Polymer Nanotechnology: Synthesis and Novel Applications

Instructors
Professor Yvon G. Durant

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

![Graph showing the relationship between particle radius and surface area.](image)

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

Characterization of Multiple Phase Particles

- Internal structure (morphology)
  Microscopy, thermal analysis

DSC graph
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

\[ \begin{align*}
\text{Initiation:} & \quad \text{acid} + M \rightarrow \text{CF}_3\text{SO}_3^- + M_{n-1}^+ \text{ and } M_n^+ \text{ and } X^- \\
\text{Propagation:} & \quad \text{CF}_3\text{SO}_3^- + M \rightarrow CF_3\text{SO}_3^- + M_{n+1}^+ \text{ and } X^- 
\end{align*} \]

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

- a linear polymer

Crosslinking

- When polymers become crosslinked, this becomes this

Entanglement versus crosslink = physics versus chemistry
Molecular weight

- Number Average Molecular Weight ($M_n$)
- Viscosity Molecular Weight ($M_v$)
- Weight Average Molecular Weight ($M_w$)
- Z-average Molecular Weight ($M_z$)

Function of solvent: $a = 0.5$ to 1

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

\[
\begin{align*}
\text{Oct 31 2005 Copyrighted - University of New Hampshire} & \\
\text{Block copolymer architecture} & \\
\text{diblock-copolymers} & \\
\text{Tri block-copolymers} & \\
\text{gradient-copolymers} & \\
\text{Block-gradient copolymers} & \\
\text{Star block copolymer} & \\
\text{Block pendant copolymer} & \\
\end{align*}
\]
Radical polymerization

Initiation

Propagation

Termination

Polycondensation -1

Trimesoyl chloride + glycerol

Terephthaloyl chloride and glycerol react to form an ester linkage.

Our third linker can react with a molecule of terephthaloyl chloride...
Polycondensation - 2

Living Polymerizations

Anionic
Cationic
Ring Opening
Ring opening metathesis
Anionic Polymerization

\[ \sim M_n^-, M^+ + M \rightarrow \sim M_{n+1}^-, M^+ \]

- Initiation: \( R^- + \text{Li}^+ \rightarrow \text{Li}^- R \)
- Propagation: \( \text{Li}^- R + \text{M} \rightarrow \text{Li}^- R \text{M} \)
- Lewis Base: \( \text{H}^- \text{O} \rightarrow \text{H}_2\text{O} \)
- Counter ion (cation): Usually Li\(^+\), Na\(^+\), K\(^+\) or Cs\(^+\)

Carbanions are:
- Not short-lived species
- Terminated by oxygen, water and many polar functionalities
- Negatively charged
- Pyrophoric (beware!)
- Tetrahedral (\( sp^3 \) hybridized)
- Very basic (conjugated acid : alkane). They can only be formed by reacting with a stronger base.
Cationic Polymerization

\[ \sim \text{M}_n^+ , X^- + M \rightarrow \sim \text{M}_{n+1}^+ , X^- \]

Initiation

\[ \text{CF}_3\text{SO}_3^- + \text{H} \rightarrow \text{CF}_3\text{SO}_3^- + \text{H} \]

Propagation

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

Ring Opening polymerization

Initiation

\[ \text{O} \quad \text{N} \quad \text{H} \]

Propagation

\[ \sim \text{A-B} \rightarrow \sim \text{A-B} \rightarrow \sim \text{A-B} \]

\[ \text{a-caprolactam} \rightarrow \text{nylon 6} \]
Ring Opening Metathesis Polymerization

Ring-Opening Polymerization

Wurtz 1879

- Ring Strain Controls the Polymerization (C2O best)

<table>
<thead>
<tr>
<th>n</th>
<th>ΔH (kJ/mol)</th>
<th>ΔS (J/K/mol)</th>
<th>ΔG (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>-113</td>
<td>-69</td>
<td>-92.5</td>
</tr>
<tr>
<td>4</td>
<td>-105</td>
<td>-55</td>
<td>-90</td>
</tr>
<tr>
<td>5</td>
<td>-21</td>
<td>-43</td>
<td>-9</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>-10</td>
<td>+6</td>
</tr>
<tr>
<td>7</td>
<td>-22</td>
<td>-16</td>
<td>-16</td>
</tr>
<tr>
<td>8</td>
<td>-34</td>
<td>-3</td>
<td>-34</td>
</tr>
</tbody>
</table>
Living Radical Polymerization

SFRP  ATRP  RAFT

Pseudo living SFRP

130°C
**Atom Transfer Radical Polymerization**

\[ IM_n^+ + MeX \rightleftharpoons IM_nX + Me \]

