Lecture 5: Controlled Release Devices

Last time: Using enzyme substrate and cytokine peptides to engineer biological recognition of synthetic polymers

Today: controlled release devices and applications
principles of controlled release devices based on degradable polymers
Synthesis of controlled release devices
Theory of polymer-based controlled release


Controlled Release Applications in Biological Engineering and Medicine

Overview

- Controlled release: Cargo molecules (small molecule drug, protein, DNA, etc.) released to physiological environment at a designed rate

- why develop controlled release systems?
  - Recent estimates from FDA: ~10 years and $150 to develop a single new drug product- looking for added value
  - Many drugs have a narrow therapeutic index (difference between toxic level and therapeutic level)
    - Requires multiple injections
    - Poor patient compliance
    - Increased incidence of infection and hemmorhages
  - Danger of systemic toxicity with more potent drugs; some drugs simply cannot be used
    - IL-2 promotes lymphocyte proliferation, useful as an anti-cancer drug but toxic at systemic level (induces fever, pulmonary edema, and vascular shock)
  - Targeted delivery possible
  - Improves availability of drugs with short half lives *in vivo*
    - Some peptides have half-lives of a few minutes or even seconds
  - Release systems can double as adjuvants for vaccines

- Show Figure 1 p. 347 Ratner

Where applicable:

<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</td>
<td>varies</td>
</tr>
</tbody>
</table>
Create gradients of a molecule in situ

One time procedure (e.g. injection) with multiple dose delivery

Gene therapy

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<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>
</tbody>
</table>

Antimalarial drugs (Life Sciences 19, 867 (1976)); contraceptive drugs ; (Am. J. Obstet. Gynec. 135, 419 (1979))

- **Delivery Sites**
  - Oral (delivery via intestinal tract)
  - Sublingual (under tongue)
  - Rectal
  - Parenteral: (injection sites other than digestive system)
    - Intramuscular
    - Peritoneal (gut)
    - subcutaneous
  - Ocular
  - (Table 1 Edlund)

**Commercial Device Examples (weave this in list below)**

Drug delivery is one of the most clinically-commercialized areas of biomaterials

Still only $30 billion/yr in 1998, modest share of world pharmaceuticals market

- **Alza ocusert**
  - Depot for ocular delivery of pilocarpine for glaucoma
- **PLGA**
  - Luteinizing hormone releasing hormone (LHRH) treatment of prostate cancer (Drug. Deliver. Ind. Pharm. 16, 2352 (1990))
- **Capronor**
- **Advanced Polymer Systems**
  - Ocular drug delivery
- **Gliadel**
  - Polyanhydride wafers for release of carmustine (anti-brain tumor drug)
Types of controlled release devices

1. Drug diffusion-controlled release
   a. Entrapped drug diffuses out of matrix at defined rate

(SLIDE)

b. Can provide release by diffusion out of polymeric matrix or diffusion through a barrier

c. Major disadvantages
   i. Nondegradable implants
   ii. Diffusion of large molecules such as proteins through the polymer is too slow to be effective
   iii. Danger of ‘dose dumping’ in barrier systems if membrane is ruptured

d. Typically nondegradable polymer
   i. Poly(dimethylsiloxane) (Norplant contraceptive- 6 flexible tubes filled with levonorgestrel)

   We will see later that eroding polymer release devices can also have diffusion-controlled release over an early timeframe, before degradation has proceeded very far

f. Release rates controlled by simple drug diffusion calculations

2. Water diffusion-controlled release
   a. Water influx controls release
b. diffusivity in swollen polymer allows diffusion of drug out of matrix

(SLIDE)

Non-erodible capsule

b. first example: Yolles Polym. News 1,9 (1971) or polym. Sci. Tecnol. 8, 245 (1975); cyclazocine in PLA sheets

c. Advantage of being injectable (microspheres) and resorbable (no retrieval surgery)

d. Disadvantage that therapy difficult to stop once injected due to difficult recovery of particles

e. clinical product examples

1. Lupron depot
   a. One month injectable PLGA microspheres containing leuprolide acetate for treatment of endometriosis and prostatic cancer
4. regulated release
   a. devices with externally-applied trigger to turn release on/off
      i. electrical
      ii. mechanical

   (SLIDE)
   
   Osmotic pump - Alza Duros® implant
   
   Semipermeable membrane
   Osmotic engine
   piston
   Drug reservoir
   Delivery orifice
   Titanium rod casing

   Osmotic pump - Alza Duros® implant
   
   Semipermeable membrane
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   piston
   Drug reservoir
   Delivery orifice
   Titanium rod casing

