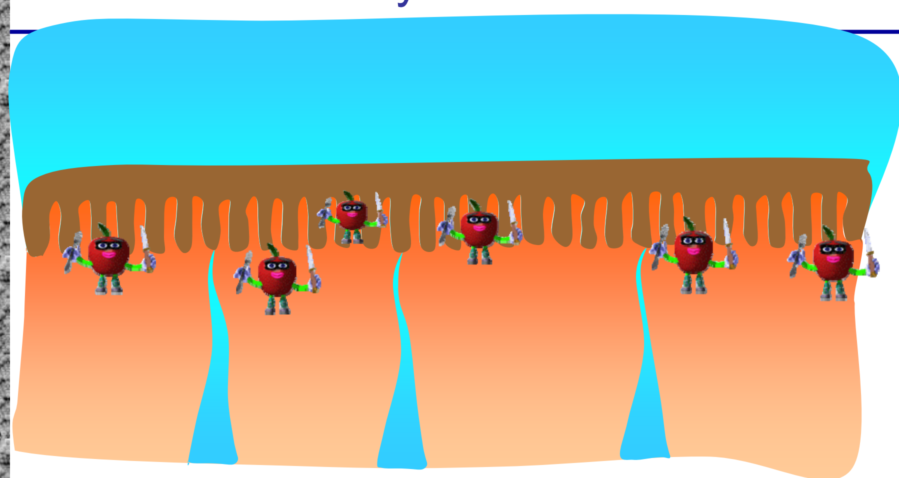
Oral Delivery of Proteins



Size issues

Hydrophobic, viscous, pH ~ 5

Oral Delivery of Proteins



Large series of digestive proteins :
- Efflux proteins
- Cytochroms
- Proteases

Oral Delivery of Insulin

Encapsulation of insulin in a vesicle (= nanobag)

What are the properties of these vesicles ?

- made of biocompatible constituents
- can be encapsulated in an enteric coating
- have an hydrophobic external layer (mucus is hydrophobic)
- have a small size (~ 100 nm)
- can release the bioactive drug
- can be used for all kind of biologically active macromolecules

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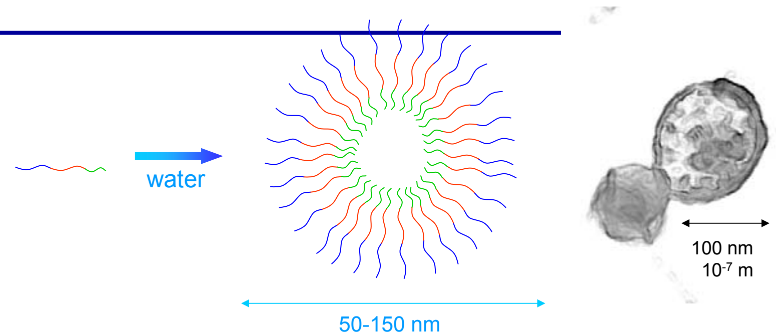
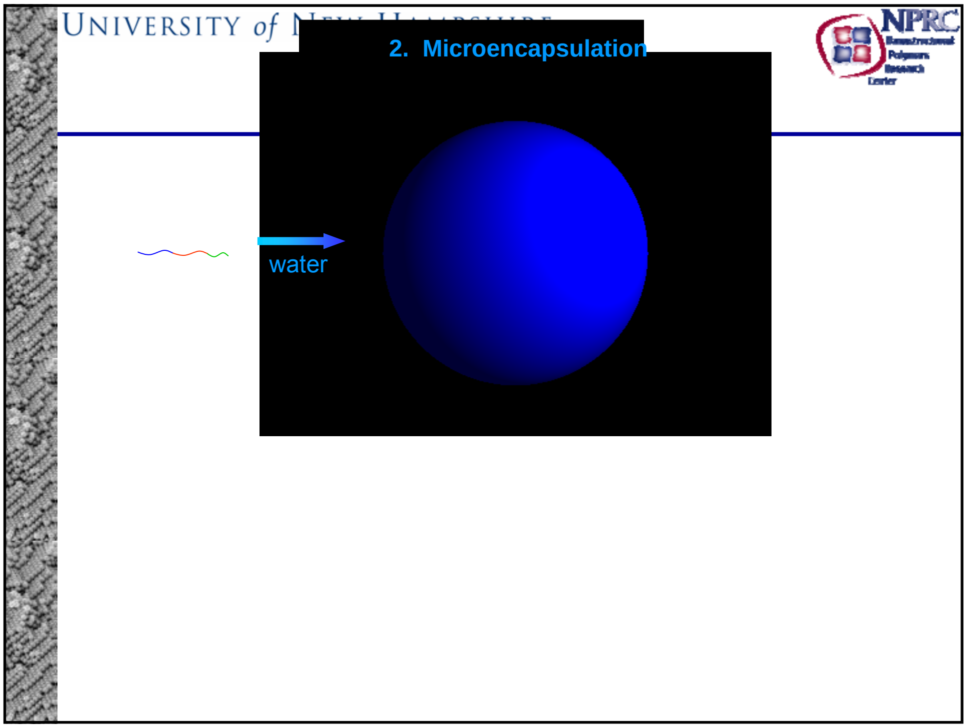
1. Self Assembly

