

# GPAT

## 2027-28



### BIOPHARMACEUTICS

CLASS- 5



TIME- 8 : 30 P.M

# ABSORPTION OF DRUGS

**UPDATED QUESTIONS TILL GPAT 2026**

# GPAT



VIDEO  
LECTURE



PDF



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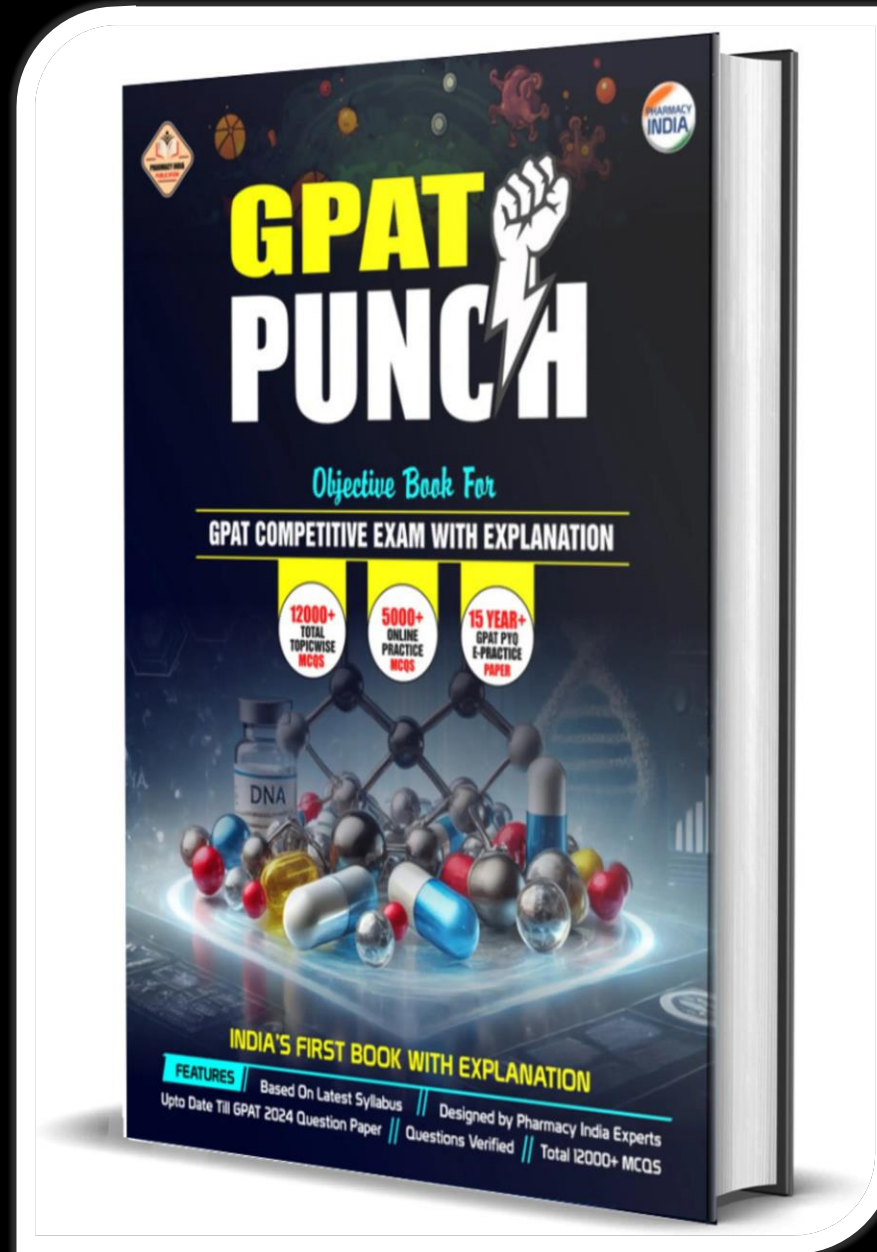




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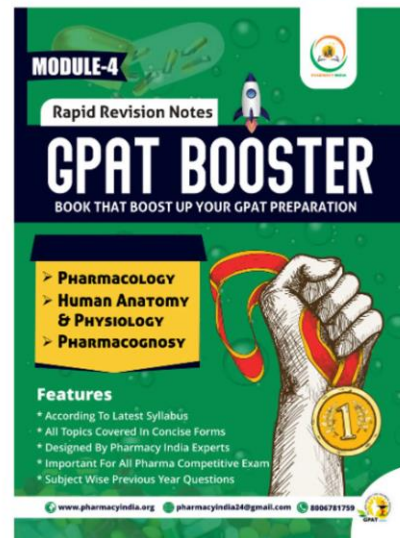
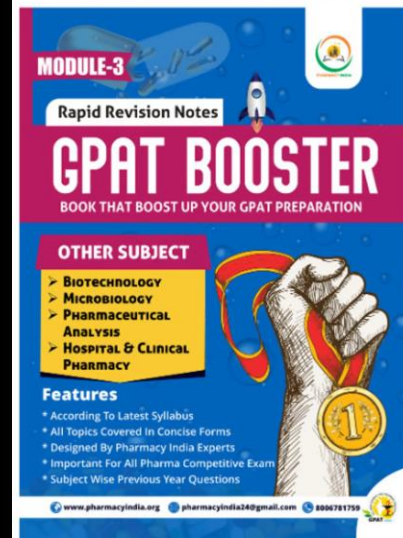
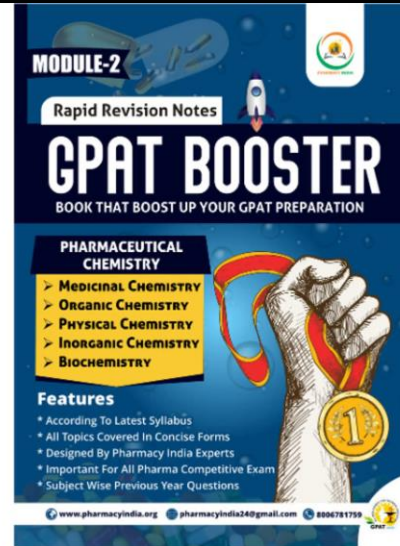
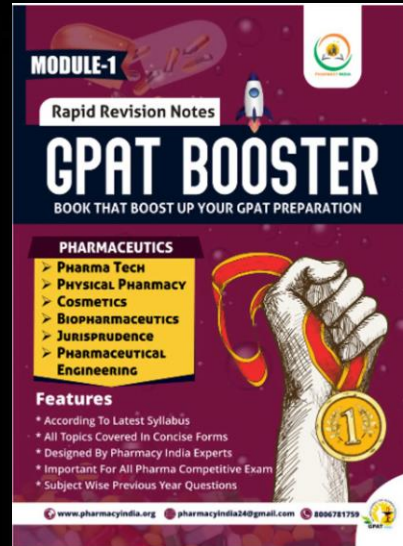
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- Includes short notes for rapid last-minute revision



1.

If the  $pK_a$  of phenobarbitone is 3.4, what fraction of drug would be ionized at pH 4.4? [GPAT 2026]

A. 0.90

B. 0.50

C. 1.00

D. 0.01



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1.

If the  $pK_a$  of phenobarbitone is 3.4, what fraction of drug would be ionized at pH 4.4? [GPAT 2026]

A. 0.90

B. 0.50

C. 1.00

D. 0.01

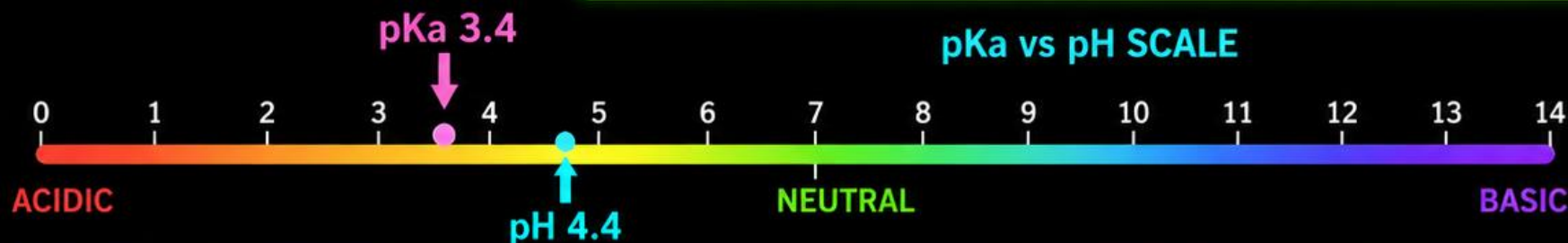


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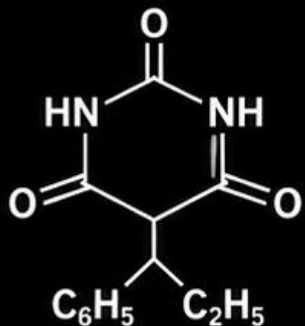


# PHENOBARBITAL IONIZATION AT pH 4.4

PHENOBARBITAL IS A **WEAK ACID** ( $pK_a = 3.4$ )

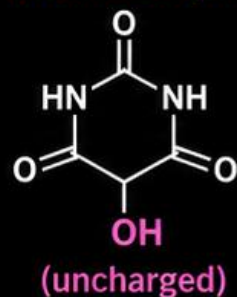


PHENOBARBITAL

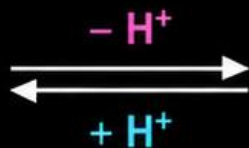
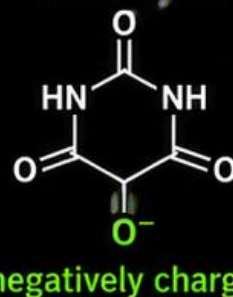


WEAK ACID EQUILIBRIUM

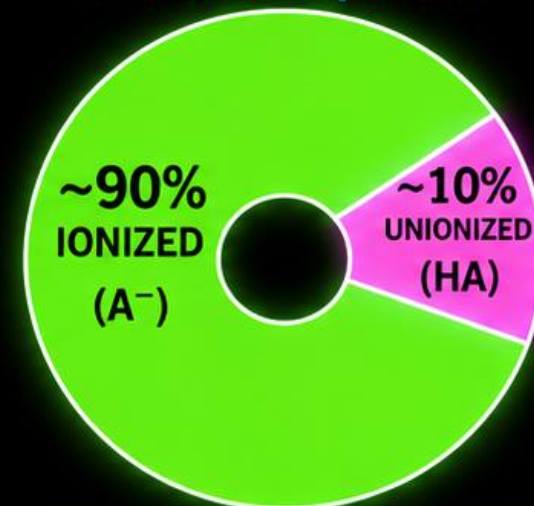
UNIONIZED (HA)



IONIZED ( $A^-$ )



SPECIES AT pH 4.4



IONIZED FORM PREDOMINATES  
 **$\approx 90\%$  IONIZED**



1) Henderson-Hasselbalch for weak acids:

$$pH = pK_a + \log \left( \frac{[A^-]}{[HA]} \right)$$



2) At pH 4.4:

$$pH - pK_a = 4.4 - 3.4 = 1$$

$$\log \frac{[A^-]}{[HA]} = 1$$

$$\Rightarrow [A^-]/[HA] = 10$$



3) Ratio of ionized to unionized:

$$[A^-]/[HA] = 10:1$$

Ionized form is 10 times more than unionized.



4) Fraction ionized:

$$\begin{aligned} \text{Fraction ionized} &= \frac{10}{10 + 1} \\ &= 0.909 \approx 0.90 \\ &\approx \mathbf{90\% \text{ ionized}} \end{aligned}$$



AT pH 4.4 (ONE UNIT ABOVE  $pK_a$ ), PHENOBARBITAL IS  **$\approx 90\%$  IONIZED.**





2.

The relationship between pH of the environment, pKa of the drug and the extent of ionization is given by: **[GPAT 2026]**

A. Fick's law

B. Henderson–Hasselbalch equation

C. Law of mass action

D. Noyes–Whitney equation



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2.

The relationship between pH of the environment, pKa of the drug and the extent of ionization is given by: **[GPAT 2026]**

A. Fick's law

**B. Henderson–Hasselbalch equation**

C. Law of mass action

D. Noyes–Whitney equation



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# HENDERSON-HASSELBALCH EQUATION

Links pH, pKa, and degree of ionization → Predicts drug absorption & membrane permeability

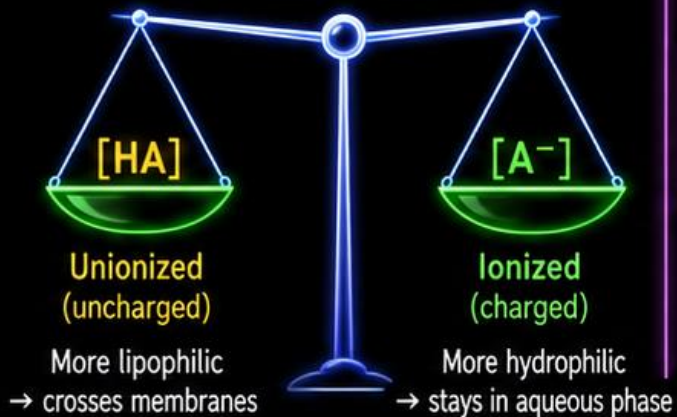
## WEAK ACIDS

$$\text{pH} = \text{pKa} + \log \frac{[\text{A}^-]}{[\text{HA}]}$$

$\text{A}^-$  = ionized (charged)

$\text{HA}$  = unionized (uncharged)

## ACID-BASE BALANCE



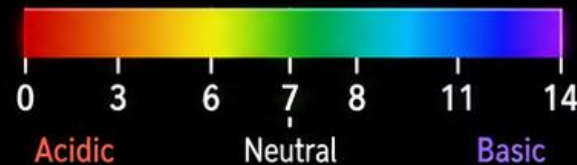
## WEAK BASES

$$\text{pH} = \text{pKa} + \log \frac{[\text{B}]}{[\text{BH}^+]}$$

$\text{B}$  = unionized (uncharged)

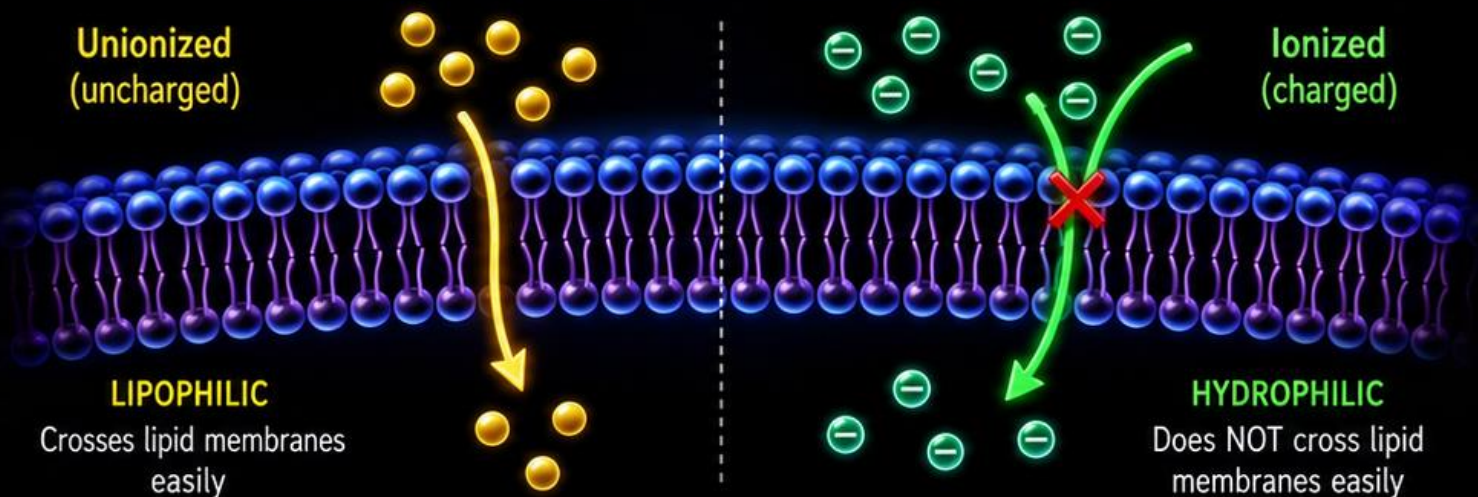
$\text{BH}^+$  = ionized (charged)

## pH SCALE (AT 25°C)



- ↑ pH > pKa → more ionized
- = pH = pKa → 50% ionized
- ↓ pH < pKa → more unionized

## IONIZED vs UNIONIZED: EFFECT ON MEMBRANE PERMEABILITY



## KEY TAKEAWAYS

- The Henderson-Hasselbalch equation quantifies the ratio of ionized to unionized drug.
- Unionized forms are lipid-soluble → better absorption.
- Ionized forms are water-soluble → less membrane permeation.
- Use it to predict absorption in different pH environments (e.g., stomach vs intestine, blood vs tissues).





3.

**The Wagner–Nelson method is used to determine which rate constant? [GPAT 2026]**

- A. Elimination rate constant**
- B. Absorption rate constant**
- C. Dissociation rate constant**
- D. Distribution rate constant**



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3.

**The Wagner–Nelson method is used to determine which rate constant? [GPAT 2026]**

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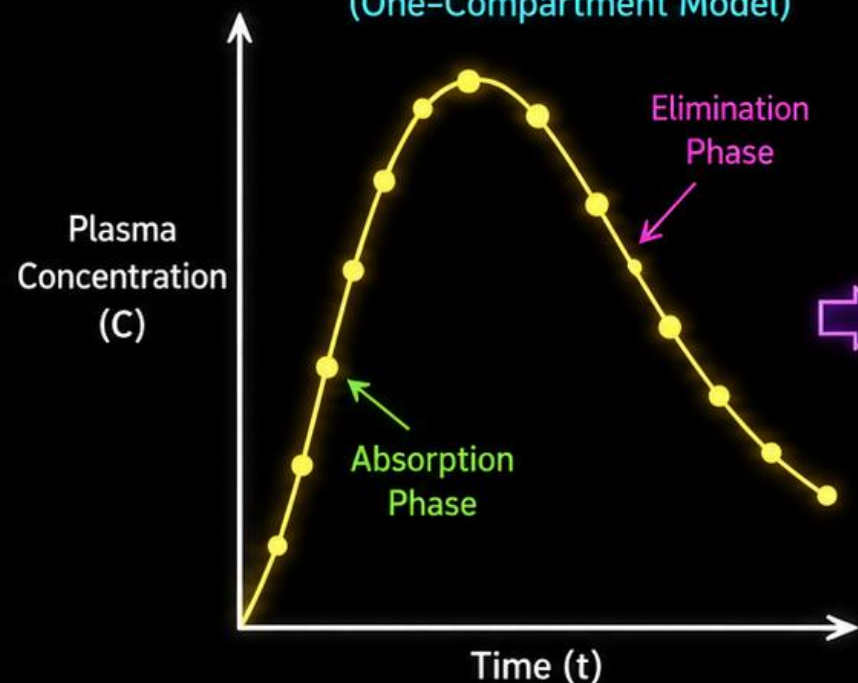


# WAGNER-NELSON METHOD



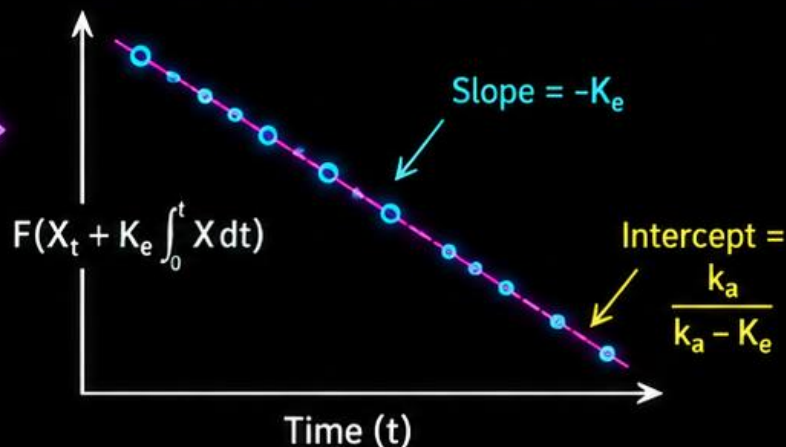
Used to estimate the **ABSORPTION RATE CONSTANT** ( $K_a$ )  
from oral plasma concentration-time data

Oral Plasma Concentration-Time Curve  
(One-Compartment Model)



Wagner-Nelson Plot  
(Linear Relationship)

$$F \left( X_t + K_e \int_0^t X dt \right) = \frac{k_a}{k_a - K_e} e^{-K_e t} + C$$



From intercept and known  $K_e$ ,  
solve for  $k_a$  (absorption rate constant)



**ESTIMATES ABSORPTION RATE  
CONSTANT ( $K_a$ )**

Determines how fast the drug  
is absorbed after oral dosing.



