dissolution and Diffusion

Outline

- Introduction
- Diffusion
- Osmosis
- Fick's laws of diffusion
- Dissolution
- Diffusion Controlled drug Delivery system
- Dissolution and Diffusion Controlled drug Delivery system
- Osmotic controlled drug delivery system

Introduction

- ✓ Diffusion can be defined as a process by which molecules transfer spontaneously from a region of higher concentration to a region of lower concentration.
- ✓ is a result of random molecular motion
- ❑ Diffusion governs the transport of the great majority of drugs across various biological barriers after administration.
- ❑ The theory of diffusion has been used :
  - ✓ in investigating the mechanism of drug transport
  - ✓ applied to the design and development of various controlled or sustained release

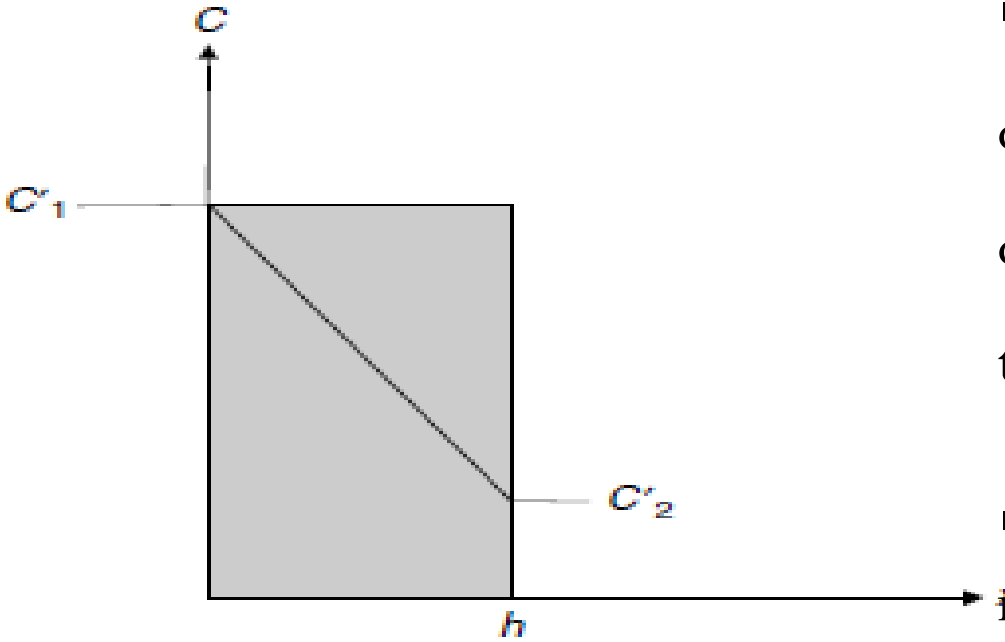
Diffusion

- The diffusion process can be abstracted to a simple system involving:
  - the molecules of interest,
  - a diffusional barrier,
  - concentration gradient within the barrier.

Diffusion…

- The molecules that migrate from one location to another are termed as diffusants,
  - ✓ called permeants or penetrants
- The medium in which the diffusant migrates is called the diffusional barrier.
- The concentration gradient is the concentration profile of the diffusant in the diffusional barrier.
  - ✓ The concentration gradient is the driving force for diffusion.

Diffusion…



- The number of molecules that diffuse through a unit area of the diffusional barrier in a given time is termed as flux, J.
- Flux is a measure of the rate of molecular diffusion

Fig. 1 Schematic representation of a diffusion system: concentration gradient in a cross section of diffusional barrier.

Factors that influence diffusion rates

- ✓ Distance -
  - The shorter the distance, the more quickly gradients are eliminated
- ✓ Molecular Size
  - Ions and small molecules diffuse more rapidly
- ✓ Temperature -
  - ↑ temp., ↑ motion of particles
- ✓ Steepness of concentrated gradient -
  - The larger the gradient, the faster diffusion proceeds
- ✓ Membrane surface area
  - The larger the area, the faster diffusion proceed

Drug transport system

- various nutrients like Carbohydrates, Amino acids, Vitamins and drugs are transported and absorbed into the blood by various mechanisms across semi permeable membrane
  - ✓ Passive diffusion
  - ✓ Facilitated transport
  - ✓ Active transport

1. Passive diffusion

- Major process for absorption of more than 90% of drugs
- Diffusion follows Fick's law:
  - The drug molecules diffuse from a region of higher concentration to a region of lower concentration till equilibrium is attained.
  - Rate of diffusion is directly proportional to the concentration gradient across the membrane.

Passive diffusion…

- Factors affecting Passive diffusion:
  - Diffusion coefficient of the drug
    - Related to lipid solubility and molecular wt.
  - Thickness and surface area of the membrane
  - Size of the molecule

Passive diffusion…

- Certain characteristic of passive diffusion can be generalized.
  a) Down hill transport
  b) Greater the surface area & lesser the thickness of the membrane, faster the diffusion.
  c) Equilibrium is attained when the concentration on either side of the membrane become equal.

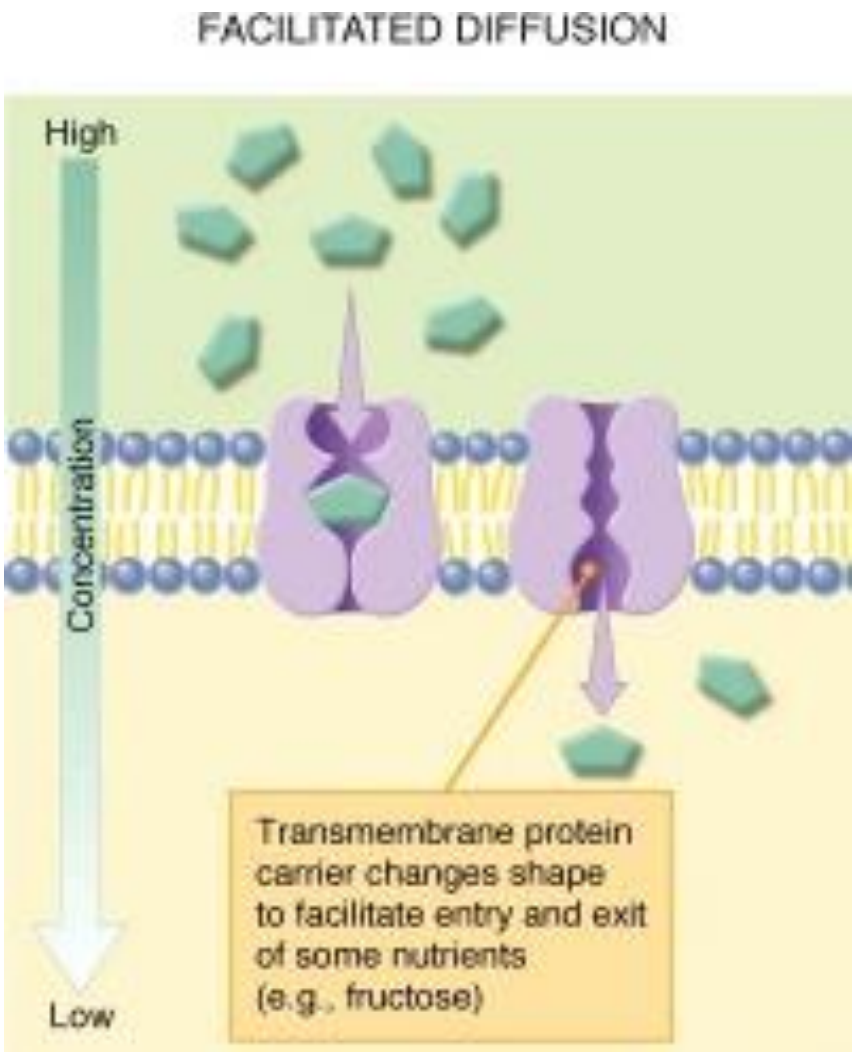
Passive diffusion…

- Greater the membrane/ water partition coefficient of drug, faster the absorption.
- Passive diffusion process is energy independent but depends more or less on the square root of the molecular size of the drugs.
- The mol. Wt. of the most drugs lie between 100 to 400 Daltons which can be effectively absorbed passively.

