

Problem Set 2 Model Solutions

Issued: 02/23/06

Due: 03/02/06

100 points total

20.462J/3.962J

Spring 2006

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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.

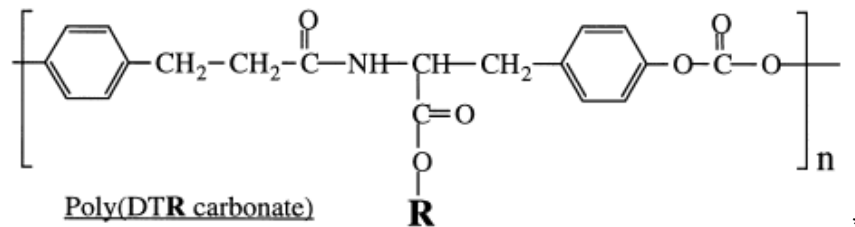
Probably the most important limitation of the strategy in this paper is the use of a nondegradable material for the vaccine—hence this approach requires recovery of the matrix at the end of its useful lifetime (which is very short). Because the material would be need to be retrieved, this also necessitates the use of a non-injectable form that is recoverable (e.g., the millirods used in this study). A second issue relates to the achievable timespan of antigen/chemokine delivery achievable by the poly(ethylene-co-vinyl acetate): diffusion of protein from this matrix is quite rapid, completing over the course of ~48 hrs, and thus, amplifying the immune response further by more sustained antigen delivery/chemoattraction is not possible with this matrix.

- 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.

A second simple approach, just as one example, could be to co-encapsulate chemokine and antigen within degradable microspheres, for example poly(lactide-co-glycolide) (or any one of numerous other materials we have discussed). These would provide an injectable, resorbable source for delivery, would co-localize the chemoattraction and antigen delivery centers, and, by using a slow-eroding material such as a polyester, release could be sustained for weeks.

As we discussed in class, a potential limitation of this alternative approach could be degradation of the proteins within PLGA over time due to buildup of an acid climate within the microspheres, which can drive protein aggregation/denaturation.

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: $\sim 8 \times 10^{-6} \text{ cm}^2/\text{s}$)

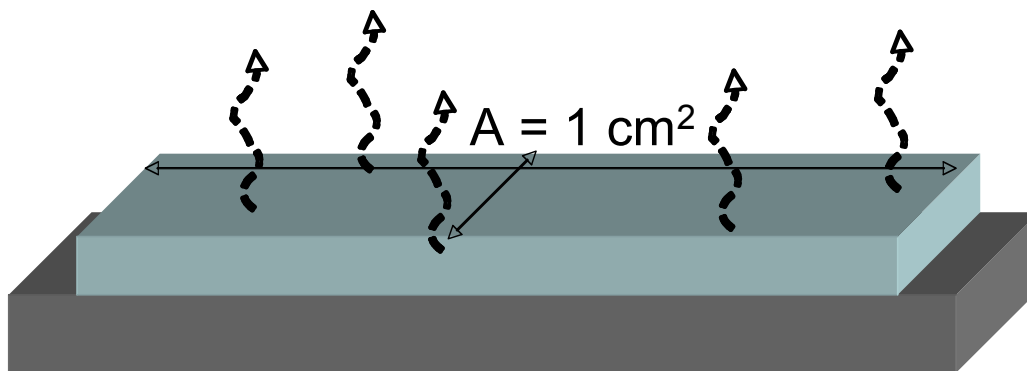
solubility of diltiazem in matrix: 0.001 g/cm^3

