

## Chapter 8

### Mathematical Models of Controlled Release

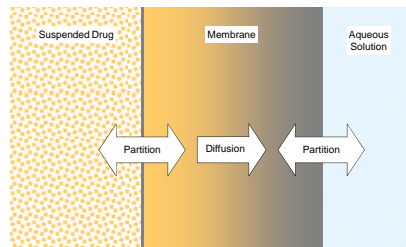
#### Solution-Diffusion Membranes

- 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

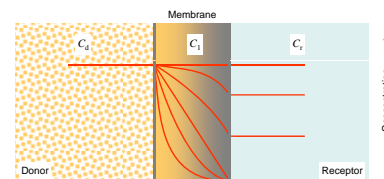
#### Diffusion through a Membrane

- 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  $t = 0$  ( $K = 1$ )

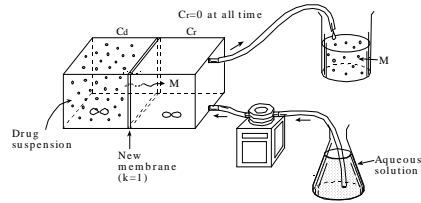
#### Diffusion through a Membrane



#### 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

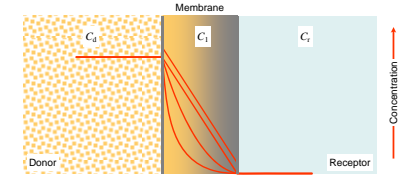
### Diffusion through a Membrane under Sink Conditions



### 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



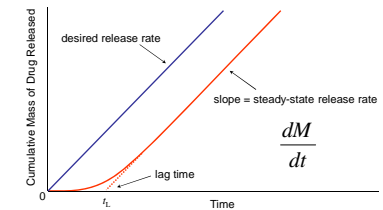
### Diffusion through a Membrane under Sink Conditions

- 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

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

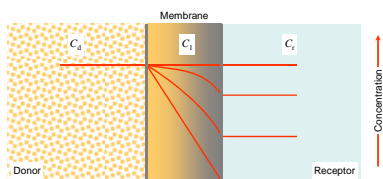
### Lag Time

- 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

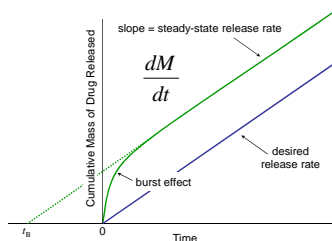
### Burst Effect

- 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  $h = 100 \mu\text{m}$
- Diffusion coefficient  $D = 1 \times 10^{-7} \text{ cm}^2/\text{s}$
- Lag time?

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

$$t_L = \frac{(100 \mu\text{m})^2}{6(1 \times 10^{-7} \text{ cm}^2/\text{s})} = 170 \text{ s} = 2.8 \text{ min}$$

$100 \mu\text{m} = 0.01 \text{ cm}$

## Effect of Diffusion Coefficient on Lag Time

- Polymer membrane thickness  $h = 100 \mu\text{m}$
- Diffusion coefficient  $D = 1 \times 10^{-10} \text{ cm}^2/\text{s}$
- Lag time?

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

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

## Effect of Diffusion Coefficient on Lag Time

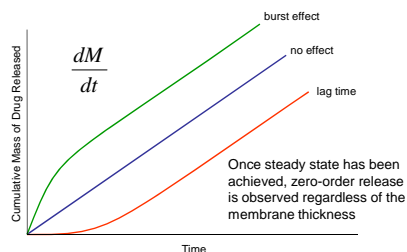
- Diffusion coefficient  $D = 1 \times 10^{-9} \text{ cm}^2/\text{s}$
- Polymer membrane thickness  $h = 10 \mu\text{m}$ ,  $100 \mu\text{m}$ ,  $1000 \mu\text{m}$ , or  $10000 \mu\text{m}$
- Lag time?

Membrane Thickness	Lag Time ( $t_L$ )
$10 \mu\text{m}$	$170 \text{ s} = 2.8 \text{ d}$
$100 \mu\text{m}$	$170000 \text{ s} = 280 \text{ min} = 4.6 \text{ h}$
$1000 \mu\text{m}$	$1.7 \times 10^6 \text{ s} = 460 \text{ h} = 19 \text{ d}$
$10000 \mu\text{m}$	$1900 \text{ d} = 5.3 \text{ y}$

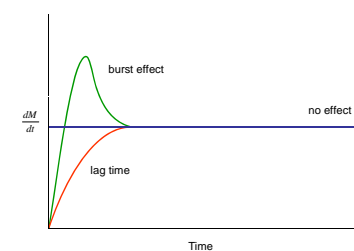
## Effect of Membrane

- 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



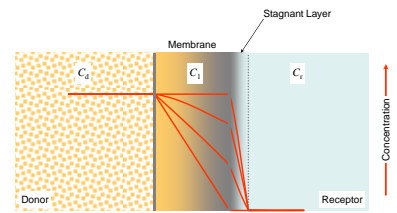
## Release Rate



### 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)