Tuning degradation through molecular structure/ Controlled Release Devices

Last time: factors controlling polymer degradation and erosion
            theory of polymer erosion

Today: degradable solid polymer molecular design
            fundamental concepts of controlled release devices and applications
            controlled release devices based on degradable polymers

         •W.M. Saltzman 'Drug administration and effectiveness,' from Drug Delivery: Engineering Principles for Drug Therapy, (2001)

Announcements:
Last time
Bulk vs. surface erosion: how do we predict it?

**Bulk erosion**

**Surface erosion**

Figures removed for copyright reasons.
Please see:


Images of Surface Erosion removed due to copyright restrictions.

Göpferich theory of polymer erosion

• If polymer is initially water-insoluble, and hydrolysis is the only mechanism of degradation, then two rates dominate erosion behavior:
Rate of water diffusion into polymer matrix

Figure by MIT OCW.

Rate of chain cleavage

t=0

Lecture 3 Spring 2006
Rate of chain cleavage

\[ p(t) = ke^{-kt} \]

Mean lifetime of one bond:

…this is the mean time I need to wait to observe one bond I am watching be broken.
Rate of chain cleavage

Mean lifetime of $n$ bonds:

$t=0$  \hspace{1cm} t
Rate of chain cleavage

Mean lifetime of $n$ bonds:

How many bonds in a depth $x$?
Comparison of water diffusion rate to bond lysis rate allows the qualitative mechanism to be predicted:

\[ \varepsilon = \text{erosion number} \equiv \frac{t_{\text{Diff}}}{t_{\varepsilon}(n)} \]

\[ \varepsilon \gg 1 \]

\[ \varepsilon \sim 1 \text{ change in erosion mechanism} \]

\[ \varepsilon \ll 1 \]
## Erosion parameters of degradable polymers

<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Polymer</th>
<th>$\lambda$ (s$^{-1}$)</th>
<th>$\epsilon$</th>
<th>$L_{\text{critical}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Poly(anhydrides)</td>
<td>$1.9 \times 10^{-3}$ Ref. [30]</td>
<td>11,515</td>
<td>75 $\mu$m</td>
</tr>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Poly(ketal)</td>
<td>$6.4 \times 10^{-3}$ Ref. [30]</td>
<td>387</td>
<td>0.4 mm</td>
</tr>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Poly(ortho esters)</td>
<td>$4.8 \times 10^{-3}$ Ref. [30]</td>
<td>291</td>
<td>0.6 mm</td>
</tr>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Poly(acetal)</td>
<td>$2.7 \times 10^{-8}$ Ref. [30]</td>
<td>0.16</td>
<td>2.4 cm</td>
</tr>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Poly(ε-caprolactone)</td>
<td>$9.7 \times 10^{-8}$ Ref. [31]</td>
<td>0.1</td>
<td>1.3 cm</td>
</tr>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Poly(ε-hydroxy-esters)</td>
<td>$6.6 \times 10^{-9}$ Ref. [30]</td>
<td>$4.0 \times 10^{-2}$</td>
<td>7.4 cm</td>
</tr>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Poly(amide)</td>
<td>$2.6 \times 10^{-11}$ Ref. [30]</td>
<td>$1.5 \times 10^{-6}$</td>
<td>13.4 m</td>
</tr>
</tbody>
</table>

*a* For a 1cm thick device, $D = 10^{-8}$ cm$^2$s$^{-1}$ (estimated from Ref. [32]) and in $\sqrt{M_{W}/N_{A}(N-1)p} = -16.5$.

*b* $D = 10^{-8}$ cm$^2$s$^{-1}$ (estimated from Ref. [32]) and in $\sqrt{M_{W}/N_{A}(N-1)p} = -16.5$.

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Figure by MIT OCW.
Dependence of erosion number on device dimensions
Testing the theory: experimental switch of a bulk-eroding polymer to a surface-eroding mechanism

PLA and PLGA degradation at pH 7.4: (bulk erosion)

Erosion profiles of poly(α-hydroxy esters) at pH 7.4.

Figure by MIT OCW.

PLA and PLGA degradation at pH 12: (surface erosion)

Erosion of poly(α-hydroxy esters) at pH > 13.

Figure by MIT OCW.

(SEM shown earlier confirms surface erosion mechanism)
Control over polymer degradation by molecular architecture
Controlling molecular architecture: self-assembly
Concepts in controlled release
Application of degradable solid polymers to controlled release

Implantable or injectable device
Therapeutic index: tailoring materials to provide release kinetics matching the ‘therapeutic window’

Bolus drug injection:

Amount of drug in tissue or circulation vs. time
Therapeutic index: tailoring materials to provide release kinetics matching the ‘therapeutic window’

Objective of controlled release:

Amount of drug released vs. time vs. Amount of drug in tissue or circulation vs. time
# Example applications of controlled release

<table>
<thead>
<tr>
<th>Application</th>
<th>Examples</th>
<th>Active concentration of cargo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide missing soluble factors promoting cell differentiation, growth, survival, or other functions</td>
<td>Replace deficient human growth hormone in children</td>
<td>1-10 pM; Hormones 5-10 nM</td>
</tr>
<tr>
<td>Sustained or modulated delivery of a therapeutic drug</td>
<td>Release of anti-cancer drugs at site of tumors to induce cancer cell apoptosis, ocular drugs for treatment of glaucoma, contraceptive drugs, antimalarial drugs</td>
<td>varies</td>
</tr>
<tr>
<td>Create gradients of a molecule in situ</td>
<td>Chemoattraction of immune cells to antigen depot for vaccines</td>
<td>1-50 pM</td>
</tr>
<tr>
<td>One time procedure (e.g. injection) with multiple dose delivery</td>
<td>Pulsatile release of antigen for vaccines</td>
<td>10-100 µg antigen</td>
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<tr>
<td>Gene therapy</td>
<td>Correction of cystic fibrosis gene defect, correction of adenosine deaminase deficiency (ADA-SCID) in lymphocytes, replace defective gene in Duchenne muscular dystrophy, cancer immunotherapy</td>
<td>1-20 µg DNA</td>
</tr>
<tr>
<td>Delivery site</td>
<td></td>
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<tr>
<td>-----------------------</td>
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<tr>
<td>Oral (delivery via digestive tract)</td>
<td></td>
<td></td>
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<tr>
<td>Sublinguinal (under tongue)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td></td>
<td></td>
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<tr>
<td>Parenteral</td>
<td></td>
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<tr>
<td>• intramuscular</td>
<td></td>
<td></td>
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<tr>
<td>• peritoneal (gut)</td>
<td></td>
<td></td>
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<tr>
<td>• subcutaneous (under skin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular</td>
<td></td>
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</tbody>
</table>
Drug diffusion-controlled release

Solid matrix

Barrier release
Drug diffusion-controlled release

Advantage:

Disadvantages:
Further Reading