**MODEL-INDEPENDENT**

Does not require knowledge of  
bioavailability ( $F$ ) or volume of  
distribution ( $V_d$ ).



**APPLICABLE TO  
ONE-COMPARTMENT DRUGS**

Assumes first-order absorption  
and elimination.



**USES ORAL PLASMA  
CONCENTRATION-TIME DATA**

Based on the area under the curve  
up to time  $t$  and observed  
concentrations.



The Wagner-Nelson method is a simple and robust approach to quantify the **rate of absorption** ( $K_a$ ) from oral data, essential for understanding **bioavailability** and **formulation performance**.





4.

When the highest dose of a drug is soluble in 250 mL or less of aqueous medium over the pH range from 1 to 6.8 at 37°C and absorption in humans is  $\geq 85\%$ , the drug is classified as: **[GPAT 2025]**

- A. BCS Class I
- B. BCS Class III
- C. BCS Class II
- D. BCS Class IV



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4.

When the highest dose of a drug is soluble in 250 mL or less of aqueous medium over the pH range from 1 to 6.8 at 37°C and absorption in humans is  $\geq 85\%$ , the drug is classified as: [GPAT 2025]

A. BCS Class I

B. BCS Class III

C. BCS Class II

D. BCS Class IV



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# BCS CLASS I DRUGS

**HIGH SOLUBILITY + HIGH PERMEABILITY = EXCELLENT ORAL ABSORPTION**

## BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

|                   | HIGH SOLUBILITY                                                                                                                              | LOW SOLUBILITY                                                                                                                              |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| HIGH PERMEABILITY | <b>CLASS I</b><br><br>HIGH SOLUBILITY<br>HIGH PERMEABILITY  | <b>CLASS II</b><br><br>LOW SOLUBILITY<br>HIGH PERMEABILITY |
| LOW PERMEABILITY  | <b>CLASS III</b><br><br>HIGH SOLUBILITY<br>LOW PERMEABILITY | <b>CLASS IV</b><br><br>LOW SOLUBILITY<br>LOW PERMEABILITY  |



### HIGH SOLUBILITY

The highest dose dissolves in **250 mL or less** of aqueous medium over **pH 1 to 6.8** at **37°C**.



### HIGH PERMEABILITY

At least **85%** of the dose is absorbed in humans.



### RESULT

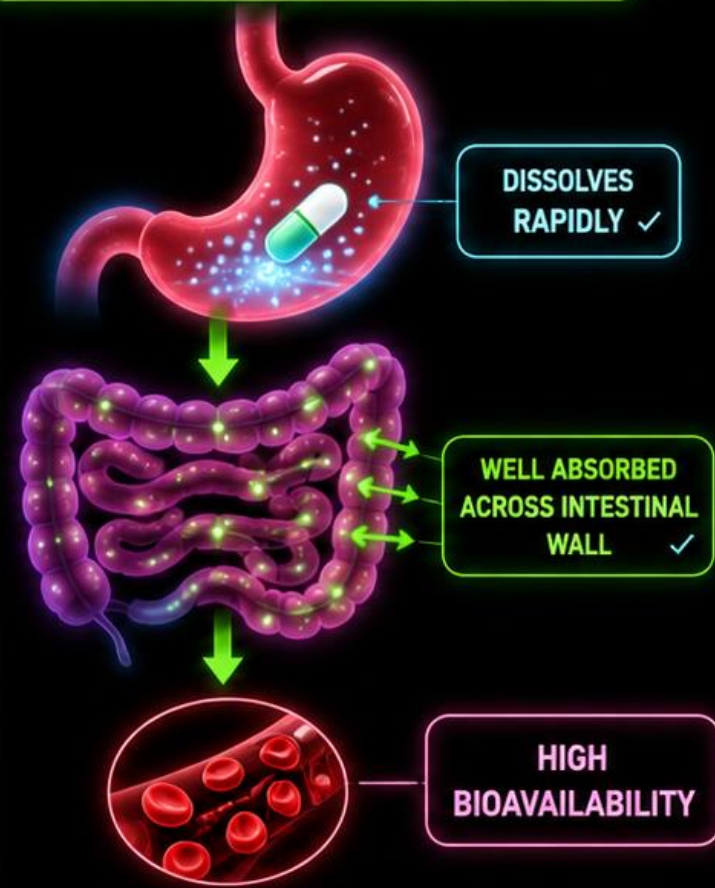
Class I drugs usually show **good oral absorption** and **high bioavailability**.



### IMPLICATION

Absorption is **not the rate-limiting** step—formulation changes rarely needed to improve bioavailability.

### SMOOTH JOURNEY TO SYSTEMIC CIRCULATION



**CLASS I = HIGH SOLUBILITY + HIGH PERMEABILITY → GOOD ORAL ABSORPTION & HIGH BIOAVAILABILITY**







5.

**Which one of the following statements holds true for passive diffusion? [GPAT-2022]**

- A. Greater the area and greater the thickness, faster is the diffusion**
- B. Rate of drug transfer is directly proportional to the concentration gradient between GI fluids and blood compartment**
- C. Rate of transfer of ionised drug species is 3–4 times the rate for unionised drug species**
- D. Greater the membrane/water partition coefficient of drug, slower is the absorption**



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5.

**Which one of the following statements holds true for passive diffusion? [GPAT-2022]**

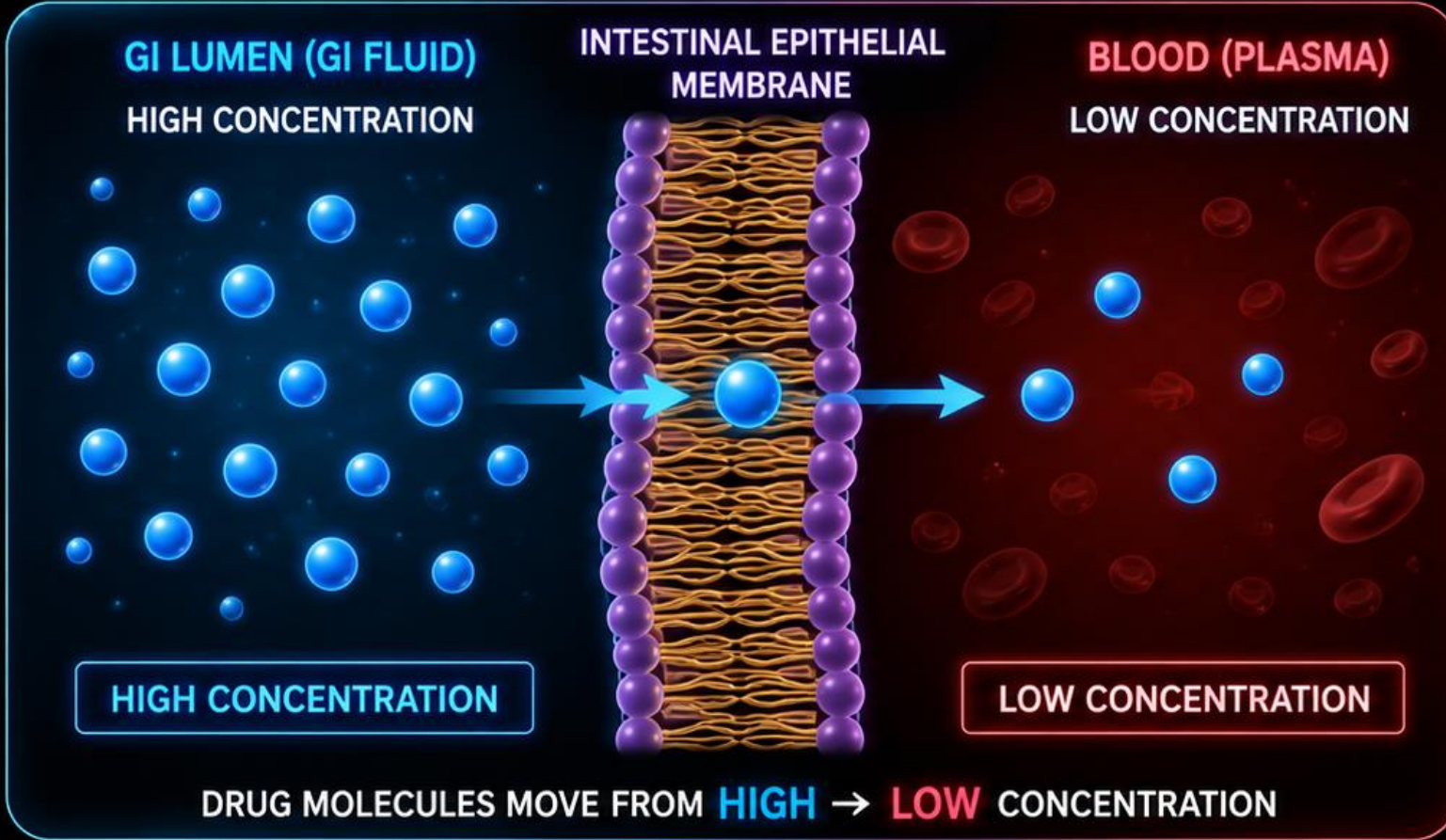
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# PASSIVE DIFFUSION PRINCIPLE

Drugs move down their **concentration gradient**—naturally, simply, effectively.



**PASSIVE DIFFUSION = SIMPLE, NATURAL, AND FUNDAMENTAL**



## DIRECTLY PROPORTIONAL

Rate of drug transfer is directly proportional to the **concentration gradient** across the membrane.



## HIGH → LOW

Drug molecules move from **higher** concentration in GI fluid to **lower** concentration in blood.



## NON-SATURABLE

No carrier is involved; increasing concentration increases the rate proportionally.



## NO ENERGY REQUIRED

A passive process driven by the natural concentration gradient.



## MAJOR ABSORPTION MECHANISM

Responsible for the absorption of many drugs, especially lipophilic and unionized forms.





6.

**Decrease in effective surface area available to the dissolution medium leading to a fall in dissolution rate may happen due to:**

**[GPAT-2022]**

- A. Addition of cyclodextrin**
- B. Addition of surfactant to increase the surface tension**
- C. Addition of hydrophilic diluent**
- D. Surface charges due to extreme particle size reduction**



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6.

**Decrease in effective surface area available to the dissolution medium leading to a fall in dissolution rate may happen due to:**

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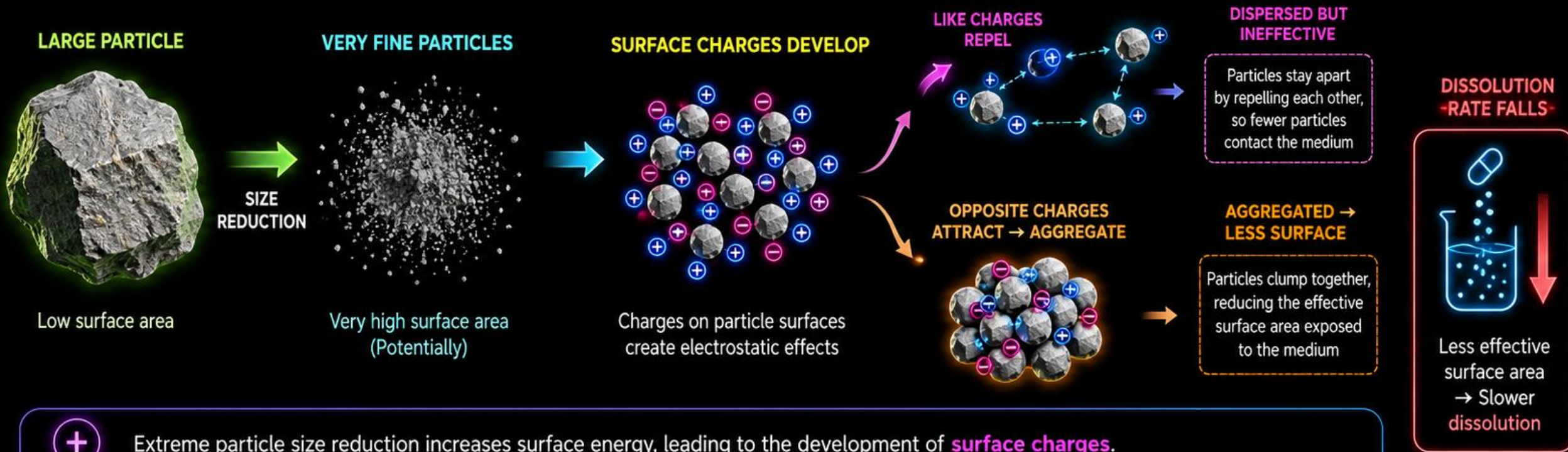
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# WHY SURFACE CHARGES CAN DECREASE DISSOLUTION RATE

Extreme size reduction → Surface charges → Less effective surface area → Lower dissolution rate



- ⊕ Extreme particle size reduction increases surface energy, leading to the development of **surface charges**.
- ↔ Like charges cause **repulsion**, keeping particles apart and **limiting the number of particles** interacting with the dissolution medium.
- ⦿ Opposite charges cause **aggregation**, forming larger clumps with much **less effective surface area**.
- ⬇️ Reduced effective surface area available to the medium → fewer molecules dissolve per unit time → **dissolution rate decreases**.





7.

**For very weak acidic drugs with  $pK_a > 8$ : [GPAT-2021]**

- A. They are unionized at all pH, hence absorption is rapid and independent of GI pH
- B. They are affected by changes in pH, hence absorption is pH dependent
- C. They are ionized in the entire pH range of GIT, hence poorly absorbed from GIT
- D. They are ionized in the gastric pH, hence better absorbed from the stomach



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7.

**For very weak acidic drugs with  $pK_a > 8$ : [GPAT-2021]**

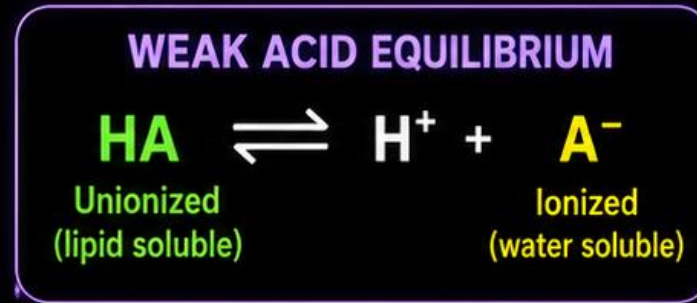
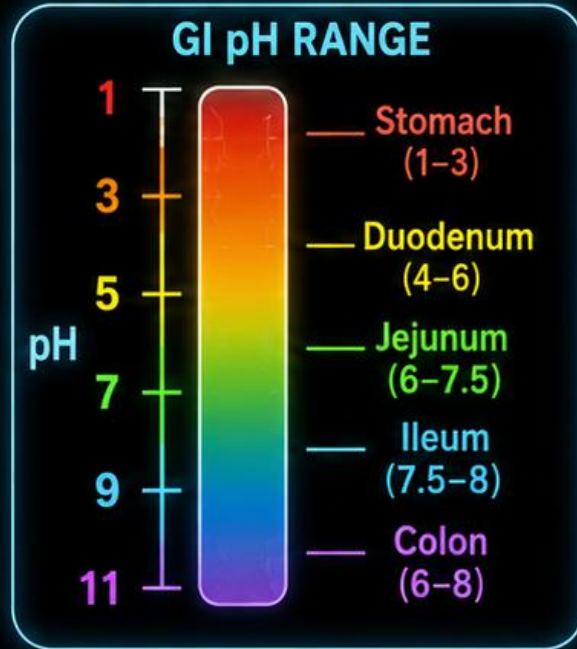
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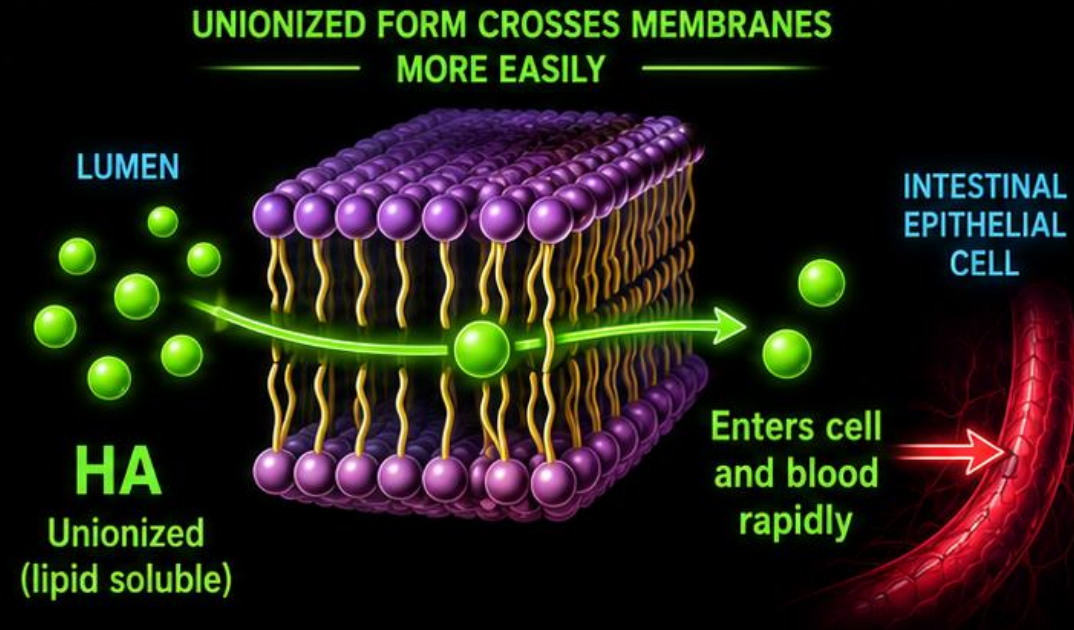
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# VERY WEAK ACIDIC DRUGS (pKa > 8)

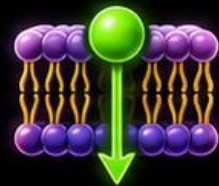
Mostly **UNIONIZED** in the GI Tract → **Rapid, pH-INDEPENDENT** Absorption



If  $\text{pKa} > 8$ , then at GI pH (1-8):  
 $\text{pH} < \text{pKa} \rightarrow \text{HA}$  predominates



**MOSTLY UNIONIZED**  
throughout the  
GI pH range  
when  $\text{pKa} > 8$ .



**UNIONIZED (HA)**  
is more lipid soluble  
and diffuses across  
membranes easily.



**RAPID ABSORPTION**  
occurs along the  
entire GI tract.



**pH-INDEPENDENT  
ABSORPTION**  
because the unionized  
fraction remains high  
across GI pH.



**Bottom Line:** Very weak acidic drugs ( $\text{pKa} > 8$ ) stay mostly **UNIONIZED** in all parts of the GI tract →  
Cross membranes easily → Absorbed **RAPIDLY** and largely **INDEPENDENT** of GI pH.