   Osmotic engine: (one form)
   
   Water driven into Engine; swelling drives piston to push drug out other end
   
   Favorable $\Delta S_{mix}$

   *DISCUSSION OF #5 NEXT DAY IN COMPLEX RELEASE PROFILES

   b. benefit of complex control
   c. generally more bulky devices and require implantation

   - Device types 1-4 generally 'pre-programmed'
   - *DISCUSSION OF #5 NEXT DAY IN COMPLEX RELEASE PROFILES
Sustained release

- Primary objective of controlled release devices: SUSTAINED RELEASE

- General rate expression:

\[
\frac{dc}{dt} = kc^n \quad n = 0 \rightarrow \frac{dc}{dt} = k
\]

- Want to match release rate to in vivo uptake/degradation rate to obtain a constant effective concentration of drug ON BOARD:

\[ c(t) \rightarrow c_{eff}(t) \]

Design of Eroding Polymer Controlled Release Devices

Continuous Release:

*Mechanism III hydrolysis*

Surface-eroding matrix

bulk-eroding matrix
Typical Release Profiles:

- **Surface eroding**
- **Bulk eroding**

(Fig. 2. Kinetics of hydrocortisone release from a half esterified copolymer of methyl vinyl ether and maleic anhydride from disks placed in the lower conjunctival cul-de-sac of rabbits. Devices removed at periodic intervals and residual hydrocortisone determined. (Garcia et al.))

- Corresponding RATES: **ON BOARD:**

![Graphs showing release profiles](Image)

- PARADOX: zero-order release best obtained from surface-eroding devices, but polymers with surface erosion mode typically also degrade very quickly—often too fast for the timescales of most interest

Factors Controlling Release:

1. Erosion mechanism
   - PH/hydrophobic contacts can cause protein degradation, aggregation, and denaturation

2. Device Microstructure
   - Burst effect often seen—controversy as to whether this is near-surface entrapped drug or surface-adsorbed drug
3. Bonding between encapsulant and matrix
   i. Proteins can adsorb to inner surfaces of degrading matrix
   ii. Ionic interactions of drug with matrix

**Mechanism II hydrolysis:**
Poly(methyl vinyl ether-co-maleic anhydride)  zero-order release
Fig. 2 Merkli et al. – release profile
Also Heller et al. JAPS 22, 1991 (1978) – mechanism of erosion

**Fabrication of Eroding Depot Devices**

**Single emulsion microparticle fabrication:**

Useful for hydrophobic, small molecule drugs

(Edlund and Albertsson⁶)
- sphere sizes ~ 0.5 – 100 µm
- Stabilizers used in microsphere fabrication:
  - Poly(vinyl alcohol)
  - Tweens
  - Poly(vinyl pyrrolidone)
  - Poly(ethylene glycol-b-propylene glycol) (e.g. Pluronics™)
- Inhibit particle coalescence by steric interference between droplets

- Factors in encapsulation efficiency: (tied to many of same molecular issues as release)
  - Bonding between drug and matrix
  - Hydrophilic proteins are poorly encapsulated

Double emulsion microparticle fabrication:
- Allows entrapment of hydrophilic molecules, proteins
• synthesis:
  1. aq. solution of protein added to organic solution of polymer; emulsify
  2. add milky W/O emulsion to large aq. phase containing stabilizer, emulsify to form second emulsion
  3. stir and evaporate organic phase to form solid polymer microspheres entrapping aq. droplets of protein solution
• issues with delivery of protein drugs
  o LOADING EFFICIENCIES TYPICALLY POOR FOR PROTEIN DRUGS
    • Difficult to achieve more than a few % by weight protein
    • Escape to aqueous phase during processing
  o Many fragile proteins denatured or irreversibly bound due to low pH, adsorption to hydrophobic polymer segments
• We will return to the topic of controlled release device synthesis when we discuss nanoparticle-based biomaterials
Theory of Controlled Release from Degradable Solids

- Release from eroding solid polymer
  - simplest important case, still a difficult problem!
  - Assume encapsulant is physically immobilized (but not covalently linked to matrix) within a water-insoluble polymer matrix

Analytical theory of controlled release from bulk-eroding solid

- List of parameters:
  - \( A \) device surface area
  - \( C_s \) concentration of drug soluble in matrix
  - \( C_0 \) initial concentration of drug encapsulated in device
  - \( M(t) \) molecular weight of matrix at time \( t \)
  - \( M_0 \) initial molecular weight of matrix
  - \( D \) Diffusion coefficient of drug in polymer matrix
  - \( h \) thickness of diffusion region in releasing sample
  - \( Q(t) \) total mass of drug released from dispersed phase from time 0 to time \( t \)

