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

Reading: 'Materials for protein delivery in tissue engineering,' S.P. Baldwin and W.M. Saltzman, *Adv. Drug Deliv. Rev.*, **33**, 71-86 (1998)

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:

Application	Examples	Active concentration of cargo
Provide missing soluble factors promoting cell differentiation, growth, survival, or other functions	Replace deficient human growth hormone in children	1-10 pM; Hormones 5-10 nM
Sustained or modulated delivery of a therapeutic drug	Release of anti-cancer drugs at site of tumors to induce cancer	varies

	cell apoptosis, ocular drugs for treatment of glaucoma, contraceptive drugs, antimalarial drugs	
Create gradients of a molecule *in situ*	Chemoattraction of immune cells to antigen depot for vaccinesk[1]	1-50 pM
One time procedure (e.g. injection) with multiple dose delivery	Pulsatile release of antigen for vaccines	10-100 μg antigen
Gene therapy	Correction of cystic fibrosis gene defect, correction of adenosine deaminase deficiency (ADA-SCID) in lymphocytes, replace defective gene in Duchenne muscular dystrophy, cancer immunotherapy[2]	1-20 μg DNA

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

- **Delivery Sites**
  - Oral (delivery via intestinal tract)
  - Sublinguinal (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
  - Polycaprolactone 1-year release of levonorgestrel (contraceptive) (C.G. Pitt in 'Long Acting Contraceptive Delivery Systems,' G.I. Zatuchni ed. (1984) p. 48-63)
  -
- Advanced Polymer Systems
  - Ocular drug delivery
- Gliadel
  - Polyanhydride wafers for release of carmustine (anti-brain tumor drug)

Types of controlled release devices[3]

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

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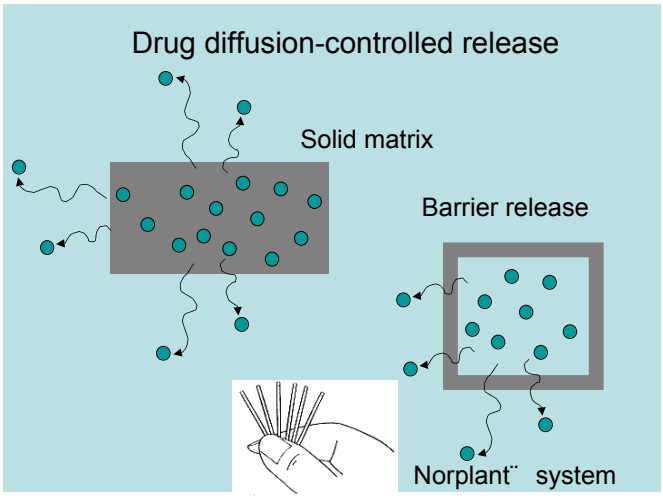
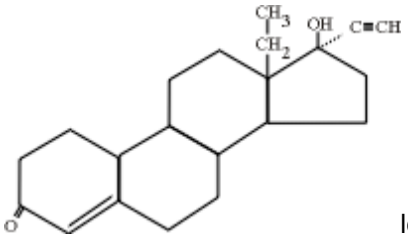


   b. Can provide release by diffusion out of polymeric matrix or diffusion through a barrier

   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)



levonorgestrel

   e. 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

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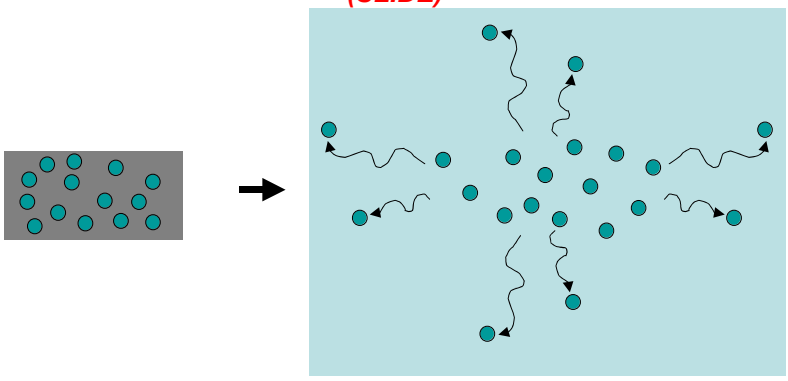

c. also nondegradable polymers typically
    i. poly(ethylene-co-vinyl acetate)