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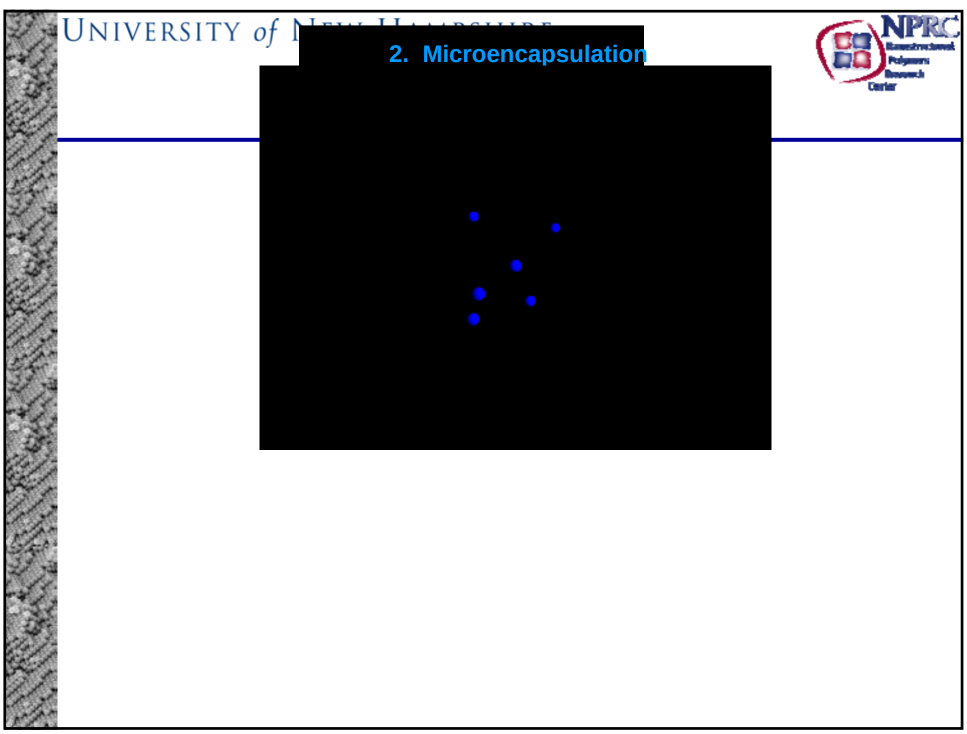
NPRC
2. Microencapsulation
water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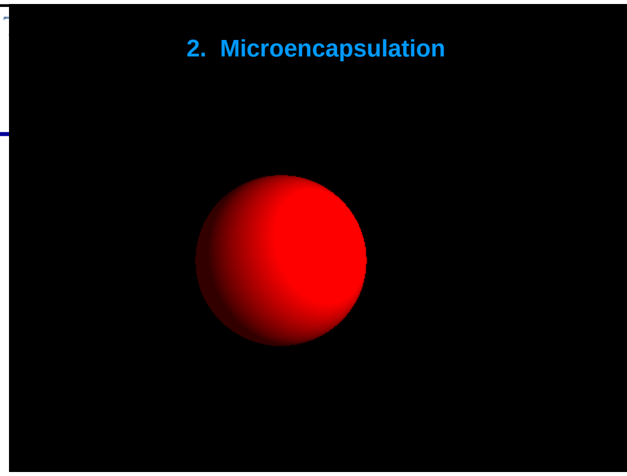
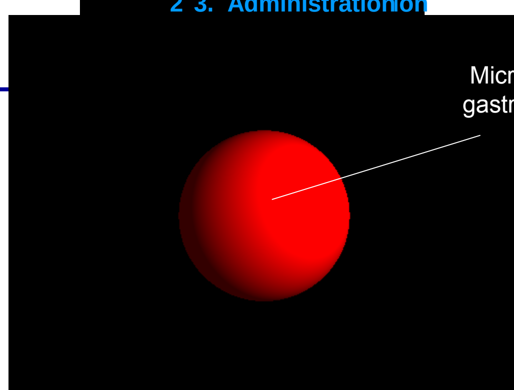
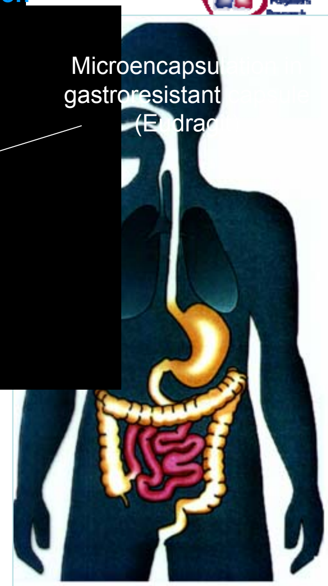
2. Microencapsulation

2. Microencapsulation

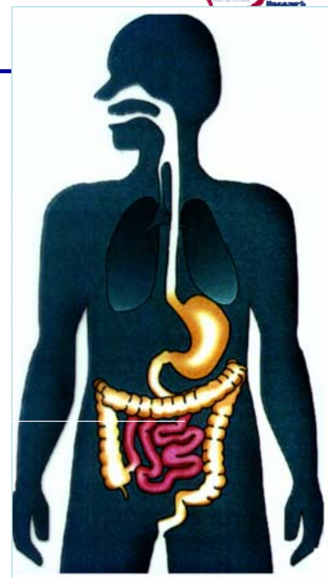


2 3. Administrationion





3. Administration



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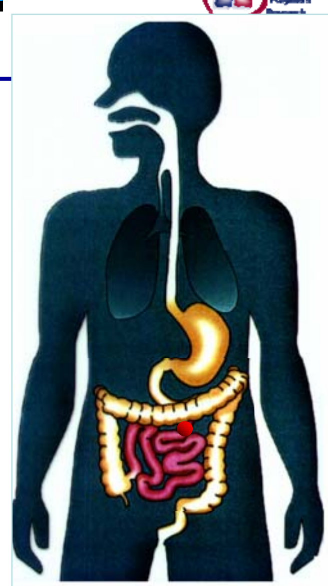
3. Administration



