NICE TO SEE YOU AGAIN
INTRODUCTION (BRIEF REVIEW OF FIRST LECTURE)
SMALL MOLECULE AMPHIPHILES AND DIBLOCK COPOLYMERS
METHODS OF PREPARATION
ACCESSIBLE MORPHOLOGIES
THermo, KINETICS AND MORPHOLOGICAL CONTROL MECHANISMS

VESICLES, PREPARATION AND THERMODYNAMICS
TYPES OF VESICLES
THERMODYNAMIC CURVATURE STABILIZATION
CONTROL OF INTERFACIAL COMPOSITION
INVERSION
EQUILIBRIUM CONTROL OF SIZES
TRIGGERS FOR MORPHOLOGICAL AND DIMENSIONAL CHANGES
(IONS, SURFACTANTANTS, WATER...)
KINETICS AND MECHANISMS OF SIZE CHANGES

VESICLES, FILLING AND NON-DESTRUCTIVE RELEASE
FILLING OF ACTIVE INGREDIENTS (DOX)
DIFFUSIONAL RELEASE OF CONTENTS (DOX)
DIFFUSION OF PROTONS THROUGH VESICLE WALLS

CONCLUSIONS
BLOCK AND GRAFT COPOLYMERS

AB Diblock

ABA

BAB

Triblock

Alternating block

Tapered block

Graft
A sodium dodecylsulfate (SDS) micelle model (n=60) drawn to scale. After Israelachvili
Morphologies of Block Copolymers in Aqueous Solutions

Star Micelle

(PS\textsubscript{23}-b-PANa\textsubscript{2400})

1 : 100

“Crew-cut” Micelle

(PS\textsubscript{420}-b-PANa\textsubscript{46})

10 : 1
Morphologies of Block Copolymers in Aqueous Solutions (Continued)
NEXT: PREP. AND MORPH.
PREPARATIVE METHODS (1)

TEMPERATURE QUENCH AND FREEZE-DRY EQUILIBRATED SOLUTIONS

- Add water to polymer solution in dioxane
- At predetermined water concentration, drop temperature to near - liquid N₂
- Warm under vacuum to sublime off dioxane and water.

WATER QUENCH EQUILIBRATED SOLUTION AND DIALYZE

- Add water to polymer solution
- At predetermined water concentration, quench into water
- Dialyze
Spherical micelles
PS(200)-b-PAA(21)

Rods
PS(190)-b-PAA(20)

Bicontinuous Rods
PS(190)-b-PAA(20)

Lamellae
PS(132)-b-PAA(20)

Lamellae
PS(49)-b-PAA(10)

Vesicles
PS(410)-b-PAA(13)

HHH
PS(410)-b-PAA(13)

LCM
PS(200)-b-PAA(4)

THERMODYNAMICS OF FORMATION OF CREW-CUT AGGREGATES

“MORPHOGENIC” CONTRIBUTIONS TO $\Delta G$

1. CHAIN STRETCHING IN CORE
2. REPULSION AMONG CORONA CHAINS
3. INTERFACIAL ENERGY

FOR EXAMPLE: AS WATER IS ADDED

1. INTERFACIAL ENERGY INCREASES
2. TOTAL INTERFACIAL AREA DECREASES
3. CORE RADIUS INCREASES
4. NUMBER OF MICELLES DECREASES
5. CORE CHAINS ARE STRETCHED
6. DISTANCE BETWEEN CORONA CHAINS DECREASES
7. CORONA CHAIN REPULSION INCREASES
8. MORPHOLOGY CHANGES AT SOME CRITICAL POINTS
MORPHOLOGY CHANGES CAN BE INDUCED BY CHANGES IN ANY OF THE THREE PARAMETERS BY DIFFERENT CONTROL MECHANISMS

- RELATIVE BLOCK LENGTHS
- WATER CONTENT
- COPOLYMER CONCENTRATION
- ADDED IONS, pH
- NATURE OF COMMON SOLVENT
- HOMOPOLYSTYRENE
- TEMPERATURE
- SURFACTANTS
- POLYDISPERSITY
Phase Diagram of Fractionated PS$_{310}$-$b$-PAA$_{52}$ in Dioxane/H$_2$O

