Hydrogels in drug delivery

Control of drug release kinetics by hydrogel structure[6,7]

- Release from stable hydrogels is controlled by diffusion of solute through the network
- Diffusion is described by Fick's second law:

Eqn 1

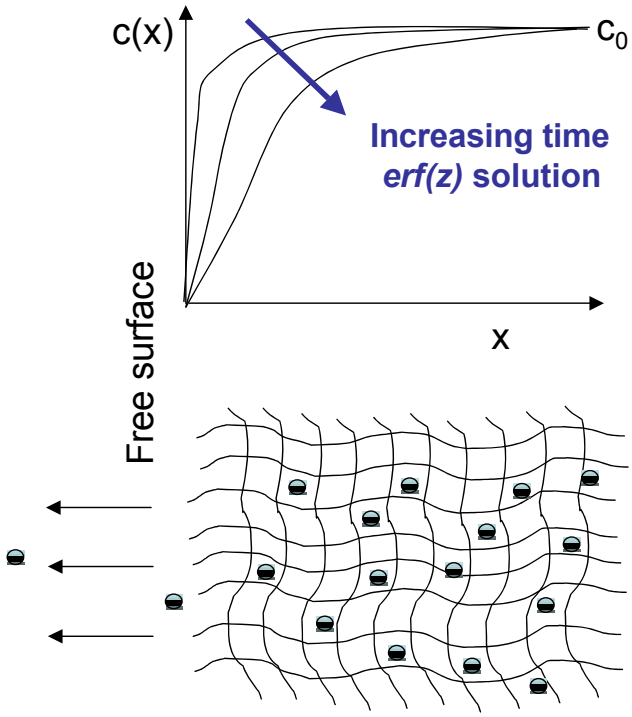
$$\frac{\partial C}{\partial t} = D_{gel}\frac{\partial^2 C}{\partial x^2}$$

- Recall the solution to Fick's second law for a semi-infinite slab contacting a perfect sink:

Eqn 2

$$\frac{c_0 - c(x)}{c_0} = 1 - erf\left(\frac{x}{2\sqrt{tD}}\right)$$

- Diffusion of drugs through a network is controlled by the mesh size (ζ)



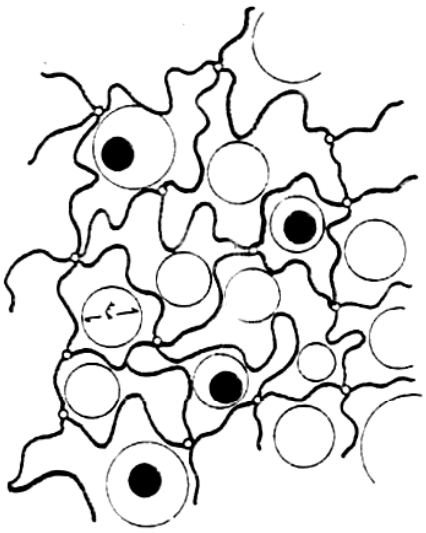
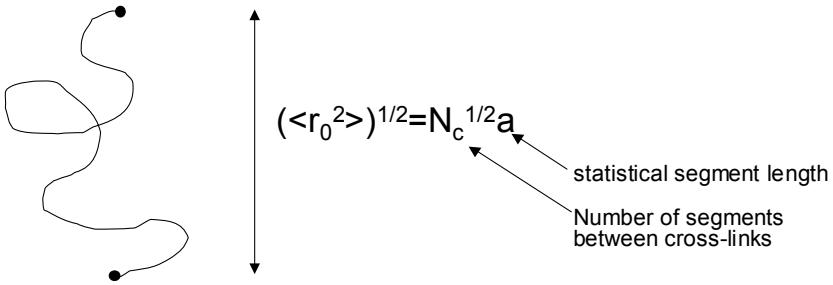


Fig. 3. Crosslinked structure of a polymer gel, showing effective chains of the structure defined by crosslinks. The effective area for diffusion for the solute is characterized by an average mesh size ξ. The smaller solutes, illustrated as dark circles, must pass between the macromolecules.

- The mesh size is related to the network swelling Q and the end-to-end distance between cross-links:



Eqn 3 $$\left(\bar{r}_0^2\right)^{1/2} = \left(\frac{2M_c}{M_0}\right)^{1/2} C_n^{1/2} l$$

- …assuming a polymer chain that has 2 carbon-carbon bonds per repeat unit
- derived from random walk chain statistics
  - Where *l* is the bond length in the polymer backbone
  - M_c is the molecular weight between cross-links
  - M_0 is the molecular weight per repeat unit
  - Where C_n is the characteristic ratio for the polymer chain

Eqn 4 $$\xi = \frac{\left(\bar{r}_0^2\right)^{1/2}}{\phi_{2,s}^{1/3}} = Q^{1/3}\left(\bar{r}_0^2\right)^{1/2} = C_n^{1/2} Q^{1/3} N^{1/2} l$$

- *Q* is the degree of swelling = $V_{\text{swollen polymer}}/V_{\text{dry polymer}}$
- *N* is the degree of polymerization between cross-links