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3. Administration

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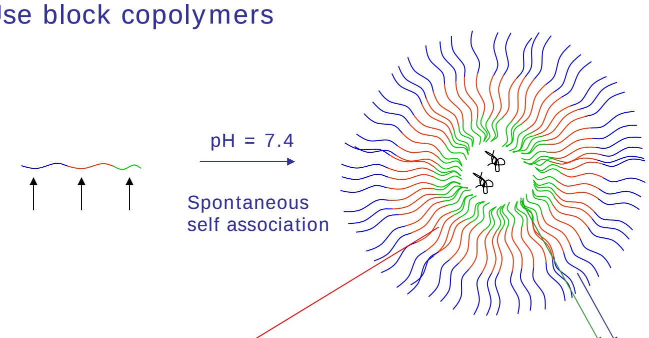
NPRC

How to make vesicles ?

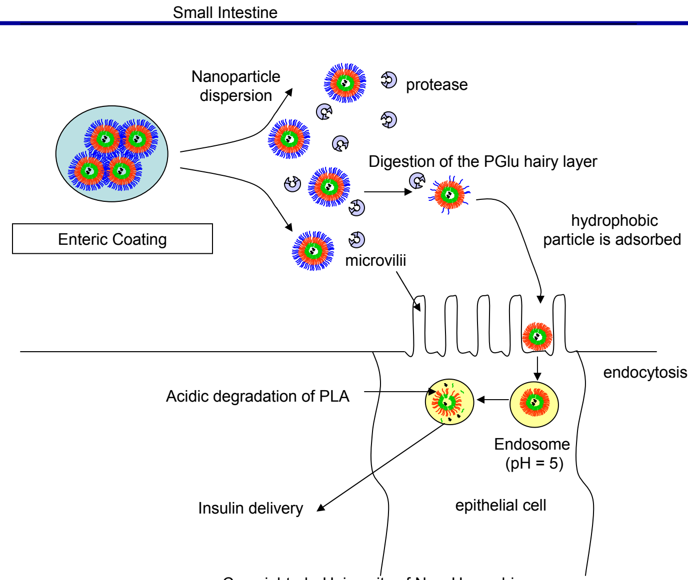
- Use phospholipids to make liposomes
- Use block copolymers



hydrophobic
Forms the wall of the vesicle
Degrades naturally

Hydrophilic polymers
necessary to form the vesicle
and prevent insulin denaturation

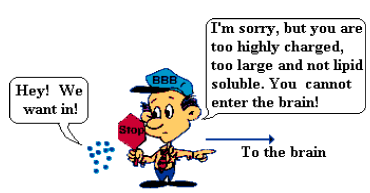
Vesicles inside the intestine



Getting around the BBB

- The blood-brain barrier (BBB)

The BBB is formed by the endothelium lining the cerebral microvessels with tight junctions in order to maintain rigorous control of the microenvironment within the brain. Even the glucose molecules need transporters to go through the BBB.



Novel pathway for drug delivery

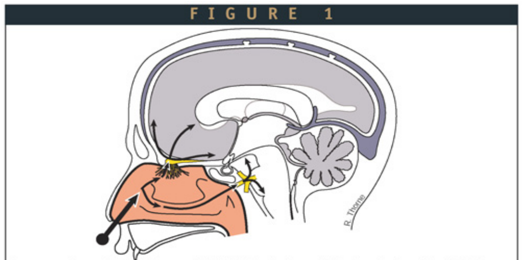
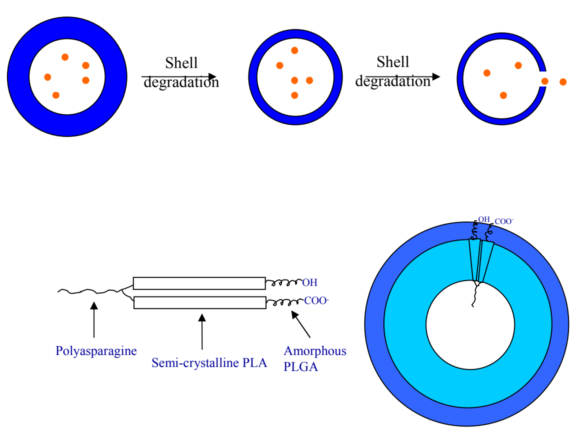


Image courtesy of Robert Thorne, PhD, Alzheimer's Research Center, Regions Hospital, St. Paul, MN.

The neural connections between the nasal mucosa and the brain provide a unique pathway for noninvasive delivery of therapeutic agents to the CNS, by bypassing blood-brain barrier.