3. erodible devices
    a. combination of polymer breakdown and drug diffusion through matrix releases cargo

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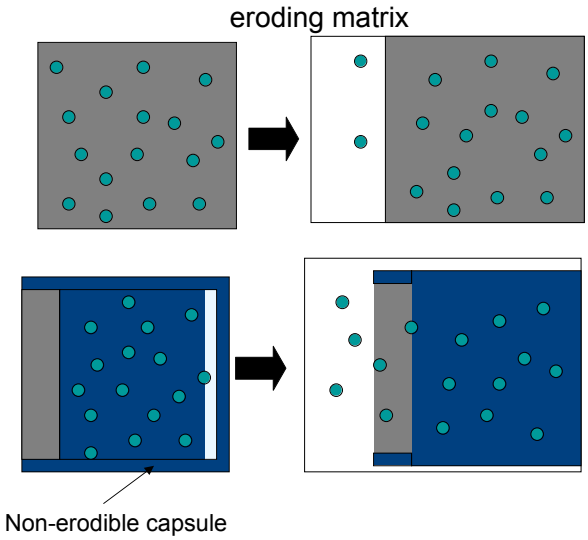

b. first example: Yolles Polym. News 1,9 (1971) or polym. Sci. Tecnol. 8, 245 (1975); cyclazocine in PLA sheets
c. Advantage of being injectable (microspheres) and resorbable (no retrieval surgery)
d. Disadvantage that therapy difficult to stop once injected due to difficult recovery of particles
e. clinical product examples
        1. Lupron depot
            a. One month injectable PLGA microspheres containing leuprolide acetate for treatment of endometriosis and prostatic cancer[4]

4. regulated release
   a. devices with externally-applied trigger to turn release on/off
      i. electrical[5]
      ii. mechanical

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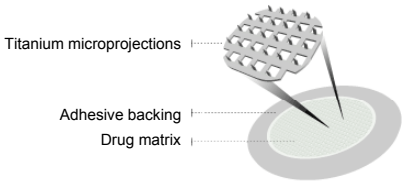
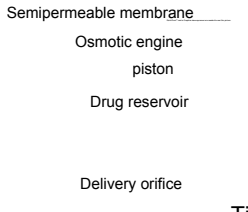
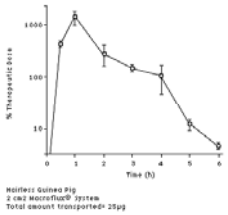
transdermal - Alza Macroflux® patch



Osmotic pump - Alza Duros¨ implant

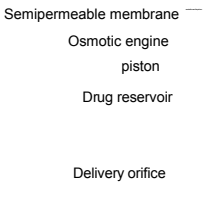


Titanium rod casing



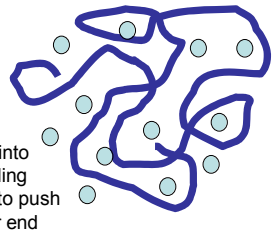
Osmotic engine: (one form)

Osmotic pump - Alza Duros¨ implant



Titanium rod casing

Favorable ΔSmix



Water driven into engine Õ swelling drives piston to push drug out other end

   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

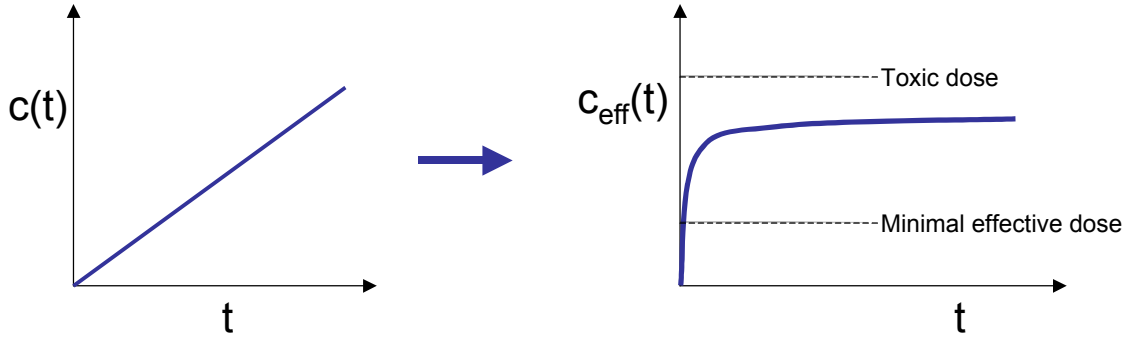
Sustained release

- Primary objective of controlled release devices: SUSTAINED RELEASE

- General rate expression:

