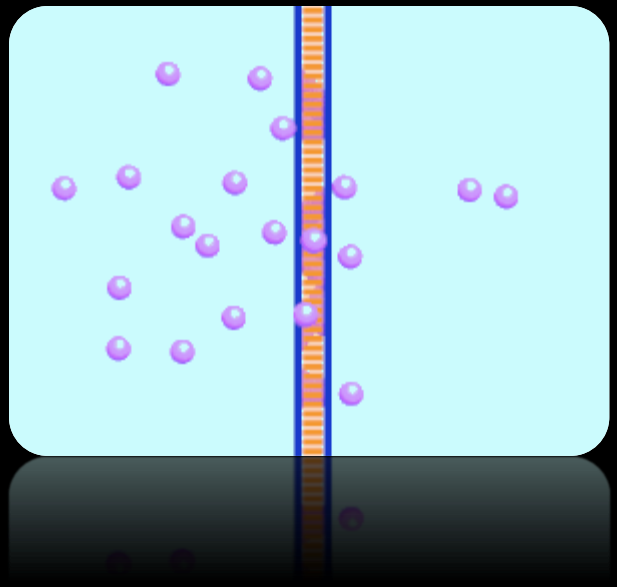
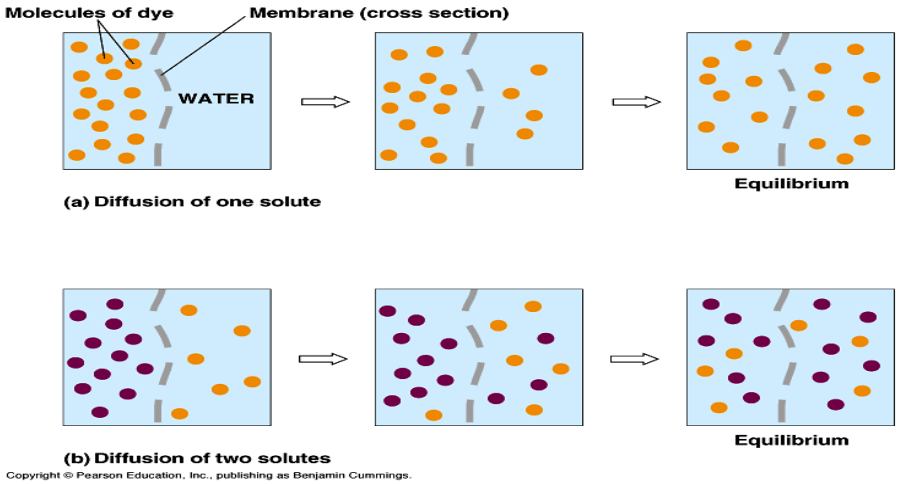
Chapter 11

Diffusion



Definition

- *Diffusion* is defined as a process of mass transfer of individual molecules of a substance brought about by random molecular motion and associated with a driving force such as a concentration gradient



Diffusion Importance

- diffusion of a drug across a biologic membrane is required for a drug to be absorbed into and eliminated from the body, and even for it to get to the site of action within a particular cell
- Drug release from a variety of drug delivery systems Depends on diffusion

Diffusion Importance

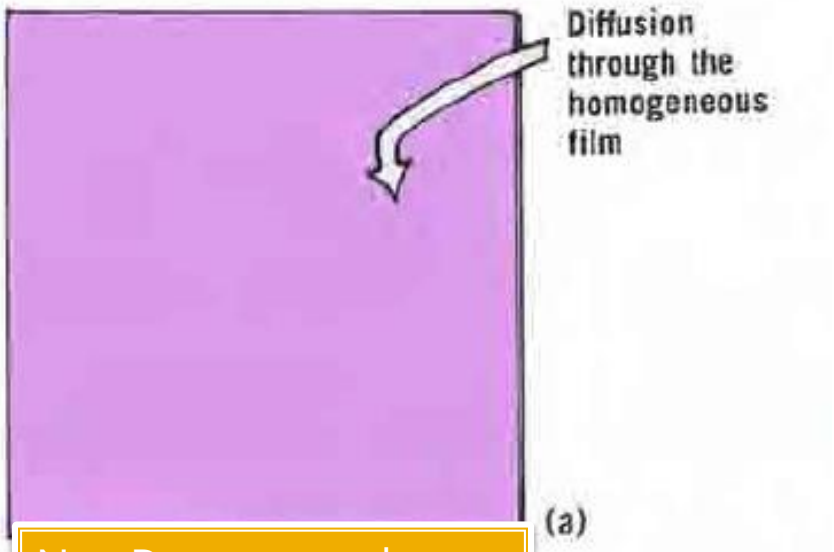
- Drug absorption, Elimination
- On the negative side, the shelf life of a drug product could be significantly reduced if a container or closure does not prevent solvent or drug loss or if it does not prevent the absorption of water vapor into the container

Diffusion Importance

- Diffusion also plays an important role in drug and nutrient transport in biologic membranes in the brain, intestines, kidneys, and liver

How to permeate through Polymeric membrane

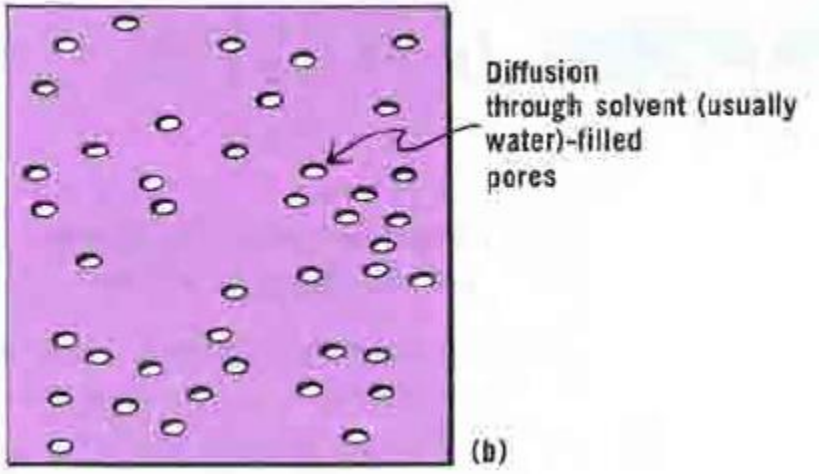
- Non Pours membrane: . Molecular diffusion or permeation through nonporous media depends on the solubility of the permeating molecules in the bulk membrane



Non Porous membrane

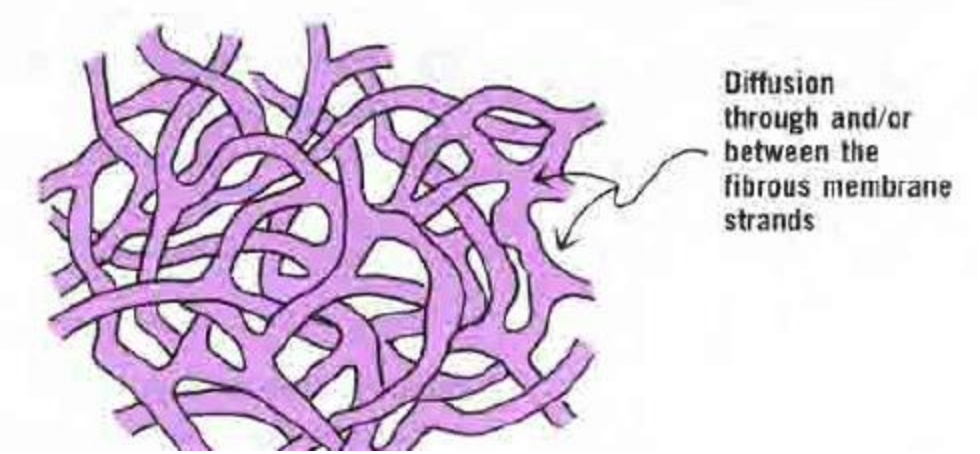
How to permeate through Polymeric membrane

- whereas a second process can involve passage of a substance through solvent-filled pores of a membrane
- It is influenced by the relative size of the penetrating molecules and the diameter and shape of the pores.



How to permeate through Polymeric membrane

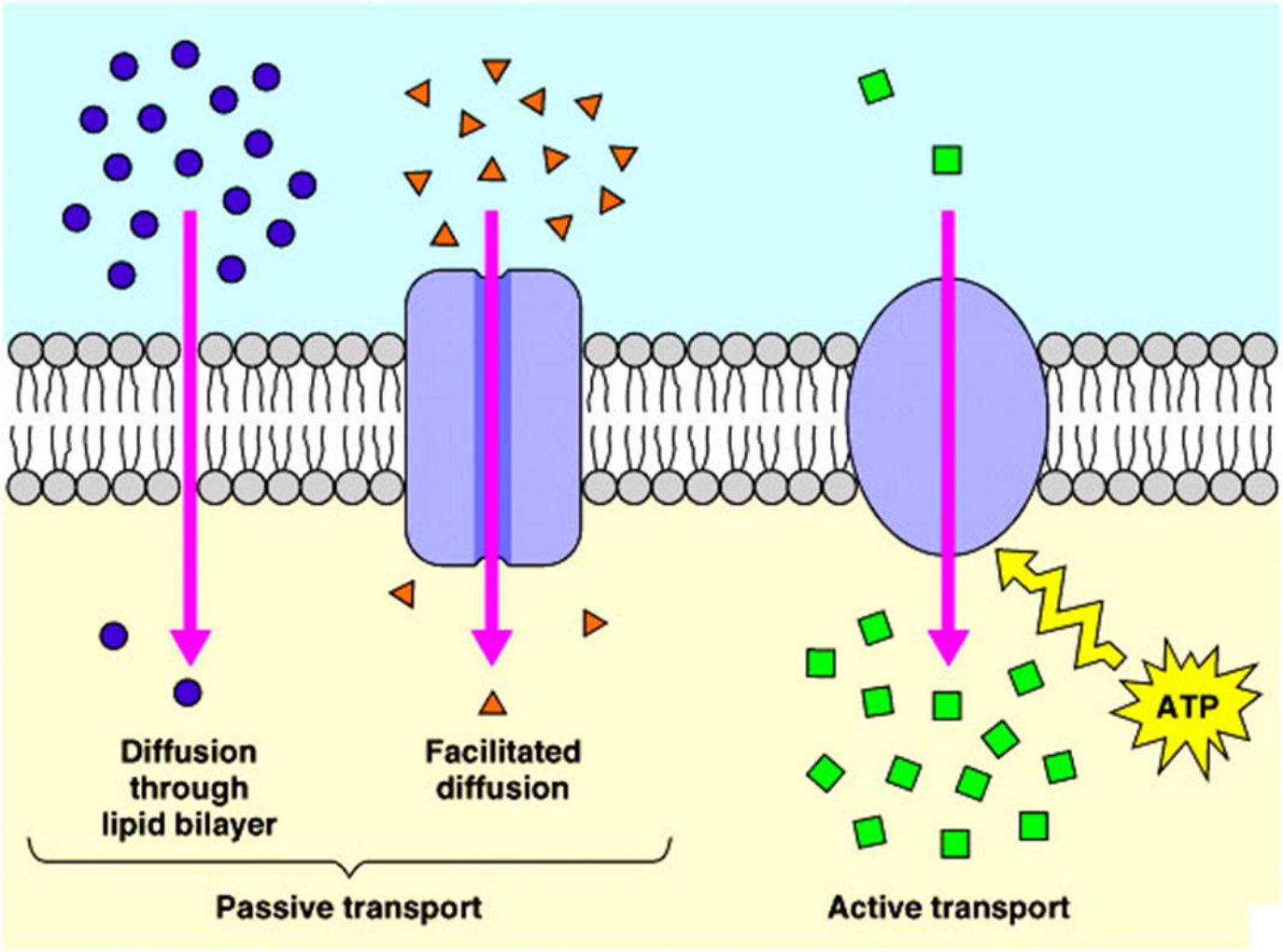
- 3rd diffusion of drug though polymer strands with branching and intersecting channels
- they may pass through the pores formed by the overlapping strands of polymer. If it is too large for such channel transport, the diffusant may dissolve in the polymer matrix and pass through the film by simple diffusion