Design to degradation



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Sensor Technology

University of New Hampshire

- **Polymeric Nanoparticles synthesis processes**
  - Emulsion Polymerization
  - Mini-emulsion Polymerization
  - Self assembly
  - Directed assembly
- **Application to biotechnologies**
  - biosensors by molecularly imprinted polymers
  - liposomes for transmembrane delivery
  - Bypassing the BBB

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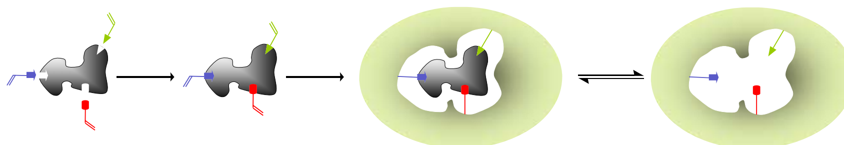
Molecularly Imprinted Polymers



1. Selection of template molecule and functional monomers
2. Self-assembly of template molecule and functional monomers
3. Polymerization
4. Analyte Extraction

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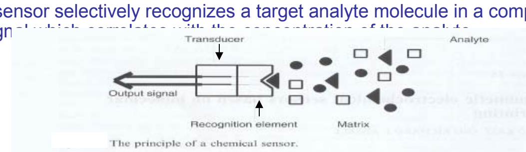
Biomimetic electrochemical sensors based on molecular imprinting

- A chemical sensor selectively recognizes a target analyte molecule in a complex matrix and gives an output sign



The principle of a chemical sensor.

The transducer: When the analyte interacts with the recognition element of a sensor, there is a change in one or more physicochemical parameters associated with the interaction. Transducer convert these parameters into an electrical output signal than can be amplified, processed and displayed in a suitable form.

⇒ Molecular imprinting use as sensing materials

Advantage: cheap, stable and robust under a wide range of conditions including pH, humidity and temperature

Problem: Signal transduction is so low that it seem to be environmental artifacts. Due to the insulating nature of the polymer constituting the MIP

Biomimetic electrochemical sensors based on molecular imprinting / Chap.18 MIP – D. Kriz, R. J. Ansell- Vol 23 -Elsevier

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NPRC Nanostructured Polymers Research Center

Preparation of a MIP

- **Choice of the target molecules**
  Wide variety of analyte molecules have been successfully used for the preparation of selective recognition matrices

Compound Class	Example		Compound Class	Example
drugs	timolol		**amino acids**[a]	phenylalanine
	theophylline			tryptophan
	diazepam			tyrosine
	morphine			aspartic acid
	ephedrine			
			carbohydrates[a]	galactose
hormones	cortisol			glucose
	enkephalin			fucose
pesticides	atrazine		**co-enzymes**	pyridoxal
proteins	RNase A		**nucleotide bases**	adenine
	Urease			

Molecular Imprinting Technology - *A Way to Make Artificial Locks for Molecular Keys http://www.smi.tu-berlin.de/story/How.htm*

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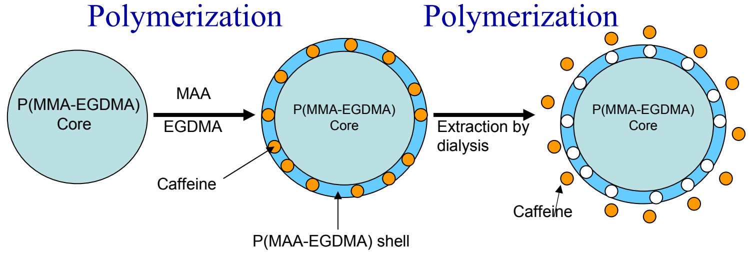
NPRC Nanostructured Polymers Research Center

SINP : Surface Imprinted NanoParticle

1st stage Miniemulsion Polymerization | 2nd stage Emulsion Polymerization



MJB-20: miniemulsion seed

Organic phase = 23% : MMA 85.5%, EGDMA 9.5%, Hexadecane 5%,

Water phase = 77% : Water 99%, SDS 0.6%, KPS 0.025%, NP-50 0.39%

Prepare the two phases, mix them together, magnetically stir them for 15 minutes, then, sonicate the resulting emulsion for 2 minutes (90%, 9) in ice.

SCexp = 22.25%, Conversion = 98.96%,

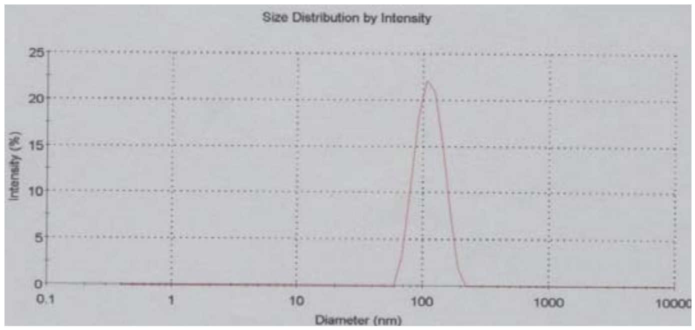
Size = Malvern Nanosizer: Dz = 107.1 nm, Dv = 111.9 nm

MJB-21: 2nd stage imprinting

Water	57.74%
MJB20 (wet)	33.44%
NaHCO3	0.042%
KPS	0.047%
Caffeine	5.78%
EGDMA	2.63%
MAA	0.31%