- **IM**
  - **Ru**
  - **PPh\(_3\)**
  - **Cl**

- **MeX**
  - **PPh\(_3\)**
  - **Cl**

Sawamoto, 1995
MMA

Teyssie, 1997
MMA

Matyjaszewski, 1995
MMA, S

**CATALYSTS**

- **Br**
- **Me**
- **H**
- **CCl\(_4\)**
- **CBr\(_4\)**

**INITIATORS**

---

**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
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)

Reversible Addition Fragmentation Chain Transfer (RAFT)

\[ \begin{align*}
&\text{1. } \text{I} \xrightarrow{k_i} \text{R}^o \\
&\text{0.01 eq} \\
&\text{2. } \text{R}^o + \text{M} \xrightarrow{k_p} \text{RM}^o \\
&\text{1000 eq} \\
&\text{3. } \text{RM}^o + \text{RM}^o \xrightarrow{k_{tr}} \text{RM}_n^o + \text{R}^o \\
&\text{1 eq} \\
&\text{4. } \text{RM}_m^o + \text{RM}^o \xrightarrow{k_{tr}} \text{RM}_n^o + \text{RM}_m^o \\
\end{align*} \]

Rizzardo, 1998

\[ C_{tr} = \frac{k_{tr}}{k_p} \approx 500 \]

Not based on a persistent radical effect
Reversible Addition Fragmentation Chain Transfer (RAFT)

The number of dead chains = I
The number of dormant chains = CS₂
Initial MW = MW₀ Cₜ⁻¹

Kinetics = Kinetics of conventional radical polymerization

Styrene/CS₂ = 1000
CS₂/AIBN = 20

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

General Mechanisms for Particle Formation

- 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

<table>
<thead>
<tr>
<th>1 mm</th>
<th>100μm</th>
<th>10μm</th>
<th>1μm</th>
<th>100 nm</th>
<th>10 nm</th>
<th>1 nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspension Polymerization</td>
<td>Emulsion Polymerization</td>
<td>Dispersion Polymerization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.
**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
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

Emulsion Polymerization

![Diagram of emulsion polymerization](image_url)
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
Emulsion Polymerization

Characteristic features of latex particles

- 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
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

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

Initiator addition
seed latex particle
surfactant molecule
monomer feed

Batch Reaction

Seed Latex
Surfactant
Water
Monomer
Initiator

Condenser
**Semi-Batch Reaction**

- Monomer
- Surfactant
- Water
- Seed
- Some Surfactant
- Some Water
- Some Monomer

**Phase Diagram**

- Polymerization Pathways
- Semi-batch
- Batch
Multiple Component Polymer Nanoparticles

Two Component Particles – Morphological Options

<table>
<thead>
<tr>
<th>THERMODYNAMIC CONTROL</th>
<th>KINETIC CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inverted Core-Shell</td>
<td>Octopus - like</td>
</tr>
<tr>
<td>Core-Shell</td>
<td>Core-Shell</td>
</tr>
<tr>
<td>Moon - like 3rd quarter</td>
<td>Raspberry - like</td>
</tr>
<tr>
<td>Moon - like 1st quarter</td>
<td>Sandwich - like</td>
</tr>
<tr>
<td>Eye-Ball - like</td>
<td>Occlusion or Salami - like</td>
</tr>
<tr>
<td>Acorn - like</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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!!
Polymer Nanotechnology: Synthesis and Novel Applications

Polymer Synthesis III

Miniemulsion Polymerization

Preparation of a miniemulsion:

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

Miniemulsion: steady state


Oct 31 2005

Copyrighted - University of New Hampshire
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 (misleading)
    - Hexadecane, Eicosane, polymer, macromonomer, macrorinitiator, CTA, ...

Miniemulsion Polymerization

Miniemulsion stability

- Water
- Surfactant(s)
- Monomer(s)
- Stabilizer

Oswald Ripening

No stabilizer

With stabilizer
Particle size control


Mini to micro emulsion

Recipe MJB-10: microemulsion (seed)
Water 82.84%
NaHCO3 0.043%
Na2OSS2 0.011%
SDS 8.27%
KPS 0.17%
Styrene 8.67%
Water, Salts, SDS, stirred, degassed. Add 20% of styrene. Heat. When at 80°C, 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