concentration of diltiazem encapsulated in matrix: 0.01 g/cm^3

surface area of matrix: 1 cm^2

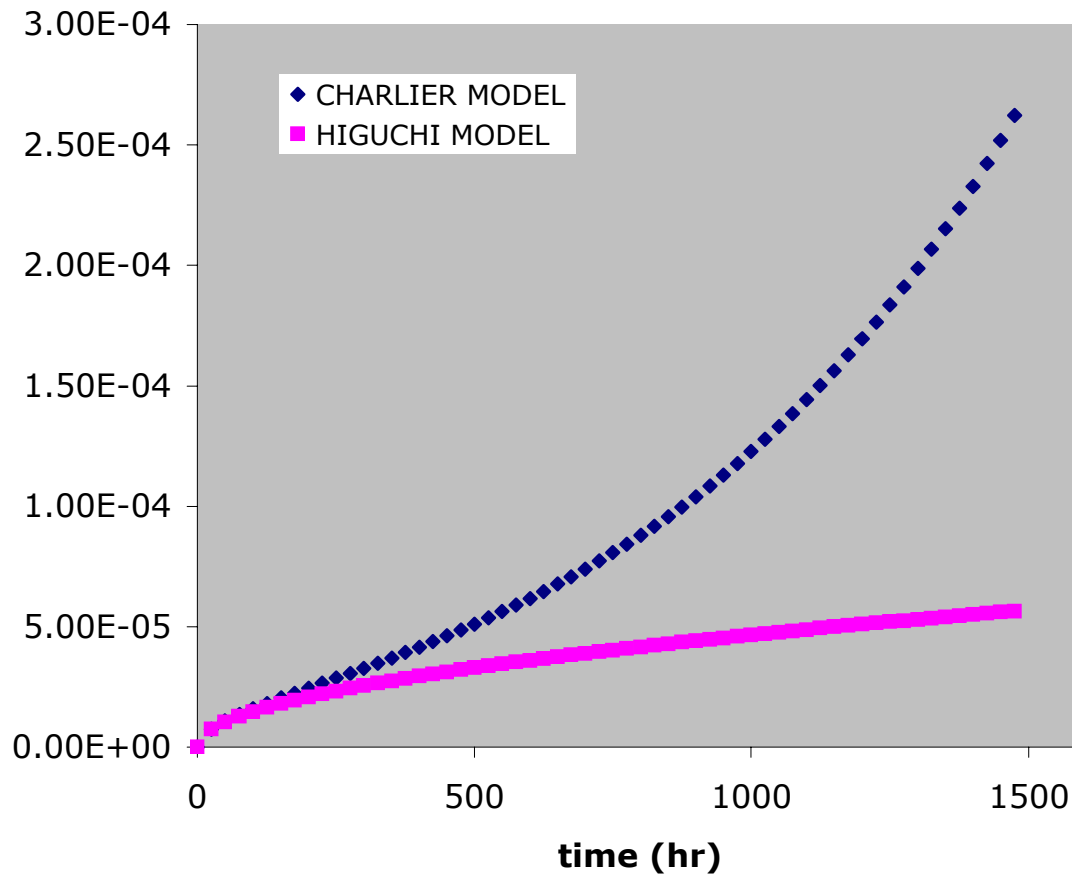
matrix thickness: $500 \text{ }\mu\text{m}$

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?

A plot of the release kinetics for the Higuchi model vs. the complete Charlier model for the given physical parameters is shown below.



By calculating the release profiles, we can determine a 10% difference between the two predictions occurs by ~125 hrs. At 125 hrs, the diffusion coefficient of drug has increased to $4.43\text{E-}11 \text{ cm}^2/\text{s}$ and the MW of the matrix has dropped to 84,600 g/mole—a change of +48% and -32%, respectively.

b. How long will this biodegradable matrix release drug?

