

## Problem Set 4 Model Solutions

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100 points total

20.462J/3.962J

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1. Physically associating polymers are used as drug carriers, tissue bulking agents, and cell delivery scaffolds.
    - a. Explain why physical hydrogels are most often formed using *block* copolymers, where polymer chains are made up of repeating stretches of monomers which can take part in physical cross-links.

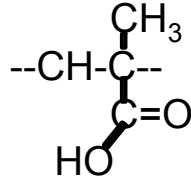
Single physical cross-links, formed by hydrophobic association/Van der Waals bonding, ionic bonding, or hydrogen bonding between two monomers in water, have significantly lower strengths than single covalent bonds (10-100-fold lower bond energies). Thus, formation of even transiently stable hydrogels (or micelles) requires block copolymer structures where cooperative binding can occur between bonding blocks of two chains. Formation of one physical bond is immediately followed by bonding of several other adjacent monomer units, 'zipping up' a physical contact between two chains.

- b. (15 points) For the 3 types of gels described below, provide the following **3** pieces of information: **(A)** State what type of polymer functional groups would be used to create physical gels with the described properties, **(B)** give one specific example of such a functional group, showing how it forms physical crosslinks, and **(C)** state how that functional group or groups provide the desired behavior:
  - i. Gels that are stable at reduced temperatures but dissolve at elevated temperature.
  - ii. Gels that are stable at elevated temperatures but dissolve at reduced temperatures.
  - iii. Gels that are stable in low ionic strength buffers but dissolve in high-ionic strength buffers.
    1. Physical gels stabilized by hydrogen bonds or polypeptide interactions are generally stable at lower temperatures, but these weak bonds are overcome if thermal energy in the system becomes too high.
    2. Physical gels stabilized by hydrophobic associations tend to be stable at elevated temperatures, where entropy has a strong contribution to the total

free energy of solutions. At low temperatures, hydrophobic groups may be hydrated and hydrophobic groups will dissociate.

3. Physical gels formed by polyelectrolytes crosslinked to oppositely-charged polymers or divalent cations are highly sensitive to ionic strength. At high ionic strengths, electrolyte ions will compete with for binding between the oppositely charged polymer chains, breaking up polyelectrolyte-polyelectrolyte complexes.

2. Consider a covalent poly(methacrylic acid) hydrogel designed to be used as a drug carrier for oral drug delivery, which has the following physical parameters:



$M$  = molecular weight of chains prior to crosslinking = 175,000 g/mole

$M_c$  = 10,000 g/mole

Molar volume of water = 18 cm<sup>3</sup>/mole

$$\phi_{2,r} = 0.4$$

Specific volume of PHEMA = 0.869 cm<sup>3</sup>/g

$\chi$  = polymer-water interaction parameter ~ 0.5

pKa methacrylic acid groups = 6.0

We will make use of Peppas theory for the swelling behavior of this ionizable gel, governed by the master swelling equation:

$$\bar{V}_1 \left( \frac{10^{-pK_a}}{10^{-pH} + 10^{-pK_a}} \right)^2 \left( \frac{\phi_{2,s}^2}{4Iv_{sp,2}^2 M_0^2} \right) = \ln(1 - \phi_{2,s}) + \phi_{2,s} + \chi \phi_{2,s}^2 + \phi_{2,r} \left( \frac{\bar{V}_1}{v_{sp,2} M_c} \right) \left( 1 - \frac{2M_c}{M} \right) \left[ \left( \frac{\phi_{2,s}}{\phi_{2,r}} \right)^{1/3} - \frac{1}{2} \left( \frac{\phi_{2,s}}{\phi_{2,r}} \right) \right]$$

- a. Suppose the gel is synthesized in the form of microspheres that have a diameter of 5  $\mu\text{m}$  at pH 7.4 and 100 mM ionic strength. What will the diameter of the particles be in the acid climate of the stomach (pH~2.0, ionic strength 20 mM)? What is the degree of ionization of the gel in the stomach?