Encapsulation of magnetite in polymer particles by miniemulsion
<table>
<thead>
<tr>
<th>Comp.</th>
<th>TRM031b</th>
<th>TRM031c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium Myrycyl Sulfate (pphm)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>di-octyl sullosuccinate (pphm)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Eicosane (pphm)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>OH-TEMPO/tBHP (mole/mole)</td>
<td>1.30</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mn (g/mole)</th>
<th>TRM031b</th>
<th>TRM031c</th>
</tr>
</thead>
<tbody>
<tr>
<td>21312</td>
<td>32815</td>
<td></td>
</tr>
<tr>
<td>Mn/Mn</td>
<td>1.54</td>
<td>1.62</td>
</tr>
<tr>
<td>Conversion</td>
<td>0.945</td>
<td>0.71</td>
</tr>
<tr>
<td>Mn (g/mole) (theoretical f=1.3)</td>
<td>33540</td>
<td>56720</td>
</tr>
<tr>
<td>Polymerization time (h:mm)</td>
<td>7:26</td>
<td>6:52</td>
</tr>
<tr>
<td>Polymerization Temperature (°C)</td>
<td>132</td>
<td>129</td>
</tr>
<tr>
<td>Polymerization Pressure (Atm)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>PD (nm) before polymerization</td>
<td>208</td>
<td>423</td>
</tr>
<tr>
<td>PD (nm) after polymerization</td>
<td>287</td>
<td>526</td>
</tr>
<tr>
<td>Coagulum</td>
<td>none</td>
<td>high</td>
</tr>
<tr>
<td>Initial monomer content (%)</td>
<td>31</td>
<td>22.2</td>
</tr>
<tr>
<td>Final solid content (%)</td>
<td>19.4</td>
<td>19.4</td>
</tr>
<tr>
<td>Tg (°C) (DSC)</td>
<td>43.7</td>
<td>43.7</td>
</tr>
<tr>
<td>Tg (°C) (calculated for blend)</td>
<td>43.7</td>
<td>43.7</td>
</tr>
<tr>
<td>Sty/BA</td>
<td>49.61</td>
<td>50.61</td>
</tr>
<tr>
<td>Block ratio (block/precursor)</td>
<td>1.84</td>
<td></td>
</tr>
</tbody>
</table>

**Block copolymer direct from miniemulsion**

**Block copolymer**

---

**Oct 31 2005**

Copyrighted - University of New Hampshire
AFM

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

Self Assembly

- Lipids
- PGlu – PLeu
- UNH tri-block
Liposomes

Lipid bilayer

Liposome

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

Self assembly of Liposome

Multi Lamellar Vesicles

Small Unilamellar Vesicles

Large Unilamellar Vesicles : LUV
Self Assembly

• PGlu - PLeu

Synthetic Scheme

\[ \text{MeO}_2C \rightarrow \text{NH}_2 + \text{HN} \rightarrow \text{CO}_2 \rightarrow \text{H}_2\text{N} \rightarrow \text{H}_2\text{O} \rightarrow \text{CO}_2 \rightarrow \text{H}^+ \]

\[ \text{CO}_2\text{Me} \rightarrow \text{HN} \rightarrow \text{HN} \rightarrow \text{H}_2\text{N} \rightarrow \text{H}_2\text{O} \rightarrow \text{CO}_2 \rightarrow \text{H}^+ \]

\[ \text{MeO}_2C \rightarrow \text{HN} \rightarrow \text{HN} \rightarrow \text{H}_2\text{N} \rightarrow \text{H}_2\text{O} \rightarrow \text{CO}_2 \rightarrow \text{H}^+ \]

\[ \text{CO}_2\text{Me} \rightarrow \text{HN} \rightarrow \text{HN} \rightarrow \text{H}_2\text{N} \rightarrow \text{H}_2\text{O} \rightarrow \text{CO}_2 \rightarrow \text{H}^+ \]
**Self-assembly in water**

![Diagram of self-assembly in water](image)

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

<table>
<thead>
<tr>
<th>Process</th>
<th>Dh (nm)</th>
<th>2*Rg (nm)</th>
<th>Mw (g/mol)</th>
<th>%α-helix</th>
<th>Crystallinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMP</td>
<td>28</td>
<td>9</td>
<td>620 000</td>
<td>&lt; 5</td>
<td>No</td>
</tr>
<tr>
<td>Dh (nm)</td>
<td>28</td>
<td>9</td>
<td>320 000</td>
<td>&lt; 5</td>
<td>No</td>
</tr>
<tr>
<td>2*Rg (nm)</td>
<td>18</td>
<td>9</td>
<td>320 000</td>
<td>85</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Nh : QELS, Rg : Zimm plot, Mw : FFF-LS, %α-helix CD at pH = 8, Crystallinity : RX*
Nanoparticles

Morphology of the Nanoparticle

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

\[ \text{d} = 1.32 \text{ nm} \]

\[ T_2 \text{ Leu} = 15 \ \mu s \]
\[ T_2 \text{ Glu} = 8 \ \text{ms} \]
\[ T_2 \text{ HS PGlu} = 150 \ \text{ms} \]

\[ \text{CD at pH = 8} \]
\[ \text{red} = \text{Pglu} \]
\[ \text{blue} = \text{NPs} \]
Aggregation Number versus L/G composition