8.

The complexation of quinine with hexyl is an example of absorption by: **[GPAT-2020]**

A. Convective transport

B. Facilitated transport

C. Pinocytosis

D. Ion pair transport



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The complexation of quinine with hexyl is an example of absorption by: **[GPAT-2020]**

A. Convective transport

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C. Pinocytosis

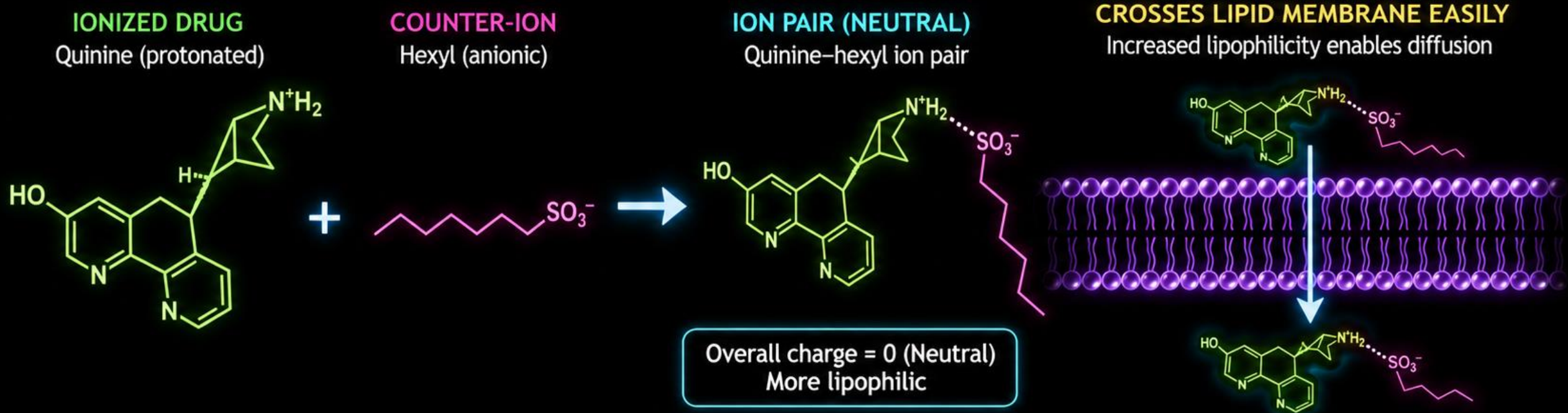
**D. Ion pair transport**



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# ION-PAIR TRANSPORT

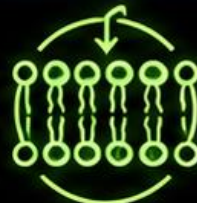
Complexation of quinine with hexyl is an example of ion-pair transport.



Ionized drug forms a neutral ion pair with an oppositely charged counter-ion.



Ion pair is more lipophilic than the ionized drug alone.



The lipophilic ion pair diffuses across the lipid membrane more easily.



Inside, the ion pair dissociates, releasing the drug in its ionized form.

ION-PAIR TRANSPORT = NEUTRAL COMPLEX FORMATION → GREATER LIPOPHILICITY → EASY MEMBRANE PERMEATION





9.

**Fraction of administered dose, which may be in the form of an ester or salt of active drug, is termed as: [GPAT-2020]**

- A. Activity factor**
- B. Formulation factor**
- C. Intrinsic factor**
- D. Salt factor**



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**Fraction of administered dose, which may be in the form of an ester or salt of active drug, is termed as: [GPAT-2020]**

**A. Activity factor**

**B. Formulation factor**

**C. Intrinsic factor**

**D. Salt factor**



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# SALT FACTOR



The **fraction** of the **administered dose** that represents the **active drug** when the product is present as a **salt or ester** form.

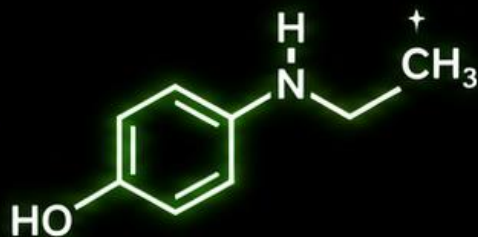
**SALT / ESTER  
FORM**



**Administered Dose**  
(contains salt/ester)



**RELEASES  
ACTIVE DRUG**



**Active Drug**  
(the therapeutic moiety)



Salt factor accounts for the difference in **molecular weight** between the **active drug** and its **salt or ester**.



It expresses the **fraction** of the total salt/ester dose that is actually **active drug**.



Used to calculate the **true amount** of **active drug** delivered to the body from a given dose of **salt or ester**.



Ensures **accurate dosing**, **potency** labeling, and **therapeutic equivalence** in formulations.

**SALT  
FACTOR**

$$= \frac{\text{Molecular Weight of Active Drug}}{\text{Molecular Weight of Salt or Ester}} \times 100$$



Salt factor **converts** the amount of **salt/ester** administered into the equivalent amount of **active drug**.



10.

**Volume of blood that flows per unit time per unit volume of tissue is: [GPAT-2019]**

- A. Residence time
- B. Elimination rate
- C. Gastric emptying rate
- D. Perfusion rate



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10.

**Volume of blood that flows per unit time per unit volume of tissue is: [GPAT-2019]**

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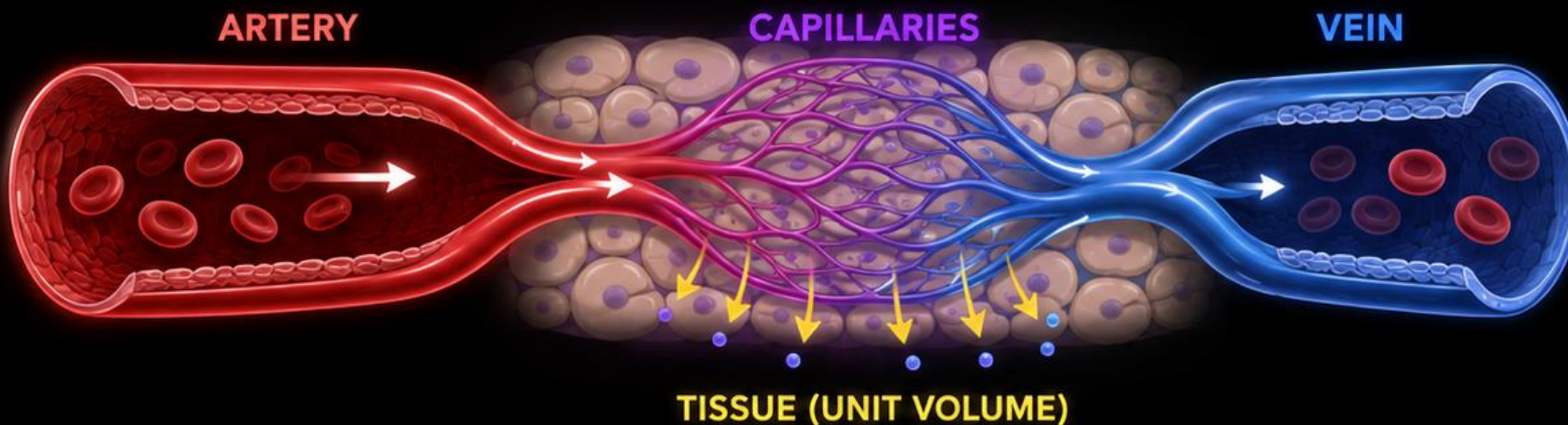
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# PERFUSION RATE



Perfusion rate is the **VOLUME OF BLOOD FLOWING** per unit time through a **UNIT VOLUME OF TISSUE**.



**PERFUSION RATE (P)**

=

**BLOOD FLOW (Q)**

**TISSUE VOLUME ( $V_T$ )**

Units: mL blood / (mL tissue · min)  
or mL / 100 g tissue / min



## MAINTAINS CONCENTRATION GRADIENT

Continuous blood flow removes drug from the absorption site, maintaining a higher drug concentration in the tissue compared to blood.



## CARRIES DRUG AWAY FROM SITE

Perfusion transports absorbed drug away from the site, reducing local saturation and back diffusion.



## INFLUENCES ABSORPTION RATE

Higher perfusion generally increases the rate and extent of drug absorption by preventing stagnation.



## AFFECTS DISTRIBUTION

Greater perfusion delivers drug more rapidly to systemic circulation, enhancing distribution to other tissues.



## FACTORS AFFECTING PERFUSION:



CARDIAC OUTPUT



VASCULAR RESISTANCE



TISSUE TEMPERATURE



PHYSICAL ACTIVITY



11.

**In plasma, phenobarbital is present as ionized and unionized forms in equal amount because: [GPAT-2018]**

- A. It is a weakly acidic drug**
- B. It is a weakly basic drug**
- C. pH of plasma is 6.8**
- D. pKa of phenobarbital is 7.4**



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11.

**In plasma, phenobarbital is present as ionized and unionized forms in equal amount because: [GPAT-2018]**

- A. It is a weakly acidic drug
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- C. pH of plasma is 6.8
- D. pKa of phenobarbital is 7.4**

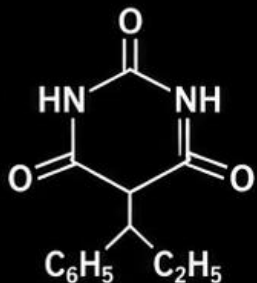




# WHY PHENOBARBITAL IS 50% IONIZED & 50% UNIONIZED

PHENOBARBITAL IS A **WEAK ACID** AND IN PLASMA ( $\text{pH} \approx 7.4$ ),  $\text{pH} = \text{pKa}$  (7.4)

## PHENOBARBITAL IS A WEAK ACID



Exists in two forms in solution:

**ionized** ( $\text{A}^-$ )  
and **unionized** ( $\text{HA}$ )

PLASMA  $\text{pH} \approx 7.4$



Physiologic plasma pH is about **7.4**

$\text{pKa}$  OF PHENOBARBITAL  $\approx 7.4$



The  $\text{pKa}$  of phenobarbital is about **7.4**

## HENDERSON-HASSELBALCH IDEA (FOR WEAK ACIDS)

Henderson-Hasselbalch equation:

$$\text{pH} = \text{pKa} + \log \frac{[\text{A}^-]}{[\text{HA}]}$$

$$\begin{aligned} \text{When } \text{pH} &= \text{pKa} \\ \Rightarrow \\ \log \frac{[\text{A}^-]}{[\text{HA}]} &= 0 \\ \Rightarrow \\ [\text{A}^-] &= [\text{HA}] \end{aligned}$$

## IN PLASMA

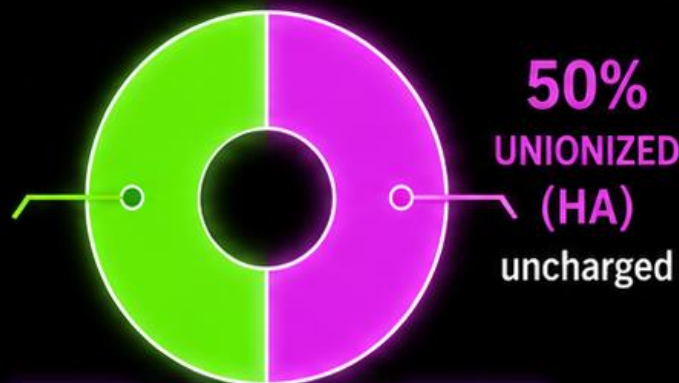
Since  $\text{pH} = \text{pKa}$  ( $7.4 \approx 7.4$ )



Phenobarbital exists in equal amounts of **ionized** ( $\text{A}^-$ ) and **unionized** ( $\text{HA}$ ) forms.

RESULT: EQUAL FORMS

**50% IONIZED** ( $\text{A}^-$ )  
charged



Equal ionized and unionized forms in plasma



**TAKEAWAY:** When  $\text{pH}$  equals  $\text{pKa}$ , a weak acid exists **50% ionized** and **50% unionized**.



**12. Very weak bases having  $pK_a < 5$ : [GPAT-2018]**

- A. Are ionized in the entire pH range of GIT**
- B. Are absorbed only in stomach**
- C. Are unionized at all pH values**
- D. None of these**



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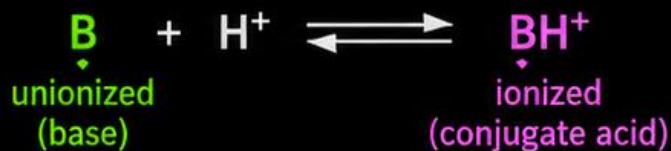
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# VERY WEAK BASES (pKa < 5)

Very weak bases have low pKa, so in the GI pH range they remain **mostly unionized**.  
The **unionized base form** is the **major form** and absorption is **generally favorable**.

## WEAK BASE EQUILIBRIUM



$$\text{pKa} = \text{pH} + \log \frac{[\text{BH}^+]}{[\text{B}]}$$

pH > pKa → mostly **B (unionized)**

pH < pKa → mostly **BH<sup>+</sup> (ionized)**

## GI pH RANGE

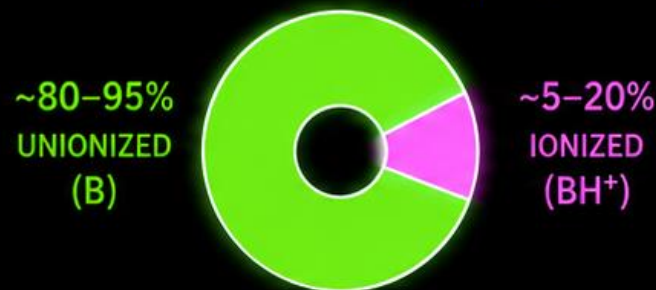
Typical pH in the GI tract



Since pKa < 5, GI pH (mostly > pKa) keeps the base **mostly unionized**.

## FORM DISTRIBUTION

In GI pH range (pH > pKa)



**MAJOR FORM:**  
**UNIONIZED BASE (B)**

## WHY THIS MATTERS



**Mostly unionized**  
→ neutral species cross membranes more easily



**Better membrane permeation**  
→ improved absorption



**Extensive absorption**  
from stomach and intestine



**Generally favorable**  
oral bioavailability



**Very weak bases (pKa < 5) stay mostly unionized across GI pH.**





**13.** If the  $pK_a$  of lidocaine is 7.9 and pH of infected tissue is 8.9, the fraction of drug in ionized form will be: **[GATE-2002, GPAT-2017]**

A. 10%

B. 1%

C. 90%

D. 99%



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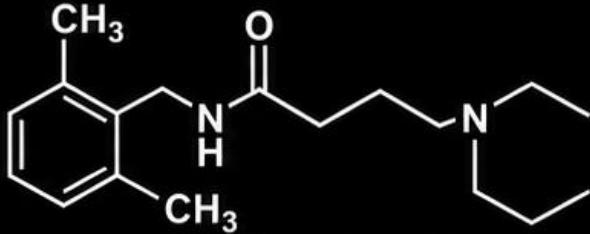


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# LIDOCAINE IONIZATION AT pH 8.9

LIDOCAINE IS A **WEAK BASE** ( $pK_a = 7.9$ )

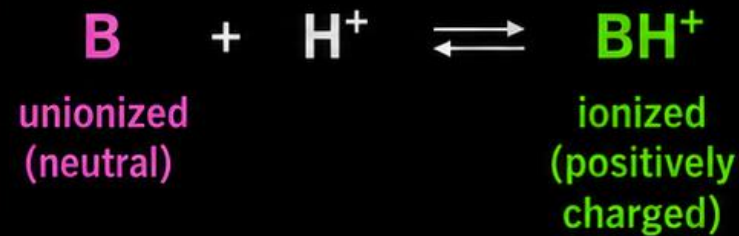
## LIDOCAINE (WEAK BASE)



**B** = unionized (uncharged)

**BH<sup>+</sup>** = ionized (positively charged)

## EQUILIBRIUM (WEAK BASE)



## HENDERSON-HASSELBALCH FOR WEAK BASES

$$\text{pH} = \text{pK}_a + \log \frac{\text{B}}{\text{BH}^+}$$

B = unionized base

**BH<sup>+</sup>** = ionized base (conjugate acid)

## CALCULATION

Given:

$pK_a = 7.9$

$pH = 8.9$

$$\text{pH} = \text{pK}_a + \log \frac{\text{B}}{\text{BH}^+}$$

$$8.9 = 7.9 + \log \frac{\text{B}}{\text{BH}^+}$$

$$8.9 - 7.9 = \log \frac{\text{B}}{\text{BH}^+}$$

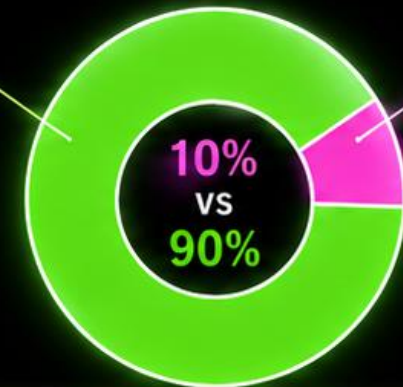
$$1 = \log \frac{\text{B}}{\text{BH}^+}$$

$$\frac{\text{B}}{\text{BH}^+} = 10$$

So, there are 10 parts unionized (**B**) for every 1 part ionized (**BH<sup>+</sup>**)

## FRACTIONS AT pH 8.9 ( $pK_a = 7.9$ )

≈**90%**  
UNIONIZED  
(**B**)  
(NEUTRAL)



≈**10%**  
IONIZED  
(**BH<sup>+</sup>**)  
(POSITIVE)



At **pH** one unit above **pK<sub>a</sub>**, a weak base is about **10% ionized** and **90% unionized**.



14.

**Hixson–Crowell's cube root law of dissolution states that: [GPAT-2017]**

- A. There is a change in particle size and surface area during dissolution of drug**
- B. Dissolution process is controlled by diffusion of molecules/ions**
- C. High free energy of activation is required for solution**
- D. Renewal of surface fluid layer around drug particle**



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# HIXSON-CROWELL CUBE ROOT LAW OF DISSOLUTION

Describes dissolution of a **SHRINKING PARTICLE**, where **SURFACE AREA DECREASES** as the solid dissolves over time.



## KEY IDEA

As dissolution proceeds, the particle gets smaller, so its **surface area continuously decreases**.



## CONSEQUENCE

The dissolution rate is **not constant** because surface area is not constant—it keeps getting smaller.