Transport through membranes

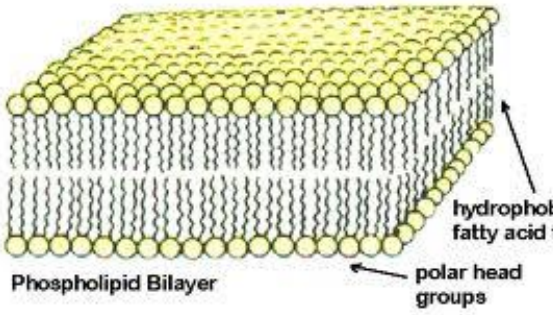
- passive diffusion
- energy-dependent carrier-mediated transport (active transport)
- energy- independent carrier-mediated transport (facilated diffusion) “large, polar molecules and ions”
- Membrane transporters are located in every organ responsible for the absorption, distribution, metabolism, and excretion (ADME) of drug substances

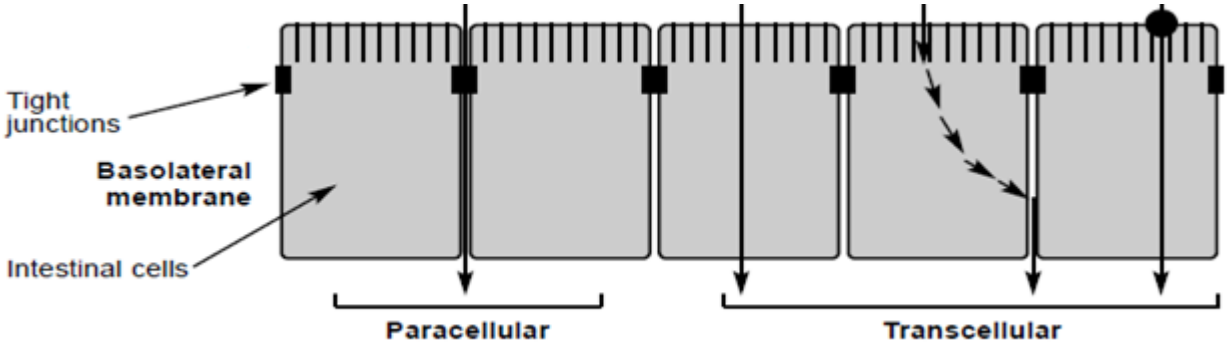
Figure 8.14 Review: A comparison of passive and active transport



Drug Absorption and Elimination

- Diffusion can occur through the lipoidal bilayer of cells. This is termed *transcellular diffusion*.
- On the other hand, paracellular diffusion occurs

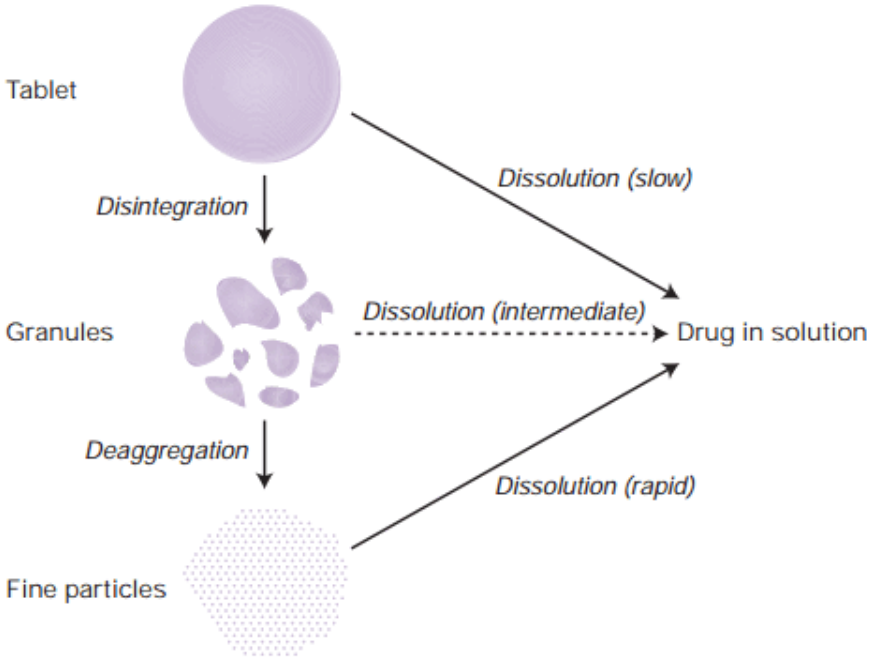




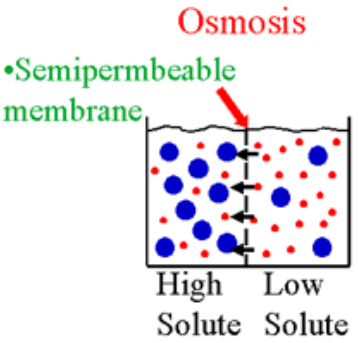
Elementary Drug Release

- ***Drug Release:*** is a very important process
- a multistep process that includes diffusion, disintegration, deaggregation, and dissolution.
- Drug release must occur before the drug can be pharmacologically active.
- This includes pharmaceutical products such as capsules, creams, liquid suspensions, ointments, tablets, and transdermal patches
- examples are the release of steroids such as hydrocortisone from topical over-the-counter creams and ointments for the treatment of skin rashes
- the release of acetaminophen from a tablet that is taken by mouth.

drug release



Osmotic drug Release



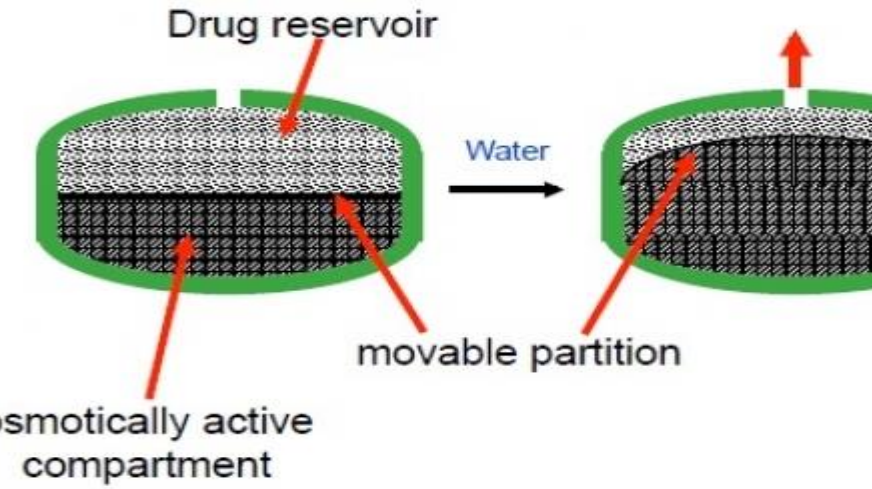
- *Osmosis* was originally defined as the passage of solvent across a semipermeable membrane
- The passage of solute together with solvent is now called *dialysis*.
- Osmotic drug release systems use osmotic pressure as a driving force for the controlled delivery of drugs. A simple osmotic pump

Osmotic drug release

- A simple osmotic pump consists of an osmotic core (containing drug with or without an osmotic agent) and is coated with a semipermeable membrane. The semipermeable membrane has an orifice for drug release from the —pump.
- The dosage form, after coming in contact with the aqueous fluids, absorbs water at a rate determined by the fluid permeability of the membrane and osmotic pressure of core formulation.
- The osmotic absorbtion of water results in high hydrostatic pressure inside the pump, which causes the flow of the drug solution through the delivery orifice

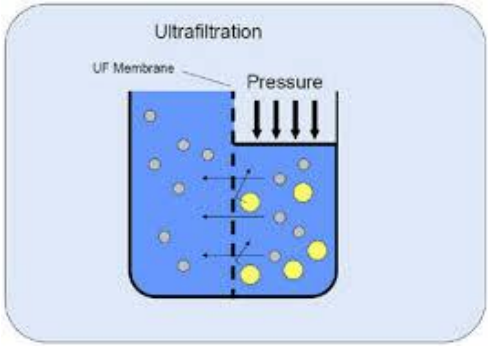
Osmotic drug release

- rigid tablet with a semi-permeable outer membrane and one or more small laser drilled holes in it. As the tablet passes through the body, water is absorbed through the semipermeable membrane via osmosis, and the resulting osmotic pressure is used to push the active drug through the opening in the tablet

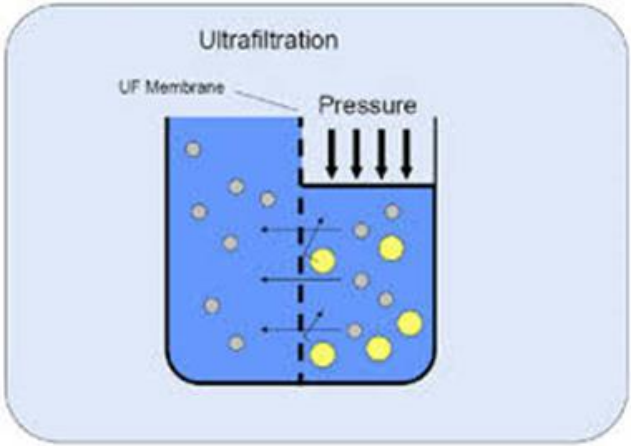


Ultrafiltration and Dialysis

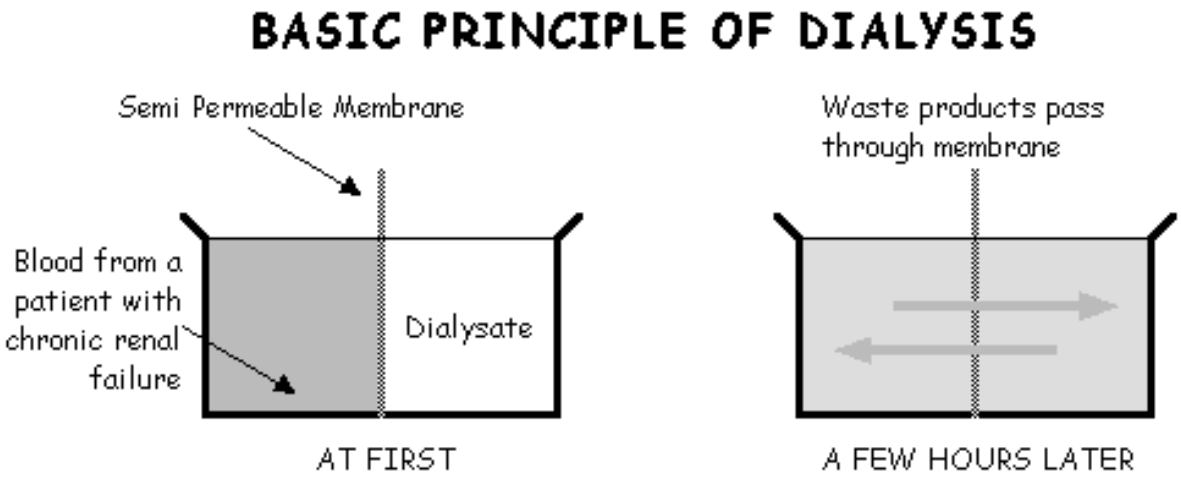
- Ultrafiltration is used to separate colloidal particles and macromolecules by the use of a membrane.
- Hydraulic pressure is used to force the solvent through the membrane, whereas the microporous membrane prevents the passage of large solute molecules
- Ultrafiltration is similar to a process called *reverse osmosis*, but a much higher pressure is developed in reverse osmosis



