

Problem Set 2

Issued: 02/23/06

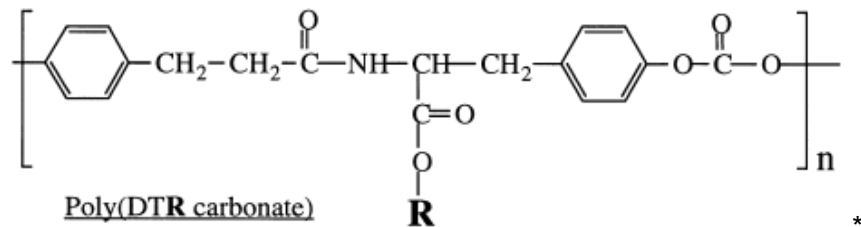
Due: 03/02/06

100 points total

20.462J/3.962J**Spring 2006**

1. From the reading for lecture 4 (Kumamoto et al., *Nat. Biotech.* **20**, 64-69 (2002)), we saw an example of how controlled release materials can be applied to create vaccines that attract immune cells to an immunization site. In this study, poly(ethylene-co-vinyl acetate) matrices were used. These are prepared by loading the polymer with a high amount of protein, such that the phase-separated protein forms a percolating network through the matrix, allowing for diffusion of the protein out of the sample once it is hydrated; as discussed in class, this leads to diffusion-based release much like a standard nondegradable matrix-based diffusion release.
 - a. Based on your reading/analysis of the paper, cite what you think are the two most important limitations of the chosen matrix material for the given application, and explain your choices.
 - b. Suggest an alternative material/release mechanism, and list two advantages and at least one potential issue with your alternative choice. Explain the advantages/issues you identify.

2. Given below are physical property data for poly(DPT-phenyl-carbonate) (PDPC), a degradable polycarbonate (note as shown below the 'R' group in the center of the structure is simply a hydrogen atom). This polymer has been shown to degrade with autocatalysis triggered by its acid breakdown products. You are going to encapsulate the small-molecule drug diltiazem within a slab matrix with dimensions as given below, and tests for the release rate of the drug will be performed with the matrix supported on an impermeable substrate as illustrated below in phosphate buffered saline at 37°C. Apply Charlier release theory for degradable polymers to answer the questions below.



(R = H) PDPC initial number average molecular weight: 125,000 g/mole

degradation rate constant: $k = 0.075 \text{ day}^{-1}$ *

approximate initial diffusion coefficient for diltiazem in the matrix: $D_0 = 3.0 \times 10^{-11} \text{ cm}^2/\text{s}$

(diffusion coefficient in water: $\sim 8 \times 10^{-6} \text{ cm}^2/\text{s}$)

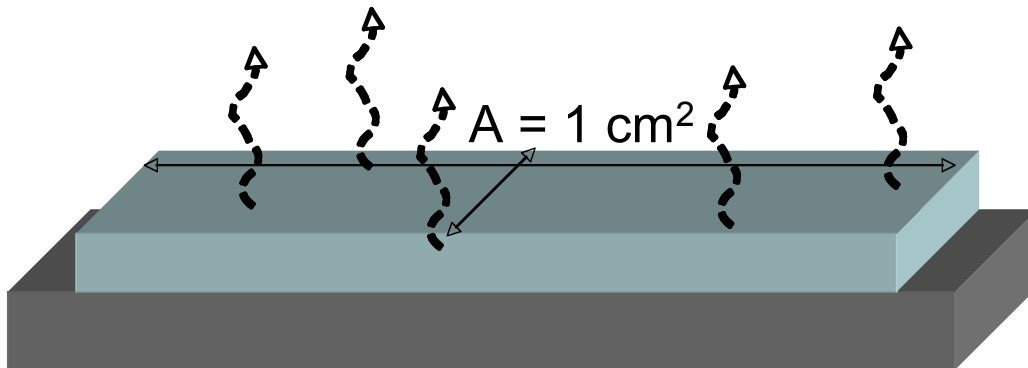
solubility of diltiazem in matrix: $0.001 \text{ g}/\text{cm}^3$

concentration of diltiazem encapsulated in matrix: $0.01 \text{ g}/\text{cm}^3$

surface area of matrix: 1 cm^2

matrix thickness: $500 \text{ }\mu\text{m}$

critical molecular weight of PDPC oligomers for solubility in saline: 2,500 g/mole



- a. At what time after the start of release will release first deviate at least 10% from the predicted Higuchi release (pure diffusion from a nondegradable matrix)? By what percent have the diffusion coefficient of the drug and the molecular weight of the matrix changed at this time?

- b. How long will this biodegradable matrix release drug?
- c. How long would the matrix release drug if it had the same initial permeability to drug but were non-degradable?
- d. Plot the drug release rate dQ/dt vs. time for the lifetime of the device.

*Tangpasuthadol, Kohn, et al. *Biomaterials* **21**, 2371-2378 (2000)

3. The basic structure of a simple osmotic pump as discussed in class is shown below. In this pump, the 'osmotic agent' is a salt rather than a polymer- here sodium chloride. The membrane separating the 'agent' chamber from the surroundings is fabricated from cellulose acetate, which has a good permeability for water but very low permeability for sodium chloride and other salts. Using our analysis from class of water flux through a membrane in response to an osmotic pressure difference, show that one can achieve a constant rate of drug release (zero-order release) if the following two conditions are met: (i) The drug solution and water solution in the 'osmotic agent' compartment are incompressible (e.g., any water entering the 'agent' compartment must push the piston and force water out of the drug compartment) and (ii) enough sodium chloride must be present in the 'osmotic agent' chamber such that even when the chamber is completely filled with water, the NaCl is forming a saturated salt solution (e.g., there is more salt than can be dissolved in the water that fills the chamber.)

Osmotic engine: (one form)

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

