Chapter 8

Mathematical Models of Controlled Release

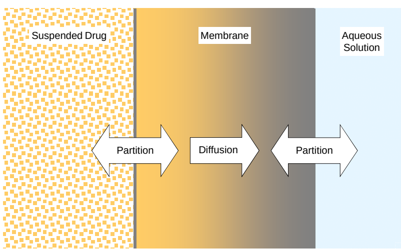
Solution-Diffusion Membranes

- Polymeric membranes can be used to control drug release
- Drug reservoir releases drug molecules by diffusion through the membrane or matrix
- Nonporous, homogeneous membranes
  - silicone rubber
  - polyethylene
  - nylon
  - etc.

Nonporous, Homogeneous Polymer Membranes

- Drug molecules from drug reservoir must partition into polymer membrane
- Drug molecules entering polymer membrane must diffuse through membrane (concentration gradient)
- Drug molecules in polymer membrane must then partition into aqueous medium

Solution-Diffusion Membranes



Solution-Diffusion Membranes

- Release of drug molecules occurs by a partition–diffusion–partition process
- Typically used for drugs with molecular weights < 400

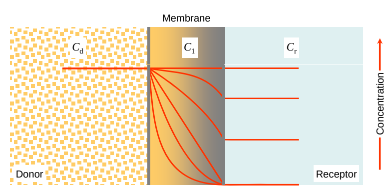
Diffusion through a Membrane

- Important phenomena in controlled drug release
  - Lag time
  - Burst effect
  - Diffusion through a polymer membrane
  - Diffusion through a polymer membrane under sink conditions

Diffusion through a Membrane

- Concentration on the donor side C_d of the polymer membrane remains constant
  - Saturated drug solution
  - Drug in suspension
- The concentration on the receptor side C_r is zero at $t = 0$
- Concentration in membrane C_1 is zero at $t = 0$ ($K = 1$)

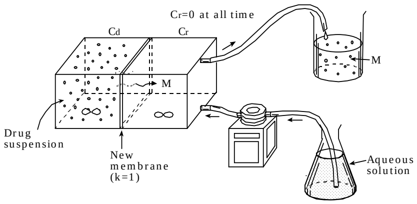
Diffusion through a Membrane



Diffusion through a Membrane under Sink Conditions

- Consider when contents of receptor compartment is continuously replenished with fresh solvent
  - Sink conditions (decrease to a lower level)
  - C_r is maintained at approximately zero

Diffusion through a Membrane under Sink Conditions

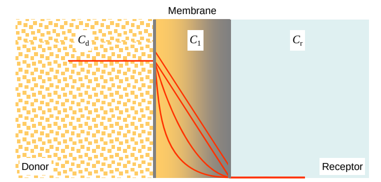


Diffusion through a Membrane under Sink Conditions

- C_d is constant (suspended drug)
- C_r is maintained at zero at all times
- A fresh, new polymer membrane is used

  ($C_1 = 0$ at $t = 0$, $K = 1$)

Diffusion through a Membrane under Sink Conditions



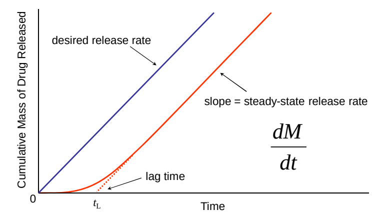
Diffusion through a Membrane under Sink Conditions

- As drug reaches other side of polymer membrane
  - Drug is released into receptor side under sink conditions
  - Concentration gradient at steady state is established
  - Concentration gradient inside membrane remains constant at all points

Lag Time

- It may take time for drug to appear from donor side to receptor side when fresh, new polymer membrane is used
- Drug is released at a constant rate into receptor side under sink conditions (steady state)
- Lag time is the time it takes to reach steady-state release rate

Lag Time



Lag Time

- Cumulative amount of drug released through membrane

$$M = S \cdot D \cdot K \frac{\Delta C}{h}(t - t_L)$$

Lag time may be expressed in terms of the diffusion coefficient and the membrane thickness

$$t_L = \frac{h^2}{6D} \Rightarrow M = S \cdot D \cdot K \frac{\Delta C}{h}\left(t - \frac{h^2}{6D}\right)$$

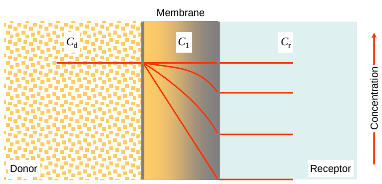
Lag Time

- Lag time may be calculated if the membrane thickness h and diffusion coefficient D are known
- Lag time may be determined experimentally
  - h may be determined if D is known
  - D may be determined if h is known