$$\frac{dc}{dt} = kc^n \qquad \text{n = 0 ->} \quad \frac{dc}{dt} = k$$

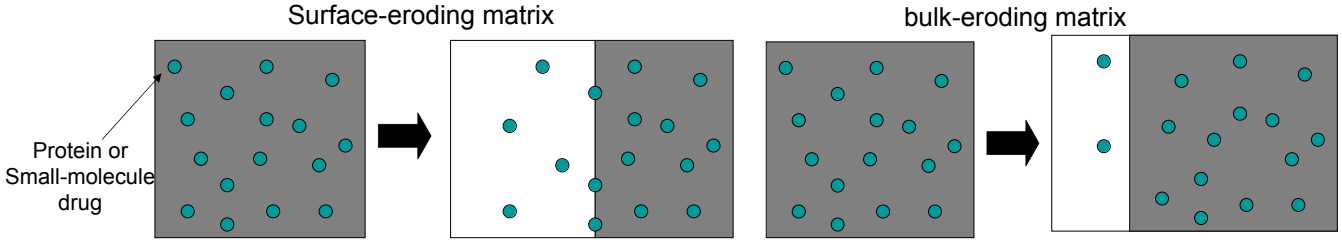
  - Want to match release rate to *in vivo* uptake/degradation rate to obtain a constant effective concentration of drug **ON BOARD:**



Design of Eroding Polymer Controlled Release Devices

Continuous Release:

Mechanism III hydrolysis



Typical Release Profiles:

Surface eroding

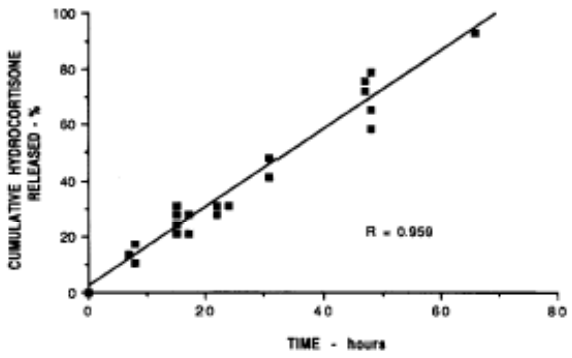


Fig. 2. Kinetics of hydrocortisone release from a half esterified copolymer of methyl vinyl ether and maleic anhydride from disks placed in the lower conjunctival cul-de-sac of rabbits. Devices removed at periodic intervals and residual hydrocortisone determined.

bulk eroding

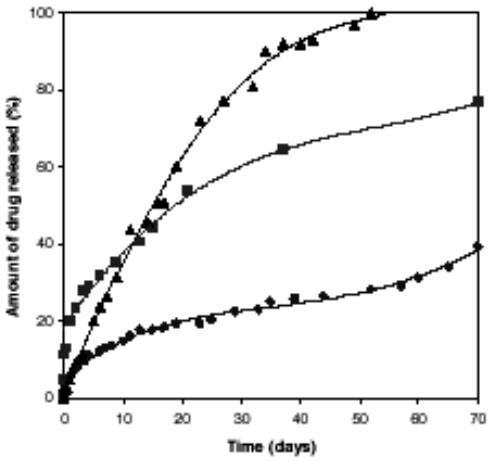
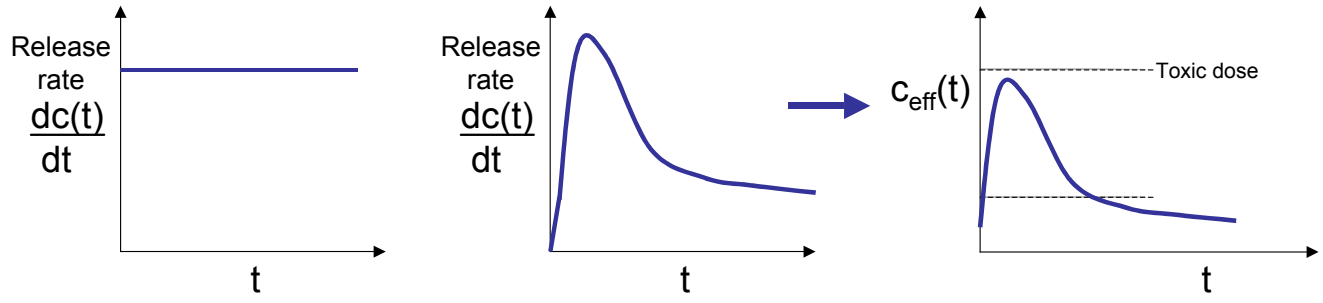


