Physical Pharmacy II

2nd stage

College of Pharmacy

Lec: 3

Diffusion

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Diffusion

- **Diffusion** is a **process of mass transfer** where molecules move from an area of **high concentration to low concentration** due to random molecular motion.
  - This movement happens naturally and does not require external energy.
  - The driving force behind diffusion is the **concentration gradient**.
- In simple terms, molecules move from where there is “more” to where there is “less” until equilibrium is reached.

Why is diffusion important?

- Diffusion plays a key role in many biological and pharmaceutical processes:
  1. **Drug absorption** – A drug must diffuse across biological membranes (like the intestinal wall) to enter the bloodstream.
  2. **Drug distribution** – After entering the blood, the drug must diffuse to reach its site of action inside tissues or cells.
  3. **Drug elimination** – Drugs also diffuse to organs like the kidneys or liver to be removed from the body.
  4. **Shelf life of products** – 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.
- Without diffusion, drugs would not be able to work effectively in the body.

Diffusion Across Biological Membranes

- Drugs cross biological membranes in two main ways:

1.Transcellular diffusion

1. Occurs through the **lipid bilayer of cells**.
2. The drug passes directly through the cell membrane.

2.Paracellular diffusion

- Occurs through the **spaces between adjacent cells**.

- Both mechanisms are essential for drug absorption and elimination.
- In addition to diffusion through the lipoidal membrane, several other transport mechanisms have been characterized in biologic membranes including energy-dependent and energy independent carrier-mediated transport

Diffusion and Drug Release

- Before a drug can act in the body, it must first be **released from its dosage form** (tablet, capsule, etc.).

  Drug release is a **multistep process**, and diffusion is one of the key steps involved.

Steady-State Diffusion

- Mass transfer is the movement of molecules in response to an applied driving force.
- Mass transfer is a kinetic process, occurring in systems that are not in equilibrium.
- An important condition in diffusion is that of the steady state.
- A system is at **steady state** when:
  - The concentration at every point does **not change with time**
  - The amount entering a membrane = the amount leaving
  - There is **no accumulation** inside the membrane
- This creates:
  - A **constant concentration gradient**
  - A **constant diffusion rate (flux)**
- So even though molecules are moving, the overall system looks stable.
- **Flux (J)** tells us **how fast diffusion occurs**.

Fick's Laws of Diffusion

- In 1855, Fick recognized that the mathematical equation of heat conduction developed by Fourier in 1822 could be applied to mass transfer.
- The amount, M, of material flowing through a unit cross section, S, of a barrier in unit time, t, is known as the flux, J:

$$J = \frac{dM}{S \cdot dt} \qquad (11\text{–}1)$$

- **Flux (J)** tells us **how fast diffusion occurs**.

- the mass, M, is usually given in grams or moles,
- the barrier surface area, S, in cm^2 , and
- the time, t, in seconds.
- The units of **J are g/cm^2 sec**. (**This means How many grams pass through 1 cm^2 in 1 second**)
- The SI units of kilogram and meter are sometimes used, and the time may be given in minutes, hours, or days.

Fick's Laws of Diffusion

Fick discovered that The flux (The rate of diffusion) is proportional to the concentration gradient, dC/dx:

Mathematically:

$$J = -D\frac{dC}{dx} \qquad (11\text{-}2)$$

D is the diffusion coefficient of a penetrant (also called the diffusant) in **cm/sec^2**,
C is its concentration in g/cm^3 ,
x is the distance in centimeter of movement perpendicular to the surface of the barrier.

- Equation (11-2) is known as Fick's first law.
- The **negative sign** of equation signifies that diffusion occurs in a direction opposite to that of increasing concentration. That is, diffusion occurs in the direction of decreasing concentration of diffusant; thus, the **flux** is always a **positive quantity**.
- Diffusion will stop when the concentration gradient no longer exists (i.e., when dC/dx = 0).

- **Diffusion Coefficient (D)** or **diffusivity** tells us **how easily a substance moves** through a medium.
  - It depends on:
    - Temperature
    - Concentration
    - Pressure
    - Solvent properties
    - Chemical nature of the diffusing molecule
  - So D is not truly constant — it changes with conditions.
  - Therefore, **D** is referred to more correctly as a **diffusion coefficient** rather than as a constant.

When Does Diffusion Stop?