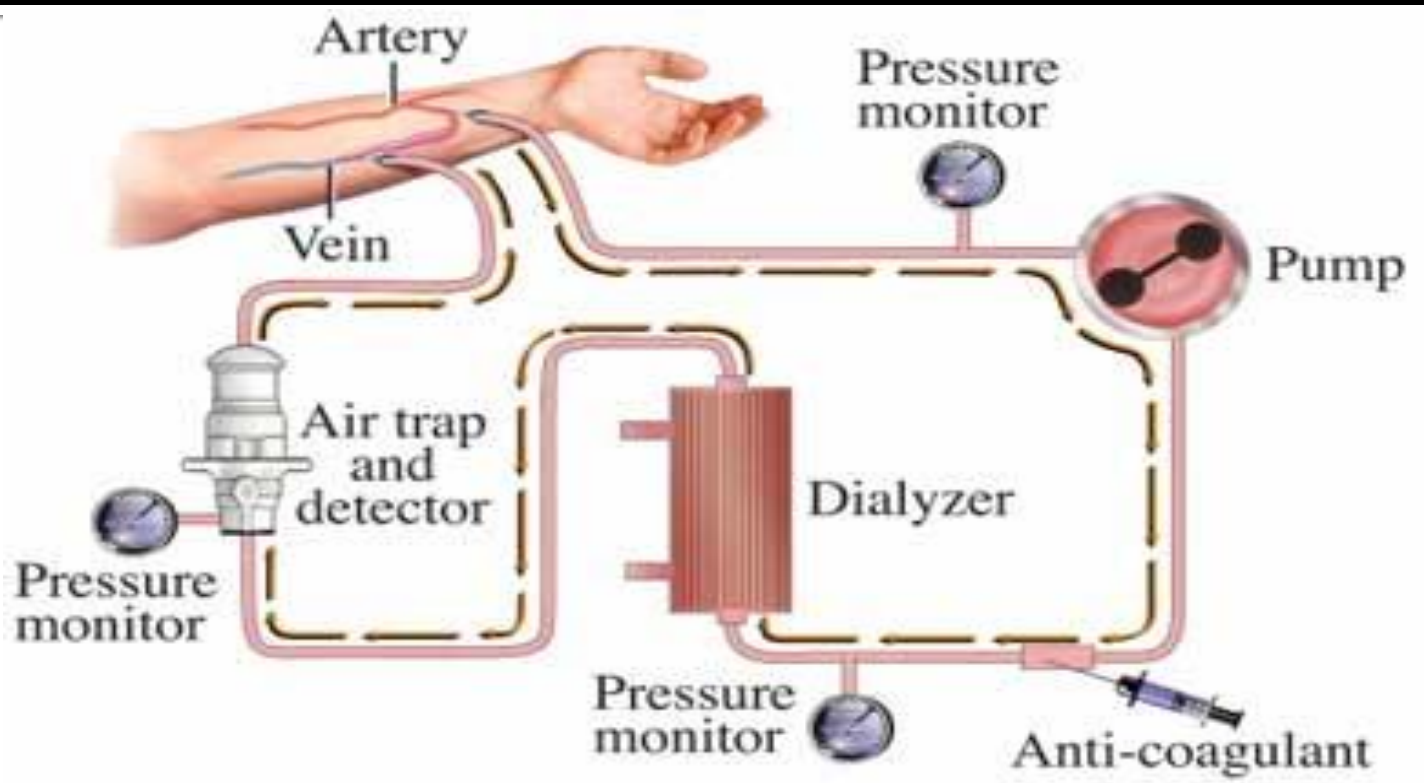
- *Microfiltration*, a process that employs membranes of slightly larger pore size, 100 nm to several micrometers, removes bacteria from intravenous injections, foods, and drinking water



- *Dialysis* as a separation process based on ability of passage of solutes through microporous membranes, carried out in batch or continuous mode (size)



- *Hemodialysis* is used in treating kidney malfunction to rid the blood of metabolic waste products (small molecules) while preserving the high-molecular-weight components of the blood


Artery
Vein
Pressure monitor
Pump
Air trap and detector
Dialyzer
Pressure monitor
Pressure monitor
Anti-coagulant

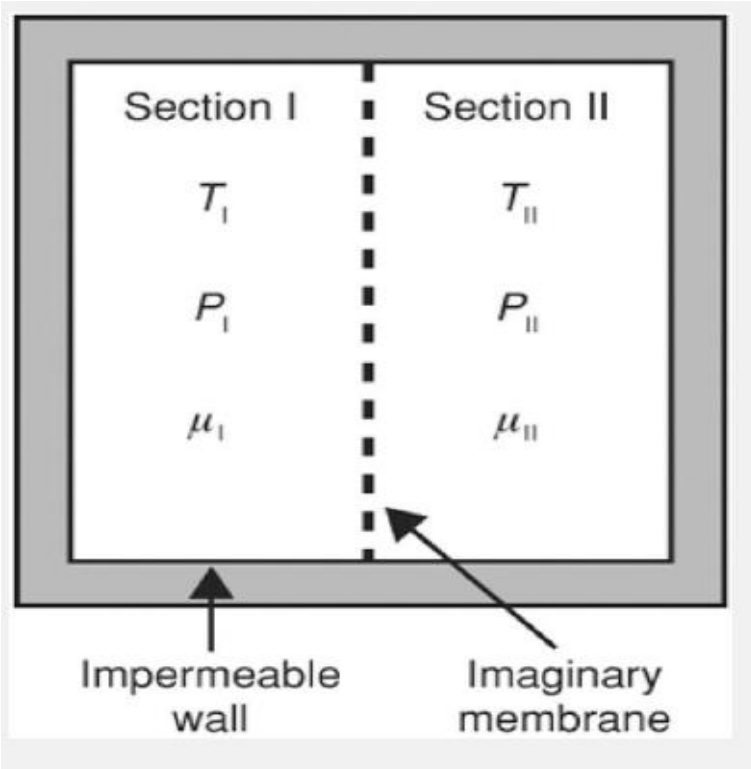
Diffusion is it Slow?

- Diffusion was proposed to happen with a speed of 0.0005cm/min
- Cell membrane thickness approx. 5nm thick
- It needs only a fraction of second to penetrate cell membrane
- For skin the thickness 3000nm it needs 600 times longer (lag time)

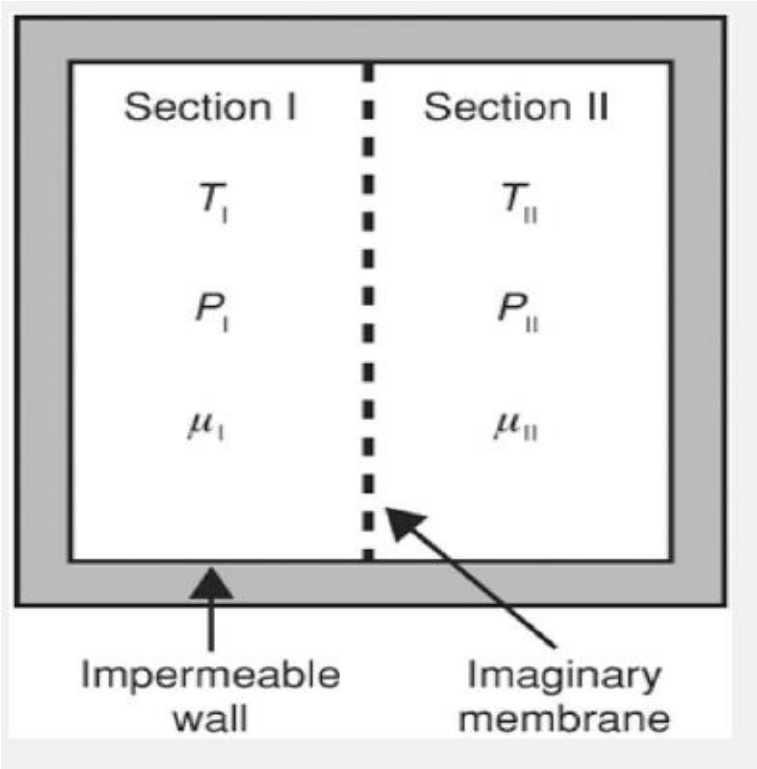
Steady-State Diffusion
Thermodynamic Basis

- Diffusion is a mass transfer process in response to a driving force (concentration gradient)
- Mass transfer is a kinetic process, occurring in systems that are not in equilibrium.
- Systems always move towards thermodynamic equilibrium

- Lets consider an isolated system
- Two compartments A, B, seperated by Permeable membrane
- At equilibrium , the temperatures, T, pressures, P, and chemical potentials, μ, of species A are equal in the two sections.

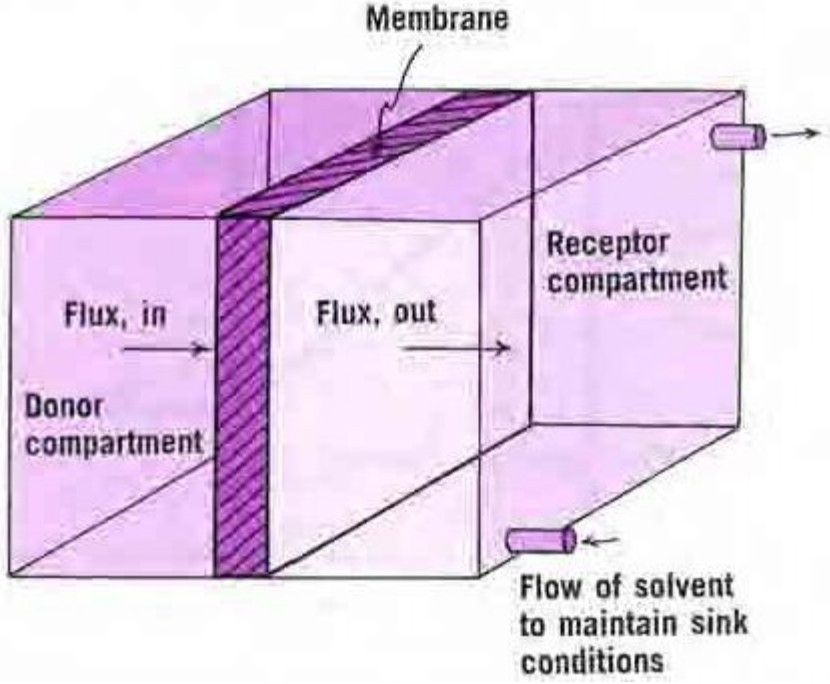


- Increase conc at any compartment will increase its chemicalpotential and affect the equilibrium of the system
- A new thermodynamic equilibrium should be achieved
- Diffusion will occur to reestablish equilbirium



