Useful Equations:

Expressions for the molecular weight (M) of degrading polymers vs. time:

\[
\frac{1}{M} = \frac{1}{M_o} + kt \\
M = M_o e^{-kt}
\]

Charlier model for controlled release; amount of drug released at time \( t \) and depth of diffusion front:

\[
Q(t) = A \left( \frac{e^{kt} - 1}{k} \right)^{1/2} = A \sqrt{2C_o D_o} \left( \frac{e^{kt} - 1}{k} \right)^{1/2} \\
h(t) = \left( \frac{2D_o C_o}{kC_o} \right)^{1/2} \left( \frac{e^{kt} - 1}{1} \right)^{1/2}
\]

Osmotic pressure developing across a membrane and resulting flux of water:

\[
\Delta \pi \cong RT(\Delta c) \\
J_{\text{water}} = \frac{L_p \left( \Delta \pi \right)}{\delta}
\]

Merrill-Peppas master equation for swelling of nonionic hydrogels:

\[
\frac{1}{M_c} = \frac{2}{M} \left( \frac{v_{sp,2}}{V_1 \phi_{2,r}} \right) \left[ \ln(1 - \phi_{2,s}) + \phi_{2,s} + \chi \phi_{2,s}^2 \right] \\
\left( \frac{\phi_{2,s}}{\phi_{2,r}} \right)^{1/3} - \frac{1}{2} \left( \frac{\phi_{2,s}}{\phi_{2,r}} \right)
\]

reduced form for highly swollen gels:

\[
\frac{1}{M_c} \cong \frac{v_{sp,2} \left( \frac{1}{2} - \chi \right) \phi_{2,s}^{5/3}}{V_1 \phi_{2,r}^{2/3}}
\]

diffusion coefficient for a drug molecule (hydrodynamic radius \( r \) ) in a hydrogel with swelling ratio \( Q \):

\[
D = D_{H,0} \left( 1 - \frac{r}{\xi} \right) e^{-\frac{1}{(Q-1)}} \text{ (cm}^2/\text{sec)}
\]
1. **(20 points total) Choosing materials for *in vivo* applications.** Answer the questions below with concise responses: 1-3 sentences or fragments, or qualitative sketches as appropriate.

   a. (5 points) Materials used *in vivo* can be placed into one of three classes, based on the ultimate fate of the material. What are these 3 classes, and what is the characteristic fate *in vivo* of materials of each type?

   **Permanent/retrievable:** These materials are not degraded/eroded *in vivo*. They will remain permanently in place until surgically removed from a patient.

   **Bioeliminable:** Biomaterials that do not degrade to completely resorbable chemical constituents but which are water soluble and can be excreted through the kidneys or faeces are termed bioeliminable.

   **Biodegradable:** Materials that break down to completely metabolized byproducts are biodegradable. These materials are typically reduced to basic byproducts of metabolism, e.g., CO₂ and water.

   b. (5 points) Draw the chemical structure and name 3 examples of bonds typically sensitive to hydrolysis under physiologic conditions; show the chemical structure of the immediately resulting products that are created by hydrolysis of each.
c. (5 points) Biodegradable solid polymers undergo two distinct modes of breakdown, surface erosion or bulk erosion. Fill in the graphs shown below with qualitative representations/annotation to show what behavior you would expect for a material undergoing surface vs. bulk erosion.

**BULK EROSION**

- Molecular weight
- Mass remaining
- time

**SURFACE EROSION**

- Molecular weight
- Mass remaining
- time

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d. (5 points) Why are physical hydrogels most commonly formed by block copolymers (copolymers where two chemically different repeat units occur in strings, e.g., AAAABBBBBAAABBBBB), rather than random copolymers (random monomer sequences, e.g., ABAABBBBBAAAAAB)? (Answer in 1-3 sentences).