2.Carrier mediated transport mechanism

- Involves a carrier which binds reversibly with the solute molecules to be transported to yield the carrier solute complex
  - ✓ which transverses across the membrane to the other side where it dissociates to yield the solute molecule
- The carrier then returns to its original site to accept a fresh molecule of solute.

2.1 Facilitated transport



✓This mechanism involves the driving force as concentration gradient

✓In this system, no expenditure of energy is involved (down-hill transport)

✓ the process is not inhibited by metabolic poisons that interfere with energy production.

Facilitated transport…

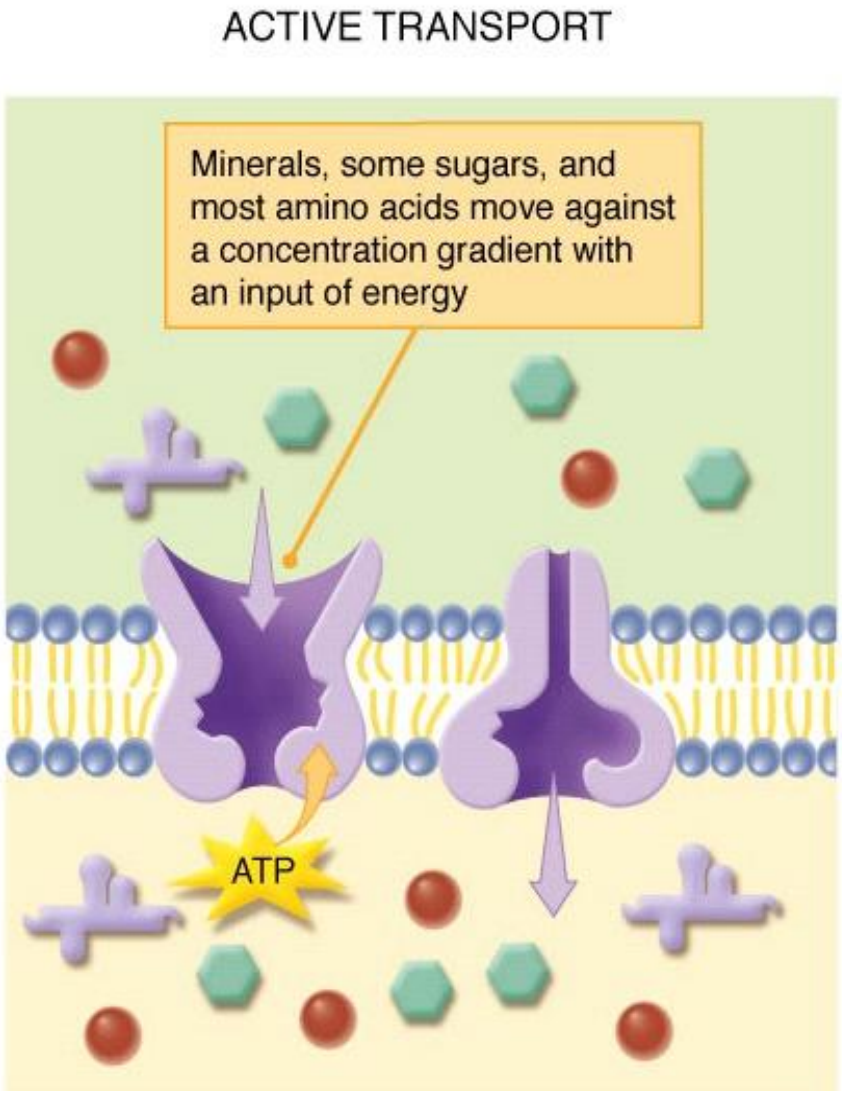
- Limited importance in the absorption of drugs.

  e.g. Such a transport system include entry of glucose into RBCs & intestinal absorption of vitamins B_1 & B_2.

- A classical example of passive facilitated diffusion is the gastro-intestinal absorption of vitamin B_{12}.

- An intrinsic factor (IF), a glycoprotein produced by the gastric parietal cells, forms a complex with vitamin B_{12} which is then transported across the intestinal membrane.

2.2 Active transport



- The driving force is against the concentration gradient or uphill transport.
- Since the process is uphill, energy is required
- As the process requires expenditure of energy
  - ✓ can be inhibited by metabolic poisons that interfere with energy production.

Active transport…

- Endogenous substances that are transported actively include sodium, potassium, calcium, iron, glucose, amino acids and vitamins like niacin, pyridoxine.
- Drugs having structural similarity to such agents are absorbed actively

  E.g. Pyrimidine transport system – absorption of 5 FU

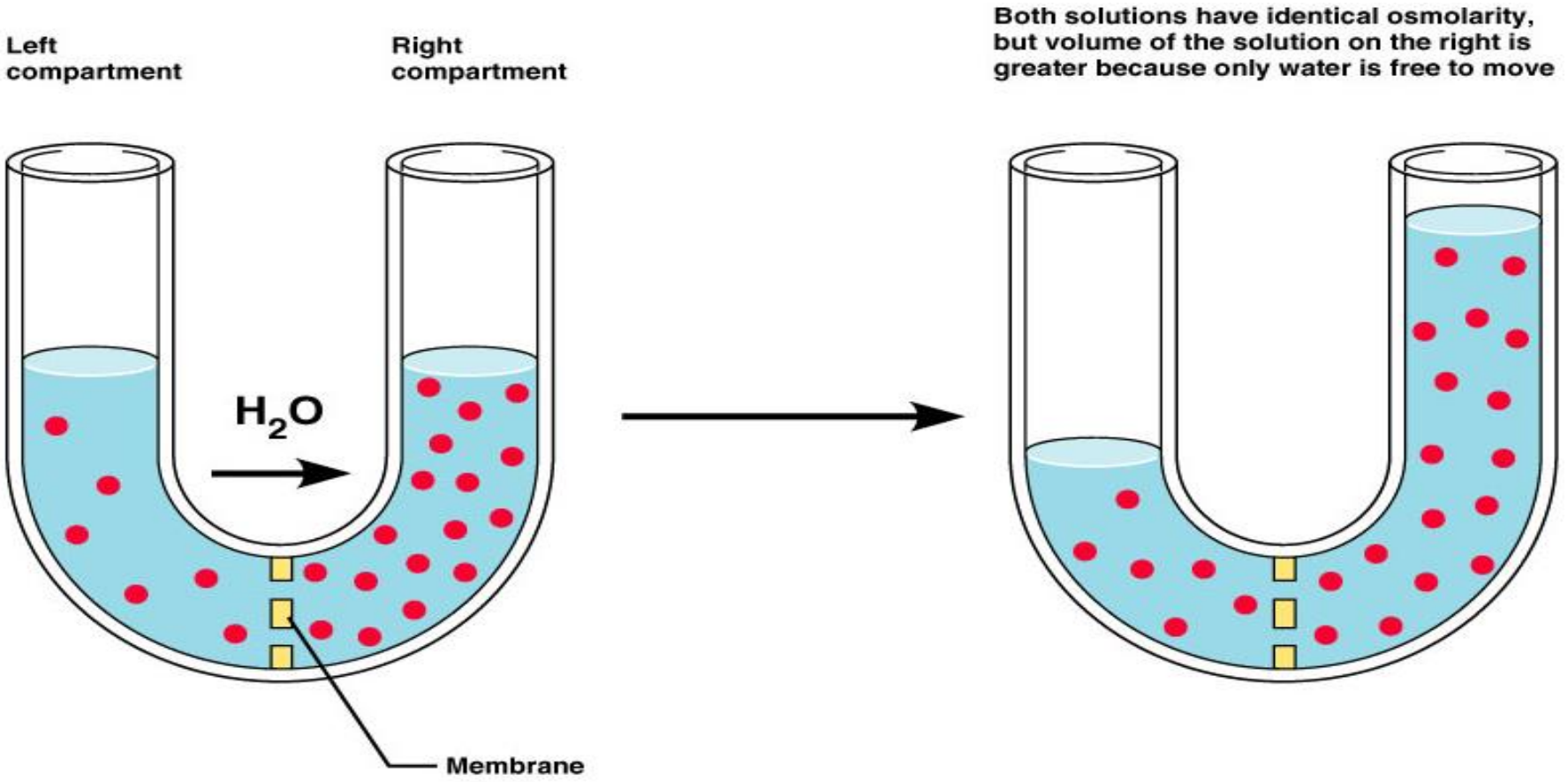
  L-amino acid transport system – absorption of

  methyldopa and levodopa

Osmosis

- Movement of water
- Across a selectively permeable membrane
- Down its concentration gradient
- Toward the solution containing the higher solute concentration
  - This solution has a lower water concentration
  - Continues until water concentrations and solute concentrations are the same on either side of the membrane