Rg

N_{agg}

N_{Leu}/N_{Glu}^{0.8}

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

UNH polymer self assembly

1. Self Assembly

Forster et al

12/18
15/35
12/35
12/21
15/30
12/50
12/40
18/35
20/40

unpolymerized

water

100 nm
10^{-7} m

50-150 nm
Electronic Microscopy

- Branched Triblock: 140nm, 100nm, 130nm
- Linear Triblock: 300nm, 160nm

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

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

Negatively-stained TEM

Can be VERY monodispersed
Branched-tri-block copolymer

\[ \text{OH} \quad \text{O} \quad \text{NH}_2 \quad \text{O} \quad \text{O} \quad \text{NH}_2 \quad \text{O} \quad \text{O} \quad \text{NH}_2 \quad \text{OH} \]

\[ \text{OH} \quad \text{O} \quad \text{N} \quad \text{H} \quad \text{O} \quad \text{O} \quad \text{NH}_2 \quad \text{OH} \quad \text{OH} \quad \text{OH} \]

\[ \text{OH} \quad \text{OH} \quad \text{OH} \quad \text{O} \quad \text{O} \quad \text{N} \quad \text{H} \quad \text{O} \quad \text{O} \quad \text{NH}_2 \quad \text{OH} \]

\[ \text{OH} \quad \text{OH} \quad \text{OH} \quad \text{O} \quad \text{O} \quad \text{N} \quad \text{H} \quad \text{O} \quad \text{O} \quad \text{NH}_2 \quad \text{OH} \]

\[ A=\text{H}, \text{glycolic acid} \quad A=\text{Me}, \text{lactic acid} \]

Directed assembly

[Diagram showing directed assembly process]

\[ \text{OH}^- \quad \text{OH}^- \quad \text{OH}^- \]

\[ \text{OH} \quad \text{OH} \quad \text{OH} \]

\[ \text{OH} \quad \text{OH} \quad \text{OH} \]

\[ \text{OH} \quad \text{OH} \quad \text{OH} \]

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

The Challenge – How to Obtain Reliable Data?

Particle Concentration in Dispersion:
1,000,000,000
000,000
Particles Per Liter
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

\[ d_n = \frac{\sum n_i d_i}{\sum n_i} \]

\[ d_w = \frac{\sum n_i d_i^4}{\sum n_i d_i^3} = \frac{\sum w_i d_i}{\sum w_i} \]

Dispersion Index = Weight Average/Number Average
Example Distributions

<table>
<thead>
<tr>
<th>System</th>
<th>di(nm)</th>
<th>ni</th>
<th>dn(nm)</th>
<th>dw(nm)</th>
<th>DI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>400</td>
<td>100</td>
<td>470</td>
<td>1890</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>100</td>
<td>10</td>
<td>550</td>
<td>999</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>1.0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Method/Instrument</th>
<th>Size range/µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sieves</td>
<td>5.0 - 5000</td>
</tr>
<tr>
<td>2. Optical microscopy</td>
<td>0.5 - 300</td>
</tr>
<tr>
<td>3. Microtome</td>
<td>1.0 - 400</td>
</tr>
<tr>
<td>4. Electron microscopy</td>
<td></td>
</tr>
<tr>
<td>4.1 Coulter Multisizer Hf</td>
<td>0.4 - 1200</td>
</tr>
<tr>
<td>4.2 Particle Data 202PC</td>
<td>0.4 - 1200</td>
</tr>
<tr>
<td>5. Soap titration</td>
<td>0.03 - 0.5</td>
</tr>
<tr>
<td>6. Light scattering</td>
<td>0.05 - 0.1</td>
</tr>
<tr>
<td>7. Electron microscope</td>
<td>0.001 - 0.1</td>
</tr>
<tr>
<td>8. Ultracentrifuge</td>
<td>0.01 - 20</td>
</tr>
<tr>
<td>9. Millipore filters</td>
<td>0.01 - 100</td>
</tr>
<tr>
<td>10. Sedigraph 3800® (Micromeritics)</td>
<td>0.1 - 300</td>
</tr>
<tr>
<td></td>
<td>0.1 - 100</td>
</tr>
<tr>
<td>11. Fractional crystallizing</td>
<td>0.05 - 1.0</td>
</tr>
<tr>
<td>12. Joyce-Loebell Disc Centrifuge DCF-4</td>
<td>0.01 - 1.0</td>
</tr>
<tr>
<td>13. Flow ultramicroscope</td>
<td>0.05 - 1.0</td>
</tr>
<tr>
<td>14. Dark field microscopy</td>
<td>0.05 - 0.8</td>
</tr>
<tr>
<td>15. Hydrodynamic chromatography (HIDCF)</td>
<td>0.03 - 1.5</td>
</tr>
<tr>
<td>Flow Size: 9600</td>
<td>0.015 - 1.1</td>
</tr>
<tr>
<td>CHDF: 1.100 (Macne)</td>
<td>0.25 - 4000</td>
</tr>
</tbody>
</table>