Water, MJB-21, NaHCO3, were mixed and heated at 80C. When at temperature, add caffeine and start degassing. After 15 minutes, add KPS and start feeding with egdma+maa. Dilute with 250g of hot water (336%) while stirring.
SCexp = 2.635% (dilution) Conversion = 57.86%
Size = Malvern nanosizer Dz= 108.4 nm, Dv = 114.2nm
Brookhaven 90+: Dz = 104.9 nm, Effective Dv = 105.2 nm

Size distribution



MJB21 by Light scattering

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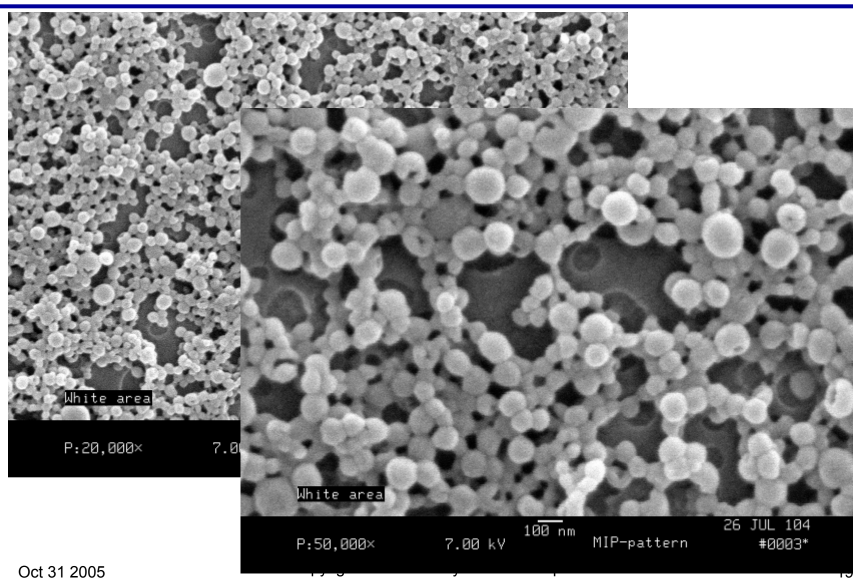
SEM of nanoparticles



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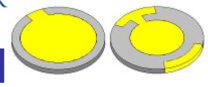
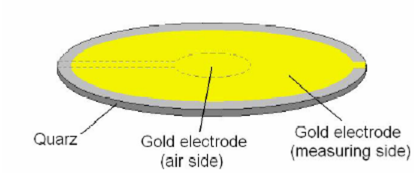
QCM



- A QCM consists of a thin quartz disc sandwiched between a pair of electrodes. Due to the piezoelectric properties of quartz, it is possible to excite the crystal to oscillation by applying an AC voltage across its electrodes.

Quartz crystal - The heart of the QCM



$\Delta f = -f_u^{2/3} [(\rho_L \eta_L) / (\pi \times (\rho_q \mu_q)]^{1/2}$, where

Δf = measured frequency shift,
f_u = resonant frequency of the unloaded crystal,
ρ_L = density of liquid in contact with the crystal,
η_L = viscosity of liquid in contact with the crystal,
ρ_q = density of quartz, 2.648 g/cm^3,
μ_q = shear modulus of quartz, 2.947×10^{11} g/cm$\times$s^2.

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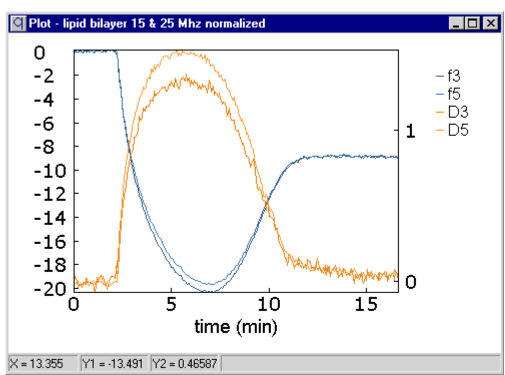
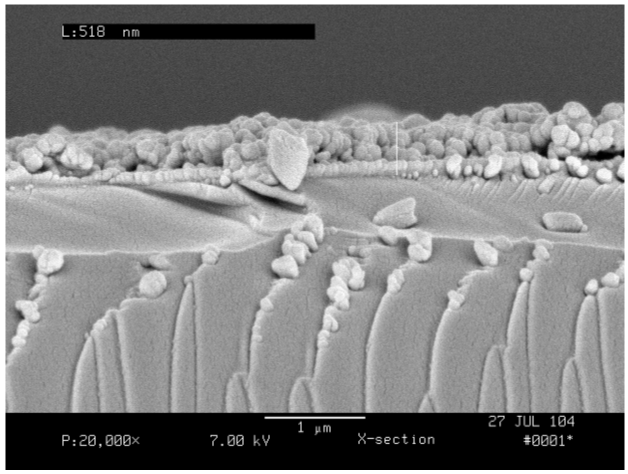
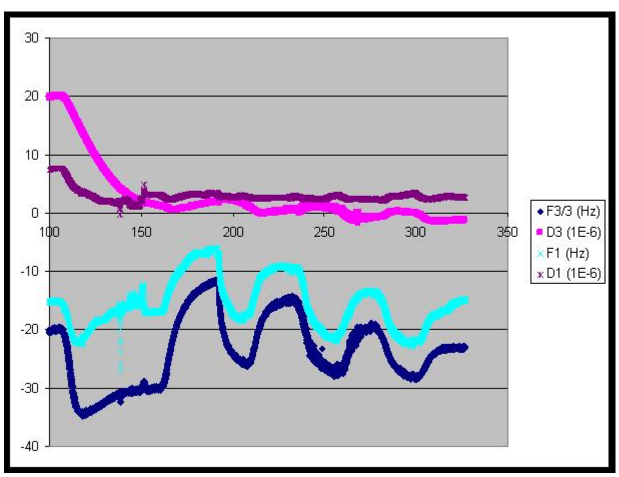
Q-Sense D300