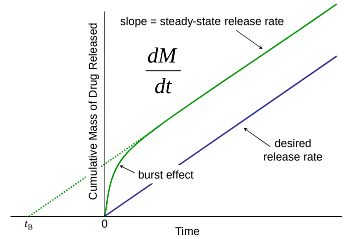
Burst Effect

- Polymer membrane saturated with drug
- Drug is released at a constant rate into membrane
- Concentration in membrane C_1 decreases
- Concentration in receptor side C_r decreases
- Initial release of drug into receptor side is at a higher rate than the steady-state release rate

Diffusion through a Polymer Membrane



Burst Effect



Burst Effect

- Cumulative amount of drug released through membrane

$$M = S \cdot D \cdot K \frac{\Delta C}{h}(t + t_B)$$

Burst effect may be expressed in terms of the diffusion coefficient and the membrane thickness

$$t_L = \frac{h^2}{3D} \Rightarrow M = S \cdot D \cdot K \frac{\Delta C}{h}\left(t + \frac{h^2}{3D}\right)$$

Effect of Diffusion Coefficient on Lag Time

- Polymer membrane thickness h = 100 μm
- Diffusion coefficient D = 1 x 10^{-7} cm^2/s
- Lag time?

$$t_L = \frac{h^2}{6D}$$

$$t_L = \frac{(100\,\mu m)^2}{6\left(1\times10^{-7}\,cm^2/s\right)} = 170\,s = 2.8\,min$$

100 μm = 0.01 cm

Effect of Diffusion Coefficient on Lag Time

- Polymer membrane thickness h = 100 μm
- Diffusion coefficient D = 1 x 10^{-10} cm^2/s
- Lag time?

$$t_L = \frac{h^2}{6D}$$

$$t_L = \frac{(100\,\mu m)^2}{6\left(1\times10^{-10}\,cm^2/s\right)} = 170000\,s = 1.9\,d$$

Effect of Diffusion Coefficient on Lag Time

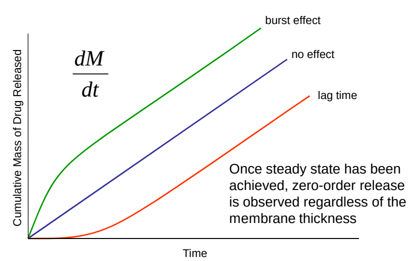
- Diffusion coefficient D = 1 x 10^{-9} cm^2/s
- Polymer membrane thickness h = 10 μm, 100 μm, 1000 μm, or 10000 μm
- Lag time?

Membrane Thickness	Lag Time (t_L)
10 μm	170 s = 2.8 d
100 μm	170000 s = 280 min = 4.6 h
1000 μm	1.7 × 10^6 s = 460 h = 19 d
10 000 μm	1900 d = 5.3 y

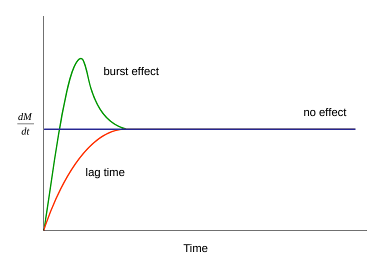
Effect of Membrane

- Thickness may be used to control the lag time of drug release (from seconds to days to weeks)
- Expect membrane to be saturated with drug (time between manufacturing and use may be up to a year or more)
- Burst effect is to be expected
- Initial release rate will be greater than desired release rate

Zero-Order Release Rate



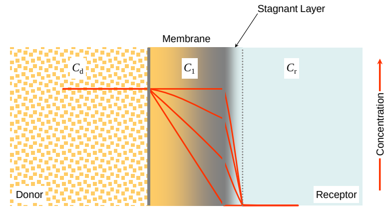
Release Rate



Boundary Layer Effect

- Bulk solution in receptor side is not well mixed (typical situation)
- Stagnant layer exists immediately adjacent to membrane
- Hydrophobic (water insoluble) drugs can reach drug solubility in aqueous solution
  - Boundary layer
  - Drug diffusion through boundary layer is a rate-limiting step

Boundary Layer Effect



Boundary Layer Effect

- Drug diffuses through boundary layer before being mixed into bulk solution
- Boundary layer acts as second membrane retarding release of drug
- Boundary layers are highly likely in the body where mixing is poor
- Drug release rate is independent of membrane thickness if boundary layer effect is significant (change surface area to change release rate)