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

Microscopy Data

TEM

SEM

AFM
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

Static Light Scattering (SLS)

Example of Turbidity

Light Scattering Behavior Non-Interacting Spherical Particles

\[ \alpha = \pi \frac{d}{\lambda_m} \]
\[ m = \frac{n}{n_0} \]

\( \lambda_m \) 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 \( \theta \) (180 degrees)
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
  \[ D = \frac{kT}{3\pi \eta d} \]
- 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 \[ t = \frac{k \eta \ln \left( \frac{rd}{ri} \right)}{\omega^2 (\Delta \rho) d^2} \]
where \( \omega \) = RPM and \( \eta \) = viscosity

- Measure the time for particle front to move across the spinning disk
- \( 10 \text{ nm} < d < 10 \mu\text{m} \) range
- Yields particle size distributions

Analytical Ultracentrifugation
Analytical Ultracentrifugation

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

Sedimentation Velocity Profile
Courtesy of Thomas Laue, Univ. of New Hampshire
Capillary Hydrodynamic Fractionation

Laminar flow through a capillary tube

[Diagram showing flow and velocity distribution]
Capillary Hydrodynamic Fractionation

Field Flow Fractionation

83 nm PS standard

Credit: E.A. Collins in "Emulsion Polymerization and Emulsion Polymers"
### Comparative Data from Different Methods

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

<table>
<thead>
<tr>
<th>Latex No.</th>
<th>TEM $d_a$</th>
<th>$d_w$</th>
<th>DCP $d_a$</th>
<th>$d_w$</th>
<th>SFF $d_a$</th>
<th>$d_w$</th>
<th>HDC $d_a$</th>
<th>$d_w$</th>
<th>Turbidity</th>
<th>QELS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>160</td>
<td>162</td>
<td>182</td>
<td>192</td>
<td>205</td>
<td>222</td>
<td>255</td>
<td>257</td>
<td>237</td>
<td>223</td>
</tr>
<tr>
<td>2</td>
<td>239</td>
<td>241</td>
<td>233</td>
<td>247</td>
<td>261</td>
<td>267</td>
<td>322</td>
<td>342</td>
<td>275</td>
<td>305</td>
</tr>
<tr>
<td>3</td>
<td>293</td>
<td>298</td>
<td>344</td>
<td>351</td>
<td>346</td>
<td>350</td>
<td>422</td>
<td>423</td>
<td>357</td>
<td>413</td>
</tr>
<tr>
<td>4</td>
<td>377</td>
<td>283</td>
<td>418</td>
<td>432</td>
<td>410</td>
<td>421</td>
<td>540</td>
<td>542</td>
<td>459</td>
<td>468</td>
</tr>
<tr>
<td>5</td>
<td>448</td>
<td>469</td>
<td>550</td>
<td>566</td>
<td>521</td>
<td>529</td>
<td>664</td>
<td>668</td>
<td>687</td>
<td>578</td>
</tr>
<tr>
<td>6</td>
<td>574</td>
<td>611</td>
<td>658</td>
<td>686</td>
<td>600</td>
<td>605</td>
<td>893</td>
<td>901</td>
<td>817</td>
<td>746</td>
</tr>
</tbody>
</table>

Credit: E.A. Collins in "Emulsion Polymerization and Emulsion Polymers"
Data from Koehler and Proctor, ACS Symp. Ser. No.332, 1987, p 231-239