## HIXSON-CROWELL EQUATION

$$W_0^{1/3} - W_t^{1/3} = kt$$

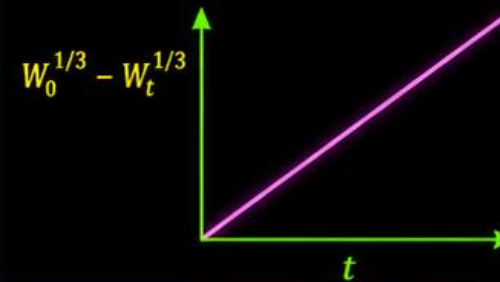
$W_0$  = initial amount of solid

$W_t$  = amount of solid remaining at time  $t$

$k$  = Hixson-Crowell rate constant

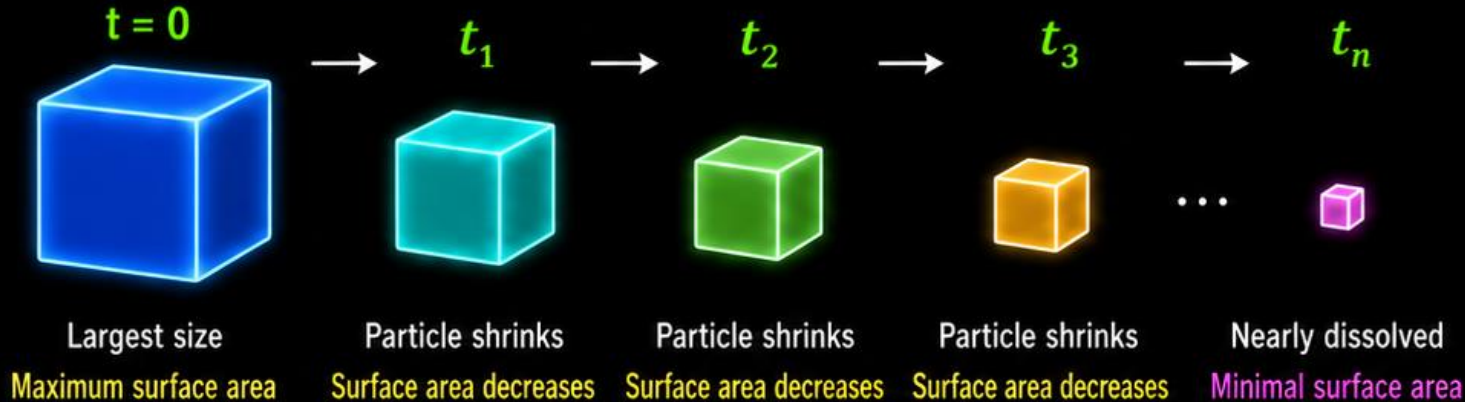
$t$  = time

## LINEAR RELATION



A plot of  $W_0^{1/3} - W_t^{1/3}$  vs.  $t$  is linear with slope =  $k$

## DISSOLUTION OVER TIME: SHRINKING PARTICLE



Hixson-Crowell law describes systems where **size** and **surface area decrease** during dissolution.





15.

**Indicate which of the following statements is true: [GPAT-2017]**

- A. A weakly acidic drug is unionized when pH of the solution is at least 2 pH units below its pKa**
- B. Acidic drugs are nonionized at pH 9**
- C. Acidic drugs are less soluble in alkaline solution**
- D. The higher the pKa of a weak acid, the stronger is acid**



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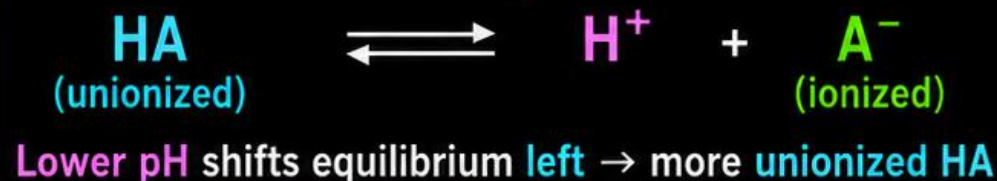
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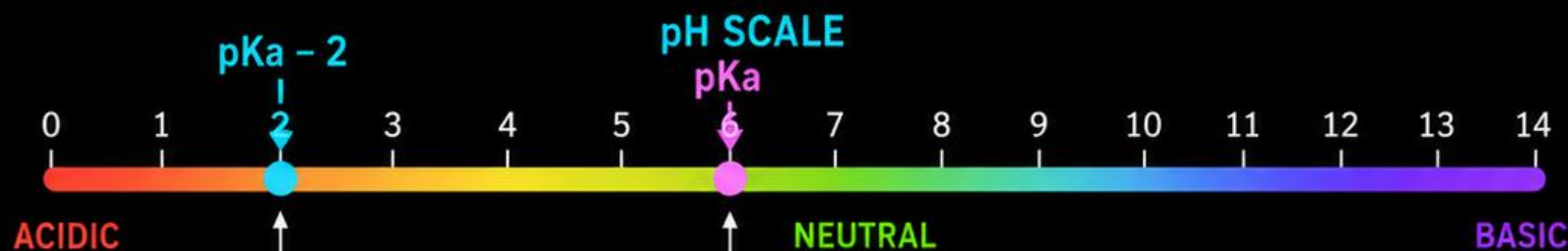
# WHEN A WEAKLY ACIDIC DRUG IS UNIONIZED

A WEAK ACID IS MORE UNIONIZED WHEN THE MEDIUM pH IS BELOW ITS pKa.

## WEAK ACID EQUILIBRIUM



At pH below pKa, the HA form predominates.  
At pH  $\geq 2$  units below pKa, the drug is predominantly unionized.



**pH  $\leq$  pKa - 2**  
Predominantly unionized HA  
(~90% or more)

**pH between pKa - 2 and pKa**  
Unionized HA > ionized A<sup>-</sup>  
(more unionized)

**pH  $\geq$  pKa**  
Ionized A<sup>-</sup> predominates  
(less unionized)

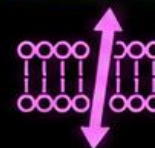
## WHY UNIONIZATION MATTERS



**UNIONIZED HA**  
(uncharged)



**MORE LIPID SOLUBLE**  
Dissolves better in lipid membranes



**BETTER MEMBRANE PERMEATION**  
Easier absorption



**Weak acids** are mainly unionized when pH is at least 2 units below pKa.





16.

**Which of the following equation is correct to determine the pH of weak base?**

**[GPAT-2016]**

- A.  $\text{pH} = \text{pK}_a + \log \text{ionized drug concentration} / \text{unionized drug concentration}$**
- B.  $\text{pH} = \text{pK}_a + \log \text{unionized drug concentration} / \text{ionized drug concentration}$**
- C.  $\text{pH} = \text{pK}_a - \log \text{ionized drug concentration} / \text{unionized drug concentration}$**
- D.  $\text{pH} = \text{pK}_a + \text{antilog unionized drug concentration} / \text{ionized drug concentration}$**



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D.  $\text{pH} = \text{pK}_a + \text{antilog unionized drug concentration} / \text{ionized drug concentration}$



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# HENDERSON-HASSELBALCH FOR WEAK BASES

pH IS DETERMINED BY THE RATIO OF **UNIONIZED BASE** TO **IONIZED FORM**

CORRECT HENDERSON-HASSELBALCH  
FORM FOR WEAK BASES

$$\text{pH} = \text{pK}_a + \log \left[ \frac{[\text{unionized}]}{[\text{ionized}]} \right]$$

COMMON NOTATION

$$\text{pH} = \text{pK}_a + \log \left[ \frac{[\text{B}]}{[\text{BH}^+]} \right]$$

WHAT DO THE TERMS MEAN?

**B** = unionized base  
(neutral form)

**BH<sup>+</sup>** = ionized form  
(conjugate acid)

KEY TAKEAWAY

↑ **[B]** → **pH** ↑

Increasing the  
**unionized**-to-**ionized** ratio  
increases **pH**.

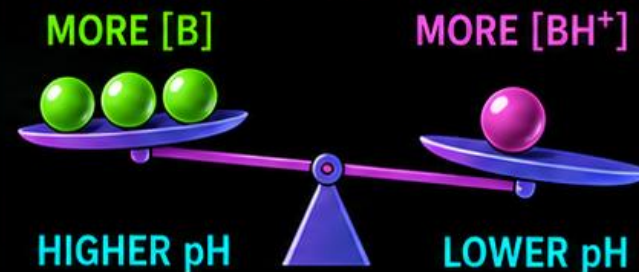
INTERPRETATION

If **[B]** = **[BH<sup>+</sup>]** → pH = pK<sub>a</sub>

If **[B]** > **[BH<sup>+</sup>]** → pH > pK<sub>a</sub>

If **[B]** < **[BH<sup>+</sup>]** → pH < pK<sub>a</sub>

RATIO VISUAL



For weak bases, pH depends on the ratio of **unionized base** to **ionized form**.







17.

Which among the following is the Henderson–Hasselbalch equation for a weak base and its salt? [GPAT-2013]

- A.  $\text{pH} = \text{pK}_a + \log [\text{salt}] / [\text{base}]$
- B.  $\text{pH} = \text{pK}_a + \log [\text{base}] / [\text{salt}]$
- C.  $\text{pOH} = \text{pK}_b + \log [\text{salt}] / [\text{base}]$
- D.  $\text{pH} = \text{pK}_b + \log [\text{base}] / [\text{salt}]$





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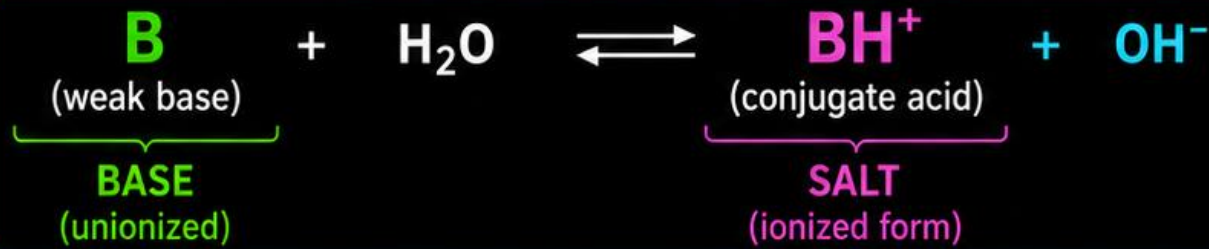
D.  $\text{pH} = \text{pK}_b + \log [\text{base}] / [\text{salt}]$



# HENDERSON-HASSELBALCH EQUATION FOR A WEAK BASE AND ITS SALT

$$\text{pH} = \text{pKa} + \log \left( \frac{[\text{BASE}]}{[\text{SALT}]}\right)$$

## GENERAL WEAK BASE SYSTEM



## BUFFER CONCEPT (NEAR pKa)

- When  $[\text{BASE}] = [\text{SALT}] \rightarrow \text{pH} = \text{pKa}$
- $[\text{BASE}] > [\text{SALT}] \rightarrow \text{pH} > \text{pKa}$  (more basic)
- $[\text{BASE}] < [\text{SALT}] \rightarrow \text{pH} < \text{pKa}$  (less basic)



A mixture of weak base and its salt resists pH changes.

## WHERE:

$[\text{BASE}]$  = concentration of the weak base (unionized form)

$[\text{SALT}]$  = concentration of its ionized salt (conjugate acid form)

$\text{pKa}$  = negative log of the base's conjugate acid dissociation constant

## BASE vs SALT

### BASE

= weak base



UNIONIZED

### SALT

= conjugate acid (ionized form)



IONIZED



**TAKEAWAY:** For a weak base system, **pH** is controlled by the **base-to-salt ratio**.





18.

**Passive diffusion follows which order of kinetics? [GPAT-2015]**

- A. Non-selective and mixed order
- B. Selective and first order
- C. Non-selective and first order
- D. Selective and mixed order



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18.

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A. Non-selective and mixed order

B. Selective and first order

**C. Non-selective and first order**

D. Selective and mixed order



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# PASSIVE DIFFUSION FOLLOWS NON-SELECTIVE, FIRST-ORDER KINETICS



## NON-SELECTIVE

Any small, uncharged lipid-soluble molecule can diffuse.



## FIRST-ORDER

Rate is proportional to concentration difference.



## NO ENERGY

No ATP required.  
Movement is down the concentration gradient.



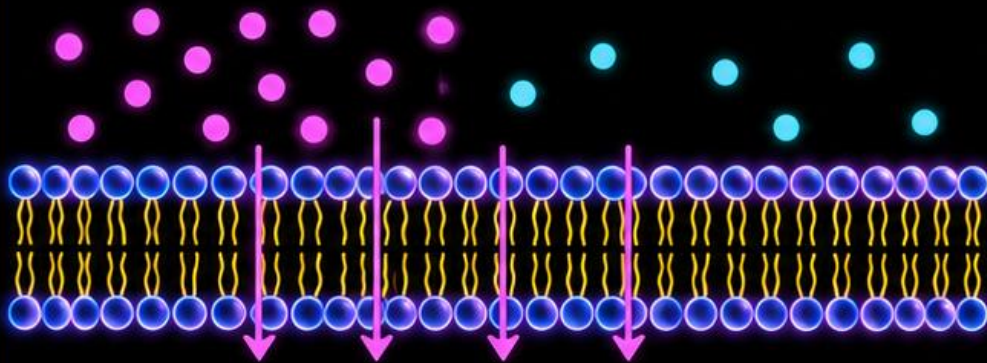
## RATE DEPENDS ON CONCENTRATION GRADIENT

Greater gradient → faster diffusion.

## HOW PASSIVE DIFFUSION WORKS

HIGH CONCENTRATION

LOW CONCENTRATION



Molecules move directly through the lipid bilayer from **high** → **low** concentration.  
No carrier or channel required.

## FIRST-ORDER KINETICS

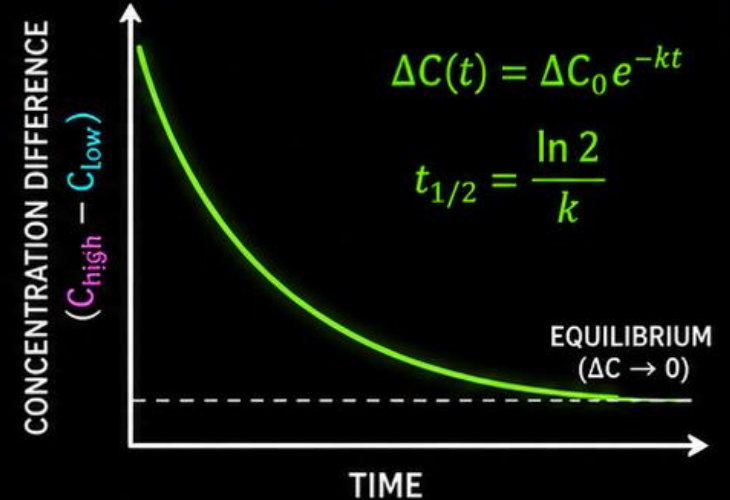
Rate of diffusion is proportional to concentration difference:

$$\text{Rate} = k (C_{\text{high}} - C_{\text{low}})$$

### Implications:

- If gradient doubles, rate doubles.
- As gradient decreases, rate decreases.
- Process naturally slows and approaches equilibrium.

## FIRST-ORDER DECAY OF GRADIENT



Passive diffusion is **non-selective** and follows **first-order** kinetics.





19.

**A good in-vitro and in-vivo dissolution correlation can be obtained when in-vitro dissolution is performed under: [GPAT-2015]**

- A. Normal condition**
- B. Sink condition**
- C. High temperature**
- D. A constant value**



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**A good in-vitro and in-vivo dissolution correlation can be obtained when in-vitro dissolution is performed under: [GPAT-2015]**

**A. Normal condition**

**B. Sink condition**

**C. High temperature**

**D. A constant value**



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# WHY SINK CONDITION

## GIVES THE BEST *IN-VITRO/IN-VIVO* DISSOLUTION CORRELATION



### SINK CONDITION

The dissolved drug concentration in the medium remains well below its saturation solubility.

$C < 10\% \text{ of } C_s$   
( $C$  = dissolved concentration,  
 $C_s$  = saturation solubility)



Maintains a high concentration gradient between dosage form and medium.



Ensures continuous dissolution throughout the test.



Better reflects the in-vivo environment where drug is rapidly removed (absorbed).

VS

### SINK CONDITION



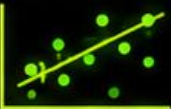
High and constant concentration gradient  
( $C_s - C$  is large and nearly constant)



Continuous, near-zero order dissolution  
Rate remains steady



Mimics in-vivo conditions  
Drug is removed by absorption,  
maintaining sink



Higher in-vitro/in-vivo correlation  
Predicts in-vivo performance better

### NON-SINK CONDITION



Gradient decreases as  $C$  approaches  $C_s$   
( $C_s - C$  becomes small)



Dissolution slows or stops early  
Rate decreases with time



Poor in-vivo mimicry  
Accumulation limits dissolution,  
does not reflect absorption



Lower in-vitro/in-vivo correlation  
Poor prediction of in-vivo performance



**TAKEAWAY:** Best IVIVC is usually obtained under **sink conditions**.





20.

**Concentration vs time curve drawn from a single oral dose is used to calculate: [GPAT-2015]**

- A. Elimination constant**
- B. Rate constant**
- C. Absorption peak**
- D. Plasma concentration**



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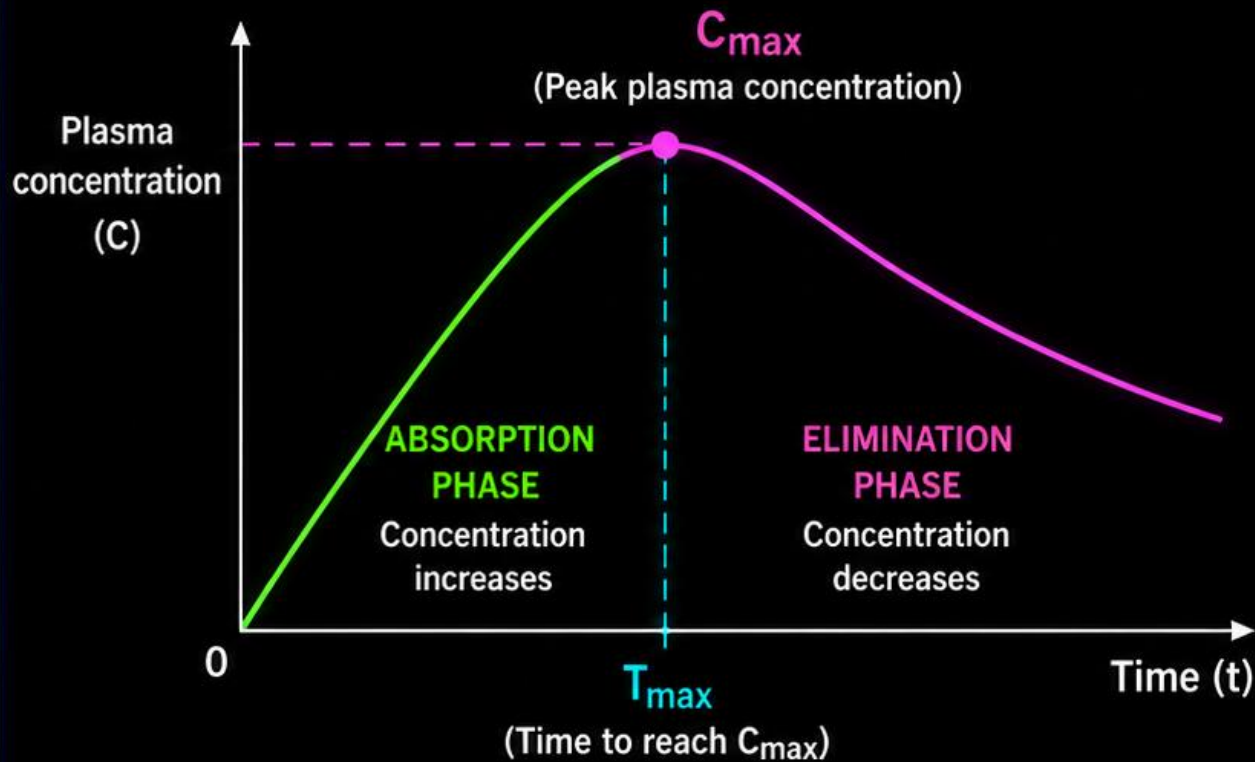
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# CONCENTRATION–TIME CURVE AFTER A SINGLE ORAL DOSE

The plasma concentration–time curve identifies the **absorption peak**.