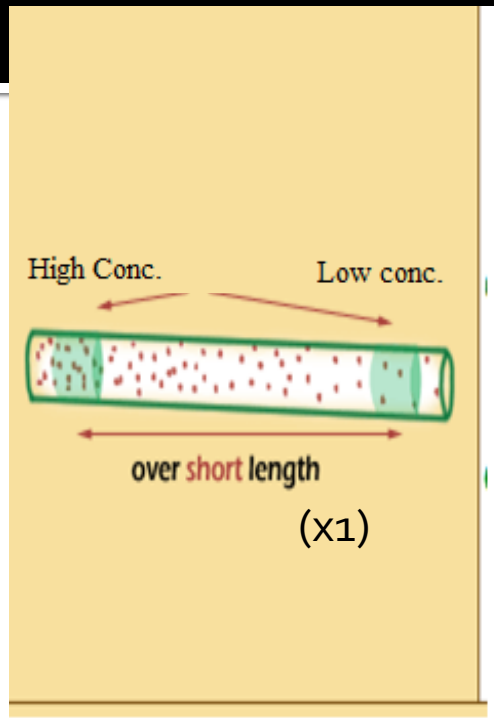
Fick's 1st Law of Diffusion

- Consider the diffusant originally dissolved in the left side compartment of the cell , solvent alone is placed on the right side of the barrier, the solute diffuses through the central barrier from solution to solvent side
- High Conc ⟹ Low Conc
- As we travel with distance x towards x axis

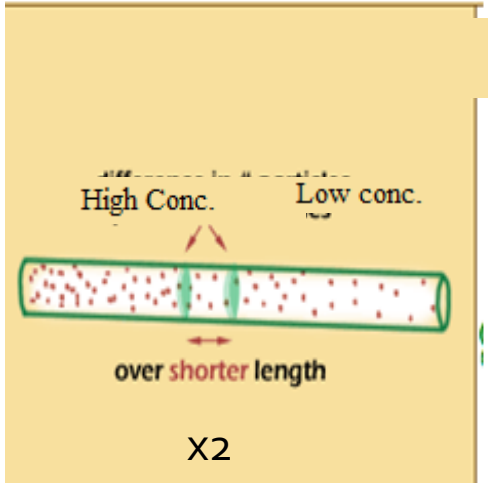


Concentration gradient:
Change in concentration of solute while travelling a unit length from the region of higher concentration to the region lower concentration within a system. Hence:

concentration gradient = dC/dx



$$\frac{C_{right} - C_{left}}{x_{right} - x_{left}} = \frac{\Delta C}{\Delta x}$$



$$\frac{C_{right} - C_{left}}{x_{right} - x_{left}} = \frac{\Delta C}{\Delta x}$$

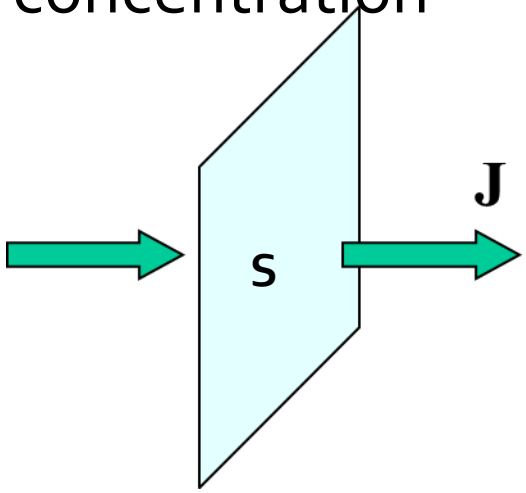
Fick's 1st Law of Diffusion

- Flux (*J*): The amount (M) of material flowing through a unit cross section, *S*, of a barrier in unit time, *t*, equals:

$$J = \frac{dM}{S \cdot dt}$$

- The flux, in turn, is proportional to the concentration gradient, *dC/dx*

$$J = -D\frac{dC}{dx}$$



- J: is flux (g/cm^2.sec)
- M: is the amount of material flowing (g)
- S: is cross sectional area of flow (cm^2)
- t: is time (sec)
- D: is the diffusion coefficient of the drug in cm^2/sec
- dC/ dx: is the concentration gradient
- C: concentration in (g/cm3)
- X: distance in cm of movement perpendicular to the surface of the barrier
- (-) towards decrease in concentration

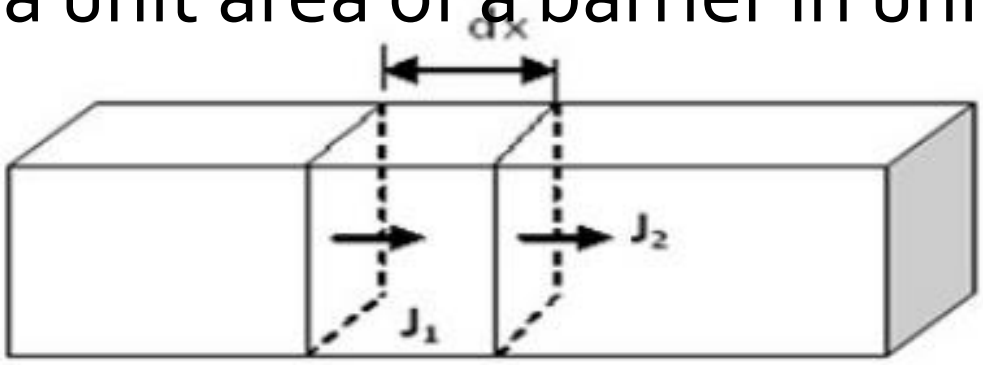
Notes on Fick's first law

- The negative sign of equation signifies that diffusion occurs in a direction opposite to that of increasing concentration
- *D* is affected by concentration, temperature, pressure, solvent properties, and the chemical nature of the diffusant. Therefore, *D* is referred to more correctly as a *diffusion coefficient* rather than as a constant.

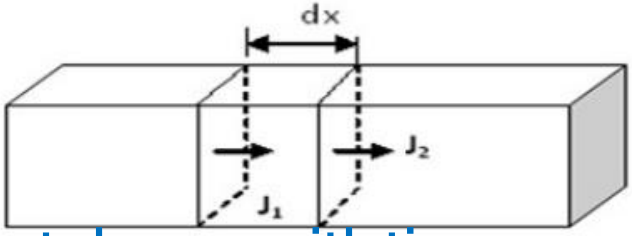
Fick's Second Law

- 1st Law $J = \frac{dM}{S \cdot dt}$
- Fick's Second Law
- An equation for mass transport that emphasizes the change in flux with time at a definite location rather than the mass diffusing across a unit area of a barrier in unit time is

(flux is not always constant):



Fick's second law:



The concentration of diffusant in the volume element changes with time, that is, $\Delta C/\Delta t$, *as* the flux or amount diffusing changes with distance, $\Delta J/\Delta x$, *in the x direction*

$$\frac{dC}{dt} = -\frac{dJ}{dx}$$

diffusion flux and the concentrations change with time. and distance

Differentiating the equation $J = -D\frac{dC}{dx}$

$$-\frac{dJ}{dx} = D\frac{d^2C}{dx^2}$$

$$\frac{dC}{dt} = D\frac{d^2C}{dx^2}$$

J: is flux (g/cm^2.sec)
M: is the amount of material flowing (g)
S: is cross sectional area of flow (cm^2)
t: is time (sec)
D: is the diffusion coefficient of the drug in cm2/sec
dC/ dx: is the concentration gradient (g/cm4)
C: is concentration

The Change in flux at a particular distance is proprtional to change of concentration diffusant within time

Summary

- **Flux**: is the rate of flow of molecules across a given surface.
- Flux is in the direction of decreasing concentration.
- Flux is always a positive quantity
- Flux equal zero (diffusion stop) when the concentration gradient equal zero.

Diffusion coefficient also called diffusivity. It is affected by:

- ✓ Chemical nature of the diffusant drug.
- ✓ Solvent properties.
- ✓ Temperature
- ✓ Pressure
- ✓ Concentration

Fick's first law

$$J = \frac{dM}{S \bullet dt} \qquad J = -D\frac{dC}{dx}$$

rate of diffusion through unit area

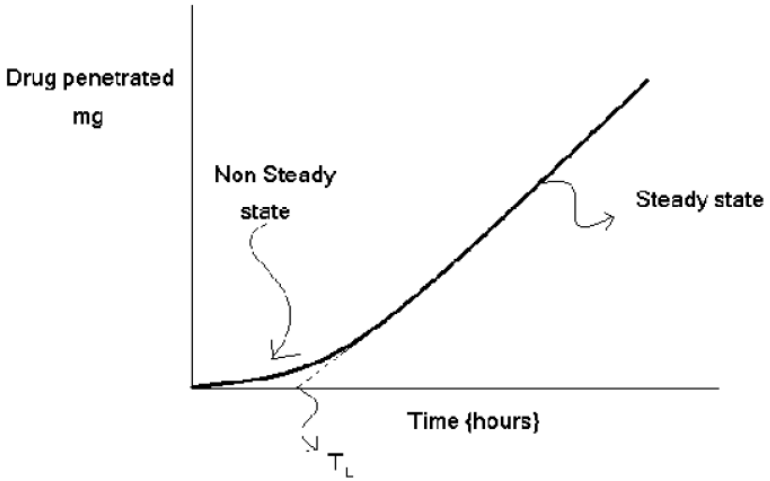
Fick's second law

$$\frac{dC}{dt} = D\frac{d^2C}{dx^2}$$

change in concentration of diffusant with time at any distance

Steady state

- Fick's first law, equation gives the flux (or rate of diffusion through unit area) in the steady state of flow
- The second law refers in general to a change in concentration of diffusant with time at any distance, *x* (i.e., a nonsteady state of flow).



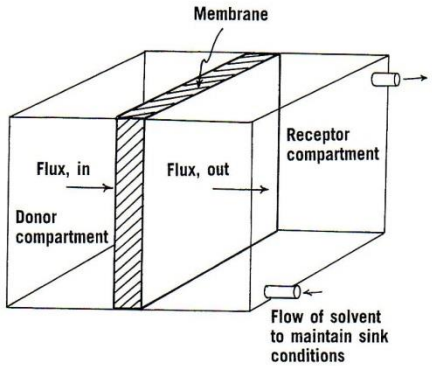


Fig. 12–3. Diffusion cell. The donor compartment contains diffusant at concentration *C*.

Steady state (flux is constant)

$$J = \frac{dM}{S \bullet dt} \qquad J = -D\frac{dC}{dx}$$

Fick's 1st law
Flux is constant
Steady state

- Steady state Could be described by fick's 2nd law
- At the steady state at each there no change in the concentration of the diffusant with time through the barrier.

$$\frac{dC}{dt} = -\frac{dJ}{dx} = 0 \qquad \frac{dC}{dt} = D\frac{d^2C}{dx^2} = 0$$

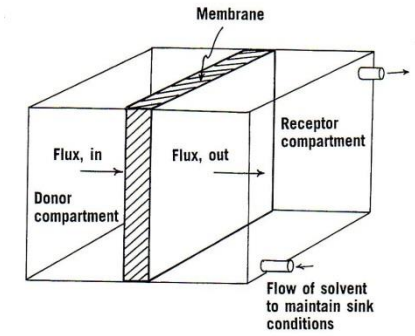


Fig. 12–3. Diffusion cell. The donor compartment contains diffusant at concentration *C*.