Osmosis…



(b) Membrane impermeable to solute molecules, permeable to water

Membrane transport

Types of membrane

- Impermeable membrane - membrane through which nothing can pass
- Freely permeable membrane - any substance can pass through it
- Selectively permeable membrane - permits free passage of some materials and restricts passage of others

✓ Plasma membrane is selectively permeable

Membrane transport…

- ✓ Distinction may be based on size, electrical charge, lipid solubility

- Cells differ in their permeabilities; depending on
  - ➢ what lipids and proteins are present in the membrane and
  - ➢ how these components are arranged
- Diffusion through lipid bilayer
  - ➢ Non polar, hydrophobic substances diffuse through lipid layer; these are "lipid soluble" or *lipophilic* substances

Membrane transport…

- Diffusion through channel proteins
  - hydrophilic and charged solutes diffuse through channel proteins; these are lipid insoluble or *lipophobic* (fat fearing) substances
- Cells control permeability by regulating number of channel proteins

Fick's laws of diffusion

- a proportional relationship between the flux and the concentration gradient.
- This relationship was expressed as:

$$J \propto \frac{dC}{dx} \qquad \text{eq. 1}$$

Fick's laws of diffusion…

- Fick described diffusion of molecules in quantitative terms
- The quantitative description of diffusion through a given unit area, expressed as follows is called *Fick's first law.*

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

eq. 2

D is the diffusion coefficient, or diffusivity

dC/dx is the concentration gradient

Fick's laws of diffusion…

- The unit for flux is the amount of diffusant per unit area per unit time (grams/square centimeters/seconds).
- The units for concentration and distance are the amount of diffusant per unit volume (grams/cubic centimeters) and length (centimeters).
- Hence, the unit for diffusion coefficient is $(\text{length})^2/\text{time}$.
- A typical unit for the diffusion coefficient is square centimeters/seconds.

Fick's laws of diffusion…

- When the concentration changes of diffusant at a given location in the diffusional barrier is of interest, Fick's first law is unable to describe the diffusion process.
- To describe the time-dependent diffusion process, the changes in concentration of diffusant with time (dC/dt) in a unit volume element along the x-direction can be expressed by the following partial differential equation:

$$\frac{dC}{dt} = D\left(\frac{d^2C}{dx^2}\right) \qquad \text{eq. 4}$$

Non steady state and steady state diffusion

- Non steady state diffusion refers to a diffusion process in which the concentration of diffusant in a given space is a function of time or the concentration of diffusant in the diffusional barrier varies with time.
- In this case, one should use Fick's second law to study the diffusion process.
  - Mathematically, this condition can be described as

$$\frac{dC}{dt} \neq 0 \qquad \text{eq. 5}$$

Non steady state and steady state diffusion

- When the amounts of diffusant enter and leave the given space at the same rate, the concentration of the diffusant in the given volume is a constant.
  - ✓ The concentration in the given space is independent of time.
- The diffusion process that meets this condition is considered a steady state diffusion.

Non steady state and steady state diffusion

$$\frac{dC}{dt} = 0 \qquad \text{eq. 6}$$

Applying this condition to above equation, we get

$$\left(\frac{d^2C}{dx^2}\right) = \frac{d}{dx}\left(\frac{dC}{dx}\right) = 0 \qquad \text{eq. 7}$$

- When a derivative of a variable is equal to zero, this variable must be a constant.
- In other words, the concentration gradient is a constant for diffusion at the steady state
  - ✓ diffusion at the steady state gives a constant flux.

Distribution or partition coefficient

- Distribution or partition coefficient is a measure of the ability of a compound to distribute in two immiscible phases.
- The partition phenomenon is of paramount importance for the diffusion across skin and other epithelia.
- Many pharmaceutical processes based on the partition principles
  - ✓ absorption from the gastrointestinal tract after oral administration

Distribution or partition coefficient…

- ✓ drug distribution following entry into systemic circulation,
- ✓ extraction and isolation of pure drugs after synthetic manufacturing or from crude plant sources,
- ✓ formulation of a stable dosage form (emulsion, etc.),

Distribution or partition coefficient…

- The ability of drugs to penetrate a biological membrane has been evaluated using its partition in an octanol and water system.
- Occasionally, other organic solvents such as chloroform, ether, and hexane have been used as a lipid vehicle.
- When a drug is placed in an immiscible system composed of octanol and water,
  - ✓ the drug distributes in each solvent and eventually reaches equilibrium.

Distribution or partition coefficient…

- The ratio of drug concentration in each phase is termed its distribution coefficient or partition coefficient (K)
  - expressed as:

$$K = \frac{\text{Concentration in Octanol}, C_o}{\text{Concentration in Water}, C_w}$$

- Practically, concentration in an aqueous phase is determined by chemical assays, such as high performance chromatography, ultraviolet spectroscopy, gas chromatography, gas chromatography–mass spectroscopy, etc.

Conce. In octanol is obtained by??

Distribution or partition coefficient…

Q1: Succinic acid (0.15 g) dissolved in 100 ml of ether was shaken with 10 ml of water at 37°C. After equilibrium was achieved, the water layer contained 0.067 g of succinic acid. What is the partition coefficient (K) of succinic acid?

Q2. The partition/distribution coefficient value of a drug will help in understanding:

(a) Its solubility

(b) Miscibility of different solvents

(c) Its permeability across biological membranes

(d) All of the above

Diffusion coefficient and permeability coefficient

- A diffusion coefficient represents the mobility of a molecule in a specific medium, the diffusional barrier.
- The mobility of a substance in a diffusional barrier is determined by:
  - ❖ the physicochemical properties of the diffusant
  - ❖ the diffusional barrier
  - ❖ temperature.

Diffusion coefficient and permeability coefficient…

- The relationship of the diffusion coefficient and these factors is expressed quantitatively in the Stokes–Einstein equation,
  - ✓ which states the diffusion coefficient as a function of temperature (T), viscosity (η), and size of the diffusant (*r*)

$$D = \frac{KT}{6\pi\eta r}$$

Diffusion coefficient and permeability coefficient…

- A set-up for studying diffusion through a diffusional barrier.