Now: Vesicles
TYPES OF VESICLES

small uniform vesicles
$\text{PS}_{410}-b-\text{PAA}_{13}$

large polydisperse vesicles
$\text{PS}_{100}-b-\text{PEO}_{30}$

entrapped vesicles
$\text{PS}_{200}-b-\text{PAA}_{20}$

hollow concentric vesicles
$\text{PS}_{132}-b-\text{PAA}_{20}$

onion
$\text{PS}_{260}-b-\text{P4VPDecI}_{70}$

tube-walled vesicles
$\text{PS}_{100}-b-\text{PEO}_{30}$

Original references given in S. Burke and A. Eisenberg *Macromolecular Symposia* (Warsaw IUPAC meeting)
THEMODYNAMICALLY STABLE VESICLES ARE PRODUCED BY WORKING IN LARGE REGION OF THE PHASE DIAGRAM WHERE VESICLES ARE THE ONLY (OR THE DOMINANT) MORPHOLOGY SIZES, WALL THICKNESS AND INTERFACE COMPOSITION CAN BE CONTROLLED BY FINE TUNING THE DETAILED PREPARATIVE CONDITIONS (WATER CONTENT, SOLVENT COMPOSITION, pH, IONIC STRENGTH, ETC.)
QUESTIONS ABOUT VESICLES (1)

- ARE VESICLES EQUILIBRIUM STRUCTURES?
- WHAT ARE KINETICS AND MECHANISMS OF FORMATION AND TRANSFORMATION?
- CURVATURE STABILIZATION MECHANISM?
- PROOF OF SEGREGATION USING LABELED BLOCK COPOLYMERS
- IS SEGREGATION SIZE DEPENDENT?
- IS SEGREGATION REVERSIBLE?
- ARE SIZES CONTROLLABLE?
- ARE SIZE CHANGES REVERSIBLE?
QUESTIONS ABOUT VESICLES (2)

- Can different groups be attached inside and outside?
- Can vesicles be inverted?
- How fast do vesicles fuse?
- What is the equilibration mechanism?
- Can wall thickness be controlled?
- Can vesicles be filled?
- Can walls be plasticized?
- Can protons diffuse through walls?
Changes in Aggregate Morphology Are Associated With Changes in Turbidity

\[ \text{PS}_{310-b-\text{PAA}_{52}} \text{ 1\% w/w in dioxane} \]

Turbidity Increase With Time After 1% Water Jump

PS$_{310}$-b-PAA$_{52}$ 1% w/w in dioxane

Chen, L.; Shen, H.; Eisenberg, A.

Fitting Quality

\[ y = y_0 + a(1 - \exp(-k_1 * t)) \]

\[ y = y_0 + a(1 - \exp(-k_1 * t)) + b(1 - \exp(-k_2 * t)) \]

Concentration of Each Species

\[
C_{rt} = C_{r0} \left[ -\frac{k_{1b}k_{2b} + k_f m_1 - m_1 m_2}{m_1(m_2 - m_1)} \exp(-m_1 t) + \frac{k_{1b}k_{2b} + k_f m_2 - m_1 m_2}{m_2(m_2 - m_1)} \exp(-m_2 t) + \frac{k_{1b}k_{2b}}{m_1 m_2} \right]
\]

\[
C_{lt} = C_{r0} \left[ -\frac{k_f (k_{2b} - m_1)}{m_1(m_2 - m_1)} \exp(-m_1 t) + \frac{k_{1f} (k_{2b} - m_2)}{m_2(m_2 - m_1)} \exp(-m_2 t) + \frac{k_{1b}k_{2b}}{m_1 m_2} \right]
\]

\[
C_{vr} = C_{r0} \left[ -\frac{k_{1f}k_{2f}}{m_1(m_2 - m_1)} \exp(-m_1 t) + \frac{k_{1f}k_{2f}}{m_2(m_2 - m_1)} \exp(-m_2 t) + \frac{k_{1f}k_{2f}}{m_1 m_2} \right]
\]