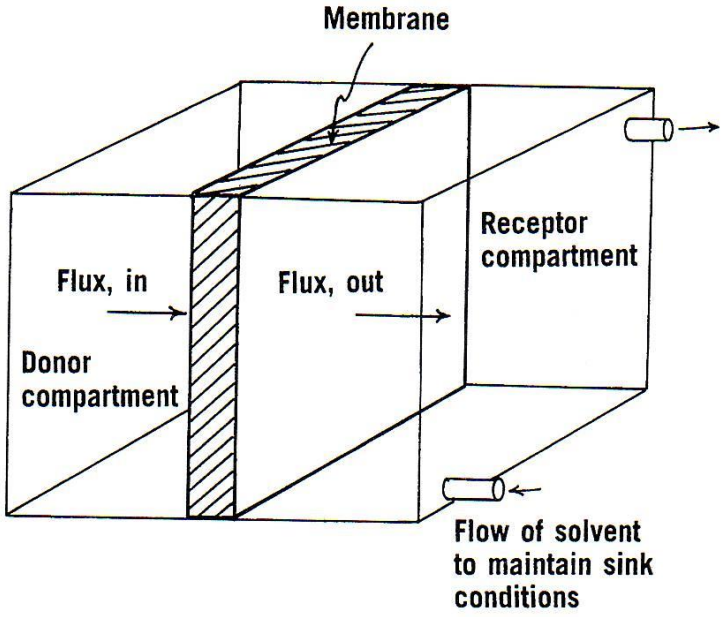
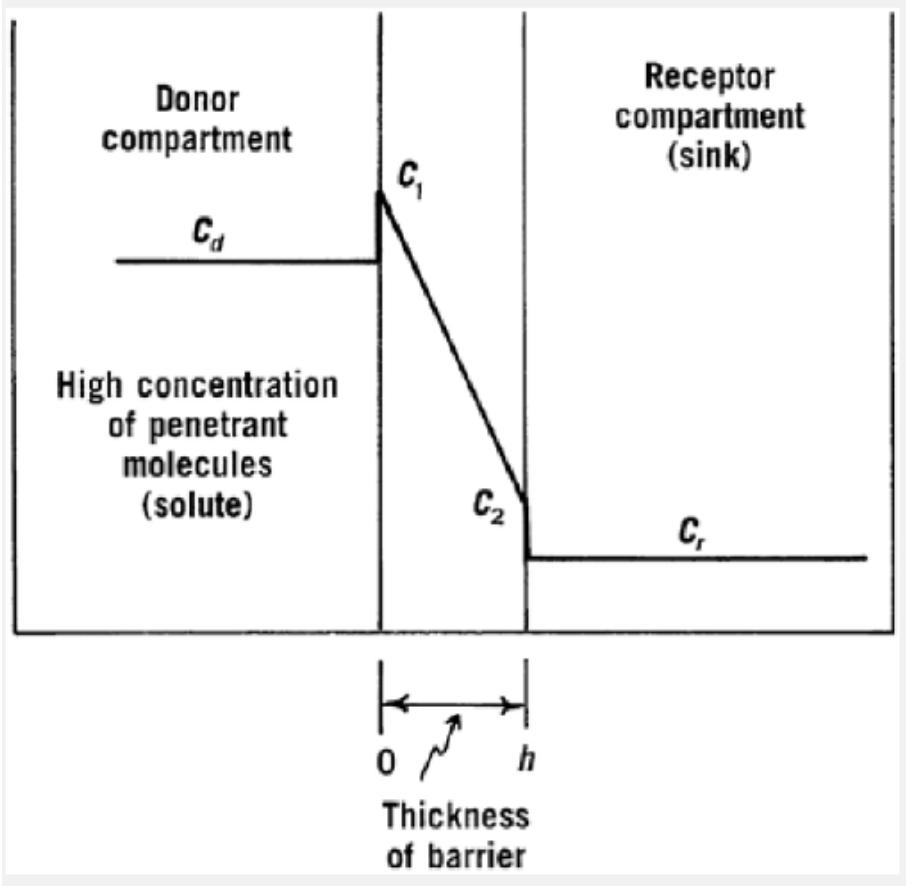


Fig. 12–3. Diffusion cell. The donor compartment contains diffusant at concentration *C*.

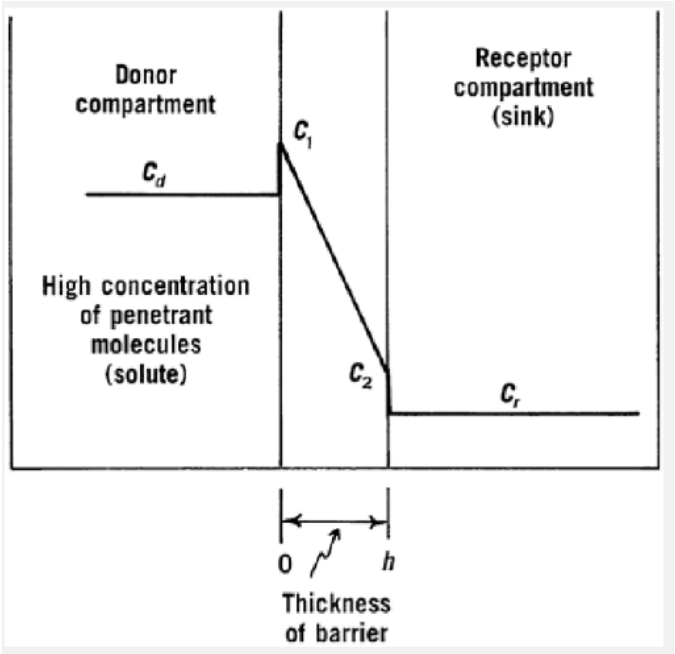


$$\frac{dC}{dt} = D\frac{d^2C}{dx^2} = 0$$

Concentration will not be rigidly constant, but rather is likely to vary slightly with time, and then *dC/dt is not exactly zero. The conditions are referred to as a* ***quasistationary state***, and little error is introduced by assuming steady state under these conditions.

Diffusion Through Membranes
Steady state diffusion through a thin film with thickness =h

- Diffusion across a thin film. The solute molecules diffuse from the well-
- mixed higher concentration, *C*1, to the well-mixed lower concentration, *C*2. The concentrations on both sides of the film are kept constant. At steady state, the concentrations remain constant at all points in the film. The concentration profile inside the film is linear, and the flux is constant.



Diffusion

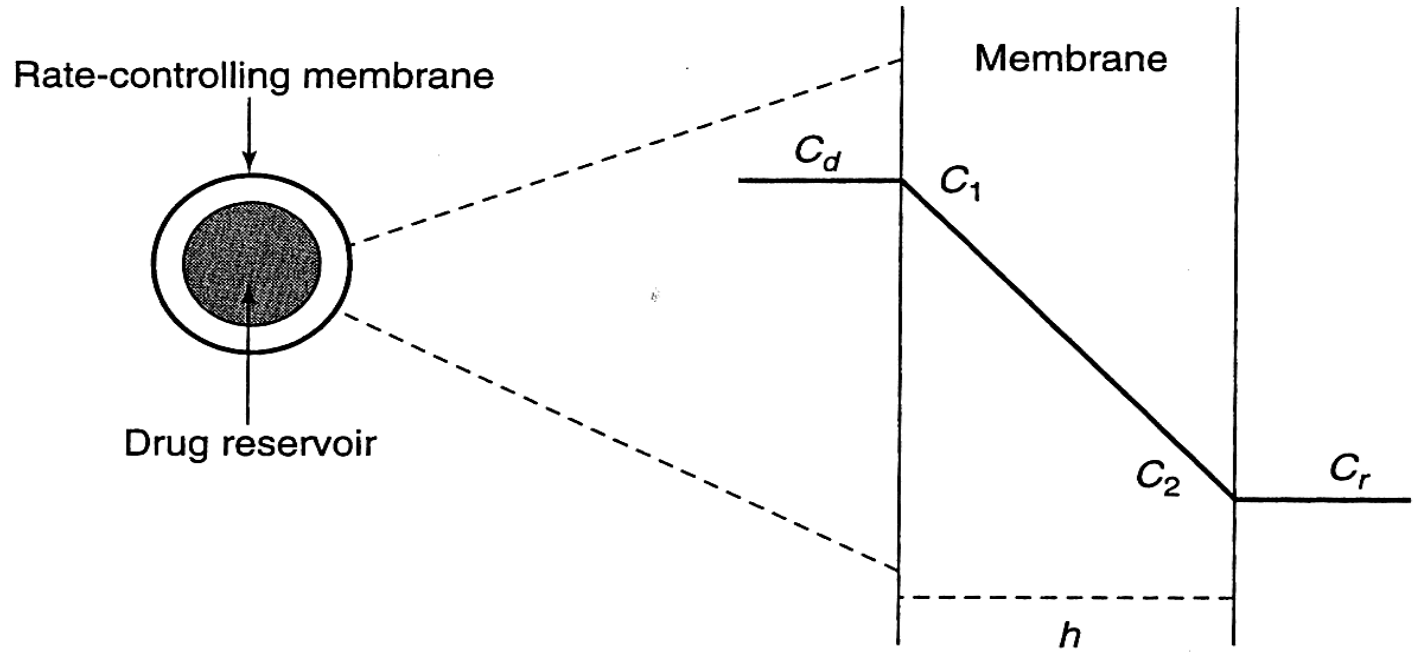
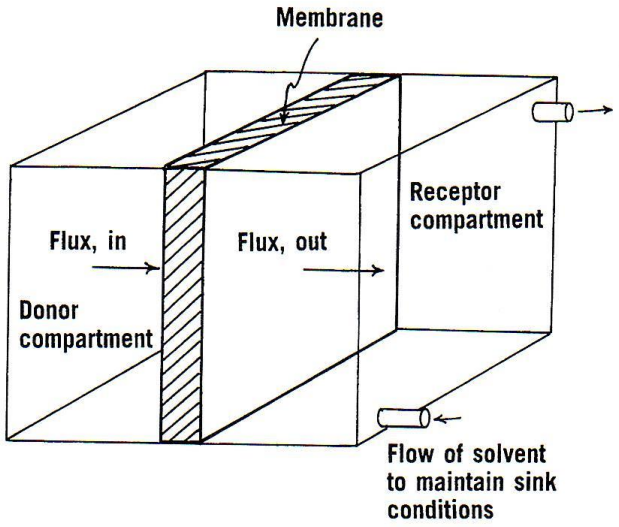


FIGURE 9-6 Diagrammatic representation of drug release from a diffusional reservoir system.