Fig. 14. Release of a therapeutic substance from (▲▲) P(L-LA-co-DXO), (■■) PDLLA-PDXO, and (●●) PLLA-PDXO microspheres with a L-LA/DXO molar ratio of 90:10

(Garcia et al.[6])

- Corresponding RATES: **ON BOARD:**

Surface eroding: **bulk eroding:**



- PARADOX: zero-order release best obtained from surface-erodiing 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
   i. PH/hydrophobic contacts can cause protein degradation, aggregation, and denaturation
2. Device Microstructure
   i. Burst effect often seen- controversy as to whether this is near-surface entrapped drug or surface-adsorbed drug[7]

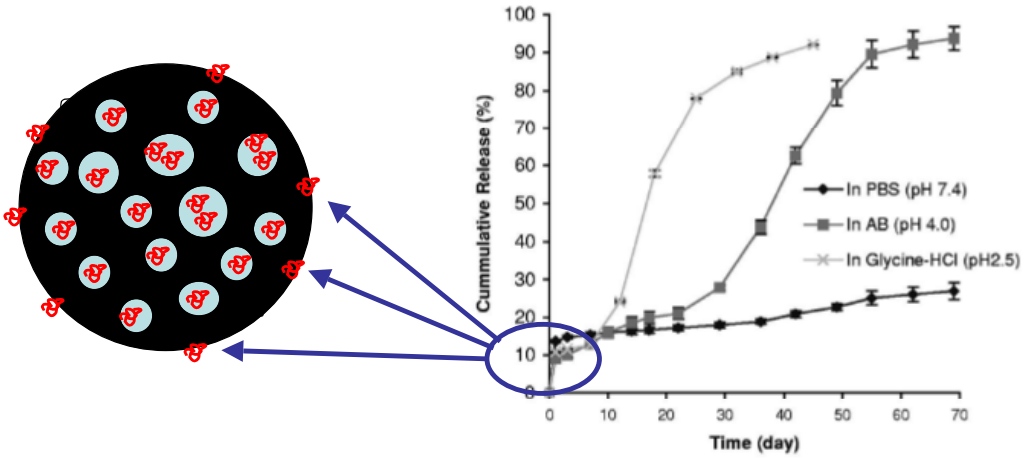


Fig. 4. In vitro release of lysozyme loaded PLGA microspheres in different release media at 37 °C for 70 days.

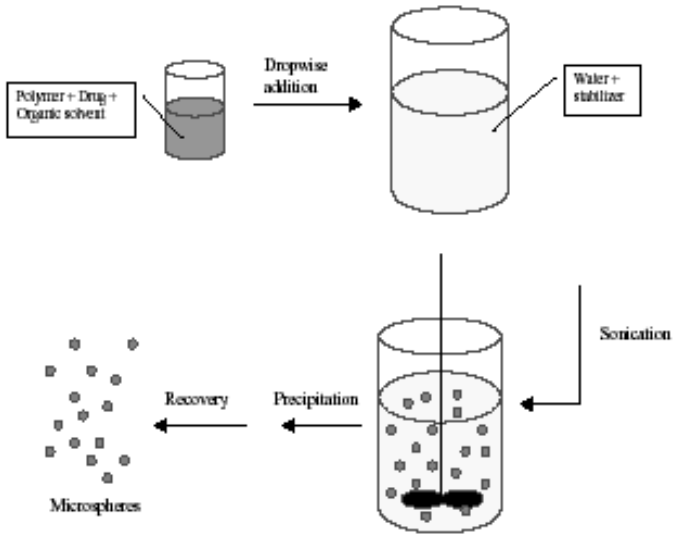
3. Bonding between encapsulant and matrix
    i. Proteins can adsorb to inner surfaces of degrading matrix
    ii. Ionic interactions of drug with matrix

Mechanism II hydrolysis:
Heller in Contr. Rel. of Bioactive Materaisls R.W. Baker ed. 1980 p. 1-17
Poly(methyl vinyl ether-co-maleic anhydride) zero-order release
Fig. 2 Merkli et al. – release profile
Also Heller et al. JAPS 22, 1991 (!978) – mechanism of erosion