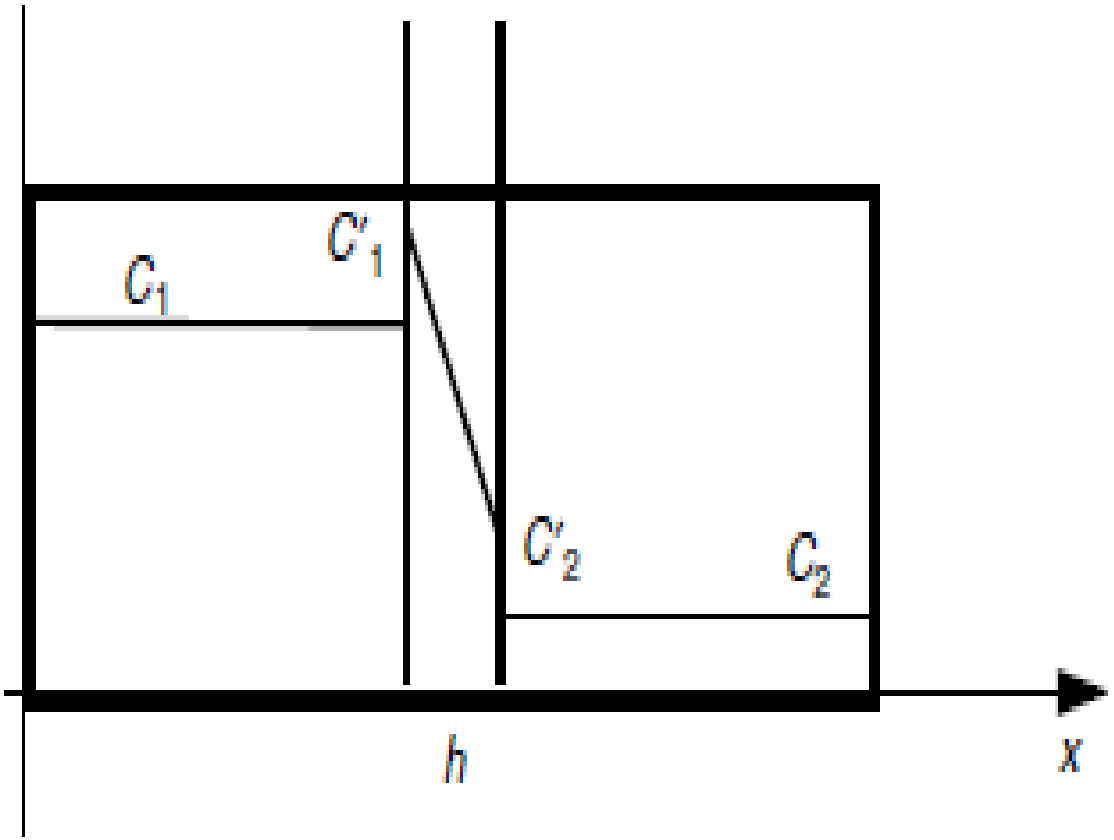


Fig. Diffusion across a membrane.

Diffusion coefficient and permeability coefficient…

- The set-up has two compartments divided by the diffusional barrier, for example, a membrane with a thickness of h.
- The concentrations of diffusion outside of a diffusional barrier or the concentrations of diffusant in each compartment are denoted C1 and C2.
- The concentrations of diffusant in the diffusional barrier are denoted C′1 and C′2 for each side of the barrier.

Diffusion coefficient and permeability coefficient…

- C1 and C2 can be determined experimentally, but C′1 and C′2 are usually not known.
- To apply Fick's laws, one must know C′1 and C′2 .
- The concentrations of a diffusant in the diffusional barrier and the adjacent medium can be related by using partition coefficients (K) as follows:

$$K = \frac{\text{Conc. in membrane}}{\text{Conc. in solution phase}} = \frac{C_1'}{C_1} = \frac{C_2'}{C_2}$$

Diffusion coefficient and permeability coefficient…

- Therefore, the concentrations of diffusant in the diffusional barrier can be expressed as:

$$C_2' = KC_1$$

$$\text{and } C_2' = KC_2$$

By replacing the concentrations of diffusant in the barrier by using these relationships, Fick's first law can be rewritten as

$$J = -\frac{DK}{h}\left(C_2 - C_1\right)$$

Since D, K, and h are constant for a given diffusional barrier, a constant permeability or permeability coefficient (P), is defined as:

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

Diffusion coefficient and permeability coefficient…

- The dimension of permeability coefficient is length per unit time,
  - ✓ for example, centimeters per second.
- Permeability coefficient is commonly used in pharmaceutical sciences to determine or compare the permeation of a drug through various biological barriers.

Q. The diffusion coefficient of a permeant depends upon:

(a) Diffusional medium

(b) Diffusional length

(c) Temperature

(d) All of the above

(e) None of the above

Experimental methods

- The diffusion process can be studied by using various methods, such as
- The most commonly used method in pharmaceutical research is the permeation method.
- The experimental set-up for this method consists of two chambers separated by a diffusional barrier.
- A drug solution is charged to the donor chamber.

Experimental methods…

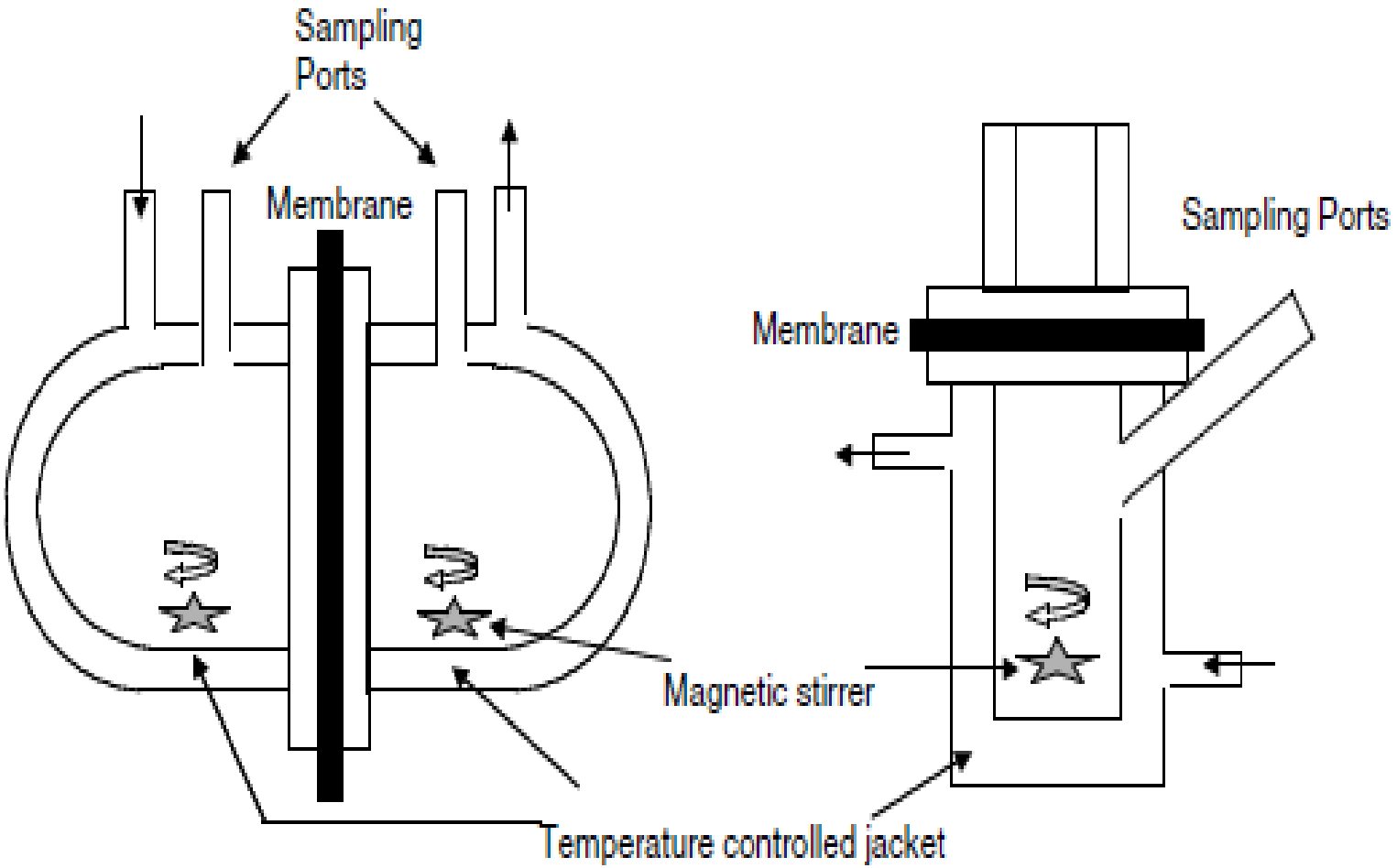


FIG. Side-by-side and vertical diffusion cells.