Coated QCM sensor Fracture SEM



Raw data



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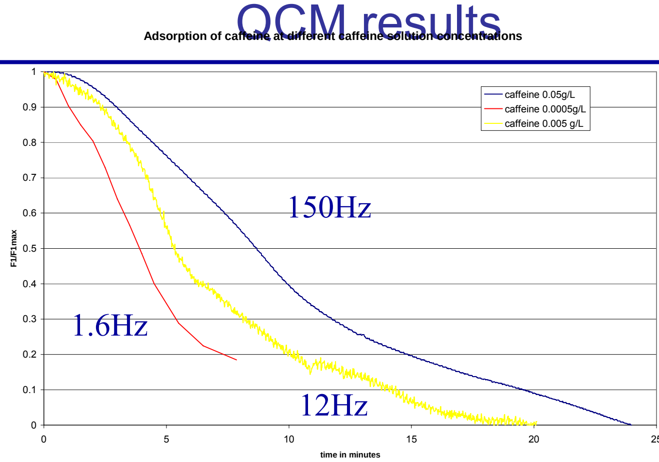
QCM results



With the Langmuir equation the quantity adsorbed can be calculated for the caffeine MIP at a concentration of 0.0005g/L. This value is found to be equal to 7.3×10-6g of caffeine per gram of MIP. The mass of MIP on the crystal is equal to 4×10-5g. With these two values, the minimum amount detected in this experiment was equal to 0.3nanogram.

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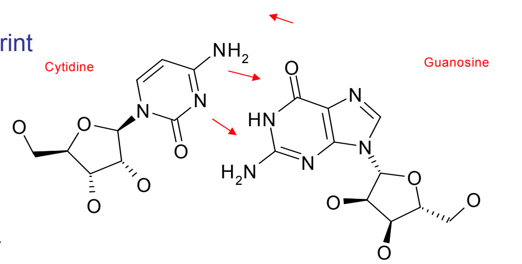
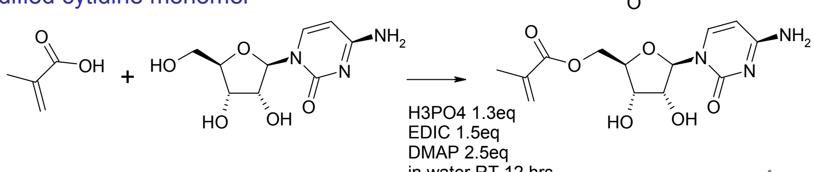
Guanosine Recognition

- Perfect complement to imprint guanosine is cytidine



- Modified cytidine monomer



EDCI: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
DAMP: 4-dimethylaminopyridine

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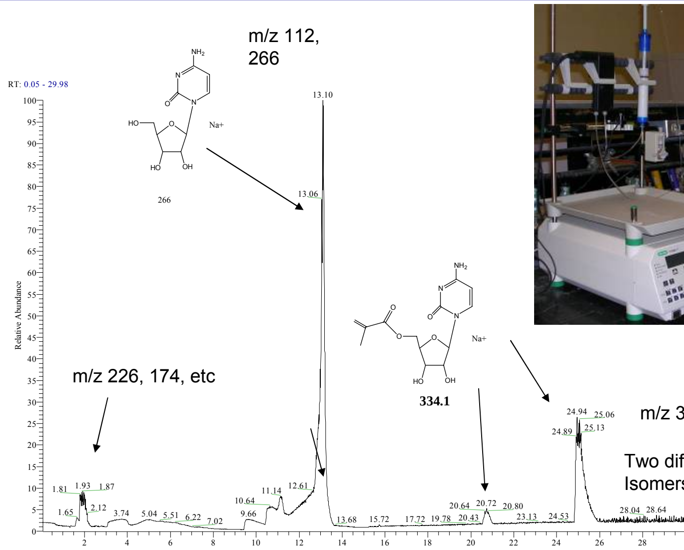
LC/MS Base peak chromatogram



m/z 334

Two different
Isomers apparently

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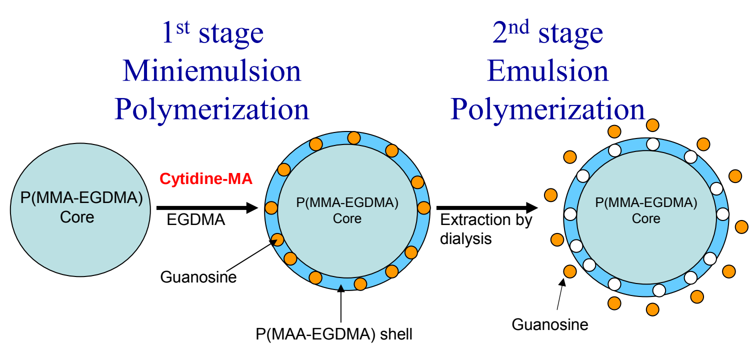
SINP : Guanosine detection