- Diffusion stops when: $dC/dx=0$, This means there is **no concentration difference**.
- If concentrations are equal everywhere → no driving force → no diffusion.

Fick's Second Law

- we studied **Fick's First Law**, which describes diffusion at steady state — when concentration does not change with time
- Fick's second law of diffusion forms the basis for most mathematical models of diffusion processes.
- Fick's second law is an equation for mass transport that focuses on how concentration changes with time at a specific location inside a system.
  - This is different from Fick's first law. Fick's First Law tells us how much drug passes through a unit area per unit time (flux).
  - Fick's Second Law tells us how the concentration at one point changes as time passes."
- Fick's second law, Equation (11-5)

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \qquad (11\text{–}5)$$

C = concentration
t = time
x = position (distance)
D = diffusion coefficient
$\partial C/\partial t$= change of concentration with time
$\partial^2 C/\partial x^2$ = how concentration changes with position

- Fick's second law looks at:
  - how concentration changes with time (t) and at a specific location (x) in the system
- 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).
- In simple words Diffusion continues until concentration becomes uniform

Using the Diagram

In the donor–membrane–receptor system:

- Initially, concentration is high in the donor compartment.
- Over time, drug diffuses across the membrane.
- Concentration in each compartment changes with time.
- Eventually, steady state may be reached.
- Fick's Second Law describes how concentration changes with time at any position during diffusion before steady state is reached.

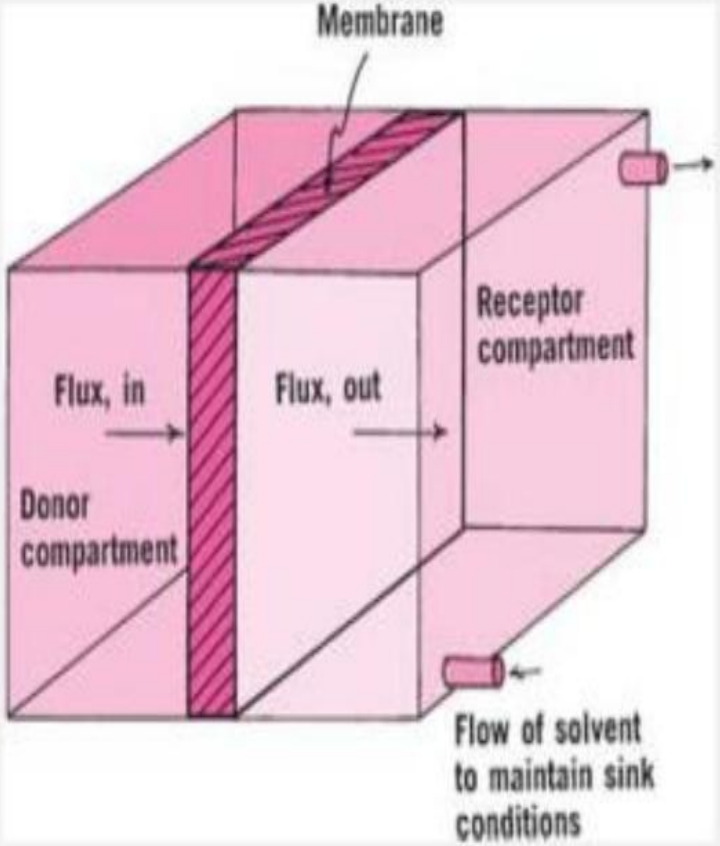

Fig. 11-3. Diffusion cell. The donor compartment contains diffusant at concentration *C*.

Diffusion Across a Thin Film

- **In the system shown:**
  - The **donor compartment** contains a high concentration of solute (**Cd**).
  - The **receptor compartment (sink)** contains a lower concentration (**Cr**).
  - Between them is a **thin membrane (or film)** of thickness **h**.
- Molecules move from **Cd → Cr** because diffusion always proceeds down a concentration gradient

We assume:

- The film has **uniform thickness (h)**.
- The solutions on both sides are **well mixed**, so Cd and Cr remain constant.
- The diffusion coefficient (D) is constant (because solutions are dilute).