\[
m_1 \text{ and } m_2 \text{ stand for:}
\]

\[
m_1 = \frac{1}{2} \left[ (k_{1f} + k_{1b} + k_{2f} + k_{2b}) - \sqrt{(k_{1f} + k_{1b} + k_{2f} + k_{2b})^2 - 4(k_{1b}k_{2b} + k_{1f}k_{2b} + k_{1f}k_{2f})} \right]
\]

\[
m_2 = \frac{1}{2} \left[ (k_{1f} + k_{1b} + k_{2f} + k_{2b}) + \sqrt{(k_{1f} + k_{1b} + k_{2f} + k_{2b})^2 - 4(k_{1b}k_{2b} + k_{1f}k_{2b} + k_{1f}k_{2f})} \right]
\]
Concentration of Each Species

Mechanistic Details for the Vesicle to Rod Transition

- 1.0 wt % PS$_{310}$-b-PAA$_{52}$ in Dioxane / Water
- Transition from 28.0 to 27.0 wt % Water
Next: Curvature stabilization mechanism
Transmission electron micrograph (TEM) of vesicles of PS$_{300}$-$b$-PAA$_{44}$

Quenched from dioxane/water (60/40) at 1 wt % polymer.
PREFERENTIAL SEGREGATION OF CORONA CHAINS:

SHORT CHAINS TO THE INSIDE
LONG CHAINS TO THE OUTSIDE
POLYMER WITH FLUORESCENT LABEL

Parent system: PS<sub>300</sub>-b-PAA<sub>44</sub>

PS<sub>295</sub>-Py-b-PAA<sub>X</sub>

X = 12, 45, 74

UV-vis spectrum of pyrene

Emission spectrum of vesicles in solution upon irradiation at 343 nm

L. Luo and A. Eisenberg, JACS 2001, 123, 1012-1013
Proof of Segregation by Block Length in Vesicles

Modified Stern-Volmer equation:

\[
\frac{I_0}{I_0 - I} = \frac{1}{\phi K Q} + \frac{1}{\phi}
\]
### Apparent $\phi$ and $K$ values of the PS-$b$-PAA Micelles and Vesicles

<table>
<thead>
<tr>
<th>system</th>
<th>micelles</th>
<th></th>
<th>vesicles</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\phi$</td>
<td>$K$(mM$^{-1}$)</td>
<td>$\phi$</td>
<td>$K$(mM$^{-1}$)</td>
</tr>
<tr>
<td>$PS_{300}$-$b$-PAA$<em>{44}$/PS$</em>{295}$-Py-$b$-PAA$_{42}$</td>
<td>0.91±0.07* (0.85)**</td>
<td>9.5±1.8 (9.9)</td>
<td>0.065±0.003 (0.065)</td>
<td>9.0±0.6 (9.0)</td>
</tr>
<tr>
<td>$PS_{300}$-$b$-PAA$<em>{44}$/PS$</em>{295}$-Py-$b$-PAA$_{45}$</td>
<td>0.92±0.07 (0.85)</td>
<td>9.2±0.9 (9.7)</td>
<td>0.53±0.02 (0.53)</td>
<td>8.9±0.4 (8.9)</td>
</tr>
<tr>
<td>$PS_{300}$-$b$-PAA$<em>{44}$/PS$</em>{295}$-Py-$b$-PAA$_{74}$</td>
<td>0.91±0.07 (0.85)</td>
<td>9.3±0.9 (9.8)</td>
<td>0.88±0.05 (0.83)</td>
<td>8.4±0.6 (8.8)</td>
</tr>
</tbody>
</table>

*: value± standard error.

**: the numbers in brackets were used to calculate the lines in the Figure. They were chosen to give the best fit. All the values are within the error limits.