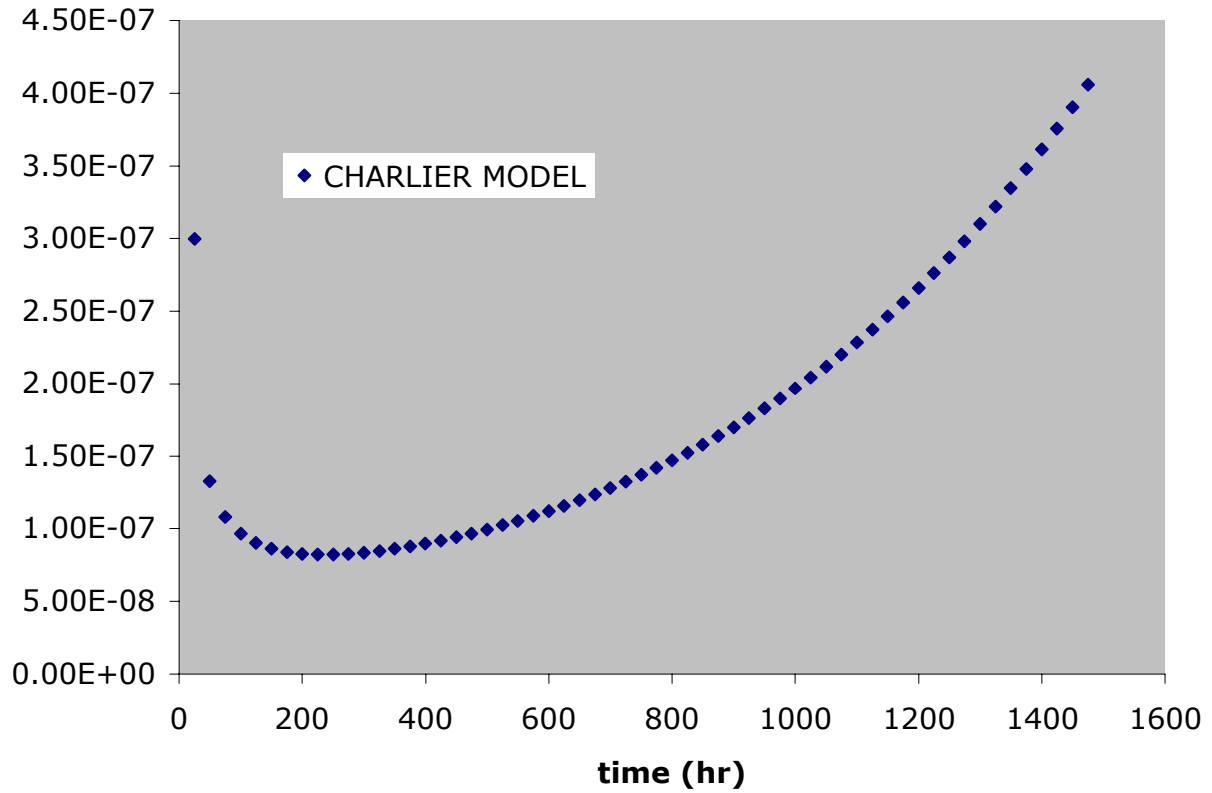
There are two possibilities: either the matrix will remain intact until all of the drug has diffused and escaped, or the alternatively, the matrix may degrade to failure prior to complete release of the drug (thus 'dumping' a certain quantity of drug at the time of failure). In this case, by solving for the release profile as a function of time, we can show that the matrix degrades to its critical molecular weight for solubility in saline (2500 g/mole) by ~1250 hrs, a timepoint at which only 37% of the encapsulated drug has been released. Thus, the matrix will only release drug for 1250 hrs, at which point the film will be solubilized and the remaining drug 'dumped' into solution.

- c. How long would the matrix release drug if it had the same initial permeability to drug but were non-degradable?

If the matrix is nondegradable, the calculation is for Higuchi release (the diffusion constant will not change with time)—in that case we find that the matrix has not released all of the encapsulated drug until 116,000 hrs!! (13 years!). However, note that the **rate** of release has dropped off so severely after even a few thousand hours that the dose delivered per unit time is likely not therapeutic.

- d. Plot the drug release rate dQ/dt vs. time for the lifetime of the device.