Concentration Gradient

- Inside the membrane, concentration decreases gradually from one side to the other.
- At steady state:
  - The concentration profile inside the film is **linear**.
  - The slope of this line represents the **concentration gradient** (**Cd – Cr**)
  - Diffusion increases when the **concentration difference increases**
  - Diffusion decreases when **membrane thickness (h) increases**

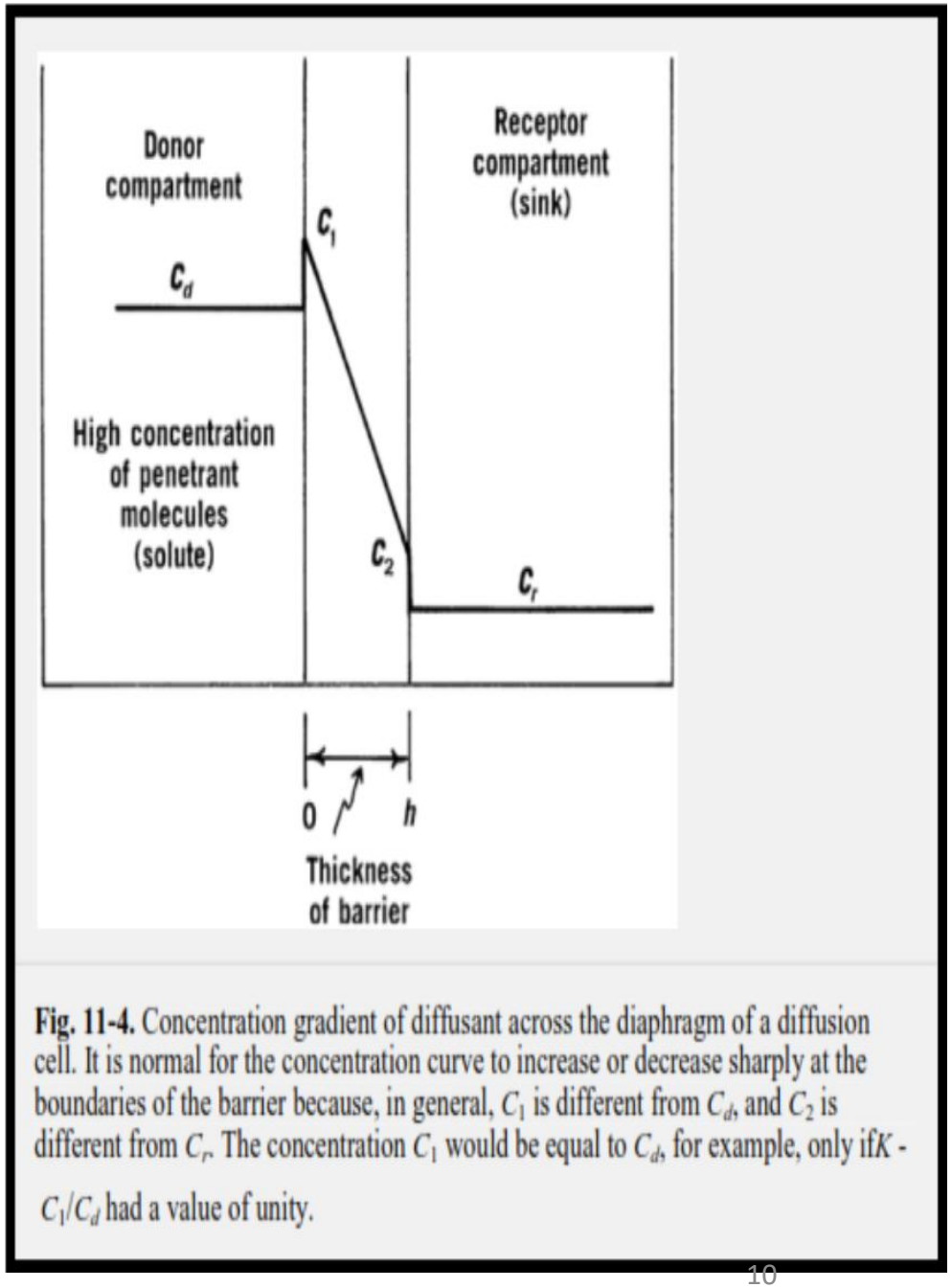

Fig. 11-4. Concentration gradient of diffusant across the diaphragm of a diffusion cell. It is normal for the concentration curve to increase or decrease sharply at the boundaries of the barrier because, in general, C_1 is different from C_d, and C_2 is different from C_r. The concentration C_1 would be equal to C_d, for example, only if $K = C_1/C_d$ had a value of unity.