#### Table 12.12 Comparison of latex particle diameter (μm) measurements

<table>
<thead>
<tr>
<th>Method</th>
<th>Latex A (PVC copolymer)</th>
<th>Latex B (PVC homopolymer)</th>
<th>Latex C (acrylic copolymer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EM, $d_a$</td>
<td>0.292</td>
<td>0.096</td>
<td>0.273</td>
</tr>
<tr>
<td>Joyce Loebel, $d_w$</td>
<td>0.274</td>
<td>0.095</td>
<td>0.273</td>
</tr>
<tr>
<td>Hovis Caps 500, $d_a$</td>
<td>0.330</td>
<td>0.100</td>
<td>0.249</td>
</tr>
<tr>
<td>Coulter N-4, $d_a$</td>
<td>0.293</td>
<td>0.095</td>
<td>0.289</td>
</tr>
<tr>
<td>99% in the range</td>
<td>0.285-0.301</td>
<td>0.0906-0.096</td>
<td>(0.282-0.295)</td>
</tr>
<tr>
<td>Nicomp 300, $d_a$</td>
<td>0.274</td>
<td>0.100</td>
<td>0.277</td>
</tr>
<tr>
<td>95% in the range</td>
<td>0.274-0.294</td>
<td>0.0906-0.110</td>
<td>(0.282-0.295)</td>
</tr>
<tr>
<td>BE-90, $d_w$</td>
<td>0.389</td>
<td>0.097</td>
<td>0.294</td>
</tr>
<tr>
<td>Polydispersity</td>
<td>0.06</td>
<td>0.078</td>
<td>0.003</td>
</tr>
<tr>
<td>$d_{50}$</td>
<td>0.259</td>
<td>0.083</td>
<td>0.292</td>
</tr>
<tr>
<td>HDC 5000</td>
<td>0.270</td>
<td>0.089</td>
<td>0.279</td>
</tr>
<tr>
<td>$d_{50}$</td>
<td>0.340</td>
<td>0.089</td>
<td>0.339</td>
</tr>
<tr>
<td>$d_{ave}$</td>
<td>BiModal</td>
<td>Narrow</td>
<td>BiModal</td>
</tr>
<tr>
<td>Range {0 below 0.200}</td>
<td>0.112-0.420</td>
<td>0.065-0.110</td>
<td>0.100-0.400</td>
</tr>
<tr>
<td>$d_f$</td>
<td>0.236</td>
<td>0.038</td>
<td>0.238</td>
</tr>
<tr>
<td>$d_{ave}$</td>
<td>0.265</td>
<td>0.066</td>
<td>0.265</td>
</tr>
<tr>
<td>SCM DCP $d_a$</td>
<td>0.279</td>
<td>0.080</td>
<td>0.306</td>
</tr>
<tr>
<td>$d_{ave}$</td>
<td>0.329</td>
<td>0.094</td>
<td>0.357</td>
</tr>
<tr>
<td>$d_{ave}$</td>
<td>0.351</td>
<td>0.125</td>
<td>0.381</td>
</tr>
<tr>
<td>$d_{ave}$</td>
<td>0.317</td>
<td>0.087</td>
<td>0.341</td>
</tr>
</tbody>
</table>

Credit: E.A. Collins in "Emulsion Polymerization and Emulsion Polymers"
Characterization of Surface Composition of Polymer Micro- and Nanoparticles

Scanning Electron Microscope
Scanning Electron Microscope

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

Backscattered electron, secondary electron, x-ray

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

\[ y = -0.0067x + 0.0148 \]
\[ R^2 = 0.9726 \]
Atomic Force Microscopy (AFM)

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

![AFM Tapping Mode Analysis](image)

"Height" Image  "Phase Contrast" Image

 Isothermal Titration Calorimetry

![Isothermal Titration Calorimetry](image)
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

JEM-1230

JEOL

Current EM

JEM-3000F

Specifications

JEM-1230

JEM-3000F

Resolutions

0.24 nm (HBD)

0.19 nm (LBD)

Accelerating Voltages

40 to 100 kV

100 to 300 kV

Magnifications

x50 to x5000

x50 to x5000
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
Examples of Potential Problems with Contrast Staining

Sample C was unstained. Sample D was over stained.

Thermal Analysis Techniques

- Differential Scanning Calorimetry (DSC), especially modulated temperature - for particles and films
- Dynamic Mechanical Analysis (DMA) for films
Figure 2  DSC trace for an acrylic copolymer seed and polystyrene composite latex.
Example of DSC Data for Composite Latex Particles

DSC results for Various Particle Morphologies

Large domains, well phase separated polymers

Very small domains, well phase separated polymers

Gradient Phase, partially phase separated polymers

Solution, non-phase separated polymers
Modulated Temperature DSC Data as a Function of Extent of Reaction

TEM Results

All acrylic (polar) seed latex
Second stage styrene monomer added slowly

After 50% monomer add
After 100% monomer add
Polymer Nanotechnology: Example of Applications

Waterborne Paints
**Film Formation**

**Waterborne Latex Coating**
- Dispersed polymer particles
- Evaporation of water
- Increasing concentration, packing of latex particles
- Particle deformation
- Particle coalescence and interdiffusion of polymer chains