Hydrogels are characterized by water-swollen chains held together by crosslinks—multiple points of interchain bonding. The noncovalent interactions that characterize physical gels are much weaker than covalent bonds (by 10-100-fold). Thus, in order for crosslinks to remain stable in the face of thermal fluctuations (particularly at the physiologic temperature of 37°C), crosslinks are typically formed by coordinated bonding between adjacent repeat units in two apposed chains. In this setting, thermal rupture of any single bond between two repeat units does not dissolve the crosslink; the remaining adjacent bonds hold the pair together until the bond can reform.
2. (30 points total) Delivery of leuprolide, a polypeptide drug used as a prostate cancer treatment (amino acid sequence shown below).

\[
\text{Glu-His-Trp-Ser-Tyr-DLeu-Leu-Arg-Pro-NHEt} \]

Leuprolide acetate

a. (10 points) Two strategies to achieve zero-order release are to use a reservoir/membrane device or to encapsulate the drug in a surface-eroding degradable polymer. Cite a principle advantage of each of these strategies for the given application (one sentence each) and a principle limitation (one sentence for each approach).

**Reservoir device:**

*Advantages:* Sustained release over very long times—up to years—is readily achieved by tuning the diffusion coefficient of drug passage through the membrane material. The kinetics of drug release are well-described by simple models that quantitatively predict device function.

*Disadvantages:* Danger of ‘dose dumping’—immediate release of the entire payload of drug if the membrane is physically compromised. By design, these membranes are prepared from permanent materials and require surgical retrieval at the end of their useful lifetime (if they were biodegradable, the release rate would vary with time). Typical solid polymer membranes used as reservoir devices (e.g., poly(dimethyl siloxane)) have very low permeability for protein drugs.

**Surface-eroding degradable matrix:**

*Advantages:* A biodegradable matrix requires no surgery for recovery, and the system is free from ‘dose dumping’ issues. By formulating matrices in the form of microspheres, this controlled release system can be injected instead of implanted by surgery.

*Disadvantages:* The key limitation of surface-eroding matrices is the intrinsic coupling between degradation rate and the surface erosion mode of degradation: surface-eroding polymers are generally fast-degrading polymers, thus limiting the time that a given matrix can continue to release a given therapeutic drug.
b. (5 points) Consider further the case of using a surface-eroding biodegradable matrix. What chemical/physical properties favor surface erosion of degradable polymers? (Answer in 2-3 sentences).

Recalling the scaling analysis from Gopferich, we know that we can semi-quantitatively understand the mode of solid polymer erosion in terms of the ‘erosion number’- dimensionless ratio of the time required for water to diffuse a characteristic distance into the polymer over the time required for the polymer in that depth to degrade to soluble fragments. An erosion number >> 1 indicates that polymer degradation is much faster than water diffusion into the matrix, thus favoring surface erosion. This situation is favored by having a polymer matrix that is highly hydrophobic (water entry slow), relatively more labile bonds, and in matrices where crystallinity is low (since water is slow to access bonds in crystalline regions).

c. (5 points) Your research group decides to first test encapsulation of leuprolide in poly(lactide-co-glycolide) (PLGA) matrices formed as implantable wafers. Explain in 1-3 sentences what your biggest concern would be with the use of PLGA encapsulation for delivery of the polypeptide and why.

PLGA degradation results in the production of acid byproducts that will remain trapped in the matrix until late in degradation. These acid conditions may accelerate hydrolysis of the peptide drug, leading to its degradation. Note that denaturation is not really expected to be an issue for a small polypeptide such as leuprolide, where sensitive tertiary/quartenary structure will not exist—only higher-molecular weight proteins have this issue. In addition, the acid/base side chains of the peptide may themselves autocatalyze degradation in the matrix, making release characteristics highly sensitive to the amount of drug loaded in the matrix.
d. (10 points) Assume release of leuprolide from the PLGA wafers can be described by the Charlier controlled release model. Calculate the amount of drug released when the molecular weight of the matrix has dropped to 30,000 g/mole, using the physical data given below. (For the given ‘2D’ system (neglecting release from the edges of the wafer), the equations for 1D release from a slab can be used simply by assuming release occurs from a 1D slab with half the thickness of the actual wafers.)