- After sufficient time, the system reaches **steady state**.
- At steady state:
  - Concentration at each point in the membrane does not change with time dC/dt=0
  - The **flux is constant throughout the membrane**.
  - The concentration profile is a straight line.
- This is extremely important in pharmaceutical systems

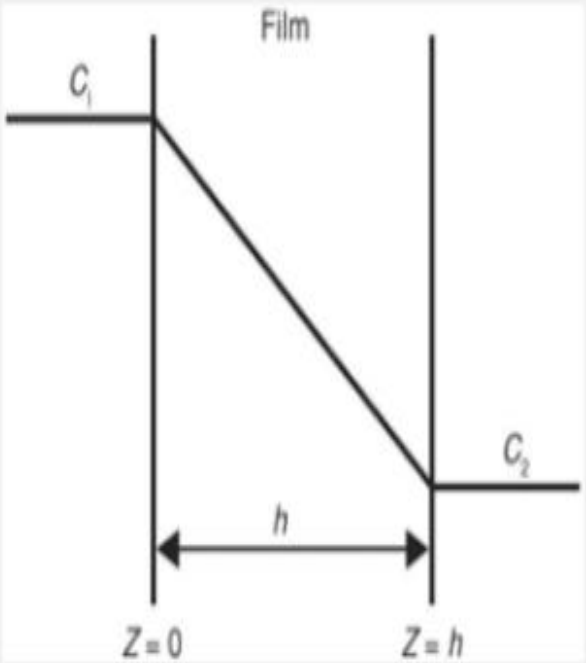

Fig. 11-5. Diffusion across a thin film. The solute molecules diffuse from the well-mixed higher concentration, C_1, to the well-mixed lower concentration, C_2. The concentrations on both sides of the film are kept constant. At steady state, the concentrations remain constant at all points in the film. The concentration profile inside the film is linear, and the flux is constant.

Membrane vs Barrier

- According to Flynn et al.:

Membrane

- A distinct physical or biological film separating two phases.
- Transport can occur by:
  - Passive diffusion
  - Facilitated transport
  - Active transport

Barrier

- A broader term.
- Includes all resistances to diffusion.
- Total barrier = sum of individual membrane resistances.

- In pharmaceutics, we often describe systems in terms of **permeability** rather than resistance
- Resistance and permeability are inversely related.
- In other words, the higher the resistance to diffusion, the lower is the permeability of the diffusing substance.
  - ↑ Thickness → ↑ Resistance → ↓ Permeability
  - ↑ Diffusion coefficient → ↓ Resistance → ↑ Permeabilit

Permeability

- Permeability (P) defined as the diffusion coefficient, D, multiplied by the partition coefficient, K, and divided by the membrane thickness, h.
- It is noteworthy that the permeability coefficient, also called the permeability, P, has units of linear velocity.

$$P = \frac{DK}{h} (\text{cm/sec}) \qquad (11\text{–}15)$$

- The distribution or partition coefficient, *K*, represents the partitioning of the solute between the material of the membrane and the fluid of the reservoir

The Partition Coefficient (K)

- Shows how much the drug "likes" the membrane.
- If K is high → drug enters the membrane easily.
- If K is low → Drug can't easily pass through.

Diffusion Coefficient (D)

- Describes how fast the drug moves inside the membrane.
- Higher D = faster movement (like a bike vs walking).

Example 11-1: Simple Drug Diffusion Through a Membrane

- A newly synthesized steroid is allowed to pass through a siloxane membrane having a thickness, h, of 0.085 cm in a diffusion cell at 25°C. The Partition coefficient K= 2.04 and Diffusion coefficient D = 4.23×10^{-7} cm²/s , Calculate the permeability, P.?

  Partition coefficient K= 2.04

  Diffusion coefficient D = 4.23×10^{-7} cm²/s

  DK= 8.6x 10-7 cm2/sec

$$P = DK/h = (8.6 \times 10^{-7}\text{cm}^2/\text{sec})/0.085\ \text{cm}$$

$$= 1.01 \times 10^{-5}\ \text{cm/sec}$$

Diffusion Driving Forces

- There are numerous diffusional driving forces in pharmaceutical systems. Examples of driving forces in pharmaceutical systems are shown in Table 11-1.