Segregation in $\text{PS}_{300}-b-\text{PAA}_{44}$ copolymer vesicles

$\text{PS}_{300}-b-\text{PAA}_{44}$

$\text{PS}_{295}-\text{Py}-b-\text{PAA}_{12}$

$\phi = 0.91$

$\phi = 0.92$

$\phi = 0.91$

$\phi = 0.53$

$\phi = 0.88$
Size-dependent segregation of hydrophilic block in PS-\textit{b}-PAA diblock copolymer vesicles

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{Quenching percentage as a function of vesicle size.}
\end{figure}

- PS_{310-\textit{b}-PAA_{28}}/PS_{295-\textit{Py-b}-PAA_{74}}
- PS_{300-\textit{b}-PAA_{44}}/PS_{295-\textit{Py-b}-PAA_{74}}
- PS_{310-\textit{b}-PAA_{28}}/PS_{295-\textit{Py-b}-PAA_{12}}
- PS_{300-\textit{b}-PAA_{44}}/PS_{295-\textit{Py-b}-PAA_{12}}
Is Size Dependent Segregation Reversible?

PS_{300-b-PAA_{44}}/PS_{295-Py-b-PAA_{12}}

- increasing water content
- decreasing water content

Run#

1 2 3 4 5 6 7 8 9

[II^+] vs. I/I_0

66.7% 50.0% 39.4% 28.6% 24.5%
Reversibility of chromophore segregation in response to change in vesicle size induced by increasing or decreasing water contents for PS$_{300}$-b-PAA$_{44}$ with 5% PS$_{295}$-Py-b-PAA$_{12}$ in 44.4/55.6 THF/Dioxane mixture

<table>
<thead>
<tr>
<th>Experiment# (direction)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water content /%</td>
<td>24.5</td>
<td>28.6</td>
<td>39.4</td>
<td>50.0</td>
<td>66.7</td>
</tr>
<tr>
<td>Vesicle size /nm</td>
<td>91±3</td>
<td>100±4</td>
<td>120±5</td>
<td>151±6</td>
<td>201±3</td>
</tr>
<tr>
<td>$\phi$ (accessibility) /%</td>
<td>4.82±0.06</td>
<td>9.73±0.09</td>
<td>13.8±0.2</td>
<td>19.8±0.2</td>
<td>25.9±0.3</td>
</tr>
<tr>
<td>Polymer concentration /%</td>
<td>7.55</td>
<td>7.14</td>
<td>6.06</td>
<td>5.00</td>
<td>3.33</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Experiment# (direction)</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water content /%</td>
<td>50.0</td>
<td>39.4</td>
<td>28.6</td>
<td>24.5</td>
</tr>
<tr>
<td>Vesicle size /nm</td>
<td>150±6</td>
<td>120±4</td>
<td>99±5</td>
<td>91±2</td>
</tr>
<tr>
<td>$\phi$ (accessibility) /%</td>
<td>20.2±0.2</td>
<td>13.9±0.2</td>
<td>9.87±0.06</td>
<td>4.95±0.04</td>
</tr>
<tr>
<td>Polymer concentration /%</td>
<td>2.50</td>
<td>1.97</td>
<td>1.43</td>
<td>1.22</td>
</tr>
</tbody>
</table>
Next: different interfaces in and out and inversion possibility
CAN DIFFERENT GROUPS BE ATTACHED INSIDE AND OUTSIDE?

GOAL: PAA inside
     P(4-VP) outside

POLYMERS USED:

\[ \text{PS}_{300-b-\text{PAA}_{11}} \] (SHORT PAA FOR INSIDE)
\[ \text{PS}_{310-b-\text{P(4-VP)}_{33}} \] (LONG P(4-VP) FOR OUTSIDE)
\[ \text{PS}_{295-\text{Py-b-\text{PAA}_{12}}} \] (LABELED SHORT PAA)
\[ \text{PS}_{300-b-\text{PAA}_{44}}^* \] (FOR ζ COMPARISON)