Experimental methods…

- ✓ Since the cumulative amount permeating the barrier (Q) at a given time (t) can be quantified and the concentration of donor chamber and the diffusional area are usually known,
  - ➢ the permeation coefficient (P) can be obtained from the slope of a plot of cumulative permeation of diffusant vs. time.
- When the diffusant appears in the receiver chamber, its amount increases gradually
- Once the diffusion reaches steady state, the concentration gradient remains constant and the amount entering the receiver chamber is also constant,

Experimental methods…

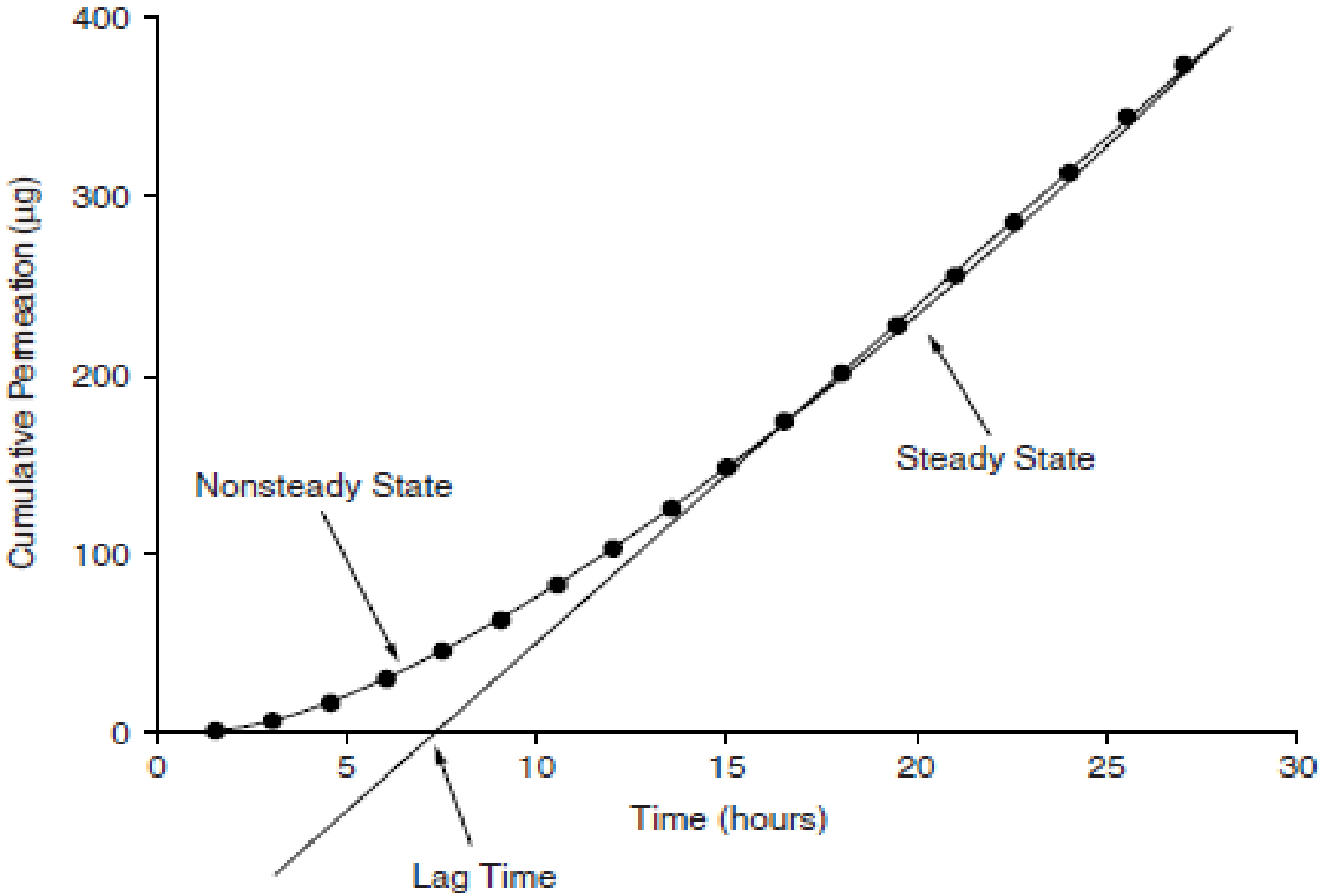


Fig. Diffusion of lidocaine through poly(vinyl alcohol acetate) membrane

Experimental methods…

- The time required to reach steady state is called the *lag time* (t_L).
- The lag time can be determined by extrapolating the linear portion of permeation vs. the time curve to the time axis.

$$Q = \frac{DKAC_1}{h}\left(t - t_L\right)$$

$$Q = PAC_1\left(t - t_L\right)$$

The lag time can be calculated by:

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

Experimental methods…

Q. A steroid permeates through a membrane with an area of 10.25 cm2 and a thickness of 0.075 cm at 25°C. The concentration of steroid in the donor chamber is 0.004 mmol/ml. The amount of the steroid across the membrane at steady state is 3.5 × 10−3 mmole in 4.5 h. The lag time is 0.4 h.

(a) Calculate the permeability coefficient.

(b) Calculate the diffusion coefficient

Experimental methods…

- The solution of the receiver chamber is removed partially or replenished with solvent or buffer solution at predetermined time intervals.
- When the receiver chamber is replenished with a solvent or a solution without a drug, the concentration of drug in the receiver chamber is maintained at a minimum level ($C_2 \approx 0$).
  - This is called sink condition.
- To maintain sink condition, the concentration of a permeant in the receiver chamber is generally kept below 10% of its concentration in the donor chamber.

Experimental methods…

- In sink condition, Fick's first law can be simplified as:

$$J = \frac{DK}{h} C_1$$

Mathematically, the amount of cumulative permeation of diffusant (Q) *can be derived from integration of the above Equation* over the time of diffusion:

$$J = \frac{dQ}{dt} \cdot \frac{1}{A} = \frac{DK}{h} C_1$$

$$Q = PAC_1 t$$

Dissolution

- Dissolution is a process in which a solid substance solubilizes in a given solvent i.e. mass transfer from the solid surface to the liquid phase.

- Rate of dissolution is the amount of drug substance that goes in solution per unit time under standardized conditions of temperature and solvent composition.

Dissolution

Diffusion layer model/Film Theory

It involves two steps :-

a. Solution of the solid to form stagnant film or diffusive layer which is saturated with the drug

b. Diffusion of the soluble solute from the stagnant layer to the bulk of the solution.