Table 11-1 Driving Forces in Pharmaceutical Systems

Driving Force	Example	Description
Concentration	Passive diffusion	Passive diffusion is a process of mass transfer of individual molecules of a substrate brought about by random molecular motion and associated with a concentration gradient
Pressure	Osmotic drug release	Osmotic drug release systems utilize osmotic pressure as the driving force
Temperature	Lyophilization	Lyophilization (freeze drying) Of a frozen aqueous solution Containing a drug
Electrical potential	Electrophoresis	Electrophoresis involves the movement of charged particles through a liquid under the influence of an applied potential difference

Procedures and Apparatus for Assessing Drug Diffusion

Simple Diffusion Cell (Karth et al.)

- One of the most commonly used and simplest designs is the **diffusion cell**
- **Structure of the Diffusion Cell**
- It consists of:
  - **Donor compartment** → Contains the drug solution
  - **Receptor compartment** → Contains a suitable receiving medium
  - **Membrane** → Placed between the two compartments
  - **Stirrer** → Maintains uniform mixing
  - **Sampling port** → For withdrawing samples
- The membrane is clamped securely (often between Teflon supports).
- They are made of glass, clear plastic, or polymeric materials, are easy to assemble and clean, and allow visibility of the liquids
- They may be **thermostated** and lend themselves to **automatic sample collection** and assay

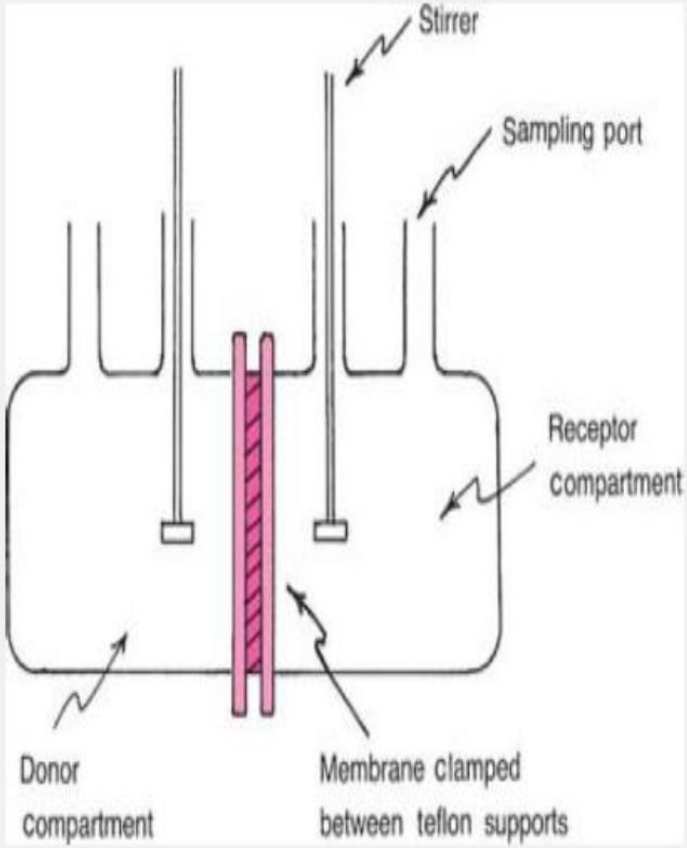

Fig. 11-11. Simple diffusion cell. (From M. G. Karth, W. I. Higuchi, and J. L. Fox, J. Pharm. Sci. **74,** 612, 1985. With permission.)

How It Works

1. The donor chamber is filled with drug solution.
2. The receptor chamber contains a medium (buffer or physiological solution).
3. Drug diffuses from:
4. **High concentration (donor) → Low concentration (receptor)**
5. Samples are withdrawn from the receptor side at specific time intervals.
6. Drug concentration is measured using analytical techniques such as:
    1. UV spectroscopy
    2. Fluorescence
    3. HPLC
    4. Liquid scintillation counting
    5. Mass spectrometry

- **Important Experimental Conditions**
    - System may be **thermostated** (maintained at 37°C for physiological relevance).
    - Stirring prevents concentration gradients within compartments.
    - Experiments may run for several hours.
- This setup allows measurement of:
    - Diffusion rate
    - Permeability coefficient
    - Steady-state flux

Use of Biological Membranes

- In many experiments, especially percutaneous absorption studies:
  - Animal or human skin (often obtained by autopsy) is used.
  - the system is called a **diffusion cell for skin penetration studies**.
- This better simulates real-life drug absorption.
- Scheuplein described a cell for skin penetration experiments made of Pyrex and consisting of two halves, a donor and a receptor chamber, separated by a sample of skin .