- The mesh size is related to the diffusion constant of a solute in the network
- Eyring theory of diffusion:

Eqn 5 $$D = T\nu e^{-\frac{\Delta G^*}{kT}} = T\nu e^{-\frac{\Delta H^*}{kT}} e^{\frac{\Delta S^*}{k}}$$

  - Where ΔG^* is the activation energy, ΔH^* is activation enthalpy, and ΔS^* is activation entropy
  - N = translational oscillating frequency of solute molecule (jump rate!)
  - T = temperature
  - k = Boltzman constant
- The ratio of diffusion constant in the gel to that in solution is:

Eqn 6 $$\hat{D} = \frac{D_{gel}}{D_0} = \frac{e^{\frac{\Delta S^*_{gel}}{k}}}{e^{\frac{\Delta S^*_0}{k}}}$$

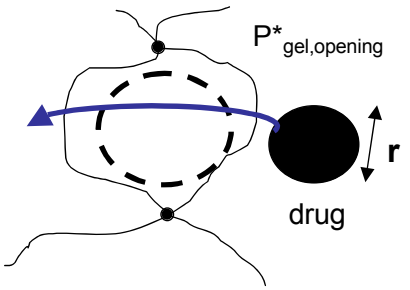
  - Where ΔS^*_{gel} is the activation entropy for diffusion in the gel and ΔS^*_0 is the activation entropy in for diffusion in the solvent
  - This assumes the activation enthalpy and oscillation frequencies for diffusion are approximately the same in the gel and pure solvent (reasonable for dilute and chemically inert systems)
- The activation entropies are:

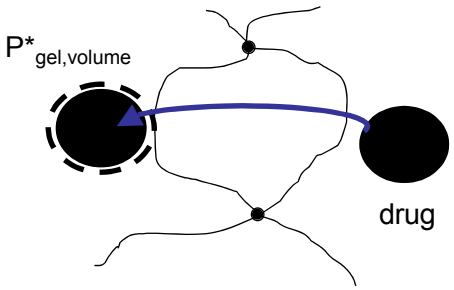
Eqn 7 $\Delta S^*_{gel} = k \ln P^* - k \ln P_0$

Eqn 8 $\Delta S^*_0 = k \ln P^*_0 - k \ln P_0$

Eqn 9
$$\hat{D} = \frac{P^*_{gel}}{P^*_0} = \frac{P^*_{gel,opening} P^*_{gel,volume}}{P^*_{0,volume}}$$

- Where P*volume is the probability that a solute-sized volume of free space exists to jump into
- P*opening is the probability that the network has a solute-sized gap to jump through





Eqn 10
$$P^*_{gel,opening} = \frac{\xi - r}{\xi} = 1 - \frac{r}{\xi}$$

- Where r is the size of the solute (drug) and ξ is the network mesh size

- The probability of a volume to jump into is an exponential of the ratio of the solute size to the available free volume per mole:

Eqn 11
$$P^*_{gel,volume} \sim e^{-\frac{v^*}{v_{free,gel}}}$$

Eqn 12
$$P^*_{0,volume} \sim e^{-\frac{v^*}{v_{free,1}}}$$

- Where vfree is the specific free volume and v* is the volume of the solute (drug)
- Refs for free volume theory applied here:
  - Yasuda et al. Makromol. Chem. 26, 177 (1969)
  - Peppas and Reinhart, J. Membrane Sci. 15, 275 (1983)

- Now:

Eqn 13
$$\frac{P^*_{gel,volume}}{P^*_{0,volume}} = e^{-\left(\frac{v^*}{v_{free,gel}} - \frac{v^*}{v_{free,1}}\right)}$$

- The free volume in a swollen gel is approximately vfree,1 since the free volume contribution from polymer is extremely low (2.5% even in solid polymers at 25°C)

Eqn 14 $v_{free,gel} = \phi_1 v_{free,1} + \phi_2 v_{free,2}$

- Therefore:

Eqn 15 $v_{free,gel} \sim \phi_1 v_{free,1} = (1-\phi_2) v_{free,1} = (1-1/Q) v_{free,1}$

- Where Q is the swelling degree = $V_{swollen\ gel}/V_{dry\ gel} = 1/\phi_2$

- Therefore:

Eqn 16
$$\frac{P^*_{gel,volume}}{P^*_{0,volume}} = e^{-\left(\frac{v^*}{(1-\frac{1}{Q})v_{free,1}} - \frac{v^*}{v_{free,1}}\right)} = e^{-\frac{v^*}{v_{free,1}}\left(\frac{1}{Q-1}\right)} \approx e^{-\left(\frac{1}{Q-1}\right)}$$

- $v^*/v_{free,1} \sim 1$ for most polymers, experimentally

- Therefore:

Eqn 17
$$\hat{D} \cong \left(1 - \frac{r}{\xi}\right) e^{\left[\frac{-1}{(Q-1)}\right]}$$

- And thus finally:

Eqn 18
$$D_{gel} \cong D_0 \left(1 - \frac{r}{\xi}\right) e^{\left[\frac{-1}{(Q-1)}\right]}$$

- Insulin: MW – 5900 g/mole; hydrodynamic radius = 16 Å

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