Thicknes of the wafer: 2 mm
Surface area of the wafer: 1 cm$^2$
Degradation rate constant for PLGA: 9.5x10$^{-3}$ hr$^{-1}$
Concentration of drug entrapped in the matrix: 1 mg/cm$^3$
Concentration of drug soluble in polymer: 50 µg/cm$^3$
Initial molecular weight of matrix: 150,000 g/mole
Initial diffusion coefficient of the drug in PLGA: 6.5x10$^{-10}$ cm$^2$/s

Solution:

Charlier theory is based on the assumption of autocatalyzed polymer degradation (a good assumption for PLGA):

$$M = M_0 e^{-kt} = 150,000 e^{-kt}$$

$$30,000 = 150,000 e^{-(9.5 \times 10^{-3} \text{ hr}^{-1}) t}$$

$$\therefore t = 169 \text{ hr} = 7 \text{ d}$$

Effective release of drug from one side of the wafer in this time:

$$Q(t) = A \sqrt{2C_o D_o \left( \frac{e^{kt} - 1}{k} \right)}$$

$$Q(t) = (1 \text{ cm}^2) \sqrt{2(50 \times 10^{-6} \frac{g}{cm^3})(0.001 \frac{g}{cm^3})(6.5 \times 10^{-10} \frac{cm^2}{s}) \left( \frac{e^{k(169 \text{ hr})} - 1}{k} \right)}$$

$$Q(t) = 9.9 \mu g$$

Since drug can be released from both sides of the wafer, the total release is:

$$Q_{total} = 2 * 9.9 \mu g = 19.8 \mu g$$
3. **(30 points total) Self-rupturing microcapsules.** Shown below is a schematic view and actual data for a recently described* self-rupturing microcapsule system for pulsatile drug delivery. The microcapsule is constructed by synthesizing a hydrogel microsphere containing an entrapped drug. The gel (see schematic/chemical structure on following page) is comprised of dextran and poly(hydroxyethyl methacrylate) chains crosslinked by degradable linkages. The gel microsphere is coated by a polyelectrolyte multilayer composed of alternating layers of the polyanion poly(styrene sulfonate) and the polycation poly(allyl amine) (3 layers of each polyelectrolyte).

The gel capsule is proposed to function in the following manner: as crosslinks in the hydrogel degrade (step II in Figure 1), free, soluble dextran and poly(hydroxyethyl methacrylate) chains are created within the structure. These soluble chains contribute to an osmotic pressure buildup within the capsule. Once a sufficient number of free chains have been created, the osmotic pressure exceeds the tensile strength of the polyelectrolyte multilayer surface membrane, and the capsule ruptures, releasing the entrapped drug in an abrupt 'pulse'. Experimental demonstration of this concept is shown in the time-lapse fluorescence images below. Use the information given below to analyze the function of this device and answer the questions on the next page.

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**Figure 1. Schematic of self-rupturing microcapsule function.**

Figure removed due to copyright restrictions. Please see: Figure 5 in


**Figure 2. Fluorescence images showing the rupture of a microcapsule encapsulating a model fluorescent drug.** The polyelectrolyte multilayer membrane at the capsule surface is also permanently labeled with a fluorophore to allow its visualization. Images are a time-lapse in 15 min intervals.

Figure removed due to copyright restrictions. Please see: Figure 1 in


**Figure 3: Structure of gel core of the microcapsule, and schematic view of its breakdown.**
Questions for problem 3:

a. (5 points) The ester linkage in the crosslinks of these gels is stabilized by its proximity to the poly(hydroxyethyl methacrylate) backbone, and resists hydrolysis over typical timescales of interest. On Figure 3, circle the other linkage in the crosslink structure that is susceptible to hydrolysis.

b. (5 points) What key design requirement must be met by the polyelectrolyte multilayer coating the dextran-gel-microcapsule for this pulsatile-release strategy to work?