Dissolution…

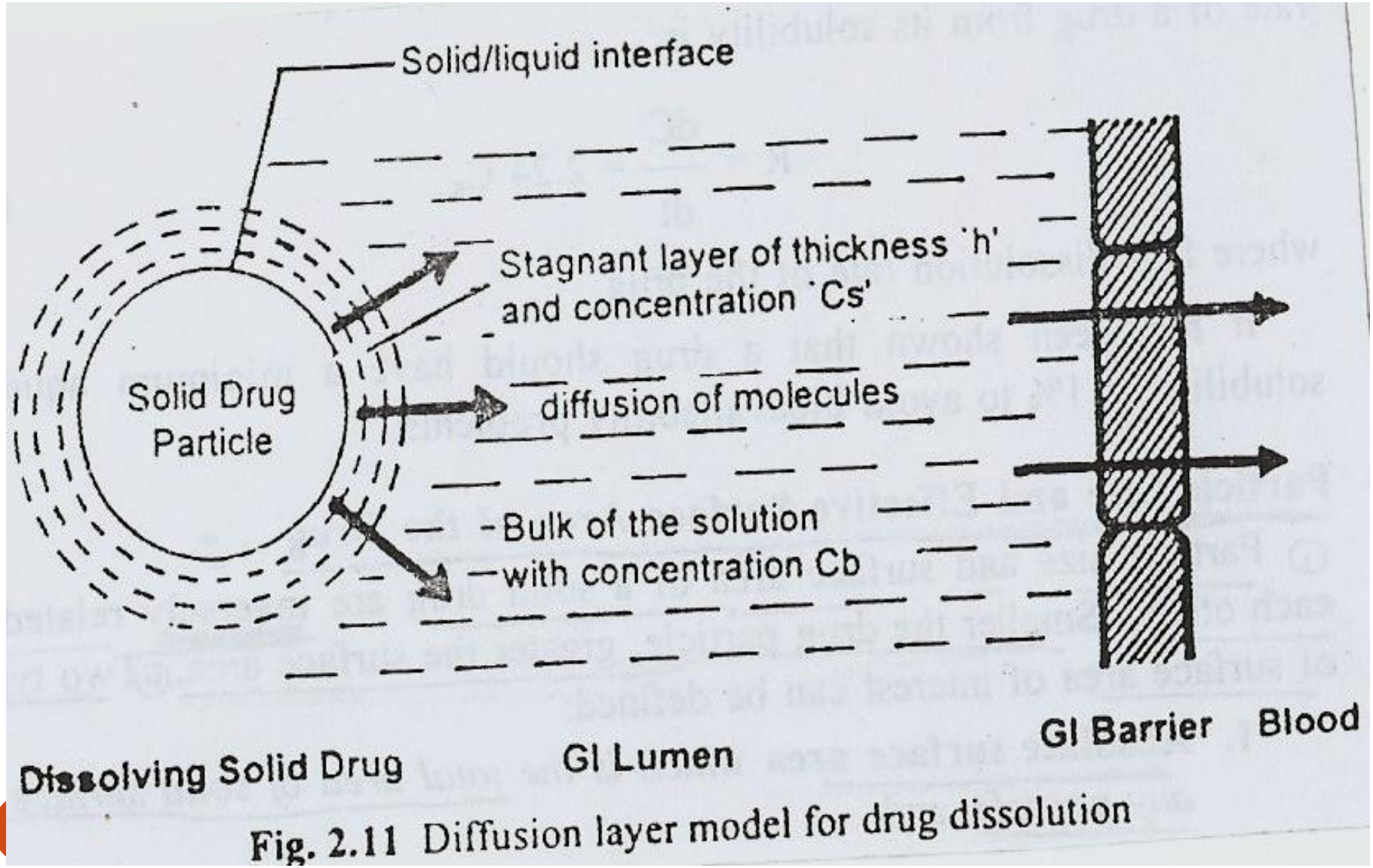


Fig. 2.11 Diffusion layer model for drug dissolution

Dissolution…

The rate of dissolution is given by Noyes and Whitney:

$$\frac{dM}{dt} = \frac{DA}{h}\left(C_s - C_t\right)$$

M = amount of drug (material) dissolved (usually mg or mmol)

t = time (seconds)

D = diffusion coefficient of the drug (cm^2/s)

A = surface area (cm^2)

H = thickness of the liquid film

Cs and ct are concentration of the drug in the diffusion layer, and Ct is the concentration of drug in bulk fluids at time t.

Dissolution…

Problem 1: Calculate the dissolution rate of a hydrophobic drug having the following physicochemical characteristics:

surface area = 2.5×10^3 cm^2

saturated solubility = 0.35 mg/mL (at room temperature)

diffusion coefficient = 1.75×10^{-7} cm^2/s

thickness of diffusion layer = 1.25 μm

conc of drug in bulk = 2.1×10^{-4} mg/mL

ans. 1.22 mg/sec

Problem 2: What would the rate of dissolution be in Problem 1 if the surface area was increased to 4.3×10^4 cm^2?

ans **21 mg/sec**

Dissolution…

- When the dissolution occurs under sink condition and controlled agitation, the rate of dissolution is:

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

where k is the dissolution rate constant, which is a constant under a given temperature and agitation condition in a defined solvent

❖ Calculate rate of dissolution if dissolution occurs under sink conditions for problem 1 & 2

Factors affecting Drug Dissolution

i. Factors relating to the physicochemical properties of drug

- ✓ Solubility-
- ✓ Particle size and effective surface area of the drug
- ✓ Polymorphism and amorphism
- ✓ Salt form of the drug
- ✓ Hydrates/solvates

Factors affecting Drug Dissolution…

Factors relating to the dosage forms.

- Vehicle
- Diluents
- Lubricants
- Binders
- Surfactants
- colorants

In-vitro dissolution testing methods

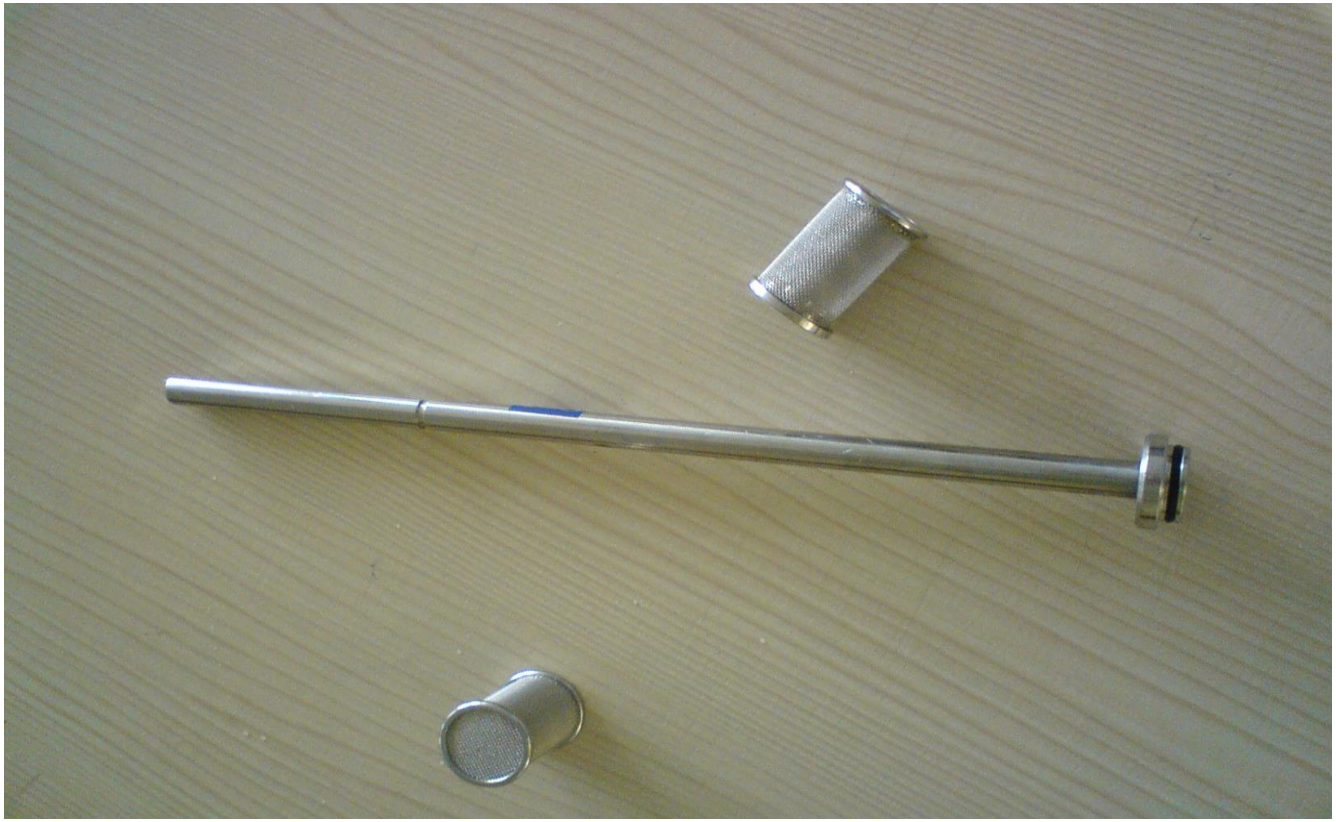
- Alternative to *in vivo* bioavailability determination
- Dissolution testing – Official in pharmacopeias
- Quantify the extent of release of drug
- Routinely used by Q.C. and R&D

i. Rotating Basket Apparatus (Apparatus 1)`

- It is basically a closed-compartment, beaker type apparatus.
- It comprising of a cylindrical glass vessel with hemispherical bottom of one liter capacity partially immersed in a water bath.
- A cylindrical basket made of #22 mesh is located centrally in the vessel at a distance of 2 cm from the bottom and rotated by a variable speed motor through a shaft.

Basket Apparatus…

- All metal parts like basket and shaft are made of stainless steel.