Permeability Cell (Wurster et al.)

- Another important apparatus is the **permeability cell**, used particularly for studying diffusion through Stratum corneum (stripped from the human forearm)
- **Experimental Conditions**
  - Constant temperature maintained.
  - Gentle shaking to ensure uniformity.
  - Samples withdrawn at predetermined intervals.
  - Drug concentration analyzed.
- **Mechanism of Drug Transport Across Membranes**
  - Drugs cross membranes by two major mechanisms:

A. Passive Transport

- No energy required.
- Driven by concentration gradient.
- Follows Fick's law.
- Most common mechanism.
- Example: in intestinal absorption, drugs move from High concentration (GI tract) To low concentration (blood circulation)

B. Carrier-Mediated Transport : Involves specific transport proteins.

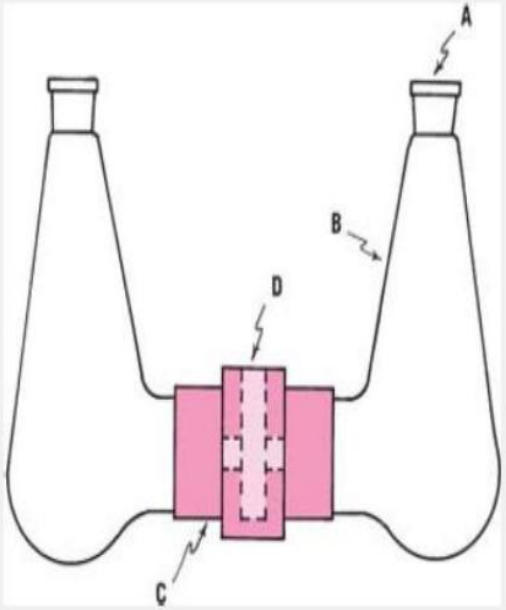

Fig. 11-12. Diffusion cell for permeation through stripped skin layers. The permeant may be in the form of a gas, liquid, or gel. Key: *A*, glass stopper; *B*, glass chamber; *C*, aluminum collar; *D*, membrane and sample holder. (From D. E. Wurster, J. A. Ostrenga, and L. E. Matheson, Jr., J. Pharm. Sci. **68,** 1406, 1410, 1979. With permission.)

Lag Time in Drug Diffusion

- When studying drug diffusion through a membrane (such as skin), we often assume steady-state conditions.
- However, **steady state is not reached immediately** after the experiment begins.
- There is an initial delay before the drug diffuses at a constant rate.This delay is called **Lag Time (tL).**

What Happens at the Beginning of the Experiment?

- When the drug is first placed in the donor compartment:
  - The membrane initially contains **no drug**.
  - Drug molecules begin penetrating into the membrane.
  - A concentration gradient is gradually formed across the membrane.
- During this early phase:
  - The system is in a **non–steady-state condition**.
  - The diffusion rate is changing with time.
  - The plot of cumulative drug permeated vs. time is curved.
- **Transition to Steady State**
- After some time:
  - A **uniform concentration gradient** is established within the membrane.
  - The diffusion rate becomes constant.
  - The cumulative amount permeated vs. time becomes **linear**.
- This linear portion represents **steady-state diffusion**.

Graphical Explanation

- Figure 11-24 is a plot of the amount of butylparaben penetrating through guinea pig skin from a dilute aqueous solution of the penetrant
- If we plot: **Amount permeated (Q) vs. Time (t)**
- We observe:
  1. Initial curved portion → Non-steady state
  2. Linear portion → Steady state
- If the steady-state portion of the line is extrapolated to the time axis, The point where it intersects the time axis is called **Lag Time (tL).**
- This is a theoretical value.
- This is the time required for a penetrant to establish a uniform concentration gradient within the membrane separating the donor from the receptor compartment