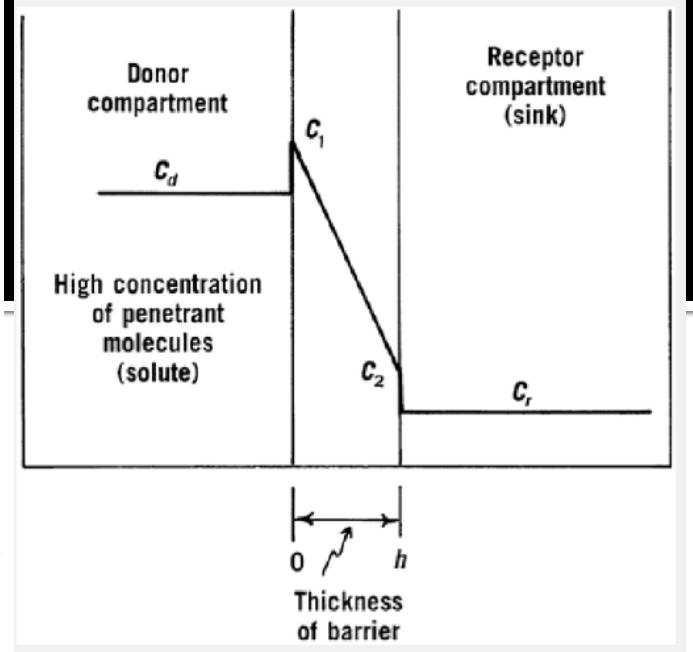
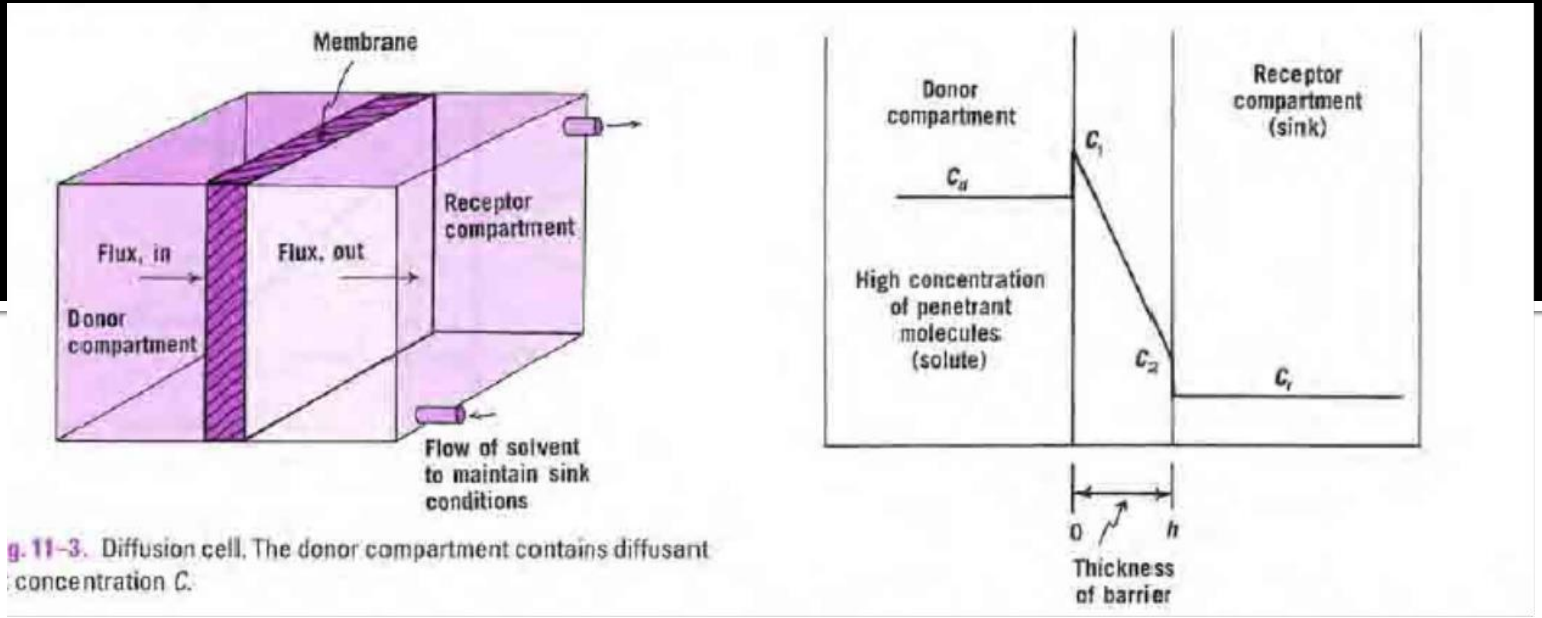


Fig. 12–3. Diffusion cell. The donor compartment contains diffusant at concentration *C*.

- If a membrane separates the two compartments of a diffusion cell of a cross sectional area S and thickness h, and if the concentrations in the membrane on the donor C1 and on thereceiver C2 respectively
- the diffusate concentration will fall in the donor compartment and will increase in
- the receiver one until the system come to equilibrium



g. 11-3. Diffusion cell. The donor compartment contains diffusant concentration C.

$$J = \frac{dM}{S \bullet dt} \qquad J = -D\frac{dC}{dx}$$

- Fick's law could be written

$$J = \frac{dM}{S \cdot dt} = D\left(\frac{C_1 - C_2}{h}\right)$$

If

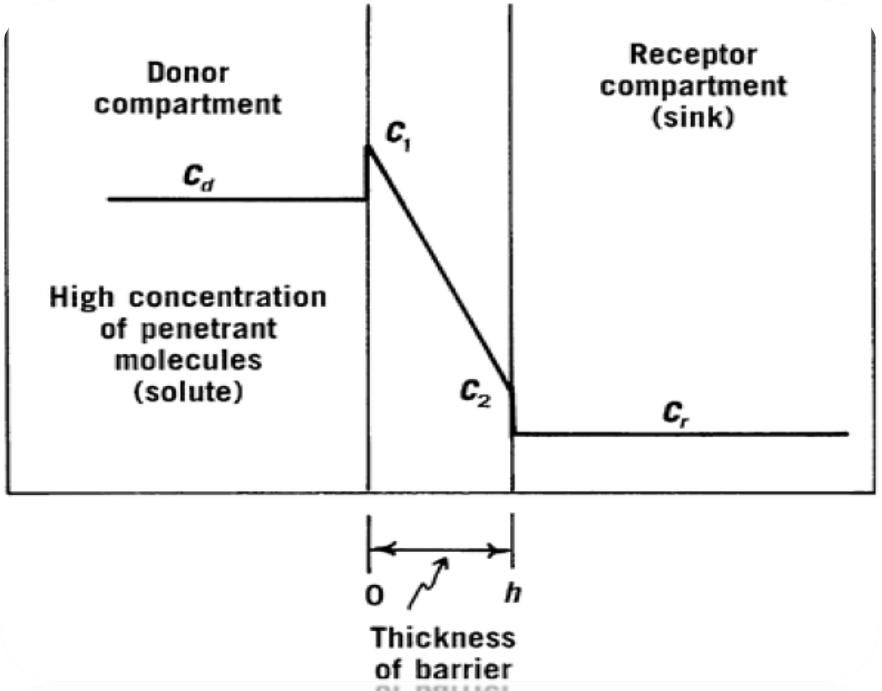
$$\frac{h}{D} = R$$

$$J = \frac{C1 - C2}{R}$$

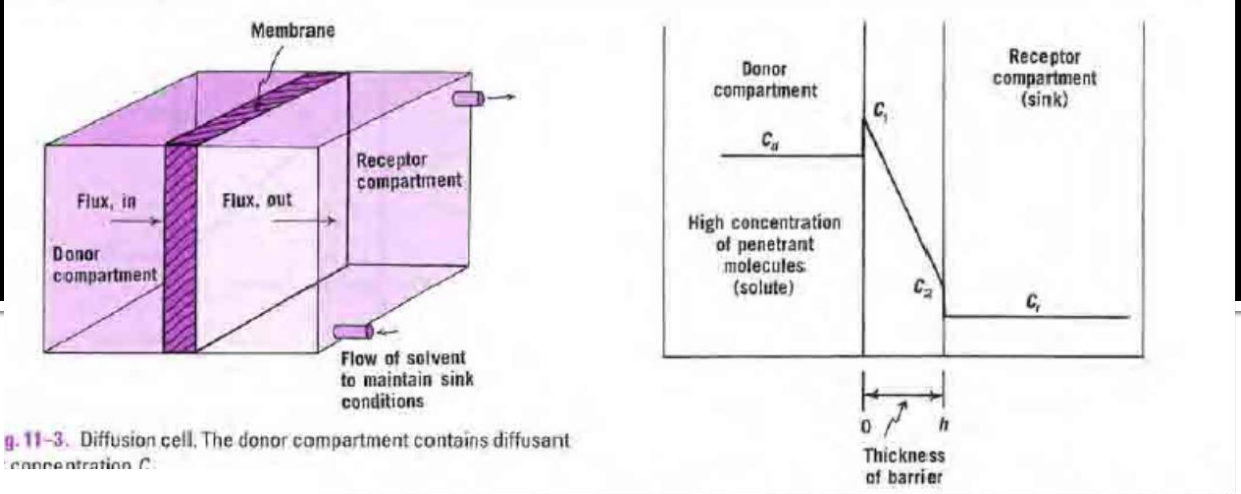
R: diffusional Resistance

The membrane can have a partition coefficient that affects the concentration of the diffusant inside it.

Therefore the concentration inside the membrane is a function of the concentration at the boundary and the partition coefficient of the membrane.



- The Concentration at the boundaries of membrane is different because of membrane partition coefficient(C1,C2) : (when Cd=C1?)
- The concentrations C1 and C2 within the membrane ordinarily are not known but can be replaced by the partition coefficient multiplied by the concentration Cd on the donor side of the membrane or Cr on the receiver side as follows



g. 11–3. Diffusion cell. The donor compartment contains diffusant concentration C_1

$$J = \frac{dM}{S \cdot dt} = D\left(\frac{C_1 - C_2}{h}\right)$$

- The concentrations C1 and C2 within the membrane ordinarily are not known but can be replaced by the partition coefficient multiplied by the concentration Cd on the donor side of the membrane or Cr on the receiver side as follows
  - $K = \frac{C_1}{C_d} = \frac{C_2}{C_r}$. $C_1 = KC_d$, $C_2 = KC_r$

Membrane permeability

$$J = \frac{dM}{S \cdot dt} = D\left(\frac{C_1 - C_2}{h}\right)$$

C_1 : Conc. in the memb. at the donor side
C_2 : Conc. in the memb. at the receptor side