There are actually three essential features for the system to function as described: (i) The polyelectrolyte multilayer must be impermeable to the encapsulated drug, (ii) the multilayer must be impermeable to degraded gel fragments prior to rupture of the membrane, and (iii) the multilayer must be permeable to water. Without all three of these conditions satisfied, release will not be zero before membrane rupture and the osmotic pressure buildup will not occur: The osmotic pressure buildup occurs because the concentration of free polymer chains in the gel is increasing with time as degradation continues, providing a steadily increasing thermodynamic driving force for water to enter the capsule.

c. (5 points) Assuming that the swelling ratio Q is large when the membrane bursts and the gel equilibrates with the surrounding solution, calculate the mesh size needed for the diffusion coefficient of a protein drug (size $r = 8$ nm) in the gel to be 90% of its value in pure water when the membrane bursts.

\[
D = D_{H_2O} \left(1 - \frac{r}{\xi}\right) e^{-\frac{1}{(Q-1)}}
\]

\[
D = 0.9D_{H_2O} = D_{H_2O} \left(1 - \frac{r}{\xi}\right) e^{-\frac{1}{(Q-1)}}
\]

\[
0.9 = \left(1 - \frac{r}{\xi}\right) e^{-\frac{1}{(Q-1)}}
\]

for $Q$ large: $e^{-\frac{1}{(Q-1)}} \approx 1$

\[
0.9 = \left(1 - \frac{r}{\xi}\right) = \left(1 - \frac{8\text{nm}}{\xi}\right)
\]

\[
\therefore \xi = 80\text{nm}
\]
d. (10 points) This delivery system is designed to provide a single ‘pulse’ of drug released at a time pre-programmed into the structure of the capsule. Cite 3 aspects of the microcapsule composition or structure that you could alter to extend the time until ‘bursting’ occurs, and explain how alterations of these parameters would influence the time-to-burst (in 1-2 sentences for each).

A few example strategies:

- Tuning the chemical structure of the degrading crosslinks to create a structure with longer-lived crosslinks would lengthen the time for generation of a rupturing osmotic pressure.

- Given the structure of the gel, decreasing Mc (increasing the crosslink density) would lengthen the time required for any individual chain to be completely freed from the network and contribute to the osmotic pressure.

- In a similar manner, increasing the molecular weight of the dextran chains used for crosslinking to form the gel will increase the time for each chain to be freed from the structure.

- If the polyelectrolyte multilayer at the surface of the capsule were only weakly permeable to water, bursting of the capsule could be limited by the time required for water to diffuse into the core and swell the capsule. (In practice, limiting water penetration of a polyelectrolyte multilayer is challenging).

- Alternatively, if the mechanical strength of the polyelectrolyte multilayer were increased (e.g., by assembly at higher overall charges), the osmotic pressure required to burst the capsule would increase and the time to burst likewise increase.
e. (5 points) Theoretically, the kinetics of swelling for nonionic or polyelectrolyte hydrogels could be influenced by (i) the time for diffusion of water and ions into/out of the gel and/or (ii) the mechanical relaxation/uncoiling of individual chains within the gel. Which of these two factors is typically seen to dominate experimentally, and what experimental data supports this finding?

The rate of hydrogel swelling is typically observed to depend strongly on the macroscopic size of the gel, and macroporous gels swell/deswell much more quickly than homogeneous hydrogels. These observations are consistent with a dominant influence of ion/water diffusion on swelling kinetics. Chain relaxation, occurring on the molecular scale, would be the same in gels of different macroscopic sizes and would be unaffected by macroporosity.

*This problem is based on: De Geest et al. Advanced Materials 17, 2357-2361 (2005) and van Dijk-Wolthuis et al. Macromolecules 30, 4639-4645 (1997)*