Latex agglutination

Medical diagnostics

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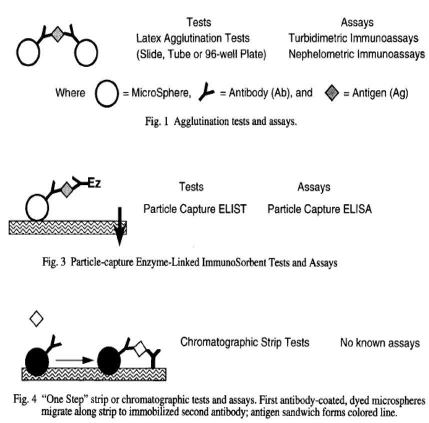
New developments in particle-based immunoassays: introduction



Pure & Appl. Chem., Vol. 68, No. 10, pp. 1873-1879, 1996.

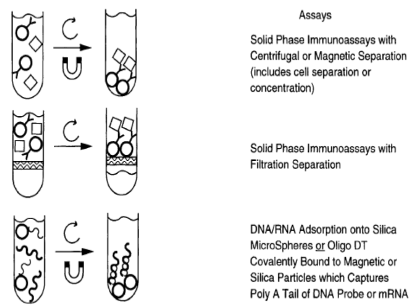


Fig. 5 Solid phase assays (requiring solid/liquid separation)

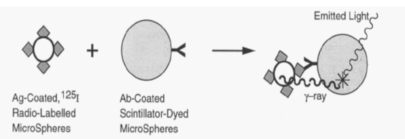
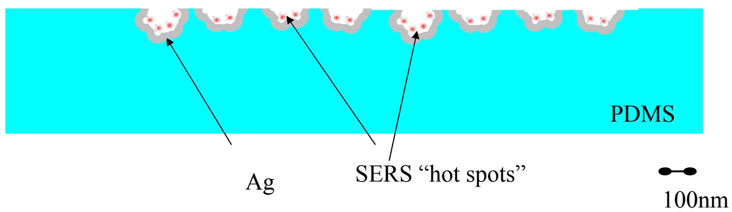


Fig. 6 Scintillation proximity assay. If Ag/Ab reaction binds particles together, light will be given off when γ-rays emitted from Ag-coated microspheres enter Ab-coated, scintillator-dyed microspheres. Free Ag in sample interferes with the two microspheres coming together and decreases light output.