**Solventborne Coating**
- Polymer molecules in solution
- Evaporation of organic solvent (VOC)

---

**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
Wear resistance improvement

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

<table>
<thead>
<tr>
<th></th>
<th>Arizona</th>
<th>Florida</th>
<th>Pennsylvania</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkyd--White</td>
<td>163</td>
<td>&gt;900</td>
<td>&gt;900</td>
</tr>
<tr>
<td>Alkyd--Yellow</td>
<td>293</td>
<td>&gt;900</td>
<td>173</td>
</tr>
<tr>
<td>Chloro Rubber--White</td>
<td>478</td>
<td>&gt;900</td>
<td>255</td>
</tr>
<tr>
<td>Chloro Rubber--Yellow</td>
<td>159</td>
<td>&gt;900</td>
<td>83</td>
</tr>
<tr>
<td>Water-base--White</td>
<td>&gt;705</td>
<td>&gt;900</td>
<td>255</td>
</tr>
<tr>
<td>Water-base--Yellow</td>
<td>&gt;705</td>
<td>&gt;900</td>
<td>474</td>
</tr>
<tr>
<td>Solv. Borne Epoxy--White</td>
<td>715</td>
<td>&gt;900</td>
<td>&gt;900</td>
</tr>
<tr>
<td>Solv. Borne Epoxy--Yellow</td>
<td>&gt;900</td>
<td>&gt;900</td>
<td>&gt;900</td>
</tr>
<tr>
<td>Urethane--White</td>
<td>863</td>
<td>&gt;900</td>
<td>&gt;900</td>
</tr>
<tr>
<td>Urethane--Yellow</td>
<td>817</td>
<td>&gt;900</td>
<td>&gt;900</td>
</tr>
<tr>
<td>Thermoplastic--White</td>
<td>&gt;900</td>
<td>&gt;900</td>
<td>&gt;900</td>
</tr>
<tr>
<td>Thermoplastic--Yellow</td>
<td>&gt;900</td>
<td>&gt;900</td>
<td>&gt;900</td>
</tr>
<tr>
<td>Cold Plastic--White</td>
<td>&gt;900</td>
<td>&gt;900</td>
<td>377</td>
</tr>
<tr>
<td>Cold Plastic--Yellow</td>
<td>&gt;765</td>
<td>&gt;900</td>
<td>625</td>
</tr>
<tr>
<td>Foil Tape--White</td>
<td>&gt;900</td>
<td>&gt;900</td>
<td>&gt;900</td>
</tr>
<tr>
<td>Foil Tape--Yellow</td>
<td>&gt;900</td>
<td>&gt;900</td>
<td>&gt;836</td>
</tr>
</tbody>
</table>

- 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

25% increase

- 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
Drug release

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

- In-vivo
  - Nature membrane
  - Peptide flux
  - Permeation enhancer
  - Peptide

- In-vitro
  - Liposome
  - Peptide
**Trigger strategy (in vitro)**

**Release study strategy**

1. Take 0.5 ml sample out periodically
2. Centrifugal extraction
3. Filtration (MWCO 10 K/50K)

**Graph**

*Adjusted Fluorescence vs. Time (hr)*

37°C
Transmembrane transport mechanism of insulin with excipient triggering

Phase I Phase II Phase III

CPE-215 molecules

Liposome

Defect

Low insulin leak rate

High insulin leak rate

Medium insulin leak rate

Low insulin leak rate

Drug delivery
Numerous barriers

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

Enzyme: trypsin, chymotrypsin, pepsin, carboxypeptidase, lipase, amylase, sucrase, maltase, lactase
Oral Delivery of Proteins

Size issues: hydrophobic, viscous, pH ~ 5

Intracellular transport

Paracellular transport through tight junctions (< 1 nm)

80 nm

700 nm

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

Oct 31 2005
Copyrighted - University of New Hampshire
Oral Delivery of Insulin

Encapsulation of insulin in a vesicle (= nanobag)

- 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

What are the properties of these vesicles?

1. Self Assembly

water

50-150 nm

100 nm

10^{-7} m
Self Assembly

2. Microencapsulation
2. Microencapsulation

Microencapsulation in gastroresistant capsule (Eudragit)
3. Administration

Nanoparticles are internalized, degraded and release insulin.

How to make vesicles?
- Use phospholipids to make liposomes
- Use block copolymers

- pH = 7.4
- Spontaneous self association
- hydrophobic
  Forms the wall of the vesicle
  Degrades naturally
- Hydrophilic polymers
  necessary to form the vesicle
  and prevent insulin denaturation
Vesicles inside the intestine

Enteric Coating

Small Intestine

Digestion of the PGlu hairy layer

Nanoparticle dispersion protease

hydrophobic particle is adsorbed

microvilli

Acidic degradation of PLA

Endosome (pH = 5)

Endocytosis

Insulin delivery

epithelial cell

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

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

- Shell degradation
- Polyasparagine
- Semi-crystalline PLA
- Amorphous PLGA
- Shell degradation
Sensor Technology