PREP: DMF, adjust pH to 3, add water to 50%, quench, dialyze
     * dioxane, add water to 40%, quench, dialyze
<table>
<thead>
<tr>
<th>BLOCK COPOLYMERS</th>
<th>RESULTING MORPHOLOGIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS_{300}-b-PAA_{11}</td>
<td>LCMs</td>
</tr>
<tr>
<td>PS_{310}-b-P(4-VP)_{33}</td>
<td>VESICLES; D=102±14nm; Wall=26±2nm</td>
</tr>
<tr>
<td>PS_{310}-b-P(4-VP)_{33} 60%</td>
<td>VESICLES; D=90±12nm; Wall=26±2nm</td>
</tr>
<tr>
<td>PS_{300}-b-PAA_{11} 40%</td>
<td>VESICLES; D=88±12nm; Wall=26±2nm</td>
</tr>
<tr>
<td>PS_{300}-b-PAA_{11} 35%</td>
<td>VESICLES; D=98±7nm; Wall=26±3nm</td>
</tr>
<tr>
<td>PS_{310}-b-P(4-VP)_{33}  5%</td>
<td>VESICLES; D=98±7nm; Wall=26±3nm</td>
</tr>
</tbody>
</table>
OUTSIDE OF VESICLES STUDIED BY pH DEPENDENCE OF $\zeta$-POTENTIAL

EXTERIOR OF MIXED VESICLES SAME AS THAT OF $\text{PS}_{310-b-P(4-VP)_{33}}$ VESICLES
F. Liu AND A. Eisenberg, Angewandte Chemie Int. Ed. 2003
PREPARATION OF THE TWO TYPES OF VESICLES

The charges are on the chains, counterions are not shown

F. Liu and A. Eisenberg, JACS 2003
NEXT:
INVERSION
INVERSION OF VESICLES, SCHEMATIC

Vesicles with PAA Outside  \rightarrow  Vesicles with both PAA and P4VP outside  \rightarrow  Vesicles with P4VP outside
Critical water content vs logarithm of the polymer concentration in various solvents or solvent mixtures. Extrapolation to 30% water gives a CMC of $10^{-60}$.
Next: control of wall thickness
## Sizes and Wall-thicknesses of Vesicles Prepared from Various PAA-b-PS block Lengths in Two Solvent Systems

<table>
<thead>
<tr>
<th>Block</th>
<th>% PAA</th>
<th>Diameter (Wall-thickness) in Dioxane</th>
<th>Diameter (Wall-thickness) in Dioxane/THF (3/1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAA$<em>{47}$-b-PS$</em>{434}$</td>
<td>9.77</td>
<td>340±149 (42±3)</td>
<td>292±118 (42±5)</td>
</tr>
<tr>
<td>PAA$<em>{47}$-b-PS$</em>{368}$</td>
<td>11.32</td>
<td>424±149 (38±4)</td>
<td>202±106 (36±4)</td>
</tr>
<tr>
<td>PAA$<em>{47}$-b-PS$</em>{356}$</td>
<td>11.66</td>
<td>301±118 (33±4)</td>
<td>147±76 (34±3)</td>
</tr>
<tr>
<td>PAA$<em>{47}$-b-PS$</em>{307}$</td>
<td>13.27</td>
<td>116±19 (28±2)</td>
<td>108±23 (28±3)</td>
</tr>
<tr>
<td>PAA$<em>{47}$-b-PS$</em>{275}$</td>
<td>14.59</td>
<td>94±16 (24±2)</td>
<td>100±19 (27±3)</td>
</tr>
<tr>
<td>PAA$<em>{47}$-b-PS$</em>{248}$</td>
<td>15.93</td>
<td>96±17 (27±3)</td>
<td>75±9 (23±2)</td>
</tr>
<tr>
<td>PAA$<em>{47}$-b-PS$</em>{197}$</td>
<td>19.26</td>
<td>Micelles (20±2)</td>
<td>Micelles (20±2)</td>
</tr>
<tr>
<td>PAA$<em>{34}$-b-PS$</em>{324}$</td>
<td>9.49</td>
<td>269±111 (39±4)</td>
<td>370±127 (39±4)</td>
</tr>
<tr>
<td>PAA$<em>{34}$-b-PS$</em>{239}$</td>
<td>12.45</td>
<td>177±85 (22±2)</td>
<td>134±60 (22±3)</td>
</tr>
<tr>
<td>PAA$<em>{34}$-b-PS$</em>{188}$</td>
<td>15.31</td>
<td>104±22 (20±2)</td>
<td>86±14 (19±4)</td>
</tr>
</tbody>
</table>
Relation between the poly(styrene) block length and the wall-thickness in vesicles made from the PAA$_{47}$-b-PS$_n$ block copolymers series