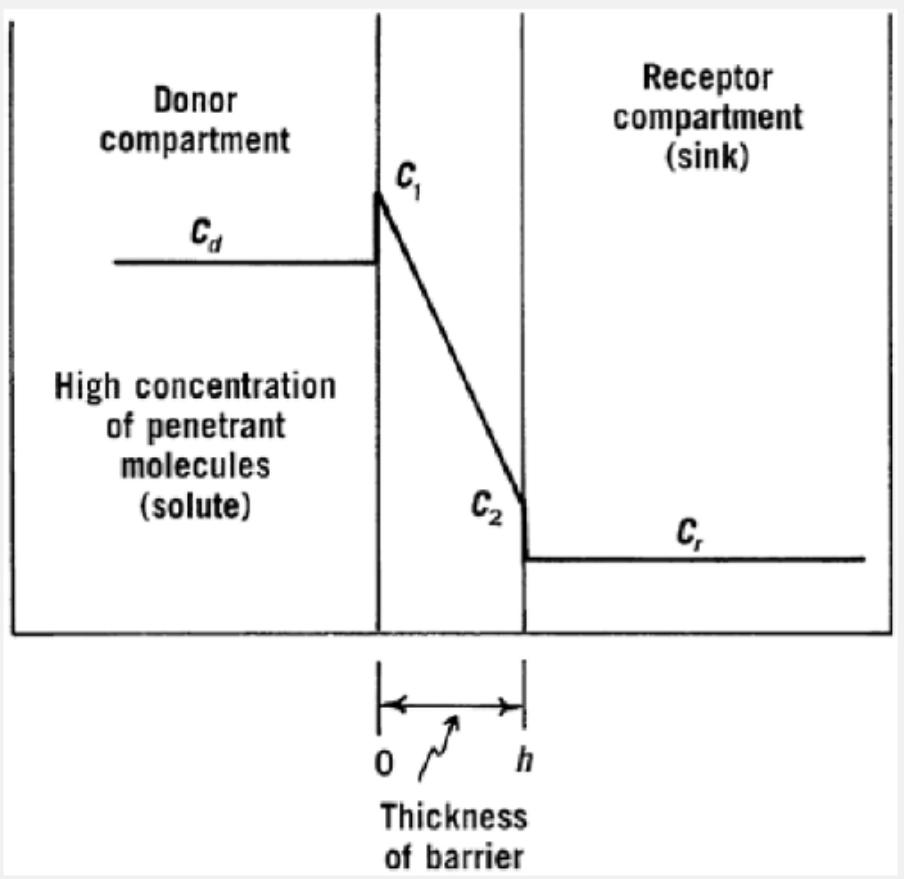
$$K = \frac{C1}{Cd} = \frac{C2}{Cr}$$

$$\frac{dM}{dt} = DSK\frac{Cd - Cr}{h}$$

$$\Rightarrow Cr = 0$$

Sink conditions cr=0

$$\frac{dM}{dt} = DSK\frac{Cd}{h}$$



Membrane permeability

$$\frac{dM}{dt} = DSK\frac{Cd}{h}$$

$$P = \frac{DK}{h}$$

$$\frac{dM}{dt} = PSCd$$

$$\frac{h}{D} = R$$

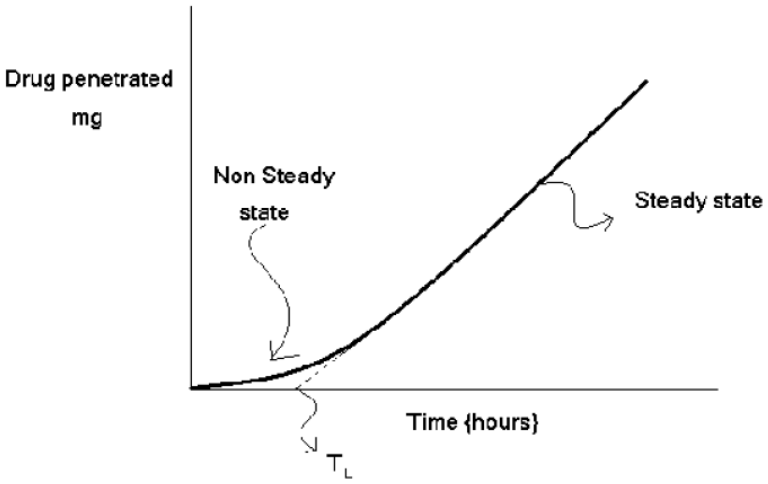
Where: R is diffusional resistance

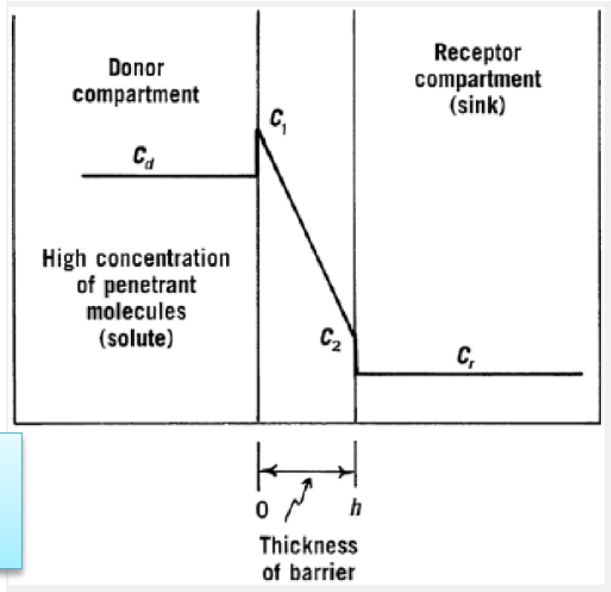
Where P is the permeability of the membrane in cm/sec.

P = *permeability coefficient* (cm/s)

- One can then obtain *P* from the slope of a linear plot of *M* versus *t*:

$$\frac{dM}{dt} = PSCd$$





provided that *C*d remains relatively constant throughout time.

$$\frac{dM}{dt} = PSCd$$

- If *C*d changes appreciably with time, one recognizes that *C*d = M_d/V_d, the amount of drug in the donor phase divided by the donor phase volume,and then one obtains *P* from the slope of log *C*d versus *t*:

$$\frac{dM}{dt} = PSCd$$

$$C_d = \frac{M_d}{V_d}$$

Diffusion

- **If the donor conc. changes with time,**

$$\log Cd_t = \log Cd(0) - \frac{PS}{2.303Vd}t$$

$$\ln Cd_t = \ln Cd(0) - \frac{PS}{Vd}t$$

$(C_d)_t$: donor conc. at any time
$(C_d)_0$: initial donor conc.
V_d : volume of the donor compartment (mL)

$$\frac{dM}{dt} = PSCd \qquad P = \frac{DK}{h}$$

Example : To study the oral absorption of paclitaxel(PCT) from an oil-water emulsion formulation, an inverted closed-loop intestinal model was used.

- surface area for diffusion = 28.4 cm^2
- concentration of PCT in intestine = 1.50 mg/ml.
- the permeability coefficient was 4.25 x 10^{-6} cm/s

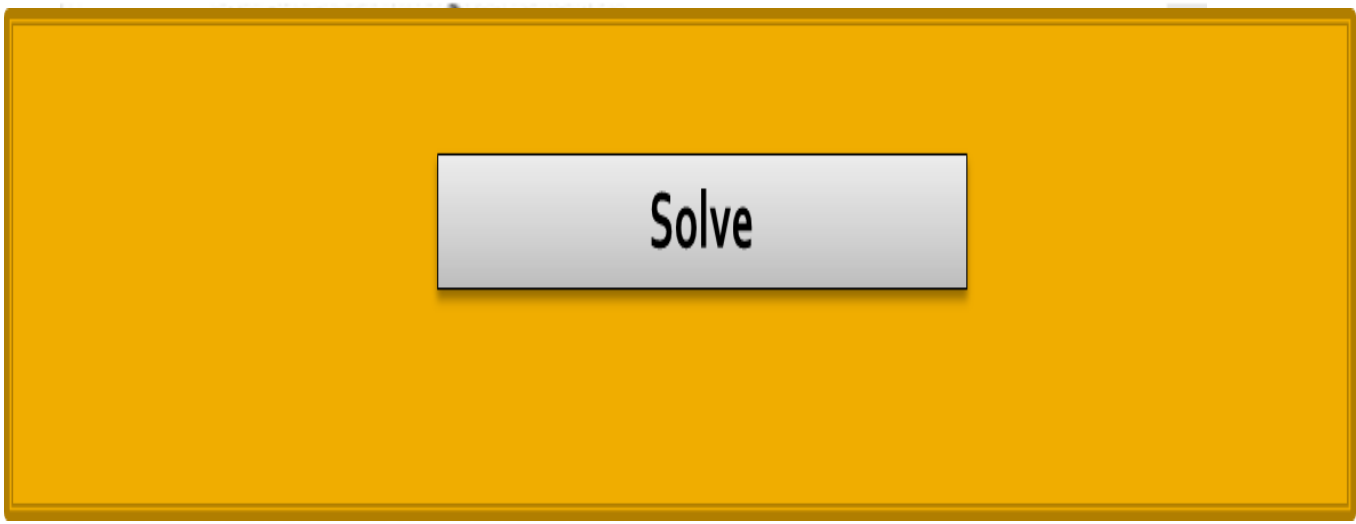
Calculate the amount of PCT that will permeate the intestine in 6 h of study (Steady state transport under sink conditions)

Solve

- A newly synthesized steroid is allowed to pass through a siloxane membrane having a cross- sectional area, *S*, of 10.36 cm2 and a thickness, *h*, of 0.085 cm in a diffusion cell at 25°C. From the horizontal intercept of a plot of $Q = M/S$ versus *t*, the lag time, t_L, is found to be 47.50min. The original concentration *C* is 0.003 mmole/cm3. The amount of steroid passing through the membrane in 4.0 hr is 3.65×10^{-3} mmole
- Calculate the parameter the permeability, *P coefficient*, *DK*

$$\frac{dM}{dt} = PSCd$$

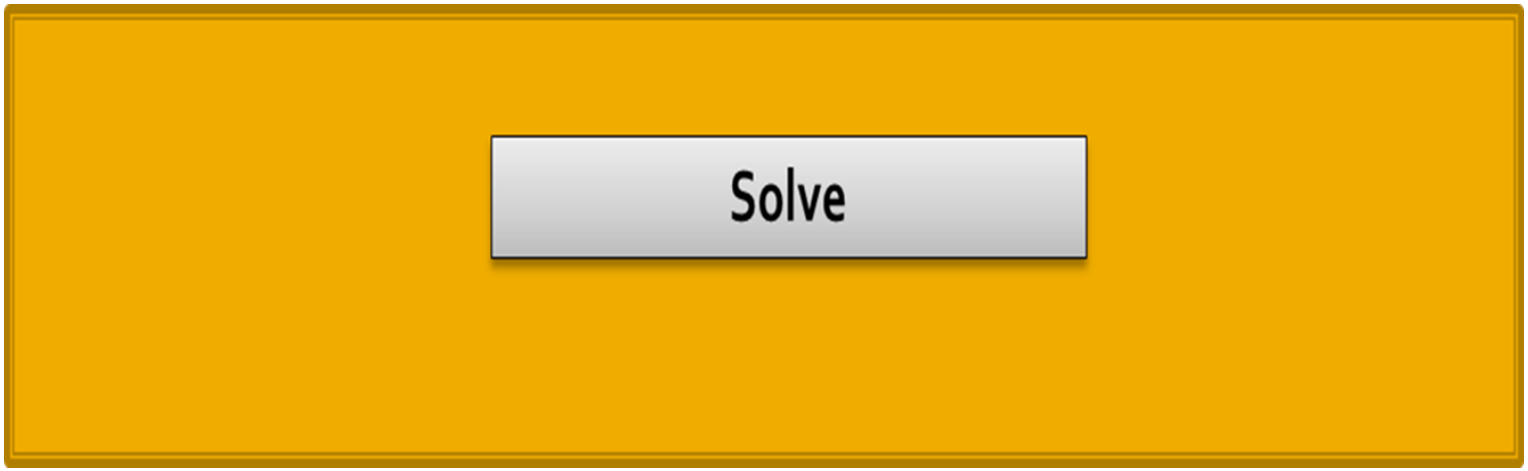
$$P = \frac{DK}{h}$$



- Using the lag time $t_l = h^2/6D$ calculate the diffusion coefficient.

Solve

- (b), calculate the partition coefficient, K.