## PLASMA CONCENTRATION–TIME CURVE AFTER A SINGLE ORAL DOSE



### ABSORPTION PEAK ( $C_{\max}$ )

The highest plasma concentration reached after the oral dose.



### TIME TO PEAK ( $T_{\max}$ )

The time required to reach  $C_{\max}$ .  
Reflects the rate of absorption.



### WHAT THE PEAK REFLECTS

Higher & earlier peak → faster absorption.  
Higher peak → greater extent of absorption.



### CLINICAL IMPORTANCE

Helps compare formulations, assess bioavailability, and guide dosing to achieve desired exposure.



A SINGLE-DOSE CONCENTRATION–TIME CURVE HELPS IDENTIFY THE **ABSORPTION PEAK ( $C_{\max}$ )**.





21.

**Match the following: [GPAT-2013]**

| Drug            | Influence of food on absorption |
|-----------------|---------------------------------|
| 1. Aspirin      | P. Decreased                    |
| 2. Erythromycin | Q. Delayed                      |
| 3. Griseofulvin | R. Unaffected                   |
| 4. Methyldopa   | S. Increased                    |

A. 1-Q, 2-P, 3-S, 4-R

C. 1-P, 2-Q, 3-R, 4-S

B. 1-P, 2-Q, 3-S, 4-R

D. 1-P, 2-R, 3-S, 4-Q



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**A. 1-Q, 2-P, 3-S, 4-R**

**C. 1-P, 2-Q, 3-R, 4-S**

**B. 1-P, 2-Q, 3-S, 4-R**

**D. 1-P, 2-R, 3-S, 4-Q**



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# FOOD EFFECT ON DRUG ABSORPTION



Aspirin



Delayed absorption



Erythromycin



Decreased absorption



Griseofulvin



Increased absorption



Methyldopa



Unaffected absorption



## TAKEAWAY



Food may **DELAY GASTRIC EMPTYING**, thus delaying absorption of some drugs.



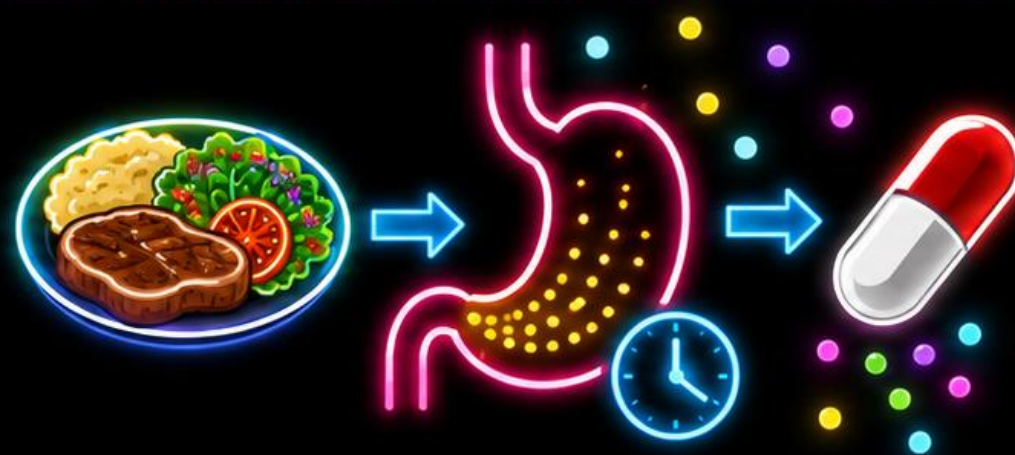
Food may **DECREASE STABILITY** or **CONTACT** of some drugs with the absorptive surface, reducing absorption.



Food (especially fats) can **IMPROVE ABSORPTION** of **LIPOPHILIC DRUGS** like griseofulvin.



Sometimes, food causes **LITTLE OR NO EFFECT** on drug absorption.





22.

**What kind of substances cannot permeate membranes by passive diffusion? [GPAT-2013]**

- A. Lipid-soluble substances**
- B. Non-ionized substances**
- C. Hydrophobic substances**
- D. Hydrophilic substances**



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**What kind of substances cannot permeate membranes by passive diffusion? [GPAT-2013]**

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**B. Non-ionized substances**

**C. Hydrophobic substances**

**D. Hydrophilic substances**



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# HYDROPHILIC SUBSTANCES DO NOT CROSS BY PASSIVE DIFFUSION



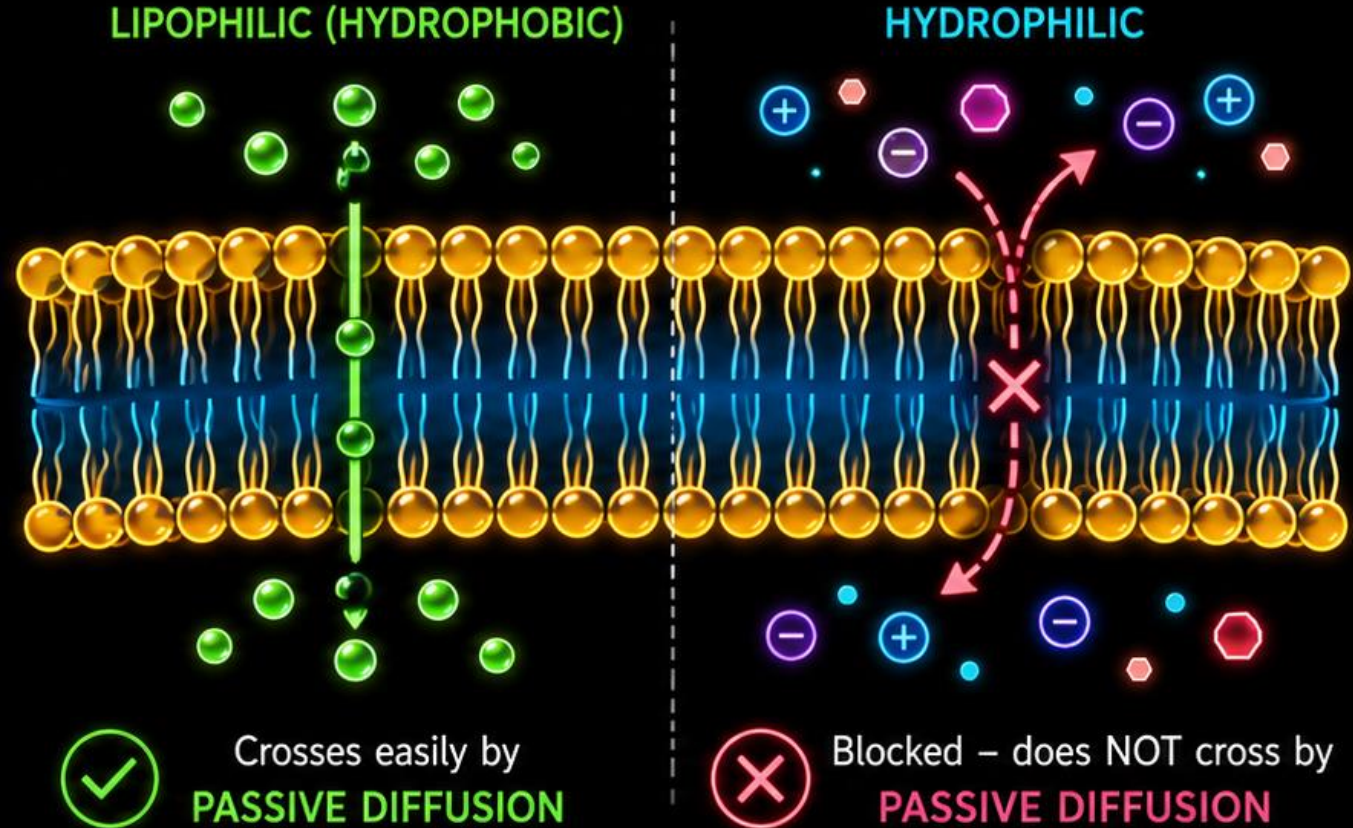
Passive diffusion across the cell membrane mainly favors **NON-IONIZED, LIPOPHILIC, HYDROPHOBIC** molecules.



The membrane is **LIPID** in nature (phospholipid bilayer with a hydrophobic core).



Hydrophilic substances are **WATER-LOVING**, **poorly partition** into the lipid bilayer, and therefore **cannot permeate efficiently** by simple passive diffusion.



**RULE:** **LIPID SOLUBLE** molecules **DISSOLVE** in the lipid bilayer and **DIFFUSE THROUGH**.  
**WATER LOVING (IONIC/POLAR)** molecules **DO NOT DISSOLVE**, so they **CANNOT DIFFUSE** across.



**23. Stokes–Einstein equation is related to: [GPAT-2013]**

- A. Energy changes in sedimentation suspension setting**
- B. Sedimentation of suspension**
- C. Diffusion coefficient**
- D. Coefficient of energy consumption**



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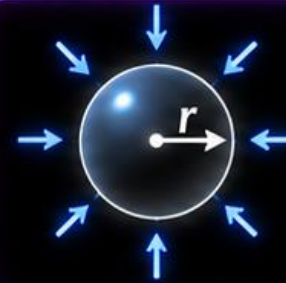
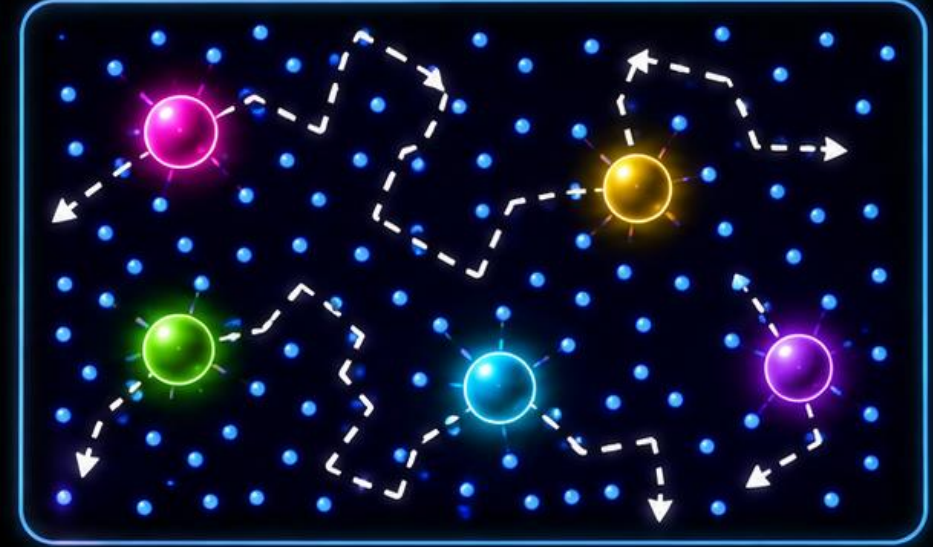


# STOKES-EINSTEIN EQUATION

This equation is related to the **DIFFUSION COEFFICIENT**.

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

- $D$  = diffusion coefficient ( $\text{m}^2 \text{s}^{-1}$ )
- $T$  = absolute temperature (K)
- $\eta$  = viscosity of the fluid ( $\text{Pa}\cdot\text{s}$ )
- $r$  = particle radius (m)
- $k$  = Boltzmann constant ( $1.380649 \times 10^{-23} \text{ J K}^{-1}$ )



Particle undergoes random **thermal motion** and experiences **viscous drag** in a fluid. Balance of these gives the **diffusion coefficient**.



## KEY TAKEAWAYS



Diffusion **increases** with **temperature**.



Diffusion **decreases** with **viscosity**.



Diffusion **decreases** with larger **particle size** (radius).



24.

What will be the urine to plasma ratio of a weakly acidic drug having  $pK_a$  5? Urine  $pH = 5$ , plasma  $pH = 7$ . [GPAT-2011]

- A. 1:101
- B. 1:201
- C. 2:101
- D. 1:202



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A. 1:101

B. 1:201

C. 2:101

D. 1:202



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# URINE : PLASMA RATIO OF A WEAK ACID

## CASE

- Weakly acidic drug
- pKa = 5
- Urine pH = 5
- Plasma pH = 7

$$\text{Urine : Plasma ratio} = \frac{1 + 10^{(\text{pH urine} - \text{pKa})}}{1 + 10^{(\text{pH plasma} - \text{pKa})}}$$

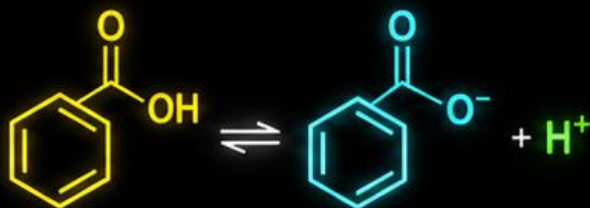
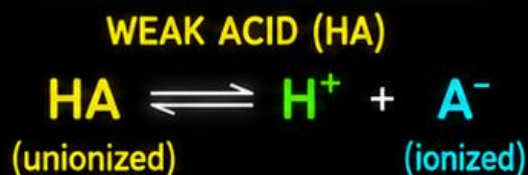
## CALCULATION

$$\frac{(1 + 10^{(5 - 5)})}{(1 + 10^{(7 - 5)})} = \frac{2}{101}$$

$$\text{Urine : Plasma} = 2 : 101$$

## ★ KEY CONCEPT ★

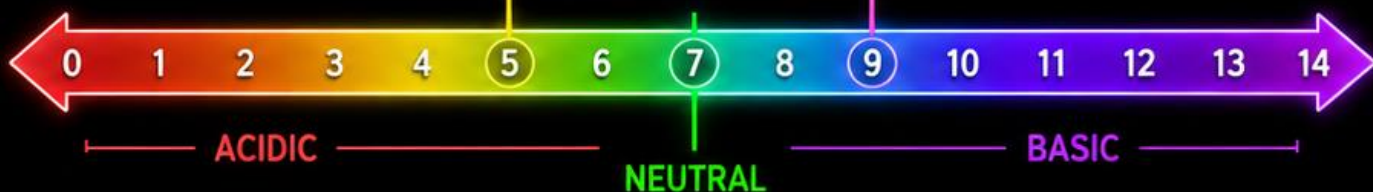
Weak acids become more **ionized** at **higher pH**.  
The ionized form ( $A^-$ ) does not readily cross membranes.  
Therefore, the **higher-pH** compartment contains **more total drug**.



## pH SCALE

Urine pH = 5

Plasma pH = 7

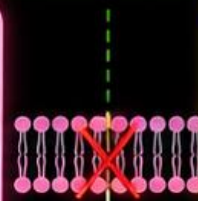


## PLASMA (pH 7)

More ionized ( $A^-$ )



More total drug



$A^-$   
does not  
cross  
membranes  
easily

## URINE (pH 5)

More unionized (HA)



Less total drug



At pH 7 (plasma), ionized form ( $A^-$ ) predominates → **more total drug** in plasma.  
At pH 5 (urine), unionized form (HA) predominates → **less total drug** in urine.







25.

If  $C$  is the concentration of dissolved drug and  $C_s$  is the saturation concentration, sink conditions are maintained when: [GPAT-2011]

- A.  $C < 20\%$  of  $C_s$
- B.  $C > 20\%$  of  $C_s$
- C.  $C < 10\%$  of  $C_s$
- D.  $C > 10\%$  of  $C_s$



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25.

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- D.  $C > 10\%$  of  $C_s$



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# SINK CONDITION

SINK CONDITIONS ARE MAINTAINED WHEN DISSOLVED DRUG CONCENTRATION  $C$  IS **LESS THAN 10%** OF SATURATION SOLUBILITY  $C_s$ .

$$C < 0.1 C_s \quad \text{OR} \quad C < 10\% \text{ OF } C_s$$



## MAINTAINS HIGH CONCENTRATION GRADIENT

$C$  remains much lower than  $C_s$ , keeping the driving force for dissolution high.



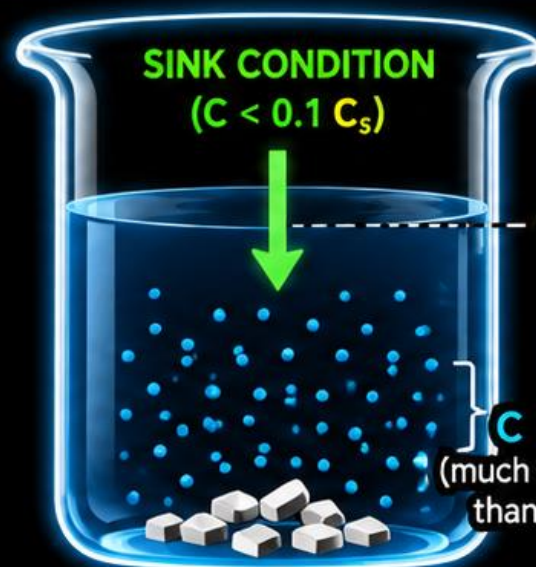
## PROMOTES CONTINUOUS DISSOLUTION

Drug keeps dissolving at its maximum rate without slowing down.



## GIVES BETTER IN-VITRO DISSOLUTION TESTING

Provides consistent, reliable and reproducible dissolution data that reflects in-vivo performance.



VS



KEEP  $C < 0.1 C_s$  (OR  $C < 10\%$  OF  $C_s$ ) TO ENSURE SINK CONDITIONS, MAINTAIN **HIGH GRADIENT**, PROMOTE **CONTINUOUS DISSOLUTION**, AND OBTAIN **BETTER IN-VITRO DISSOLUTION RESULTS**.





26.

**According to pH partition theory, a weakly acidic drug will most likely be absorbed from the stomach because the drug exists primarily in: [GATE-1993]**

- A. Un-ionised, more lipid soluble form**
- B. Ionised, more water-soluble form**
- C. Form of weak acid and more soluble in acid media**
- D. Ionic form of the drug which facilitates diffusion**



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26.