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

Biomimetic electrochemical sensors based on molecular imprinting

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

**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
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

<table>
<thead>
<tr>
<th>Compound Class</th>
<th>Example</th>
<th>Compound Class</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>drugs</td>
<td>timolol</td>
<td>amino acids*</td>
<td>phenylalanine</td>
</tr>
<tr>
<td></td>
<td>theophylline</td>
<td>tryptophan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>diazepam</td>
<td>tyrosine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>morfine</td>
<td>aspartic acid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ephedrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hormones</td>
<td>cortisol</td>
<td>carbohydrate*</td>
<td>galactose</td>
</tr>
<tr>
<td></td>
<td>enkephalin</td>
<td>glucose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>fructose</td>
<td></td>
</tr>
<tr>
<td>pesticides</td>
<td>atrazine</td>
<td>co-enzymes</td>
<td>pyridoxal</td>
</tr>
<tr>
<td>proteins</td>
<td>RNase A</td>
<td>nucleotide bases</td>
<td>adenine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>urease</td>
<td></td>
</tr>
</tbody>
</table>


SINP: Surface Imprinted NanoParticle

1st stage

Miniemulsion Polymerization

<table>
<thead>
<tr>
<th>MJB-20: miniemulsion seed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic phase = 23% : MMA 85.9%, EGDMA 9.5%, Hexadecane 5%</td>
</tr>
<tr>
<td>Water phase = 77% : Water 99%, SDS 0.6%, KPS 0.025%, NP-50 0.39%</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>SCexp = 22.25%, Conversion = 98.96%</td>
</tr>
<tr>
<td>Size = Malvern Nanosizer: Dz = 107.1 nm, Dv = 111.9 nm</td>
</tr>
</tbody>
</table>

2nd stage

Emulsion Polymerization

Extraction by dialysis

<table>
<thead>
<tr>
<th>MJB-21: 2nd stage imprinting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
</tr>
<tr>
<td>MJB20 (wet)</td>
</tr>
<tr>
<td>NaHCO3</td>
</tr>
<tr>
<td>KPS</td>
</tr>
<tr>
<td>Caffeine</td>
</tr>
<tr>
<td>EGDMA</td>
</tr>
<tr>
<td>MAA</td>
</tr>
<tr>
<td>Water, MJB-21, NaHCO3 were mixed and heated at 80C</td>
</tr>
<tr>
<td>When at temperature, add caffeine and start degassing. After 15 minutes, add KPS and start feeding with egdma+maa</td>
</tr>
<tr>
<td>Dilute with 250g of hot water (336%) while stirring</td>
</tr>
<tr>
<td>SCexp = 2.635% (dilution) Conversion = 57.86%</td>
</tr>
<tr>
<td>Size = Malvern nanosizer Dz = 108.4 nm, Effective Dv = 105.2 nm</td>
</tr>
</tbody>
</table>

Brookhaven 90+ : Dz = 104.9 nm, Effective Dv = 105.2 nm
Size distribution

MJB21 by Light scattering

SEM of nanoparticles
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.

\[ \Delta f = \Delta f_0 \left( \frac{\rho_a / \eta_a}{\rho_i \eta_i} \right)^{1/2}, \]

where:
- \( \Delta f \) = measured frequency shift,
- \( f_0 \) = resonant frequency of the unloaded crystal,
- \( \rho_i \) = density of liquid in contact with the crystal,
- \( \eta_i \) = viscosity of liquid in contact with the crystal,
- \( \rho_a \) = density of quartz, \( 2.648 \ \text{g/cm}^3 \),
- \( \eta_a \) = shear modulus of quartz, \( 2.947 \times 10^{11} \ \text{g/cm} \cdot \text{s}^2 \).

Q-Sense D300
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.

Guanosine Recognition

- Perfect complement to imprint guanosine is cytidine
- Modified cytidine monomer

EDCI: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
DAMP: 4-dimethylaminopyridine
Two different Isomers apparently

m/z 112, 266

m/z 226, 174, etc

m/z 334

SINP : Guanosine detection

1st stage
Miniemulsion
Polymerization

2nd stage
Emulsion
Polymerization
Latex agglutination

Medical diagnostics

New developments in particle-based immunoassays: introduction

Fig. 1. Agglutination test and assays

Fig. 2. Particle Capture ELISA

Fig. 3. Particle-capture enzyme-linked immunosorbent tests and assays

Fig. 4. "One step" rapid chromatographic tests and assays. First antibody-coated, dried nanoparticles to pull along strip to immobilize second antibody, antigen sandwich forms colored line.
BioSensors
for Medical Diagnostic
SERS-MIP strategy

Microfluidic channel

Class

Microfluidic channel

Ag SERS “hot spots” 100nm

PDMS
SERS-MIP strategy

Analyte receptor site = synthetic antibody

Analyte

Ag

Glass

Microfluidic channel

PDMS

SERS “hot spots”

SERS “super hot spots”

100nm

Oct 31 2005
SERS-MIP strategy

PDMS
Ag SERS "hot spots"
100nm

Analyte receptor site = synthetic antibody

Future...
(Source: Luke Lee)

*Bio-Polymer Opto-Electro Mechanical Systems*