- Schematic illustration of model:

- Primary simplifying assumptions
  - Drug is encapsulated in matrix above its solubility limit: (forms a separate phase)
    - When matrix first contacts release medium, surface layer dissolves and concentration drops to \( C_s \)- the level of drug soluble in the polymer matrix
    - Extraction of drug from the dispersed phase does not occur at a given depth in the matrix until the extraction front contacts that position, creating 'space' for the drug to dissolve
      - The rate of this process of dissolution into the polymer matrix is assumed to be >> the process of diffusion through the matrix
    - Creates discontinuity in concentration profile once diffusion begins: once free, drug concentration immediately drops to \( C_s \)
  - \( D \) (drug diffusion coefficient in polymer matrix) is correlated with polymer molecular weight
  - Hydrolysis of bonds in the matrix occurs simultaneously throughout sample with first-order kinetics
  - Surrounding environment acts a sink for released drug
Pseudo steady-state diffusion of drug toward surface occurs in region between diffusion front and the surface.

**Derivation of drug release profile:**

- Amount of drug freed as diffusion front moves into sample by an amount \( dh \):

\[
\text{Eqn 1} \quad dQ = C_0 A dh
\]

- Chain cleavage occurs homogeneously through bulk as a first-order reaction:

\[
\text{Eqn 2} \quad \frac{dM}{dt} = -kM \quad \text{M}(t) = M_0 e^{-kt}
\]

This assumption is consistent with experimental measurements on PLGA microspheres:

- An exponential/first-order mode of breakdown indicates that for microspheres, autocatalysis is not a significant factor—since autocatalysis would change the order of reaction.

- Now assume \( D \sim M^{-1} \)

\[
\text{Eqn 3} \quad \frac{D}{D_0} = \frac{M_0}{M}
\]

- within the diffusion region, Fick’s first law describing steady-state diffusion is applied:

\[
\text{Eqn 4} \quad J = D(t) \frac{dc}{dx}
\]

\[
\text{Eqn 5} \quad J = \text{flux} = \left[ \frac{\text{mass drug}}{\text{area} \cdot \text{time}} \right] = \frac{1}{A} \frac{dQ}{dt} = D(t) \frac{(C_s - 0)}{(h - 0)} = D(t)C_s
\]

\[
\therefore \quad dQ = \frac{AD(t)C_s dt}{h}
\]
• Using Eqn 1 with Eqn 6:

\[
\frac{AD(t)C_s dt}{h} = C_0 Adh
\]

\[
D \frac{C_s}{C_0} dt = h dh
\]

• Integrating:

\[
\int_0^h D \frac{C_s}{C_0} e^{kt} dt = \int_0^{h(t)} h' dh'
\]

\[
D_0 \frac{C_s}{C_0} e^{kt} - 1 = \frac{h^2}{k}
\]

\[
h(t) = \frac{2D_0 C_s (e^{kt} - 1)}{kC_0}
\]

\[
J = \frac{1}{A} \frac{dQ}{dt} = \frac{DC_s}{h} = \left( \frac{D_0 e^{2kt} C_s k}{2(e^{kt} - 1)} \right)^{1/2}
\]

• Integrating, we get total drug released over time:

\[
Q(t) = A \left( 2C_0 C_s D_0 (e^{kt} - 1) \right)^{1/2} = \tilde{A} \left( \frac{e^{kt} - 1}{k} \right)^{1/2}
\]

where \(\tilde{A} = S \sqrt{2C_0 C_s D_0}\)

At early times, \(t\) small: \(e^{kt} \sim 1 + kt\):

\[
Q \approx \tilde{A} \sqrt{t}
\]

...this is the **Higuchi equation**, which describes release by pure diffusion of a drug out of an encapsulating matrix (no erosion occurring)

• The analytical expression allows experimental determination of \(\tilde{A}\) from early release curves when Higuchi conditions are still prevailing:

![Graph showing Higuchi regime and Diffusion/Erosion model](from file ‘Charlier contr rel.xls’)

Lecture 5 – Controlled Release Devices  13 of 14
Comparison with experimental data:

- Release from 50/50 PLGA copolymers with different molecules weights cast as 80 µm-thick films encapsulating model drug mifepristone (antiprogesterone norsteroid) (relatively hydrophobic small molecule)

References