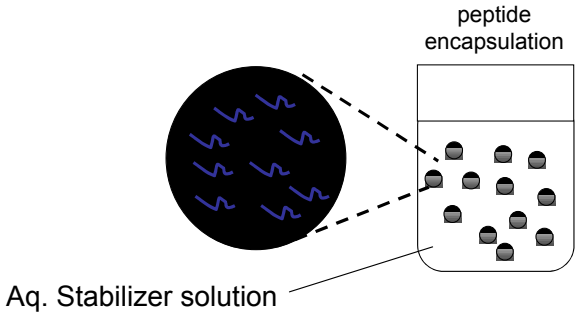
Fabrication of Eroding Depot Devices

Single emulsion microparticle fabrication:

Useful for hydrophobic, small molecule drugs



(Edlund and Albertsson[8])

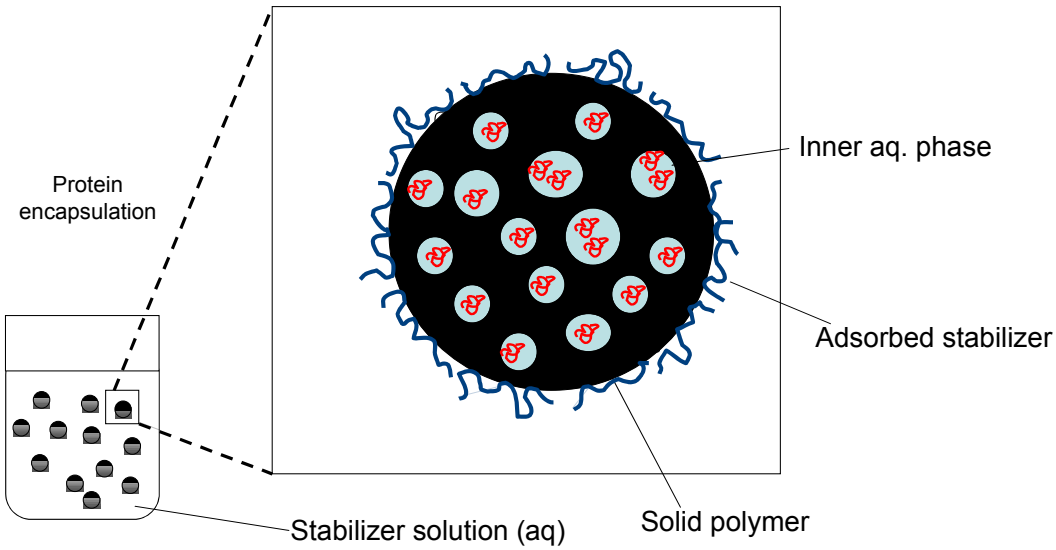


- sphere sizes ~ 0.5 – 100 μm
- Stabilizers used in microsphere fabrication:
    - Poly(vinyl alcohol)
    - Tweens
    - Poly(vinyl pyrrolidone)
    - Poly(ethylene glycol-b-propylene glycol) (e.g. Pluronics^{TM})
    - Inhibit particle coalescence by steric interference between droplets