\[ y = 0.1014x - 1.9141 \]

\[ R^2 = 0.9876 \]
Relation between the square root of the poly(styrene) block length and the wall-thickness in vesicles made from the PAA_{47}-b-PS_{n} block copolymers series.

\[ y = 0.2665x + 9.6846 \]

\[ R^2 = 0.9851 \]
Relationship between Average Vesicles wall-thickness (d) and the Degree of Polymerization of Styrene block (DP_{Styrene}) or (DP_{Styrene})^{1/2} for PAA_{47-b-PS_n}

\[ y = 0.2665x + 9.6846 \]
\[ R^2 = 0.9851 \]

\[ y = 9.7445x + 22.758 \]
\[ R^2 = 0.9876 \]
Next: Size control
Average Vesicle Diameter of PAA$_{47}$-b-PS$_n$ Block Copolymers as a Function of DP$_{\text{Styrene}}$
Polydispersity vs. Vesicle Sizes

Size Standard Deviation ($\sigma$) vs. Average Vesicles Diameter (D, nm)

- $\text{PAA}_{47}$-b-$\text{PS}_n$ in Dioxane
- $\text{PAA}_{47}$-b-$\text{PS}_n$ in Dioxane/THF (3/1)
- $\text{PAA}_{34}$-b-$\text{PS}_n$ in Dioxane
- $\text{PAA}_{34}$-b-$\text{PS}_n$ in Dioxane/THF (3/1)
The size change of PS$_{300}$-b-PAA$_{44}$ diblock copolymer vesicles with changing water content and organic solvent composition.
Reversibility of vesicle sizes in response to increasing or decreasing water contents for PS$_{300}$-b-PAA$_{44}$ vesicles in THF/Dioxane (44.4/55.6) solvent mixture

SIZE DISTRIBUTIONS OF PS$_{310}$-b-PAA$_{28}$ VESICLES (FROM TEM)

D = 90±3nm; $\sigma/D = 0.03$
Prepared in DMF/THF (79.6/20.4 w/w)

D = 1010±340nm; $\sigma/D = 0.34$
Prepared in DMF/THF (38.8/61.2 w/w)
TOTAL INTERFACIAL AREA VS. VESICLE SIZE

Outside Surface  \[ = 4\pi R^2 \]

Inside Surface  \[ = 4\pi (R - d)^2 \]

Total Surface  \[ = 4\pi \left[ R^2 + (R - d)^2 \right] \]

Volume of Wall  \[ = \frac{4}{3} \pi R^3 - \frac{4}{3} \pi (R - d)^3 \]
\[ = \frac{4}{3} \pi \left[ R^3 - (R - d)^3 \right] \]

Number of Vesicles  \[ = \frac{V_{\text{Total Wall}}}{\frac{4}{3} \pi \left[ R^3 - (R - d)^3 \right]} \]

Total Surface Area  \[ = \frac{V_{\text{Total Wall}}}{\frac{4}{3} \pi \left[ R^3 - (R - d)^3 \right]} * 4\pi \left[ R^2 + (R - d)^2 \right] \]
\[ = 3V_{\text{Total Wall}} \frac{R^2 + (R - d)^2}{\left[ R^3 - (R - d)^3 \right]} \]
\[ = 3V_{\text{Total Wall}} \frac{2R^2 + 2Rd + d^2}{3R^2d - 3Rd^2 + d^3} \]
WHY DO VESICLE SIZES INCREASE WITH INCREASING WATER CONTENT?