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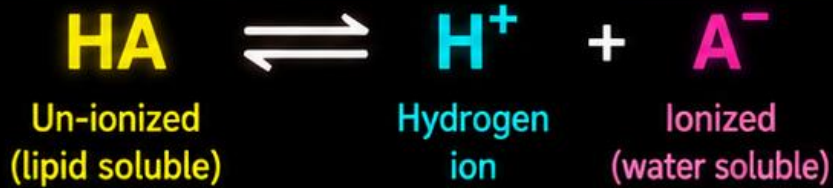
**D. Ionic form of the drug which facilitates diffusion**



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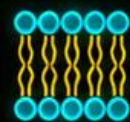
# WHY WEAK ACIDS ARE ABSORBED FROM THE STOMACH

## pH-PARTITION THEORY

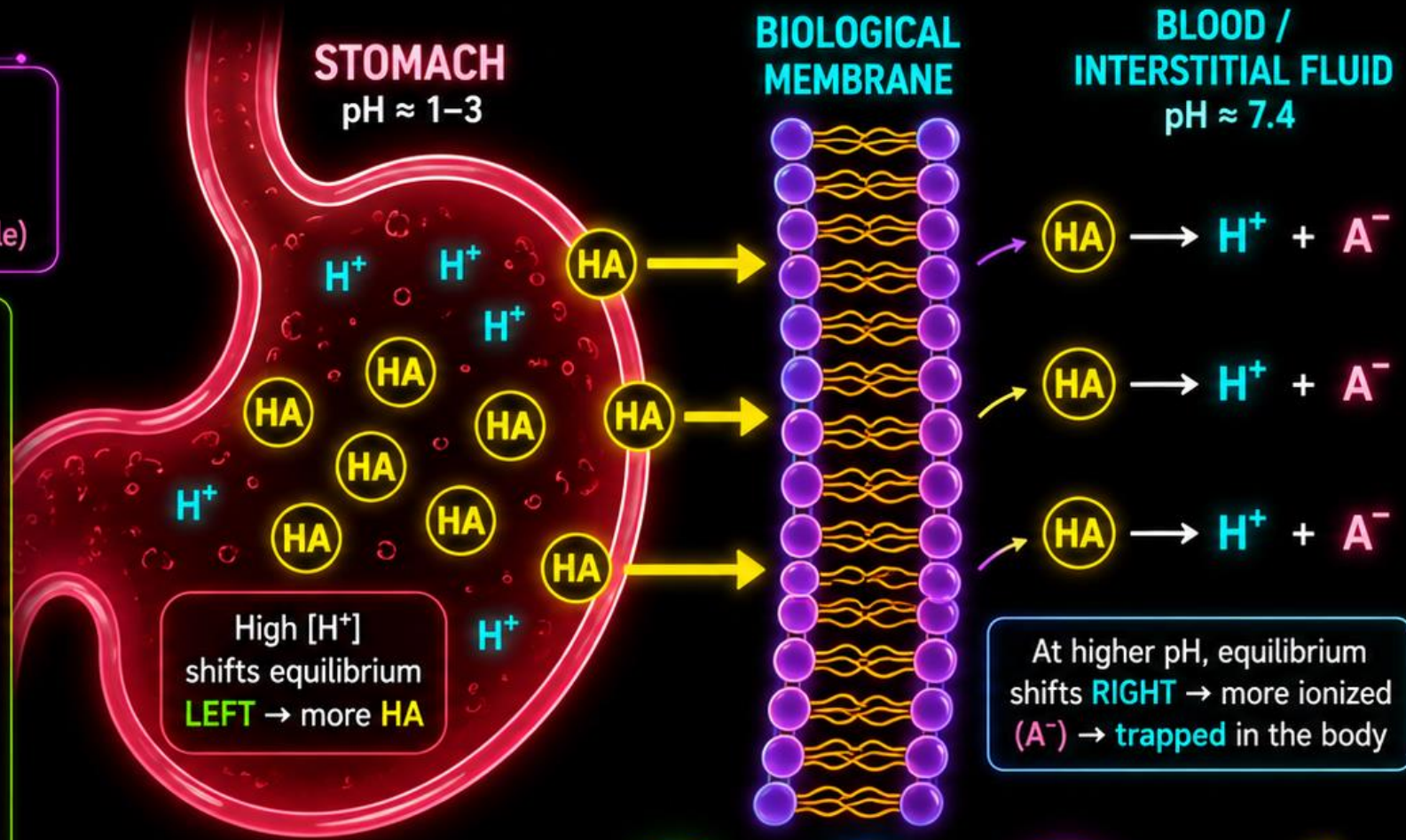


**H<sup>+</sup>** • The stomach has an acidic pH (≈ 1–3). High [H<sup>+</sup>] shifts the equilibrium to the **LEFT**.

**HA** • Weak acids exist mostly in the **UN-IONIZED** form (**HA**) in gastric pH.

 Un-ionized HA is more **LIPID SOLUBLE** and crosses biological membranes more easily.

 Therefore, **ABSORPTION OF WEAK ACIDS** from the **STOMACH** is **FAVORED**.



★ **ACIDIC STOMACH pH** → **MORE UN-IONIZED (HA)** → **BETTER MEMBRANE PERMEATION** → **IONIZATION IN BLOOD** → **TRAPPING** → **ENHANCED ABSORPTION**





**27.** The applicability of Noyes–Whitney equation is to describe: **[GPAT-2010]**

- A. First order kinetics**
- B. Zero order kinetics**
- C. Mixed order kinetics**
- D. Dissolution rate**





**27.** The applicability of Noyes–Whitney equation is to describe: **[GPAT-2010]**

- A. First order kinetics**
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- C. Mixed order kinetics**
- D. Dissolution rate**





# NOYES-WHITNEY EQUATION



The Noyes-Whitney equation describes the **DISSOLUTION RATE OF A SOLID DRUG**.

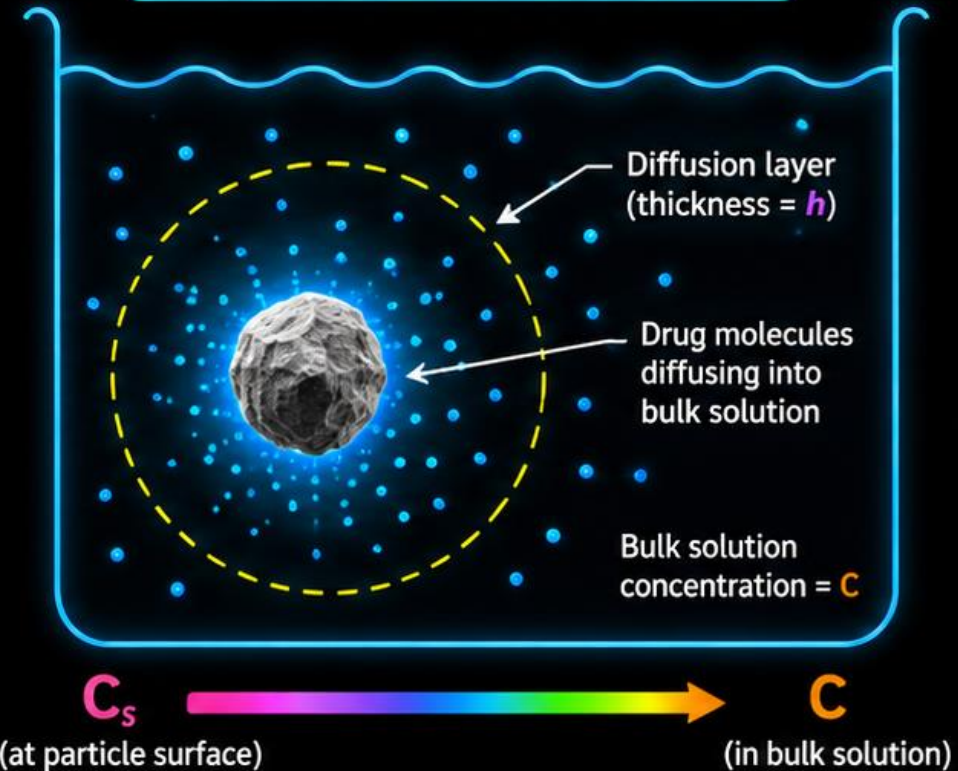
$$\frac{dC}{dt} = \frac{DA(C_s - C)}{h}$$

Rate of change of drug concentration (**C**) in the bulk solution with time (**t**).

## WHERE:

- D** Diffusion coefficient of the drug in the medium (cm<sup>2</sup>/s)
- A** Surface area of the solid drug (cm<sup>2</sup>)
- C<sub>s</sub>** Saturation solubility (equilibrium solubility) of the drug (mg/mL)
- C** Concentration of the drug in the bulk solution at time **t** (mg/mL)
- h** Thickness of the diffusion layer (cm)

## DISSOLVING SOLID PARTICLE



## KEY TAKEAWAYS



Dissolution rate **INCREASES** with larger surface area (**A**)



Dissolution rate **INCREASES** with higher diffusion coefficient (**D**)



Dissolution rate **INCREASES** with higher saturation solubility (**C<sub>s</sub>**)



Dissolution rate **DECREASES** with thicker diffusion layer (**h**)



28.

**Which of the following has the highest degree of ionization in an aqueous solution? [GATE-1997]**

- A. Aspirin,  $pK_a = 3.5$**
- B. Indomethacin,  $pK_a = 4.5$**
- C. Warfarin,  $pK_a = 5.1$**
- D. Ibuprofen,  $pK_a = 5.2$**



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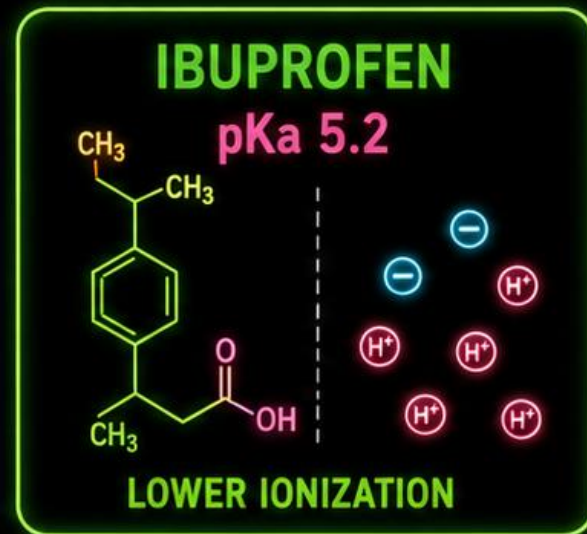
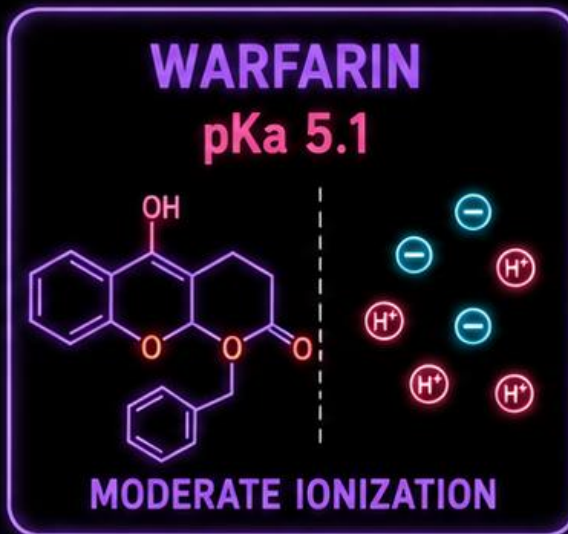
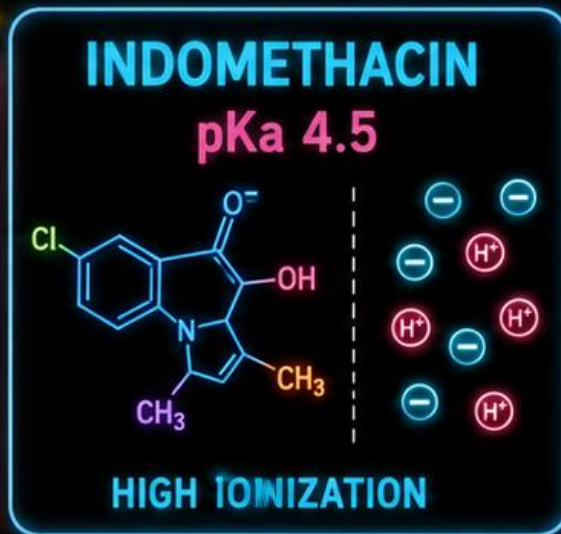
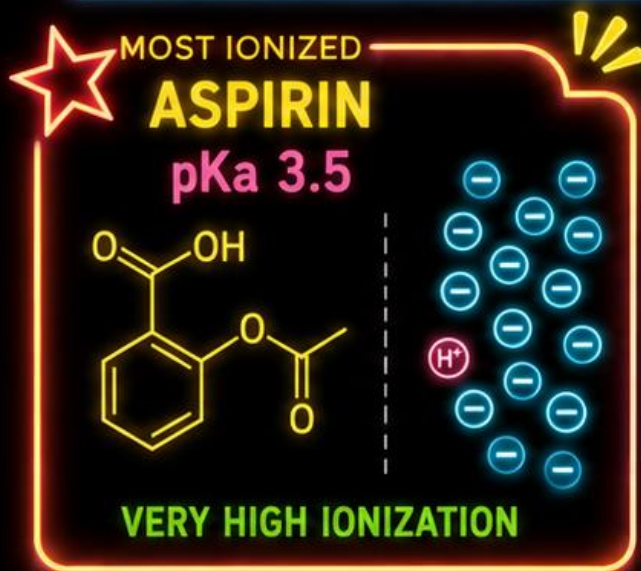


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# LOWEST pKa = HIGHEST IONIZATION

For **weak acids** at the **SAME** aqueous pH,  
the acid with the **LOWEST pKa** ionizes the **MOST**.



💡 **KEY TAKEAWAY**  
Among weak acids  
at the **SAME** pH,  
the **LOWER** the pKa,  
the **MORE** it ionizes.





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29.

**BCS Class III drugs can be described as drugs having:**

- A. High solubility and high permeability**
- B. Low solubility and high permeability**
- C. High solubility and low permeability**
- D. Low solubility and low permeability**



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**BCS Class III drugs can be described as drugs having:**

- A. High solubility and high permeability
- B. Low solubility and high permeability
- C. High solubility and low permeability**
- D. Low solubility and low permeability



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# BCS CLASS III DRUGS



**DEFINING FEATURE:**  
**HIGH SOLUBILITY AND LOW PERMEABILITY**

|            |      | PERMEABILITY         |                     |
|------------|------|----------------------|---------------------|
|            |      | LOW                  | HIGH                |
| SOLUBILITY | HIGH | <b>CLASS I</b><br>   | <b>CLASS II</b><br> |
|            | LOW  | <b>CLASS III</b><br> | <b>CLASS IV</b><br> |



These drugs **DISSOLVE EASILY** in gastrointestinal fluids.



However, **ABSORPTION** is **LIMITED** by membrane **PERMEATION**.



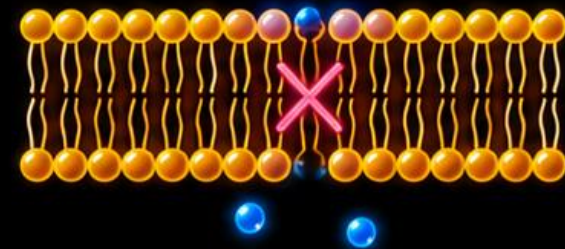
**PERMEABILITY** is the **RATE-LIMITING FACTOR** for absorption.

**DISSOLVES EASILY**



**HIGH SOLUBILITY**

**POOR PERMEATION**



**LOW PERMEABILITY**



**BCS CLASS III DRUGS** have **HIGH SOLUBILITY** but **LOW PERMEABILITY**.  
Their absorption is **LIMITED** by membrane permeation—**PERMEABILITY** is the **RATE-LIMITING FACTOR**.





30.

**Which of the following is not a characteristic of facilitated diffusion?**

- A. Carrier-mediated transport**
- B. Concentration gradient is required**
- C. Structural specificity**
- D. Non-saturable**



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30.

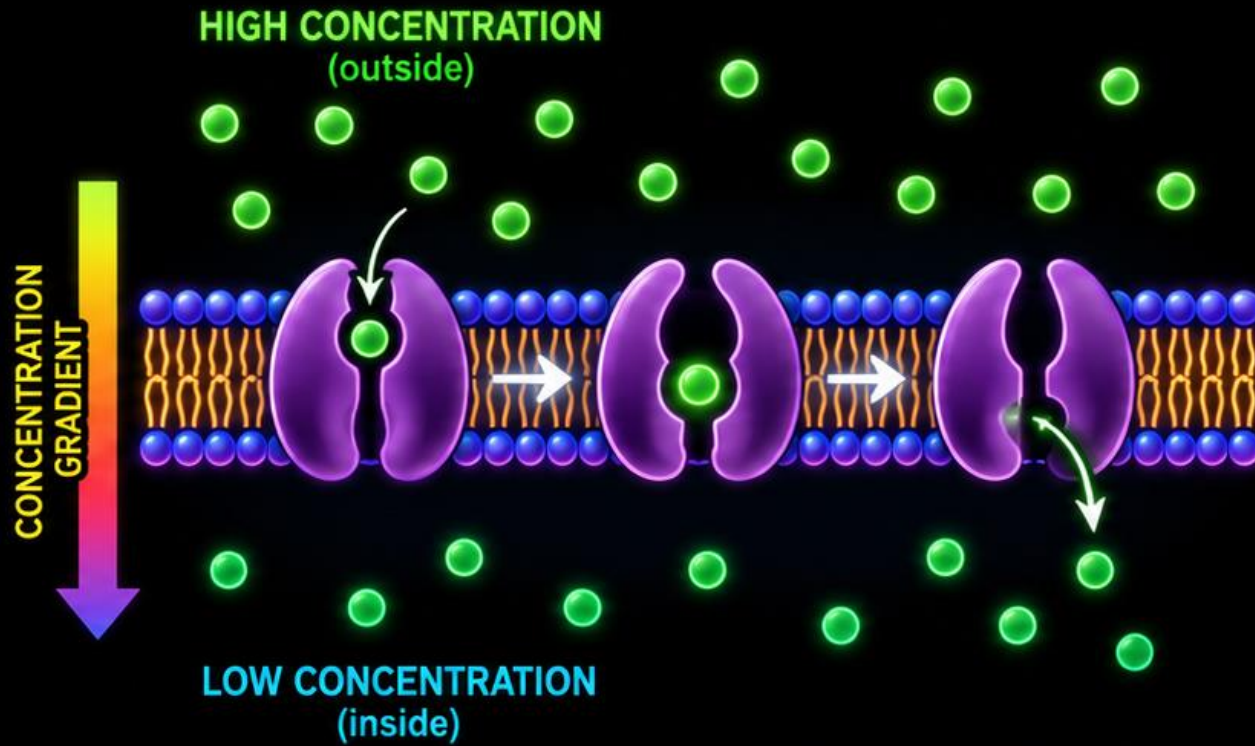
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- A. Carrier-mediated transport**
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- C. Structural specificity**
- D. Non-saturable**



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# FACILITATED DIFFUSION IS SATURABLE



Because **CARRIERS** are **LIMITED**, facilitated diffusion is **SATURABLE**.



**NON-SATURABLE** is **NOT** a characteristic of facilitated diffusion.



**CARRIER-MEDIATED:**

Solute binds to a specific carrier protein.



**SPECIFIC:**

Only certain solutes fit the carrier.



**DOWN CONCENTRATION GRADIENT:**

Moves from high to low concentration.