- 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



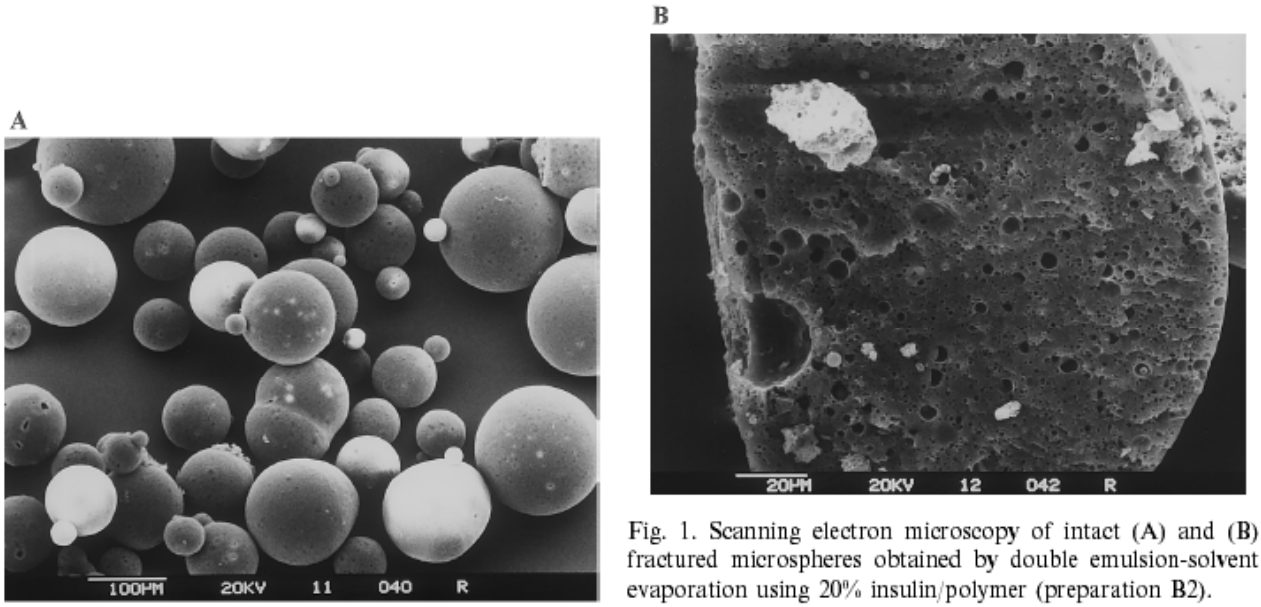


Fig. 1. Scanning electron microscopy of intact (A) and (B) fractured microspheres obtained by double emulsion-solvent evaporation using 20% insulin/polymer (preparation B2).

- 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
  - LOADING EFFICIENCIES TYPICALLY POOR FOR PROTEIN DRUGS
    - Difficult to achieve more than a few % by weight protein
    - Escape to aqueous phase during processing
  - 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[9]

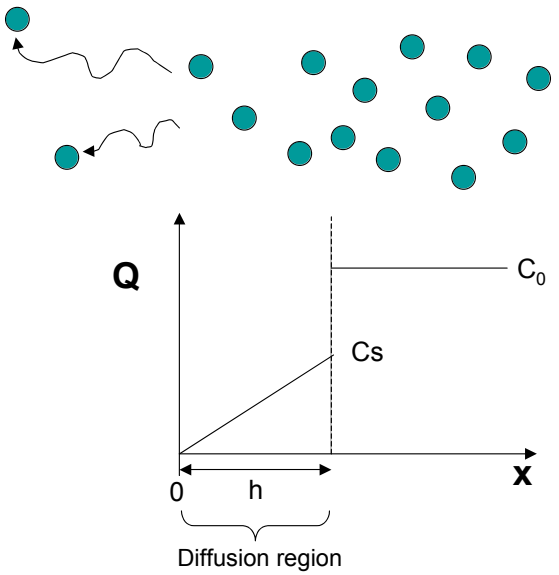
- Release from eroding solid polymer
  - simplest important case, still a difficult problem!
  - Assume encapsulant is physically immobilized (but not covalently linked to matrix) within a water-insoluble polymer matrix

Analytical theory of controlled release from bulk-eroding solid[10,11]

- List of parameters:

A	device surface area
Cs	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 Cs- 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 processs of diffusion through the matrix
    - Creates discontinuity in concentration profile once diffusion begins: once free, drug concentration immediately drops to Cs
  - 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:[12]

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

Eqn 1 $dQ = C_0 A dh$

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

Eqn 2 $\frac{dM}{dt} = -kM$ $M(t) = M_0 e^{-kt}$

- This assumption is consistent with experimental measurements on PLGA microspheres[13]:

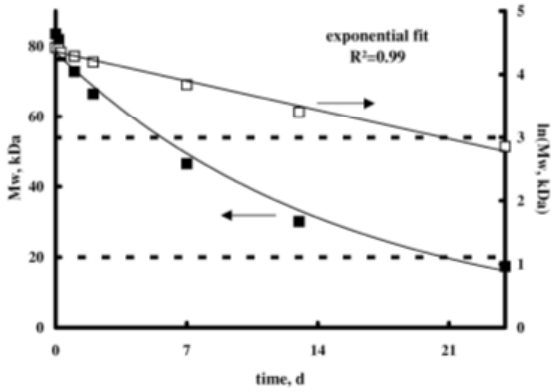


Fig. 8. Evolution of the polymer molecular weight (*Mw*) in 5-FU-loaded PLGA microparticles upon exposure to phosphate buffer pH 7.4 at 37 °C: normal–normal plot (left *Y*-axis) and semi-logarithmic plot (right *Y*-axis). The solid curve and solid line represent exponential fits, the broken lines critical threshold values (discussed in the text).