Rotating Paddle Apparatus (Apparatus 2)

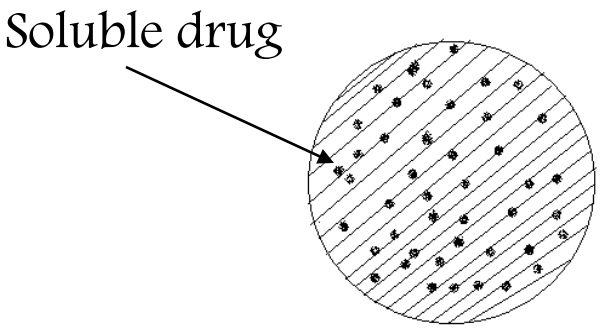
- Here, basket is replaced with a stirrer.
- A small, loose, wire helix may be attached to the dosage form that would otherwise float.
- The position and alignment of the paddle are specified in the official books.

Diffusion Controlled drug Delivery system

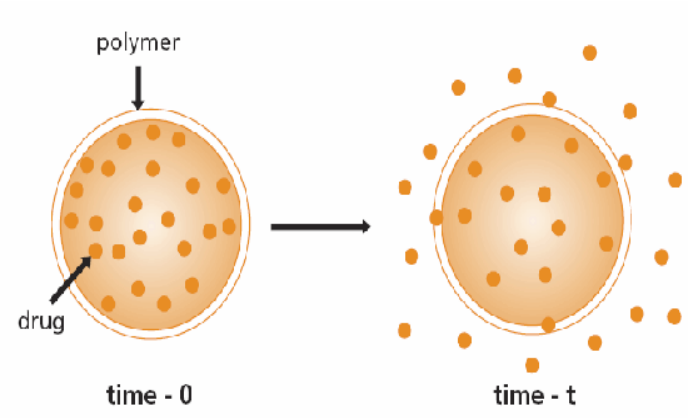
- polymers function as physical barriers to drug transport and hence control the rate of release of a drug when administered orally.
- Generally, diffusion controlled systems are of two types:

a. reservoir devices

b. matrix devices.



matrix devices.



reservoir devices

Diffusion Controlled…

Reservoir devices

Drug release is believed to involve the following processes:

- ✓ Water, gastric juices, or intestinal juices penetrate the coating and the drug dissolves to produce a saturated solution
- ✓ the drug diffuses though the polymeric coating
- ✓ A fairly constant rate of drug release occurs if the concentration of drug in the core remains at saturation

Diffusion Controlled…

- the release of solutes from polymeric drug delivery systems are based on Fick's laws of diffusion.
- Fick's first law states that the flux (J) is proportional to the concentration gradient across the area:

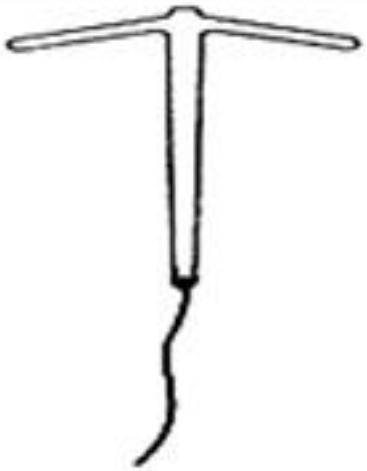
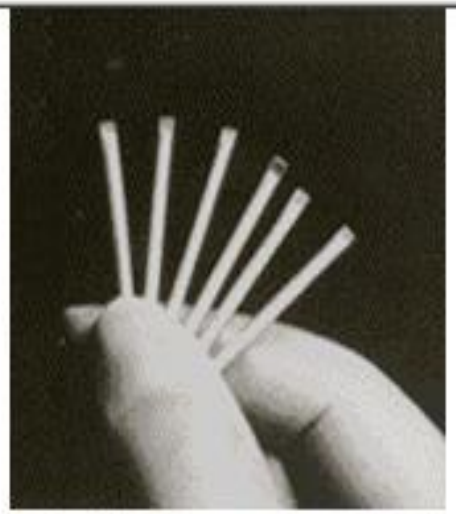
$$J = -D\,(dc/dx)$$

- Fick's first law can be simplified as shown

$$J = DK\Delta C/d$$

- K is the partition coefficient
- d is the thickness of the diffusion layer (the diffusion path).

4. Examples of reservoir system

Ocusert (Alza)	Progestasert	Norplant
Pilocarpine (20ug or 40ug/h for 7days)	Progesterone (for 1year)	Levonorgesterol (for 5years)
		

Diffusion Controlled…

Matrix Devices

- A matrix (monolithic) device consists of an inert polymeric matrix in which a drug is uniformly distributed.
  - ✓ Drugs can be dissolved in the matrix
  - ✓ the drugs can be present as a dispersion
- The state of presentation leads to different release characteristics.

Diffusion Controlled…

i. Dissolved Drug

- When the system is a homogeneous matrix containing a dissolved drug, the release can be described by a solution to Fick's second law of diffusion,
  - ✓ states that the rate of change of concentration with time (t) at a particular level is proportional to the rate of change of the concentration gradient at that level.

Fick's second law of diffusion is

$$dc/dt = D\,(d^2c/dx^2)$$

Diffusion Controlled…

ii. Dispersed Drug

- If a drug is dispersed as a solid in the homogeneous matrix (monolith) instead of being completely dissolved, the release kinetics are altered.
- The derivation of the release rate expression is based on

  Fick's first law of diffusion
- Higuchi developed a model for the analysis of a homogeneous polymer matrix containing a suspended drug.

- The expression of the amount of drug released per unit area is : $Mt = (CsD(2A - Cs)t)^{1/2}$

  where Mt is the amount of drug released per unit area at time t, D and Cs are the diffusion coefficient and solubility of the drug in the polymer, respectively, and A is the concentration of drug initially present in the matrix.

When $A >> Cs$, the equation reduces to $Mt = (2CsDAt)^{1/2}$

Route of Administration	Product	Active Ingredient	Therapeutic Indication(s)
Oral	Desoxyn-Gradumate	Methamphetamine hydrochloride	Attention-deficit hyperactivity disorder and narcolepsy
	Fero-Gradumate	Ferrous sulfate	Iron supplement
	Proscan SR	Procainamide hydrochloride	Arrhythmia
	Choledyl SA	Oxytriphylline	Bronchodialator for asthma, bronchitis, emphysemia, and chronic obstructive pulmonary disease
Transdermal	Nitrodur	Nitroglycerin	Angina