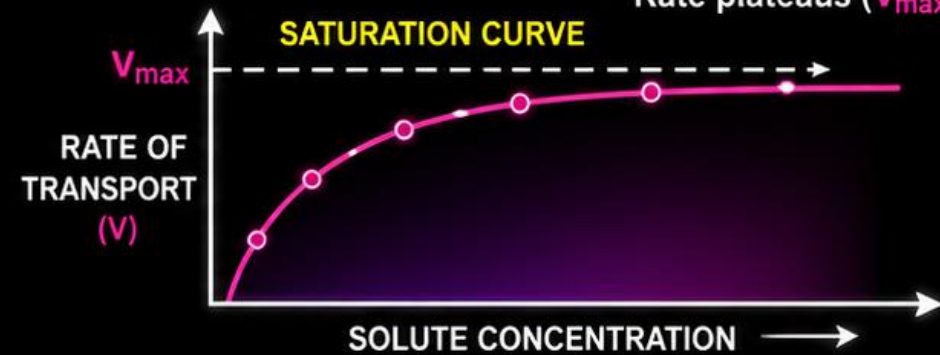
**NO ENERGY REQUIRED:**

Passive process.

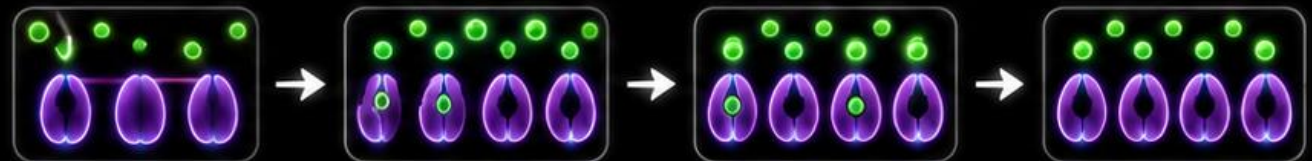


**SATURABLE:**

Carriers are limited. At high solute levels, all carriers are occupied. Rate plateaus ( $V_{max}$ ).



**CARRIER OCCUPANCY AS SOLUTE CONCENTRATION INCREASES**



LOW

INCREASING CONCENTRATION

HIGH



31.

**Which theory of dissolution is known as limited solvation rate theory?**

- A. Surface renewal theory**
- B. Diffusion layer model**
- C. Hixson–Crowell cube root model**
- D. Interfacial barrier model**



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31.

**Which theory of dissolution is known as limited solvation rate theory?**

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**B. Diffusion layer model**

**C. Hixson–Crowell cube root model**

**D. Interfacial barrier model**



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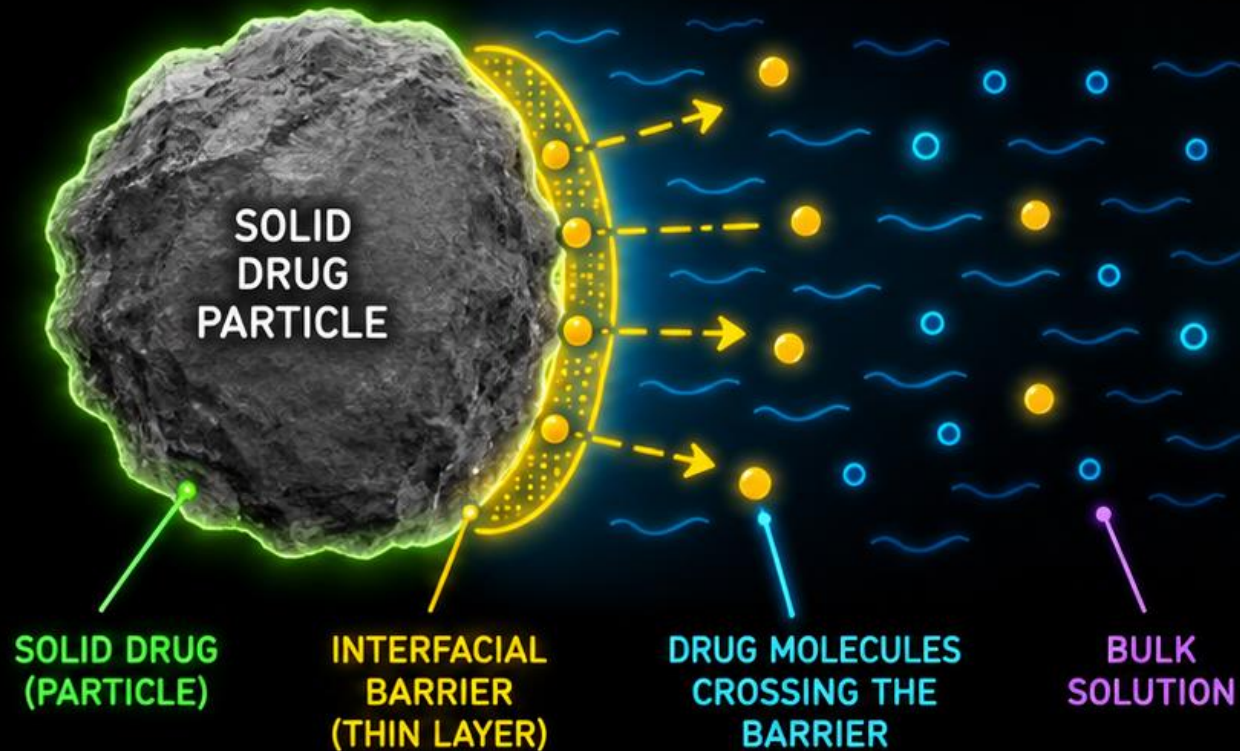


# INTERFACIAL BARRIER MODEL

DISSOLUTION THEORY = LIMITED SOLVATION RATE THEORY



## DISSOLVING SOLID PARTICLE



### BARRIER FORMS AT THE SURFACE

A thin interfacial layer (barrier) forms at the solid-liquid interface.



### DRUG MOLECULES MUST CROSS

Drug molecules must cross this barrier before entering the bulk solution.



### BARRIER CAN SLOW DISSOLUTION

The barrier offers resistance and can limit or control the dissolution rate.



### USEFUL WHEN INTERFACIAL RESISTANCE IS IMPORTANT

Important for sparingly soluble drugs, high surface tension systems, etc.



### KEY TAKEAWAY

Interfacial Barrier Model  
= Limited Solvation Rate Theory



**IN SHORT:** A thin **interfacial barrier** at the solid-liquid interface must be **crossed by drug molecules**; this limited solvation step can be the **rate-limiting step** in dissolution.





**32.** A test drug has higher absorption number and lower dissolution number. The tested drug comes under which BCS class?

- A. Class I
- B. Class II
- C. Class III
- D. Class IV



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**32.** A test drug has higher absorption number and lower dissolution number. The tested drug comes under which BCS class?

A. Class I

**B. Class II**

C. Class III

D. Class IV



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# BCS CLASS II DRUGS

A drug with **HIGH ABSORPTION NUMBER** (high permeability) and **LOW DISSOLUTION NUMBER** (low solubility) belongs to **BCS CLASS II**.



## BCS 2x2 CLASSIFICATION

| SOLUBILITY (DISSOLUTION) |                                                             |
|--------------------------|-------------------------------------------------------------|
| HIGH                     | LOW                                                         |
| HIGH PERMEABILITY        | <b>CLASS II</b><br>Low Solubility<br>High Permeability<br>  |
| LOW PERMEABILITY         | <b>CLASS IV</b><br>Low Solubility<br>Low Permeability<br>   |
| HIGH PERMEABILITY        | <b>CLASS I</b><br>High Solubility<br>High Permeability<br>  |
| LOW PERMEABILITY         | <b>CLASS III</b><br>High Solubility<br>Low Permeability<br> |

## KEY POINTS



### LOW SOLUBILITY

Dissolves poorly in GI fluids.



### HIGH PERMEABILITY

Easily absorbed across intestinal membrane.



### ABSORPTION IS LIMITED BY DISSOLUTION

Slow dissolution limits the amount available to absorb.



### IMPROVING DISSOLUTION IMPROVES BIOAVAILABILITY

More drug dissolves → more absorbed → higher bioavailability.



**KEY TAKEAWAY:** **HIGH ABSORPTION NUMBER** + **LOW DISSOLUTION NUMBER** = **BCS CLASS II**





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33.

**Furosemide comes under which BCS class?**

- A. Class I
- B. Class II
- C. Class III
- D. Class IV



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33.

**Furosemide comes under which BCS class?**

A. Class I

B. Class II

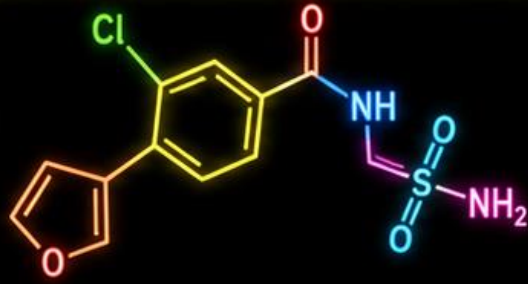
C. Class III

**D. Class IV**



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# FUROSEMIDE AND BCS CLASSIFICATION



**FUROSEMIDE**

Loop Diuretic



**FUROSEMIDE IS A BCS CLASS IV DRUG**



## LOW SOLUBILITY

Poorly soluble in water across pH range.



## LOW PERMEABILITY

Limited ability to cross intestinal membrane.



## POOR AND VARIABLE ABSORPTION

Low extent and variable bioavailability.

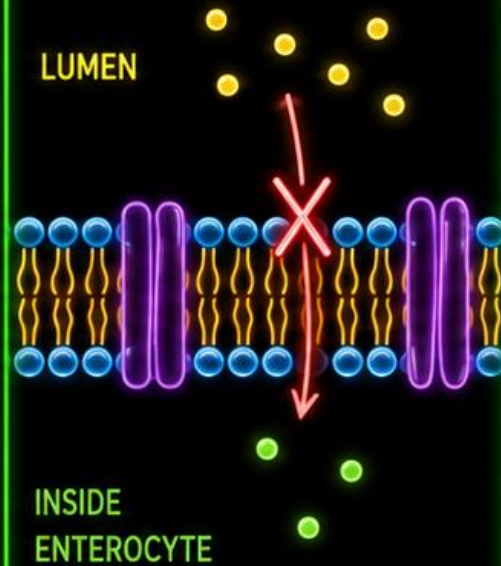


## DIFFICULT TO FORMULATE

Challenging to achieve good and consistent oral bioavailability.

## MEMBRANE CROSSING CHALLENGE

Low permeability →  
Less drug absorption



Minimal drug reaches the  
systemic circulation

## BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

|                   | HIGH SOLUBILITY                                         | LOW SOLUBILITY                                         |
|-------------------|---------------------------------------------------------|--------------------------------------------------------|
| HIGH PERMEABILITY | <b>CLASS I</b><br>High Solubility<br>High Permeability  | <b>CLASS II</b><br>Low Solubility<br>High Permeability |
| LOW PERMEABILITY  | <b>CLASS III</b><br>High Solubility<br>Low Permeability | <b>CLASS IV</b><br>Low Solubility<br>Low Permeability  |



## KEY TAKEAWAY

**FUROSEMIDE IS CLASS IV**  
BECAUSE BOTH SOLUBILITY  
AND PERMEABILITY ARE **LOW**.



34.

**For determination of dissolution profile of microspheres, which is the best dissolution model?**

- A. Peppas model**
- B. Hixson–Crowell model**
- C. Higuchi model**
- D. Noyes–Whitney equation**



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34.

**For determination of dissolution profile of microspheres, which is the best dissolution model?**

A. Peppas model

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**C. Higuchi model**

D. Noyes–Whitney equation



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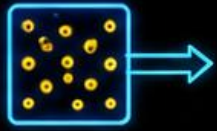
# HIGUCHI EQUATION AND DRUG RELEASE MECHANISM



When a dosage form follows Higuchi's equation, drug release is **DIFFUSION-RATE CONTROLLED**.



## DRUG RELEASE MECHANISM



Diffusion through the matrix **CONTROLS** drug release.



Release **SLOWS** as the diffusion path length increases with time.



Common in **MATRIX TABLETS** and **SEMISOLIDS**.

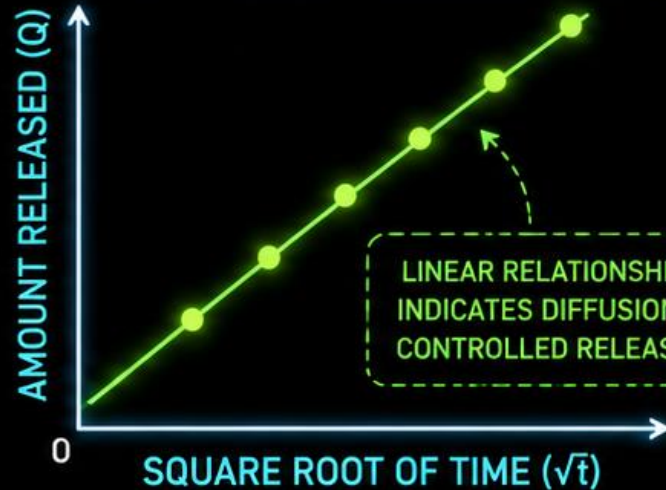


Applies when initial drug concentration is **much higher** than solubility.

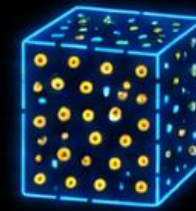
## HIGUCHI EQUATION

$$Q = k_H \sqrt{t}$$

$Q$  = Amount of drug released per unit area  
 $k_H$  = Higuchi dissolution constant  
 $t$  = Time

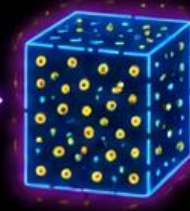


## MATRIX SYSTEM RELEASING DRUG



$t = 0$

Drug uniformly dispersed in matrix



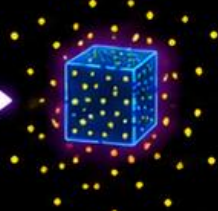
Early time

Drug diffuses to the surface and releases



Later time

Diffusion path increases, release slows



Extended time

Most drug released, rate very slow

## FACTORS AFFECTING HIGUCHI RELEASE



Porosity



Tortuosity



Moisture penetration



Particle size



Drug solubility



Temperature



**KEY TAKEAWAY:** Higuchi equation indicates **DIFFUSION-CONTROLLED** drug release.





35.

**When release of drug from a dosage form satisfies Higuchi's equation, the release of drug is considered as:**

- A. Absorption rate controlled**
- B. Diffusion rate controlled**
- C. Dissolution rate controlled**
- D. Dosing rate controlled**



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35.

**When release of drug from a dosage form satisfies Higuchi's equation, the release of drug is considered as:**

- A. Absorption rate controlled**
- B. Diffusion rate controlled**
- C. Dissolution rate controlled**
- D. Dosing rate controlled**



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# Higuchi Equation – Key Explanation



$$Q \propto \sqrt{t}$$

1 Drug release increases with **square root** of time



2 Typical of **matrix-based dosage forms**



3 Release is governed by **diffusion** of drug through the **matrix**



4 Common in **sustained / controlled release** systems



Capsule



Tablet



Drug particles



Diffusion



Dissolution medium

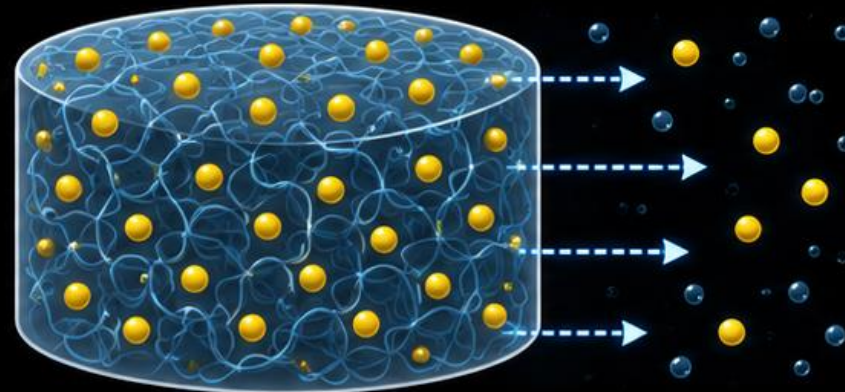


Molecule



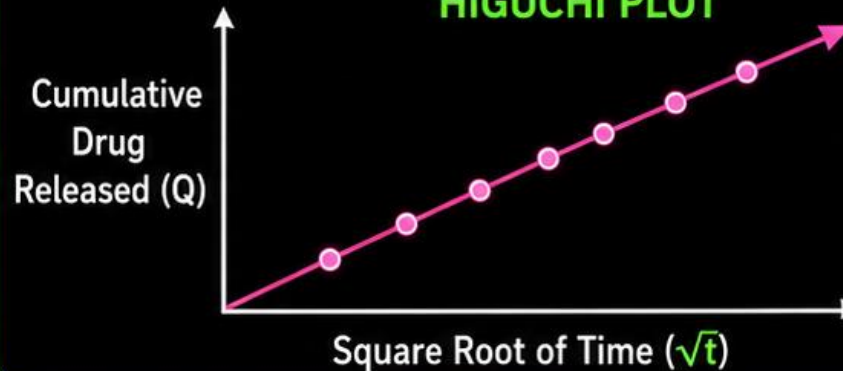
Sustained Release

MATRIX TABLET (POLYMER MATRIX)



- Drug particle
- ~ Polymer matrix
- - - Diffusion path
- Dissolution medium

HIGUCHI PLOT



Linear relationship confirms Higuchi model



**Quick clue:**

Higuchi model = **diffusion-controlled release**



36.

**Which is the major process of absorption for more than 90% of drugs?**

**A. Facilitated diffusion**

**B. Active transport**

**C. Endocytosis**

**D. Passive diffusion**



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36.

**Which is the major process of absorption for more than 90% of drugs?**

**A. Facilitated diffusion**

**B. Active transport**

**C. Endocytosis**

**D. Passive diffusion**



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# PASSIVE DIFFUSION

## AS THE MAJOR ABSORPTION PROCESS

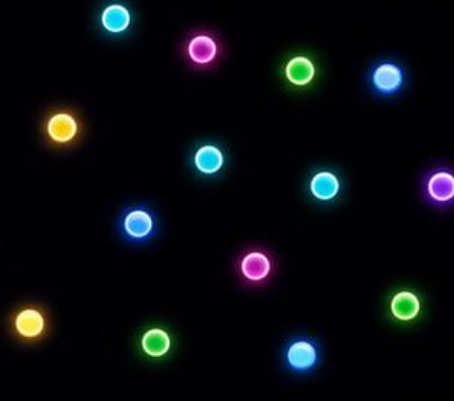
>90%

More than 90% of drugs are absorbed mainly by **PASSIVE DIFFUSION**.

**HIGH CONCENTRATION**  
(Outside)



**LOW CONCENTRATION**  
(Inside)



Moves from **HIGH** to **LOW** concentration down the concentration gradient.



**NO ENERGY REQUIRED**

Does not use ATP.



**NO CARRIER NEEDED**

Diffuses directly through the lipid bilayer.



**MOVES DOWN CONCENTRATION GRADIENT**

From high concentration to low concentration.



**BEST FOR LIPID-SOLUBLE, UNIONIZED DRUGS**

Easily crosses the lipid membrane.



**SIMPLE, EFFICIENT, AND WIDELY OCCURRING**

The natural way most drugs cross biological membranes.



**KEY TAKEAWAY:**

**PASSIVE DIFFUSION IS THE MOST COMMON MECHANISM OF DRUG ABSORPTION.**







37.