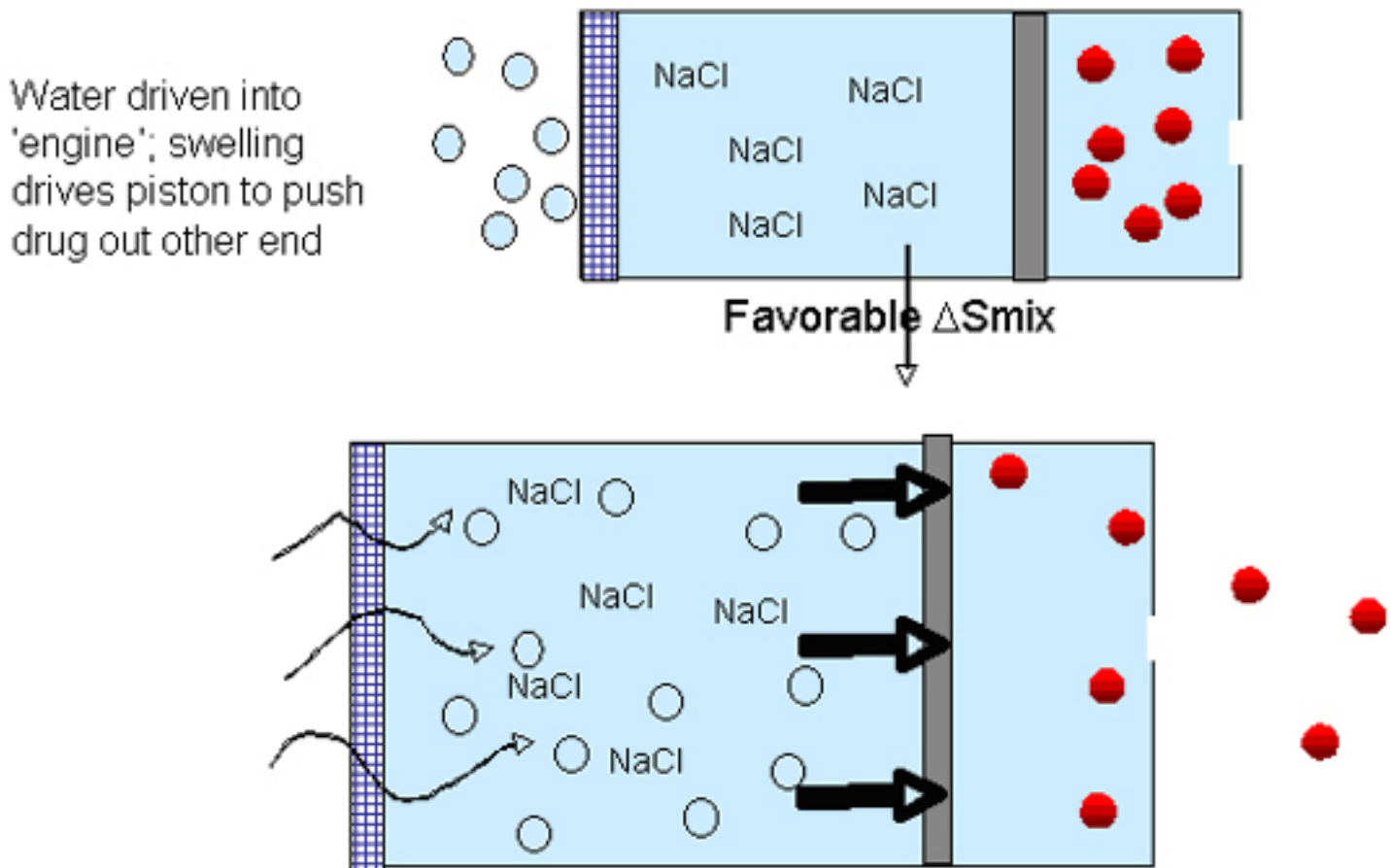
As expected, the release rate first declines in the Higuchi regimen, and then climbs as degradation becomes prominent and the diffusion coefficient begins to rise:



*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)



Assuming a saturated salt solution and compressibility of the fluids, we can solve this problem in the following fashion:

Incompressibility of the fluids ensures that the flux of water through the semipermeable membrane (J_W above) must equal the flux of drug out of the chamber (J_D above), because any volume of water that enters the osmotic chamber must displace the piston to the right and drive an equal volume of drug solution out of the device:

$$J_W = -J_D$$

The difference in sign tells us that positive flux through the osmotic membrane is opposite in direction to the flux of drug out of the device. Next, we look at how the concentration of salt in the osmotic chamber relates to JW: Based on our analysis of osmotic pressure through a membrane in class, we can write:

$$J_{w\Box} = \frac{L_p}{\delta} (\Delta\pi - \Delta P)$$

...where L_p is the permeability of the membrane, δ is the thickness of the membrane, $\Delta\pi$ is the difference in osmotic pressure inside the osmotic chamber and outside in the surrounding solution ($\pi_i - \pi_o$) and ΔP is the difference in hydraulic pressure inside/outside the chamber. If the fluids are incompressible, $\Delta P \sim 0$ (no pressure difference can build up if the fluids cannot be compressed). The osmotic pressure gradient is related to the concentration of NaCl forming a solution within the osmotic chamber:

$$\Delta\pi = -\frac{\Delta\mu}{v_{m\Box}} \cong -RT\Delta c\Box$$

Now, if we assume a saturated salt solution forms in the osmotic chamber, the concentration of salt in solution within the chamber is constant, at an amount c_s , the maximum amount of salt that can dissolve. This condition is easily met because we simply enclose enough salt so that as the piston is pushed out and more water comes into the osmotic chamber, excess salt in the chamber immediately keeps the water saturated. Putting this all together we have:

$$\begin{aligned} \Delta\pi &= -RT\Delta c\Box \cong -RT(c_{i\Box} - c_o) \cong -RTc_i \\ \therefore J_{D\Box} = -J_{w\Box} &= -\left(-\frac{RTL_p\Box}{\delta} c_s\right) = \frac{RTL_p}{\delta} c_{s\Box} = \text{constant} \end{aligned}$$

The simple conditions required to achieve zero-order release from osmotic pumps have made them a successful commercial product for clinical delivery of drugs over times up to a year or more.