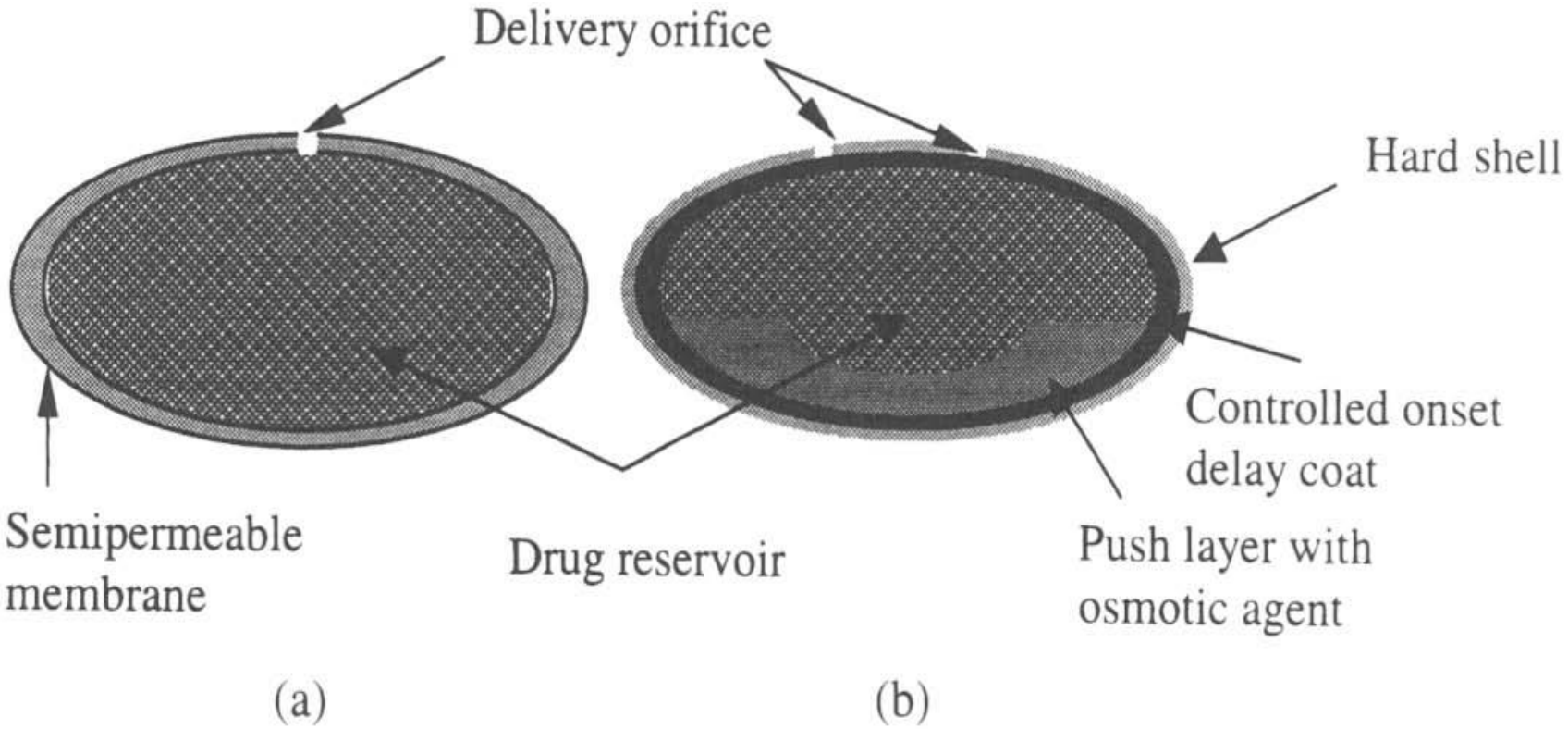
Osmotic controlled drug release

- This type of delivery device has a semipermeable membrane that allows a controlled amount of water to diffuse into the core of the device filled with a hydrophilic component.
- A water-sensitive component in the core can either dissolve or expand to create osmotic pressure
  - ✓ push the drug out through a small delivery orifice

Osmotic controlled drug release

- The main advantage of the osmotic pump system
  - ✓ constant release rate can be achieved, since it relies simply on the passage of water into the system
- The release rate of the device is affected by:
  - ➢ the amount of osmotic agent,
  - ➢ surface area and thickness of semipermeable membrane,
  - ➢ the size of the hole.

Osmotic controlled drug release



Osmotic controlled drug release

- The rate at which drug is pumped out of the osmotic system through the orifice is the same as the volume flow rate of water into the core multiplied by drug concentration

$$dM/dt = (dV/dt)\, Cs$$

dM/dt is the amount of drug (mgs) delivered per unit of time (hours)

dV/dt is the volume flow rate [milliliters per unit of time (hours)

Cs is the concentration of the saturated solution

Osmotic controlled drug release

- The volume flow rate of water into the osmotic device can be expressed in terms of:

membrane permeability (K),

semipermeable membrane surface area (A),

thickness (h) of the membrane,

osmotic pressure difference ($\Delta\pi$),

$dV/dt = (AK/h)(\Delta\pi)$

Therefore, $dM/dt = (AK/h)(\pi)\ Cs$

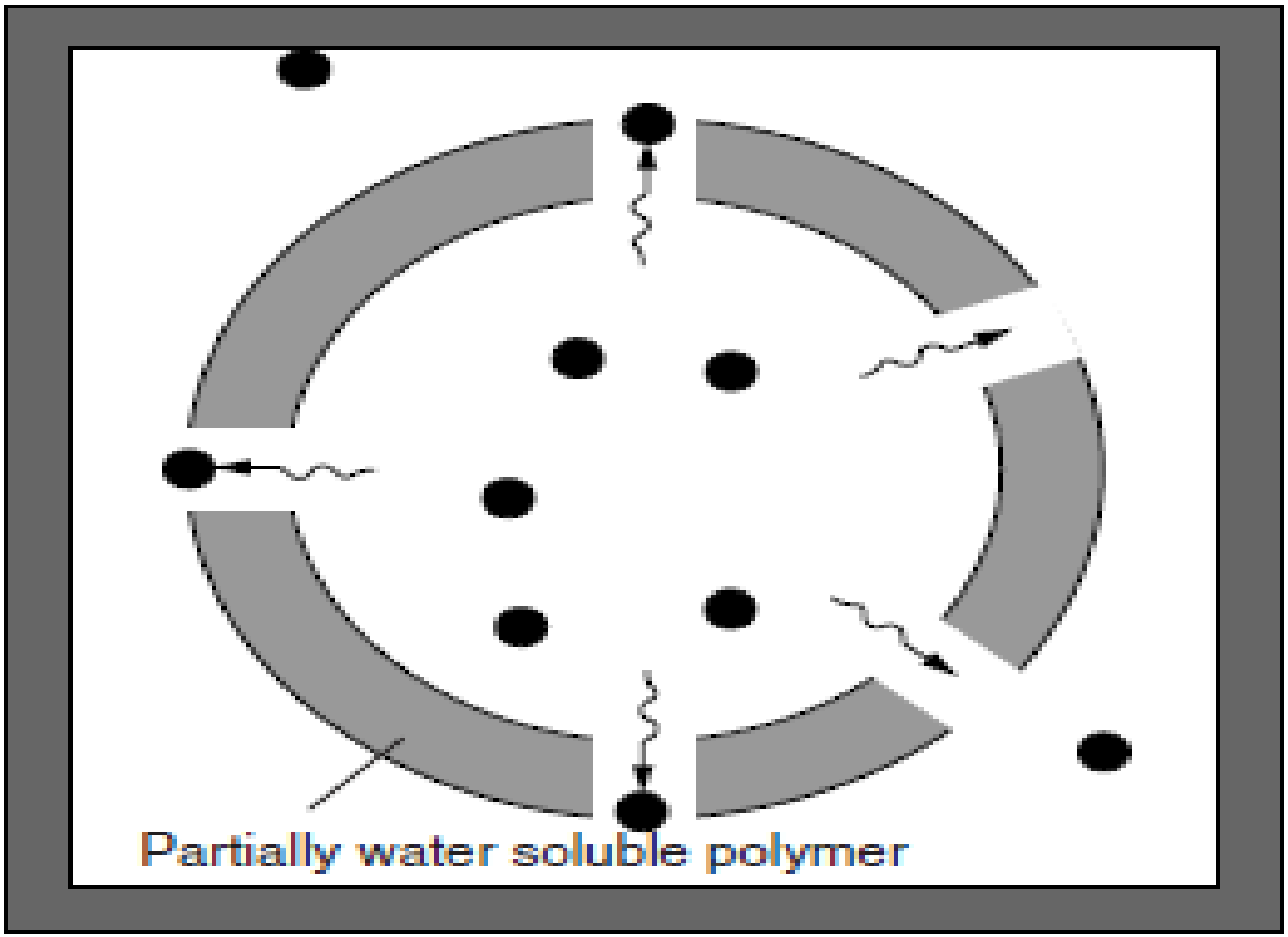
Dissolution and Diffusion Controlled Systems

- In this system, the drug forms the core, which is surrounded by a partially water-soluble polymer.
- Drug release is triggered by the dissolution of the water-soluble part of the polymer membrane
  - ✓ diffusion of the drug through the holes or pores in the polymer.
- achieved by incorporating water-soluble additives in the polymer coating.

Dissolution and Diffusion Controlled Systems

- When placed in an aqueous environment, the water-soluble additives (often called pore-formers) in the polymer coating dissolve to leave pores.
- The process is also used to increase the permeability of drugs through reservoir delivery systems.

Dissolution and Diffusion Controlled Systems



Schematic representation of dissolution and diffusion controlled system

Dissolution and Diffusion Controlled Systems

- The kinetics of the release of drugs from dissolution-controlled systems is often described by the Noyes-Whitney equation: $dC/dt = k\,A/V\,(Cs - C)$

Where:

dC/dt is the dissolution rate;

V is the volume of the solution;

k is the dissolution rate constant,

A is the surface area of the exposed solid.

Cs is the saturated solubility of the drug,

C is the concentration of the drug in the bulk solution.