BioSensors for Medical Diagnostic

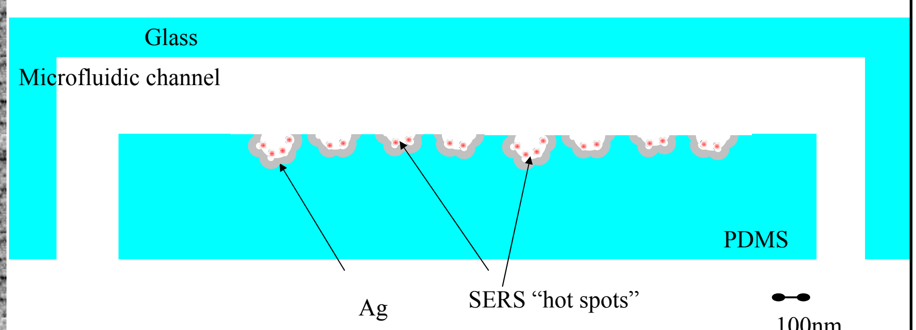
University of New Hampshire

SERS-MIP strategy

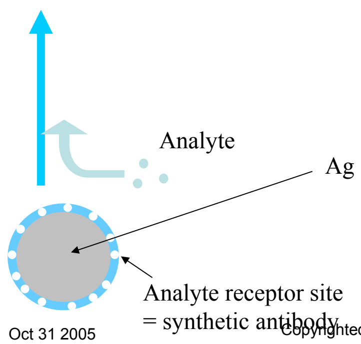


University of New Hampshire

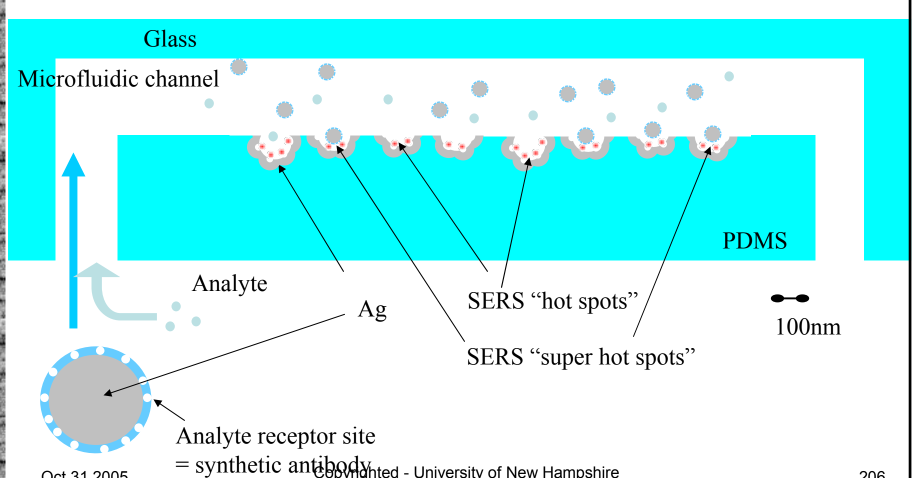
SERS-MIP strategy

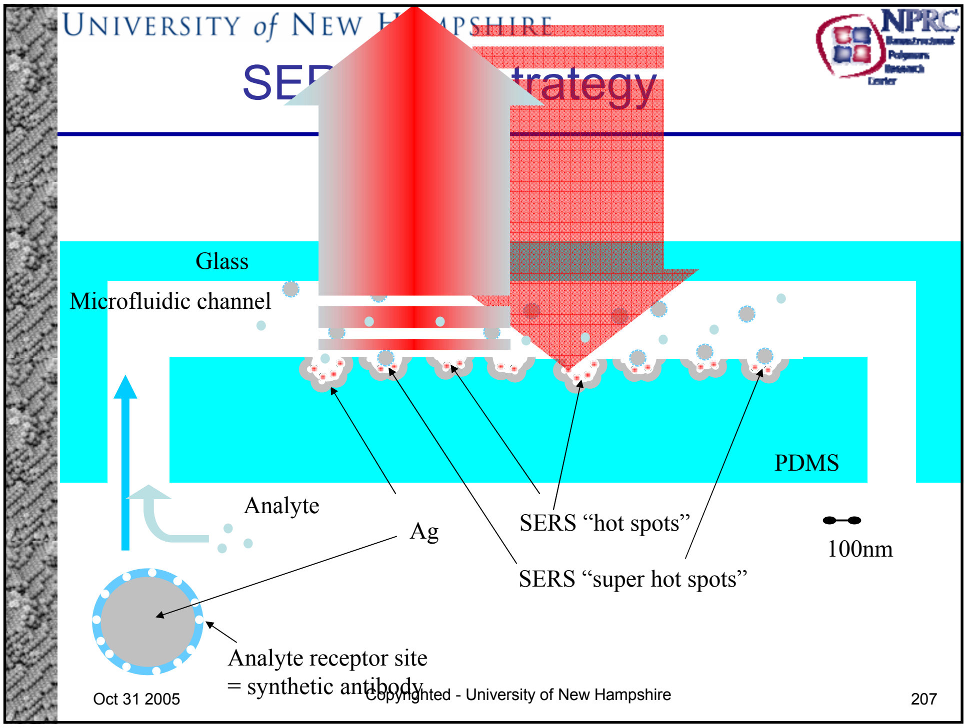


SERS-MIP strategy



SERS-MIP strategy

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SE… …trategy
Glass
Microfluidic channel
PDMS
Analyte
Ag
SERS "hot spots"
SERS "super hot spots"
100nm
Analyte receptor site
= synthetic antibody
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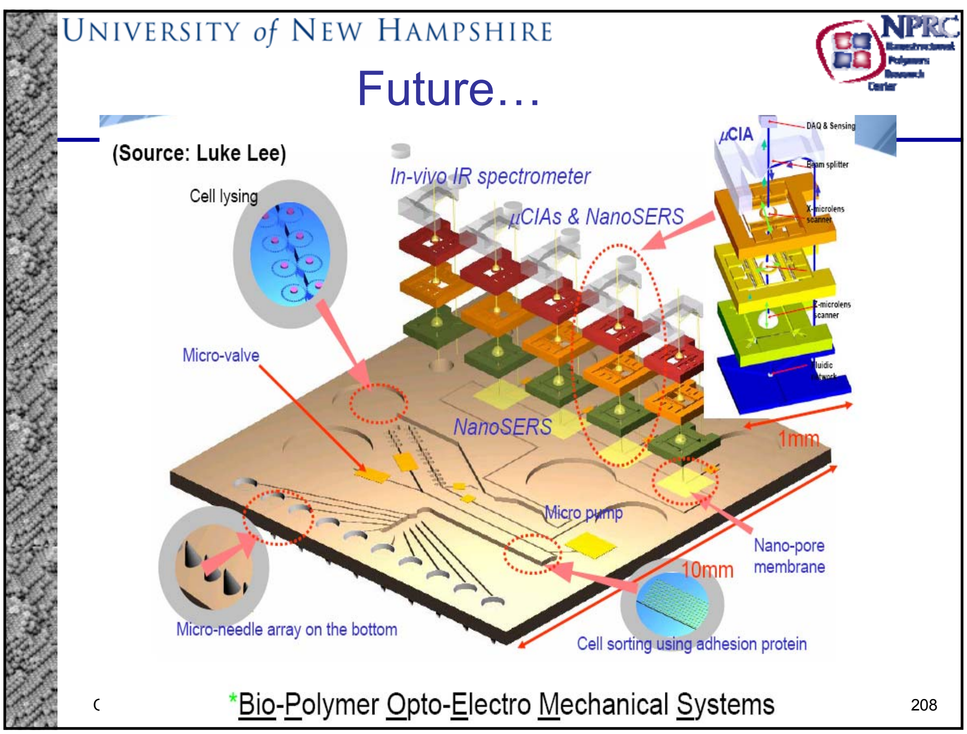
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Future…
(Source: Luke Lee)
Cell lysing
In-vivo IR spectrometer
µCIAs & NanoSERS
µCIA
Micro-valve
NanoSERS
1mm
Micro pump
Nano-pore membrane
10mm
Micro-needle array on the bottom
Cell sorting using adhesion protein
*Bio-Polymer Opto-Electro Mechanical Systems
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