- 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 $D \sim M^{-1}$

Eqn 3 $\frac{D}{D_0} = \frac{M_0}{M}$ $D(t) = D_0 e^{kt}$

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

Eqn 4 $J = D(t)\frac{dc}{dx}$

Eqn 5 **J = flux =** $\left[\frac{massdrug}{area \bullet time}\right] = \frac{1}{A}\frac{dQ}{dt} = D(t)\frac{(C_s - 0)}{(h - 0)} = D(t)C_s$

Eqn 6 $\therefore dQ = \frac{AD(t)C_s dt}{h}$

- Using Eqn 1 with Eqn 6:

$$\frac{AD(t)C_s dt}{h} = C_0 A dh$$

$$D\frac{C_s}{C_0}dt = hdh$$

- integrating:

$$\int_0^t D_0 \frac{C_s}{C_0} e^{kt} dt = \int_0^{h(t)} h'\,dh'$$

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

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

$$J = \frac{1}{A}\frac{dQ}{dt} = \frac{DC_s}{h} = \left(\frac{D_0 e^{2kt} C_s C_0 k}{2(e^{kt}-1)}\right)^{1/2}$$

- integrating, we get total drug released over time:

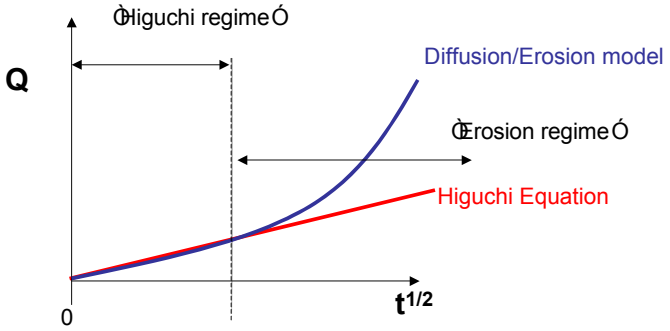
$$Q(t) = A\left(\frac{2C_0 C_s D_0 (e^{kt}-1)}{k}\right)^{1/2} = \tilde{A}\left(\frac{e^{kt}-1}{k}\right)^{1/2} \quad \text{where } \tilde{A} = S\sqrt{2C_0 C_s D_0}$$

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

$$Q \cong \tilde{A}\sqrt{t}$$

…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 A-tilde from early release curves when Higuchi conditions are still prevailing:



(from file 'Charlier contr rel.xls')

- Comparison with experimental data:

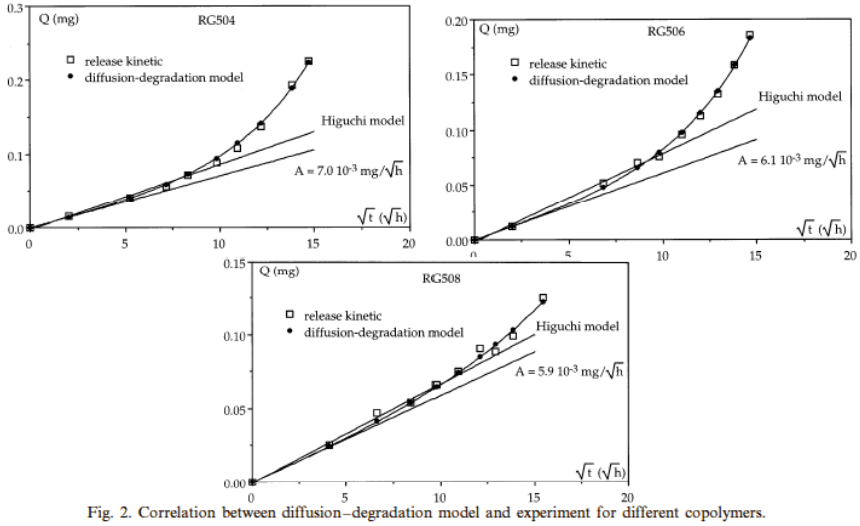


Fig. 2. Correlation between diffusion–degradation model and experiment for different copolymers.

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

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