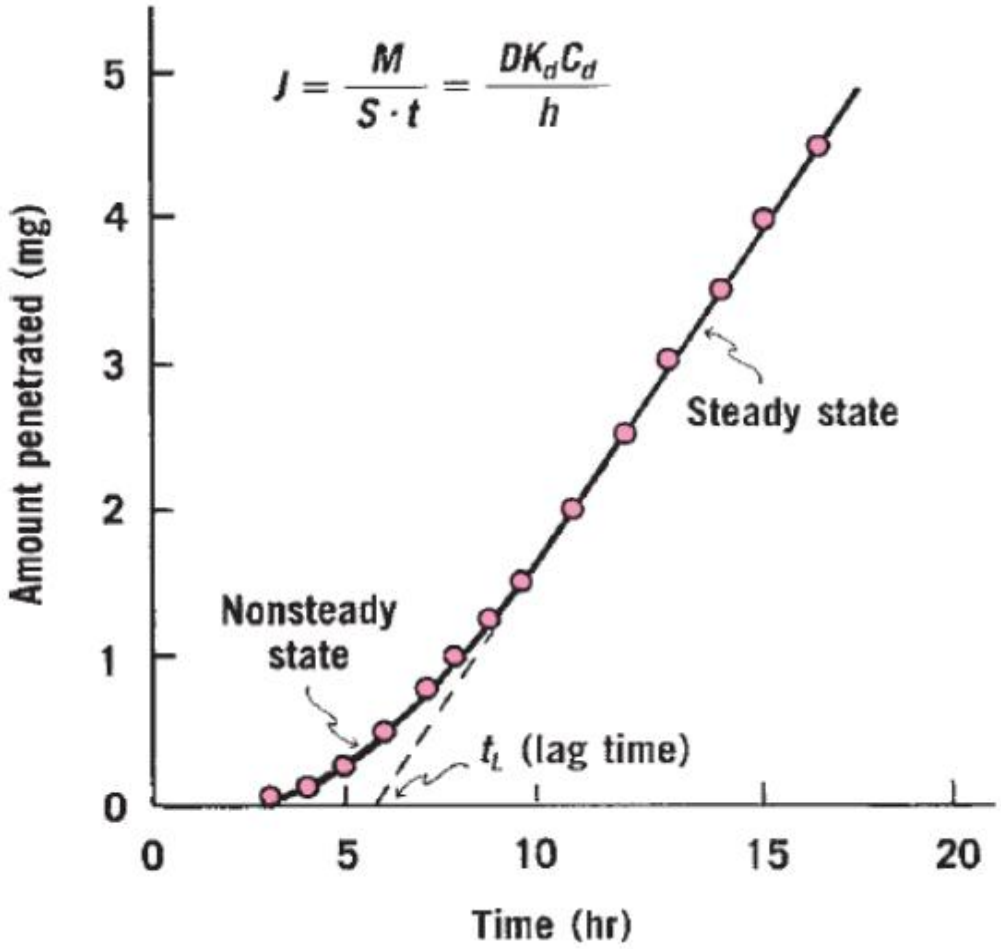

Fig. 11–24. Butyl paraben diffusing through guinea pig skin from aqueous solution. Steady-state and nonsteady-state regions are shown.

Definition of Lag Time

- *A drug dosage form may not reach steady-state diffusion immediately.*
- *Early in the experiment, the system is in a non-steady-state condition.*

- **Lag time (tL)** is:The time required for the penetrant (drug) to establish a uniform concentration gradient within the membrane and reach steady-state diffusion.

Mathematical Expression of Lag Time

- For diffusion through a membrane of thickness **h**:

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

t_L = lag time (time to reach steady-state)
h = membrane thickness
D = diffusion coefficient of the penetrant

Interpretation of the Equation

- From the equation:

❑ **Effect of membrane thickness (h)**

- Lag time is proportional to **h^2**.
- If thickness doubles → lag time increases four times.
- Thicker membrane → longer delay before steady state.

❑ **Effect of diffusion coefficient (D)**

- Lag time is inversely proportional to D.
- If diffusion coefficient increases → lag time decreases.
- Faster diffusing drug → shorter lag time.


תודה
Dankie
Gracias
Спасибо
شكراً
Merci
Takk
Köszönjük
Terima kasih
Grazie
Dziękujemy
Dėkojame
Ďakujeme
Vielen Dank
Paldies
Kiitos
Täname teid
谢谢
Thank You
Tak
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Obrigado
Teşekkür Ederiz
감사합니다
Σας Ευχαριστούμ
ขอบคุณ
Bedankt
Děkujeme vám
ありがとうございます
Tack