

Useful Equations:

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

$$\frac{1}{M} = \frac{1}{M_o} + kt \qquad M = M_o e^{-kt}$$

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

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

$$h(t) = \left(2 \frac{D_o C_s}{k C_o} \frac{(e^{kt} - 1)}{1} \right)^{1/2}$$

$$\Delta\pi \cong RT(\Delta c)$$

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

$$J_{water} = \frac{L_p (\Delta\pi)}{\delta}$$

Merrill-Peppas master equation for swelling of nonionic hydrogels:

$$\frac{1}{M_c} = \frac{2}{M} - \left(\frac{v_{sp,2}}{\bar{V}_1 \phi_{2,r}} \right) \frac{(\ln(1 - \phi_{2,s}) + \phi_{2,s} + \chi \phi_{2,s}^2)}{\left[\left(\frac{\phi_{2,s}}{\phi_{2,r}} \right)^{1/3} - \frac{1}{2} \left(\frac{\phi_{2,s}}{\phi_{2,r}} \right) \right]}$$

reduced form for highly swollen gels:
$$\frac{1}{M_c} \cong \frac{v_{sp,2} \left(\frac{1}{2} - \chi \right) \phi_{2,s}^{5/3}}{\bar{V}_1 \phi_{2,r}^{2/3}}$$

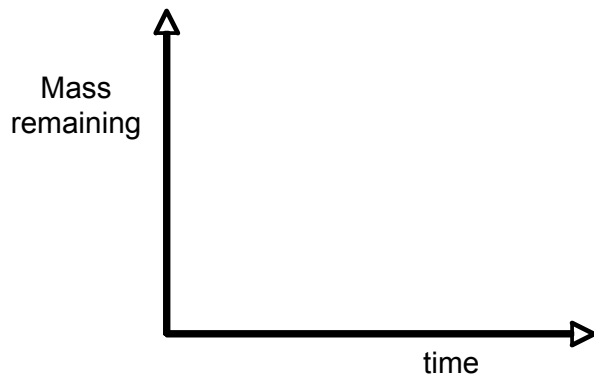
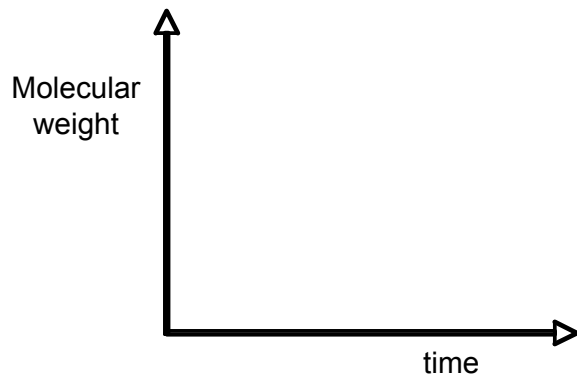
diffusion coefficient for a drug molecule (hydrodynamic radius r) in a hydrogel with swelling ratio Q:

$$D = D_{H_2O} \left(1 - \frac{r}{\xi} \right) e^{-\frac{1}{(Q-1)}} \text{ (cm}^2\text{/sec)}$$

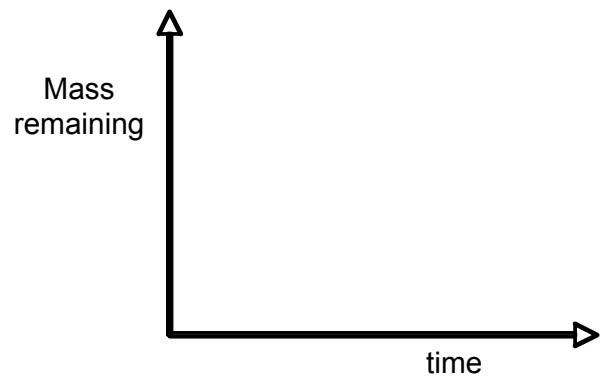
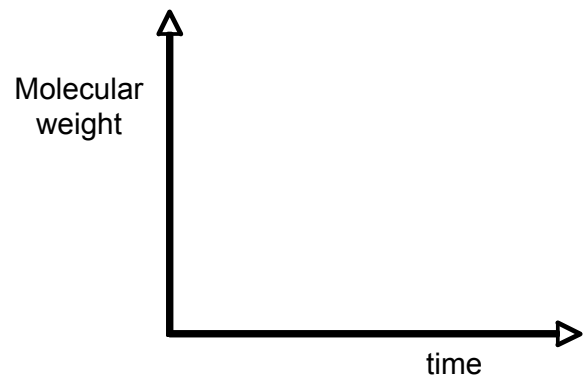
1. **(20 points total) Choosing materials for *in vivo* applications.** Answer the questions below with concise responses: 1-3 sentences or fragments, or qualitative sketches as appropriate.
- a. (5 points) Materials used *in vivo* can be placed into one of three classes, based on the ultimate fate of the material. What are these 3 classes, and what is the characteristic fate *in vivo* of materials of each type?
- 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



SURFACE EROSION



- 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., AAAABBBBBAAAABBBB), rather than random copolymers (random monomer sequences, e.g., ABAABBABBBAAAAB)? (Answer in 1-3 sentences).

2. **(30 points total) Delivery of leuprolide, a polypeptide drug used as a prostate cancer treatment** (amino acid sequence shown below).

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).

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**).

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.

- 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.)

Thickness of the wafer: 2 mm

Surface area of the wafer: 1 cm²

Degradation rate constant for PLGA: $9.5 \times 10^{-3} \text{ hr}^{-1}$

Concentration of drug entrapped in the matrix: 1 mg/cm³

Concentration of drug soluble in polymer: 50 μg/cm³

Initial molecular weight of matrix: 150,000 g/mole

Initial diffusion coefficient of the drug in PLGA: $6.5 \times 10^{-10} \text{ cm}^2/\text{s}$

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.

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

Geest, B. G. De, C. Déjugnat, G. B. Sukhorukov, K. Braeckmans, S. C. De Smedt, and J. Demeester. "Self-Rupturing Microcapsules." *Advanced Materials* 17, no. 19 (2005): 2357-2361.

Figure 1. Schematic of self-rupturing microcapsule function.

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Geest, B. G. De, C. Déjugnat, G. B. Sukhorukov, K. Braeckmans, S. C. De Smedt, and J. Demeester. "Self-Rupturing Microcapsules." *Advanced Materials* 17, no. 19 (2005): 2357-2361. 2005.

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

Dijk-Wolthuis, W. N. E. van, J. A. M. Hoogeboom, M. J. van Steenberg, S. K. Y. Tsang, and W. E. Hennink. "Degradation and Release Behavior of Dextran-Based Hydrogels." *Macromolecules* 30, no. 16 (1997): 4639-4645.

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?

- 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. (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).

- 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?

*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)