Total Surface Area vs. Vesicle Size

1. For Radius (R) >> Wall thickness (d),
   \[ A = \frac{2V_{TOTALWALL}}{d} \]

2. For R ~ d,
   \[ A = 3V_{TOTALWALL} \frac{2R^2 + 2Rd + d^2}{3R^2d - 3Rd^2 + d^3} \]

Assume \( V_{TOTALWALL} = 10^{-6} m^3 (= 1 cm^3) \), \( d = 27 \text{nm} \)

![Graph showing Total Surface Area vs. Vesicle Radius]
II- Effect of HCl

In the presence of acid we observe:

- no shift in CWC (ca. 10.5% w/w)
- after vesicle formation (ca. 11.5 % w/w) turbidity ↑ i.e. bigger vesicles form

0.5% solutions of PS_{310-b-PAA_{36}} in dioxane
Why does NaCl or HCl cause larger vesicles to form?

In the absence of additives, poly(acrylic acid) is slightly ionized

The electrostatic repulsion between chains is reduced by adding

Salt, shields the charges

or

Acid, protonates the carboxyl groups

When repulsion among chains decreases
Aggregation number increases
Larger vesicles form
Effect of additives on vesicle size

Data points:  
- HCl = 64 μM
- NaCl = 2.7 mM
- Polymer only

Materials:  
- PS$_{310}$-$b$-PAA$_{36}$
In the presence of base we observe that:

- for NaOH \(>16.4\) uM, no self-assembly
- for NaOH = 16.4 uM, CWC shifts (10.5 \(\rightarrow\) 12.5 % water)
- after vesicle formation,  
  - turbidity ↓  
  i.e. smaller vesicles form 
  - turbidity increases ONLY slightly with water content
Why does NaOH cause smaller vesicles to form?

NaOH deprotonates poly(acrylic acid)

Electrostatic repulsion among chains ↑

For NaOH >16.4 uM,
the high ion content decreases solubility

For NaOH = 16.4 uM,
chain repulsion is high
aggregation number ↓
smaller vesicles form
Next: fission and fusion mechanisms and fusion kinetics
MECHANISM OF VESICLE FUSION

- CONTACT AND ADHESION
- COALESCENCE AND FORMATION OF CENTER WALL
- DESTABILIZATION OF CENTER WALL
- ASYMMETRIC DETACHMENT OF CENTER WALL
- RETRACTION OF CENTER WALL INTO OUTER WALL
- FORMATION OF UNIFORM OUTER WALL

MECHANISM OF VESICLE FISSION

- SPHERICAL VESICLE
- ELONGATION
- INTERNAL WAIST FORMATION
- NARROWING OF EXTERNAL WAIST
- COMPLETE SEPARATION
Effect of SDS on Morphology

System: 1.0 wt % $\text{PS}_{310}-b-\text{PAA}_{52}$ in dioxane/water (11.5%)

MORPHOLOGICAL PHASE DIAGRAM

System: 1.0 wt % $\text{PS}_{310}-b-\text{PAA}_{52}$ in dioxane/water in the presence of SDS

Effect of SDS on Morphological Transitions

System: 1.0 wt % PS$_{310}$-b-PAA$_{52}$ in dioxane/water

TWO EXAMPLES OF KINETIC RUNS OF VESICLE SIZE CHANGES

15 to 16 wt.% H2O for PS310-b-PAA36 in Dioxane

\[ y = y_0 + A(1-e^{-tb}) \]

- \( R^2 = 0.98 \)
- \( y_0 = 0.969 \pm 0.001 \)
- \( A = 0.061 \pm 0.001 \)
- \( b = 0.066 \pm 0.002 \)

22 to 23 wt.% H2O for PS310-b-PAA36 in Dioxane

\[ y = y_0 + A(1-e^{-tb}) \]

- \( R^2 = 0.93 \)
- \( y_0 = 1.296 \pm 0.001 \)
- \( A = 0.044 \pm 0.001 \)
- \( b = 0.040 \pm 0.003 \)
An example of change in turbidity as a function of time upon 5wt% water jumps

0.5 wt.% PS310-b-PAA36 in Dioxane

T = A (1-e^{-bt})
Effect of the magnitude of the water jump

0.5wt.% of PS310-PAA36 in Dioxane $R^2 = 0.90$

$R^2 = 0.9171$

$R^2 = 0.9084$

Avg. Relaxation time (sec.) vs. Water Content (wt.%)
Length Segregation of Corona Chains Decreases Vesicle Sizes

Effect of Corona Block Polydispersity on Sizes of Vesicles Made from Polystyrene-\textit{b}-Poly(acrylic acid)

Solvent content, number average molecular weight, and polymer concentration were kept constant.