Using the given data, we can directly calculate the predicted swelling ratio in the acid conditions of the stomach, by plugging into the expression for swelling in a polyelectrolyte hydrogel. One simple approach is to use a nonlinear equation system optimization routine (e.g., in Mathematica, Matlab, Excel, etc. - which all have built-in nonlinear equation set solvers) to find the set of values for  $\phi_{2,s}$  that make the left-hand side of the equilibrium expression equal to that on the right. A solution can rapidly be found if one divides both sides of the equation through by  $\phi_{2,s}^2$ , to avoid  $\phi_{2,s} = 0$  as a possible solution:

$$\bar{V}_1 \left( \frac{10^{-pK_a}}{10^{-pH} + 10^{-pK_a}} \right)^2 \left( \frac{1}{4Iv_{sp,2}^2 M_0^2} \right) = \frac{\ln(1 - \phi_{2,s}) + \phi_{2,s} + \chi \phi_{2,s}^2}{\phi_{2,s}^2} + \frac{\phi_{2,r}}{\phi_{2,s}^2} \left( \frac{\bar{V}_1}{v_{sp,2} M_c} \right) \left( 1 - \frac{2M_c}{M} \right) \left[ \left( \frac{\phi_{2,s}}{\phi_{2,r}} \right)^{1/3} - \frac{1}{2} \left( \frac{\phi_{2,s}}{\phi_{2,r}} \right) \right]$$

Be careful of units! Be sure the units for the constants all match up to give the right expression on each side; this is one of the most common errors. Solving this equation for the stomach conditions, we find  $Q = 9.888$  ( $\phi_{2,s} = 0.1011$ ). Next, to calculate the diameter of the particles in this condition, we need to get the dry volume of the particles using the data given for pH 7.4 100 mM ionic strength. Under these conditions, the predicted swelling ratio is  $Q = 218$  ( $\phi_{2,s} = 0.00459$ ). We can then extract the dry volume of polymer in the gel:

$$Q = 218 = \frac{V_{swollen}}{V_{dry}} = \frac{\frac{4}{3}\pi r_{swollen}^3}{V_{dry}} = \frac{\frac{4}{3}\pi(2.5\mu m)^3}{V_{dry}}$$

$$\therefore V_{dry} = 0.300\mu m^3$$

Using this value for  $V_{dry}$ , we can determine the final dimensions of the particles in the stomach:

$$Q_{stomach} = 9.888 = \frac{V_{swollen}}{V_{dry}} = \frac{\frac{4}{3}\pi r_{swollen}^3}{V_{dry}} = \frac{\frac{4}{3}\pi(r)^3}{0.300\mu m^3}$$

$$\therefore r = 0.891\mu m$$

$$d = 2r = 1.78\mu m$$

We can calculate the degree of ionization of the gel in the stomach directly from the equation given in class:

$$i = \left( \frac{10^{-pK_a}}{10^{-pH} + 10^{-pK_a}} \right) = \frac{10^{-6}}{10^{-2} + 10^{-6}} = 9.99 \times 10^{-5}$$

...thus the gel is almost completely uncharged.

- b. What % change in diameter will these microspheres undergo on passing from the stomach to the intestine (pH 7.2, ionic strength 20 mM)?

Solving for swelling in the conditions of the intestine, we have  $Q = 553$  ( $\phi_{2,s} = 0.00181$ ). Taking the ratio of  $Q$  in the stomach to that in the intestine:

$$\frac{Q_{intestine}}{Q_{stomach}} = \frac{553}{9.888} = \frac{V_{swollen,intestine}}{V_{swollen,stomach}} = \frac{\frac{4}{3}\pi\left(\frac{d}{2}\right)_{swollen}^3}{\frac{4}{3}\pi(0.891\mu m)^3}$$

$$\therefore d_{intestine} = 6.81\mu m$$

$$\%change = \frac{d_{intestine} - d_{stomach}}{d_{stomach}}(100\%) = \frac{6.81 - 1.78}{1.78}(100\%) = 283\%$$

- c. Basic ionic swelling theory neglects interactions between monomer units in the gel. Would you expect any such interactions are possible in this hydrogel? What effect could they have on swelling?

Strong specific interactions between functional groups are not accounted for in Peppas-Merrill theory (or its predecessor, the Flory-Rehner theory). So for example, hydrogen bonding that will occur among the methacrylic acid groups when they are protonated at low pH will drive further collapse of the hydrogel, and such driving forces will be neglected by the theory. Copolymer hydrogels that have hydrogen bonding groups thus often have more complex behavior as a function of pH and temperature, which is not as well predicted by this theory.