Example

$$\frac{dM}{dt} = PSCd$$

$$P = \frac{DK}{h}$$

The lag time of methadone, a drug used in the treatment of heroin addiction, at 25°C (77°F) through a silicone membrane transdermal patch was calculated to be 4.65 min. The surface area and thickness of the membrane were 12.53 cm^2 and 100 µm, respectively.

a. Calculate the permeability coefficient of the drug at 25°C (77°F) (K = 10.5).

b. Calculate the total amount in milligrams of methadone released from the patch in 12 h if the concentration inside the patch was 6.25 mg/mL.

$t_L = h^2 / 6D$

Diffusion

$$\frac{dM}{dt} = PSCd$$

$$P = \frac{DK}{h}$$

- The surface area 12.53 cm^2
- thickness of the membrane 100 um
- lag time, 4.65 min and K = 10.5

Solution

Solve

$t_L = h^2 / 6D$

Diffusion

$$\frac{dM}{dt} = PSCd$$

$$P = \frac{DK}{h}$$

b. Calculate the total amount in milligrams of methadone released from the patch in 12 h if the concentration inside the patch was 6.25 mg/mL.

Solve

Fick's first law

$$J = \frac{dM}{S \bullet dt} \qquad J = -D\frac{dC}{dx}$$

Fick's second law

$$\frac{dC}{dt} = D\frac{d^2C}{dx^2}$$

Diffusion Through Membranes with thickness =h

$$J = D\frac{C1 - C2}{h}$$

Rate of transport

$$\frac{dM}{dt} = DSK\frac{Cd - Cr}{h}$$

Sink Conditions

$$\frac{dM}{dt} = DSK\frac{Cd}{h}$$

Membrane permeability

$$P = \frac{DK}{h} = \frac{1}{R}$$

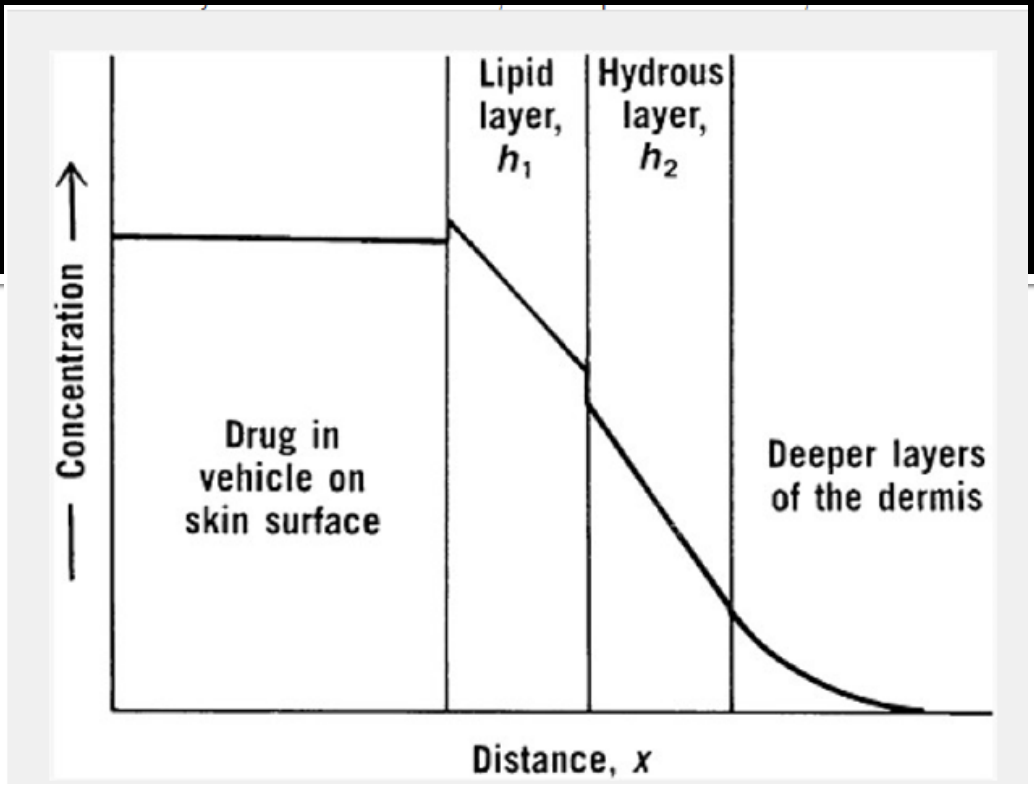
$$\frac{dM}{dt} = PSCd$$

$Cd @ constant$  $Cd \neq constant$

$$M = PSCd \bullet t$$

$$\log Cd_t = \log Cd(0) - \frac{PS}{2.303Vd}t$$

$$\ln Cd_t = \ln Cd(0) - \frac{PS}{Vd}t$$



- Two layers
- Two h
- Two Partition coefficient

Multilayer Diffusion

$$P = \frac{DK}{h} \quad \Longleftrightarrow \quad R_i = \frac{1}{P_i} = \frac{h_i}{D_i K_i} =$$

The total resistance, *R*

$$R = R_1 + R_2 + \ldots\ldots + R_n \quad \Longrightarrow \quad \frac{1}{P} = \frac{1}{P_1} + \frac{1}{P_2} + \ldots.. + \frac{1}{P_n}$$

The total permeability for the two layers

$$P = \frac{D_1 K_1 D_2 K_2}{h_1 D_2 K_2 + h_2 D_1 K_1}$$

Procedures and Apparatus For Assessing Drug Diffusion

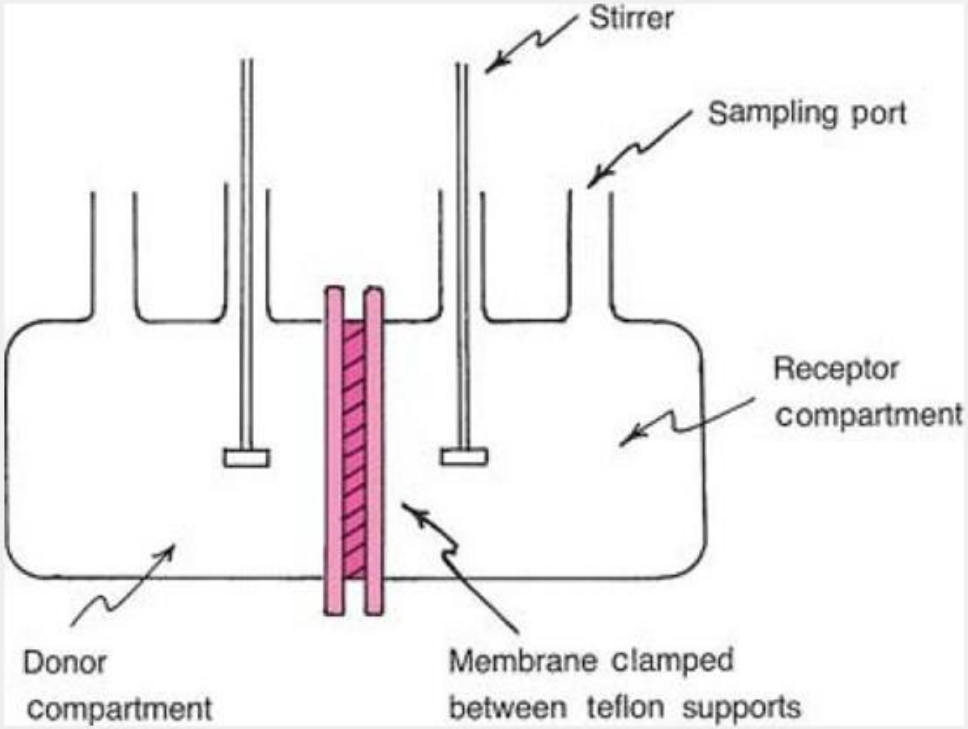
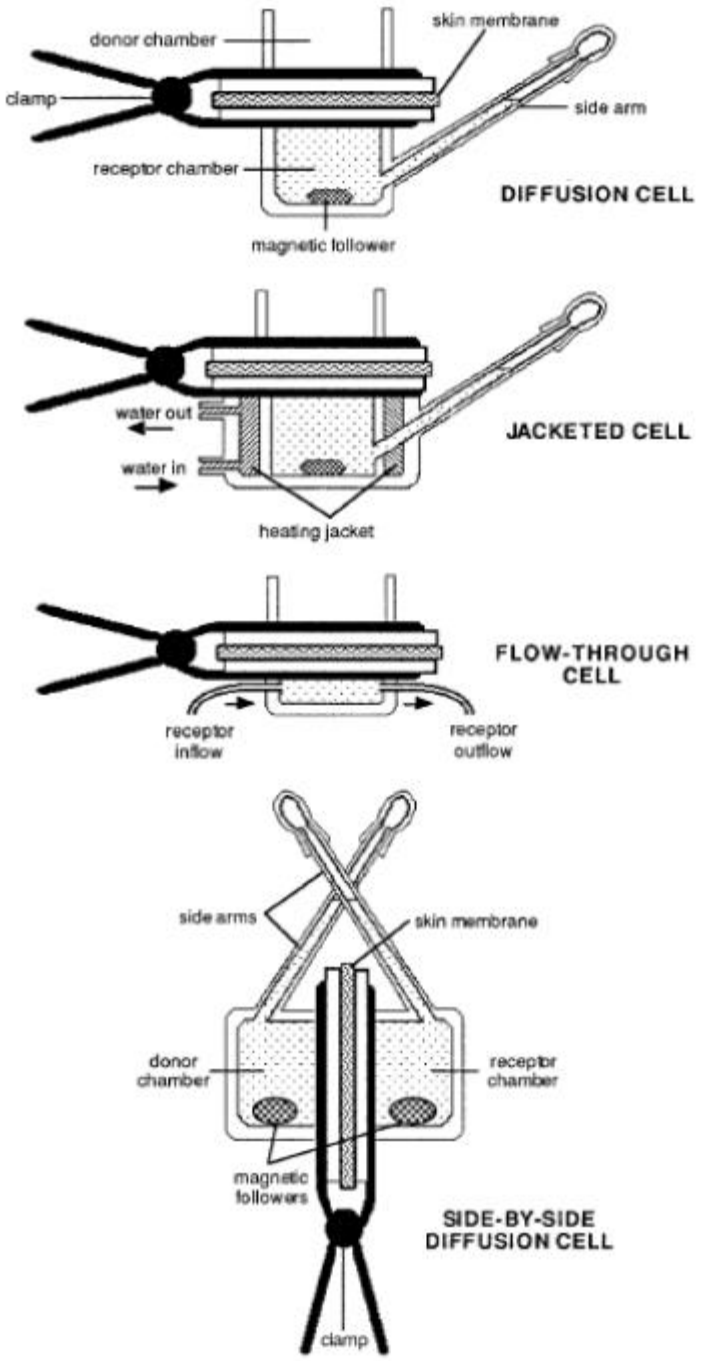


Fig. 11-11. Simple diffusion cell. (From M. G. Karth, W. I. Higuchi, and J. L. Fox, J. Pharm. Sci. **74**, 612, 1985. With permission.)

- The main difference in the application of these two static cell types is that side-by-side cells can be used for the measurement of permeation from one stirred solution to another stirred one

Flow-through cells can be useful when the permeant has a very low solubility in the receptor medium
However, the dilution produced by the continuous flow can raise problems with analytical sensitivity,

Upright cells are particularly useful for studying absorption from semisolid formulations(spread on the membrane)



Thank you