Next: filling and release
What’s DXR

- DXR.HCl: doxorubicin hydrochloride

- Anti-cancer drug
- Molecular weight = 580 (g/mol)
- Water soluble (50 mg/ml)
Active Loading into Vesicles

Use vesicles as model carriers for Doxorubicin
Induce loading by creating a transmembrane pH gradient
“Active” vs. “Passive” Loading

ΔpH ≈ 4

As a function of the wall permeability

(Addition of dioxane as a plasticizer)

ΔpH = 0
Solvent content in the PS$_{200}$-rich phase as a function of the water content (dotted lines extrapolate the cwc). The insert shows the plot against the water increment beyond the cwc.
Active vs. Passive Loading

Vesicles prepared from PS$_{310}$-b-PAA$_{36}$

Common solvent: dioxane
Loading Mechanism

\[ \text{neutral form is permeable} \]

\[ \text{protonated form is NOT permeable} \]

\[ \text{pH} = 2.5 \]

\[ \text{pH} = 6.3 \]
Release of DOX from PS$_{310}$-b-PAA$_{36}$ vesicles

Lim Soo, P.; Choucair, A.; Eisenberg, A.; In Press
Excitation spectra of 8-hydroxypyrene-1,3,6-trisulphonate (HPTS)
Calibration profiles of HPTS curves were taken as $I_{454}/I_{403}$ or $I_{403}/I_{454}$ vs. pH.
Time evolution of fluorescence excitation spectra from vesicle solutions with added HPTS at different dioxane contents;

A: 0 wt%; B: 7 wt%; C: 14 wt%; D: 28 wt%; E: 40 wt%;
Plots of proton concentration $[H^+]$ against the square root of diffusion time $t$. 
Plot of $\log[D^*(\Phi)/D^*(7\%)]$ against dioxane content.
Many types of vesicles can be prepared (equilibrium)

Sizes can be thermodynamically and reversibly controlled by

Water content, ion content, solvent composition, molecular weight distribution of corona block, relative block length, polydispersity, etc

Part of a morphological continuum spheres → rods → vesicles

Kinetics and mechanisms of transitions are known

Vesicle curvature stabilized by chain segregation:
Longer chains outside, shorter chains inside.

Segregation is size dependent and reversible.
Vesicles – Summary (2)

- Interface compositions can be controlled by using diblock mixtures,
  for example: PS-\(b\)-PAA with PS-\(b\)-PVP.
- Vesicles with opposite interfaces from ABC triblocks
  (PAA-\(b\)-PS-\(b\)-PVP)
- Triggered inversion is possible.
- Wall thickness is controllable
- (Small molecules inside vesicles)
- (Active loading is possible. Release occurs by diffusion)
- (Wall permeability can be controlled (by 100x))
COWORKERS

Z. GAO (高植生)  L. LUO (罗来斌)
L. ZHANG (张黎峰)  P. LIM SOO
H. SHEN (沈红卫)  A. CHOUCAIR
K. YU (余茭)  O. TERREAU
Y. YU (于一松)  I. RIEGEL
L. CHEN (陈雷)  R. VYHNALKOVA
G-E. YU (余嘎尔)  C. BARTELS
S. BURKE  F. LIU
A. KYCIA  N. DUXIN
N. CAMERON

FUNDING

NSERC  PRF
MERCK FROSST  RHODIA
“PARTING IS SUCH SWEET SORROW”
Thank you  Good Bye

200 nm