**Fick's law of diffusion can be described as:**

- A.  $\text{Area} \times \text{Permeability coefficient} / \text{Thickness} \times (C_1 - C_2)$
- B.  $\text{Area} \times \text{Permeability coefficient} \times (C_1 - C_2) / \text{Thickness}$
- C.  $\text{Permeability coefficient} \times (C_1 - C_2) / \text{Thickness} \times \text{Area}$
- D.  $\text{Area} \times (C_1 - C_2) / \text{Thickness} \times \text{Permeability coefficient}$



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37.

**Fick's law of diffusion can be described as:**

A. Area  $\times$  Permeability coefficient / Thickness  $\times (C_1 - C_2)$

**B. Area  $\times$  Permeability coefficient  $\times (C_1 - C_2)$  / Thickness**

C. Permeability coefficient  $\times (C_1 - C_2)$  / Thickness  $\times$  Area

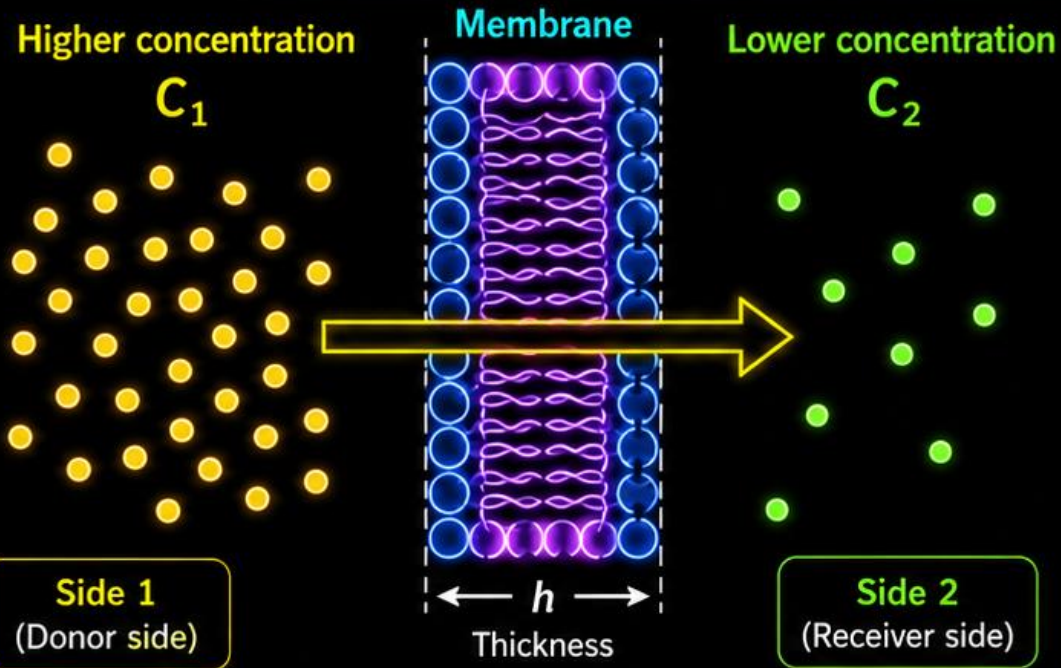
D. Area  $\times (C_1 - C_2)$  / Thickness  $\times$  Permeability coefficient



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# FICK'S FIRST LAW OF DIFFUSION

Rate of diffusion across a membrane is **directly proportional** to membrane area and concentration gradient, and **inversely proportional** to membrane thickness.



$$\text{Rate} = \frac{\text{Area} \times \text{Permeability coefficient} \times (C_1 - C_2)}{\text{Thickness}}$$

| Symbol         | Meaning                         | Units           |
|----------------|---------------------------------|-----------------|
| Rate           | Rate of diffusion (amount/time) | Amount / Time   |
| A              | Membrane surface area           | cm <sup>2</sup> |
| P              | Permeability coefficient        | cm/s            |
| C <sub>1</sub> | Concentration on donor side     | Amount / Volume |
| C <sub>2</sub> | Concentration on receiver side  | Amount / Volume |
| h              | Membrane thickness              | cm              |



**Rate increases with membrane area**

Larger area → more diffusion.



**Rate increases with concentration gradient**

Greater (C<sub>1</sub> - C<sub>2</sub>) → more diffusion.



**Rate decreases with membrane thickness**

Thicker membrane → less diffusion.



**Explains membrane diffusion of drugs**

Basis for drug absorption across biological membranes.



Fick's First Law helps predict how easily a drug diffuses across a membrane—key in **absorption**, **distribution** and **permeability** studies.



38.

**Which of the following is one of the rules in Lipinski's rule of five?**

- A. A molecular weight equal to 500**
- B. No more than five hydrogen bond acceptor groups**
- C. No more than 10 hydrogen bond donor groups**
- D. A calculated logP value less than +5**



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38.

**Which of the following is one of the rules in Lipinski's rule of five?**

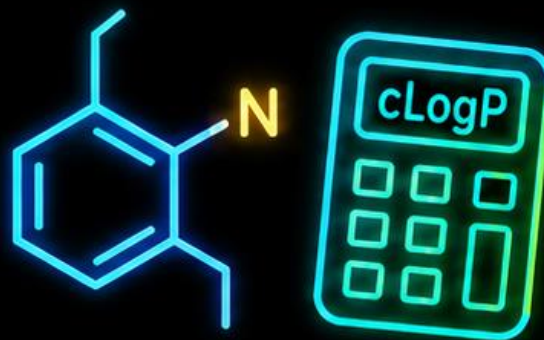
- A. A molecular weight equal to 500**
- B. No more than five hydrogen bond acceptor groups**
- C. No more than 10 hydrogen bond donor groups**
- D. A calculated logP value less than +5**



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# LIPINSKI RULE OF FIVE

GUIDELINES FOR DRUG-LIKENESS



## RULE OF FIVE



MOLECULAR WEIGHT  
UNDER 500



HYDROGEN BOND  
DONORS  
NO MORE THAN 5



HYDROGEN BOND  
ACCEPTORS  
NO MORE THAN 10



LOGP (CALCULATED)  
LESS THAN 5

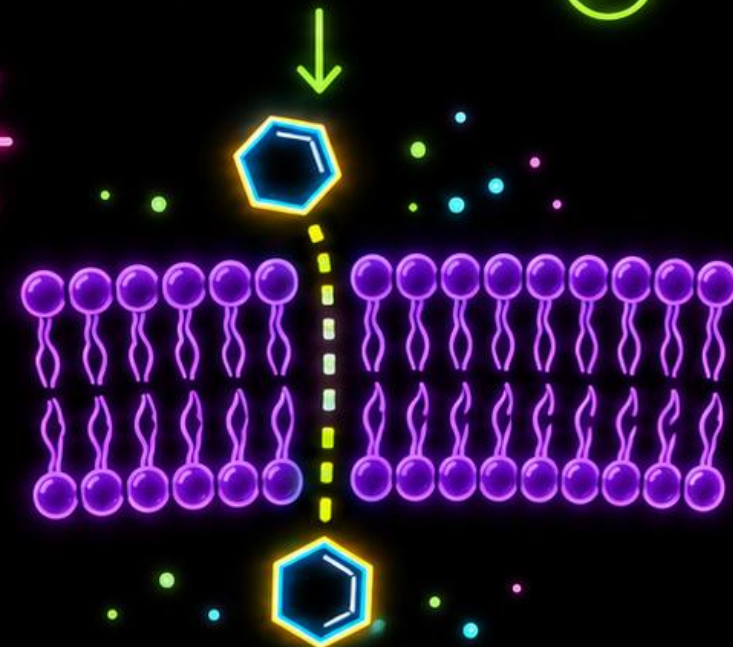
$$\text{cLogP} < 5$$



Lipinski's rules help  
**PREDICT ORAL DRUG-LIKENESS**



They estimate the ability of a  
COMPOUND TO CROSS MEMBRANES  
and be **ABSORBED ORALLY**



**CROSSES MEMBRANE  
BETTER WHEN cLogP < 5**



**KEY TAKEAWAY: cLogP < 5 IS ONE OF LIPINSKI'S RULES**





39.

**Which theory takes into account that a thin film is created by solution of the solid at the solid-liquid interface?**

- A. Interfacial barrier model**
- B. Diffusion layer model**
- C. Penetration or surface renewal theory**
- D. Danckwert's model**



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39.

**Which theory takes into account that a thin film is created by solution of the solid at the solid-liquid interface?**

**A. Interfacial barrier model**

**B. Diffusion layer model**

**C. Penetration or surface renewal theory**

**D. Danckwert's model**



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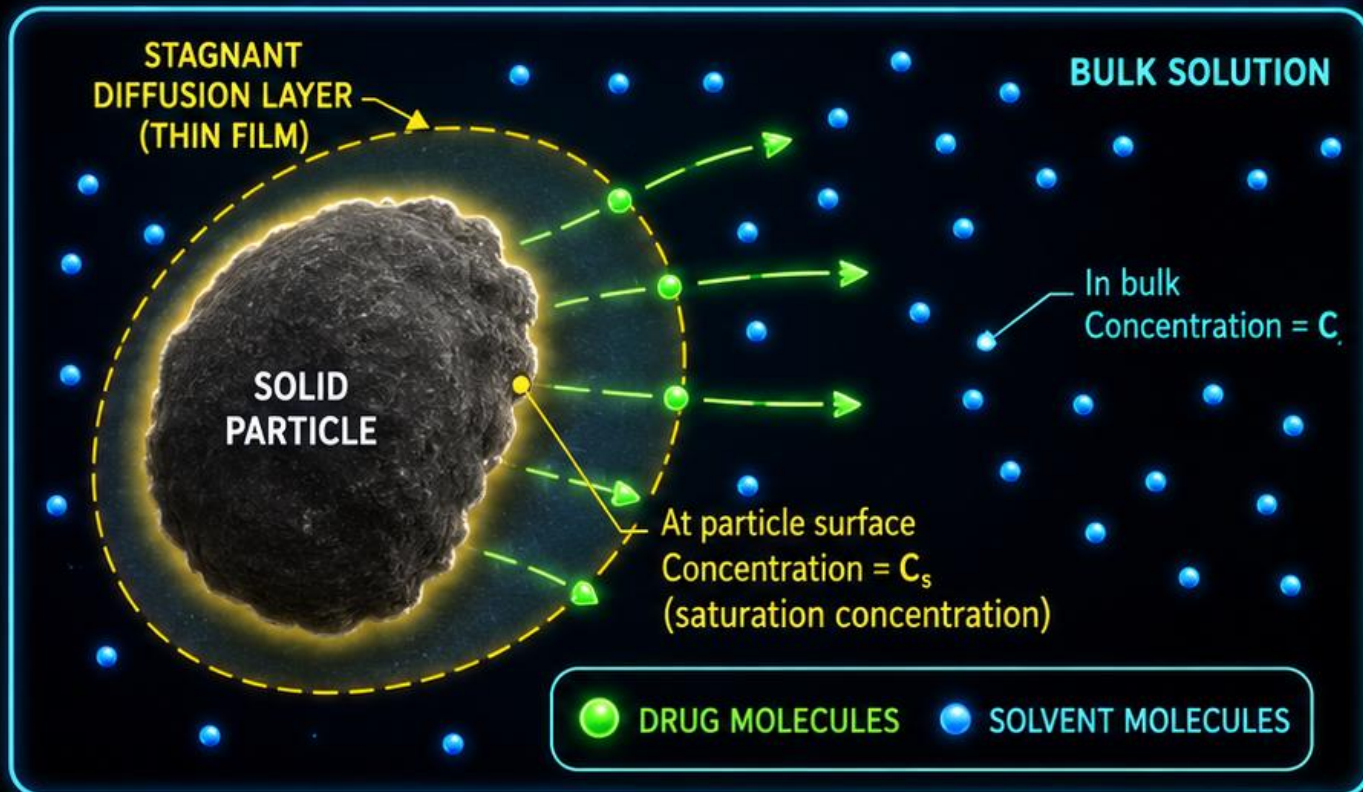




# — DIFFUSION LAYER MODEL —



The diffusion layer model assumes a **thin stagnant film** forms around a solid at the **solid-liquid interface**.



Concentration at particle **surface** is **saturation concentration  $C_s$** .



Concentration in the **bulk** solution is  **$C$**  (less than  $C_s$ ).



Drug molecules **diffuse** across the stagnant diffusion layer to the bulk.



Dissolution rate **increases** if the diffusion layer becomes **thinner**.



## KEY TAKEAWAY:

The diffusion layer model considers a **thin stagnant film** around the dissolving solid that **controls the rate of diffusion and dissolution**.



**40. If gut motility is increased, then:**

- A. Drug absorption is decreased**
- B. Drug absorption is increased**
- C. Drug absorption is not affected**
- D. None of the above**



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**40.** If gut motility is increased, then:

- A. Drug absorption is decreased**
- B. Drug absorption is increased**
- C. Drug absorption is not affected**
- D. None of the above**







# INCREASED GUT MOTILITY AND DRUG ABSORPTION



WHEN GUT  
MOTILITY  
INCREASES



DRUG  
ABSORPTION  
USUALLY  
DECREASES



FAST-MOVING  
GI TRACT



REDUCED  
CONTACT TIME



REDUCED RESIDENCE TIME  
in stomach and intestine.



LESS TIME FOR DISSOLUTION  
and absorption.



FASTER TRANSIT LOWERS  
contact with absorptive surface.



LESS OPPORTUNITY FOR DRUG  
to cross the intestinal wall.



**KEY TAKEAWAY:**  
**INCREASED GUT MOTILITY**  
GENERALLY **DECREASES** DRUG ABSORPTION.





41.

**In sink condition, dissolution rate follows:**

- A. First order kinetics**
- B. Zero order kinetics**
- C. Mixed order kinetics**
- D. None of the above**



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41.

**In sink condition, dissolution rate follows:**

- A. First order kinetics
- B. Zero order kinetics**
- C. Mixed order kinetics
- D. None of the above



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# SINK CONDITION & DISSOLUTION RATE



1



$$C \ll C_s$$

bulk concentration stays very low

2



**High concentration gradient**

drug keeps moving into solution

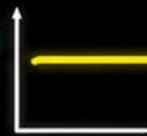
3



$$(C_s - C) \approx \text{constant}$$

driving force remains almost unchanged

4



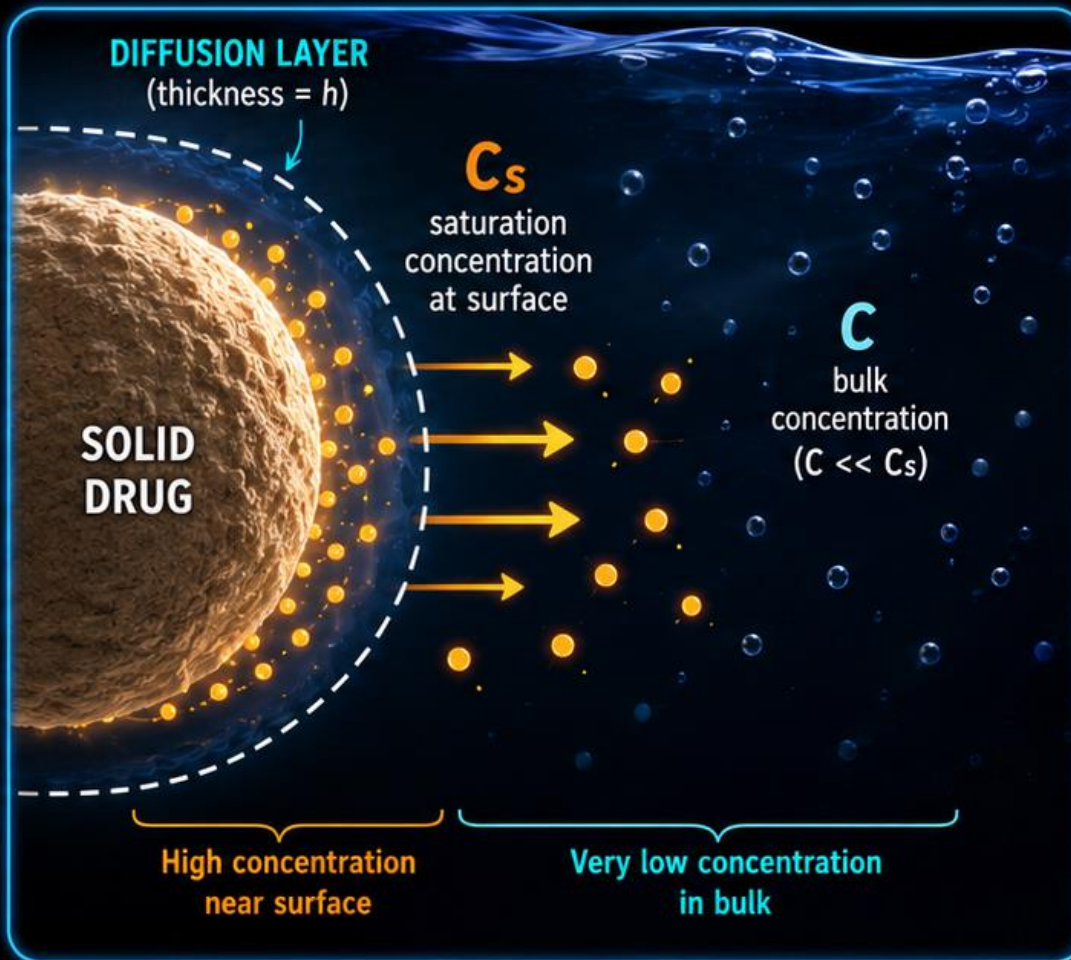
**Nearly constant dissolution rate**

apparent zero-order behavior

5



**Valid while surface area is unchanged**



**NOYES-WHITNEY EQUATION**

$$\frac{dC}{dt} = \frac{DA}{h} (C_s - C)$$

$D$  = diffusion coefficient

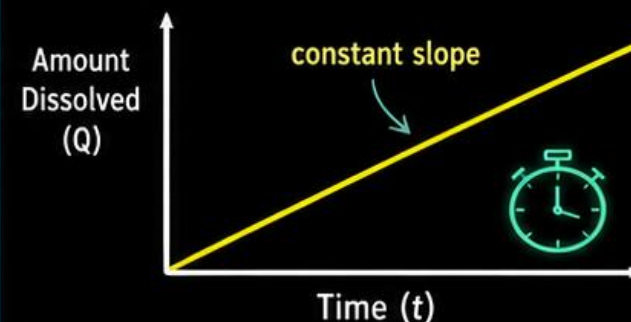
$A$  = surface area

$h$  = diffusion layer thickness

$C_s$  = saturation concentration

$C$  = bulk concentration

**RATE vs TIME (Sink Condition)**



SOLID DOSAGE FORM



IN CONTACT WITH DISSOLUTION MEDIUM



DRUG MOLECULES DISSOLVE



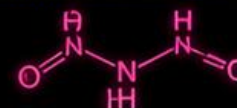
MOLECULES DIFFUSE INTO BULK



SINK CONDITION MAINTAINED



As long as surface area remains constant, dissolution proceeds at an **almost constant rate**.





**42. Dissolution may be described by using which equation or law?**

- A. Fick's second law**
- B. Noyes–Whitney equation**
- C. Stoke's law**
- D. Poiseuille's law**







**42.** Dissolution may be described by using which equation or law?

A. Fick's second law

**B. Noyes–Whitney equation**

C. Stoke's law

D. Poiseuille's law



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# DISSOLUTION IS DESCRIBED BY NOYES-WHITNEY EQUATION

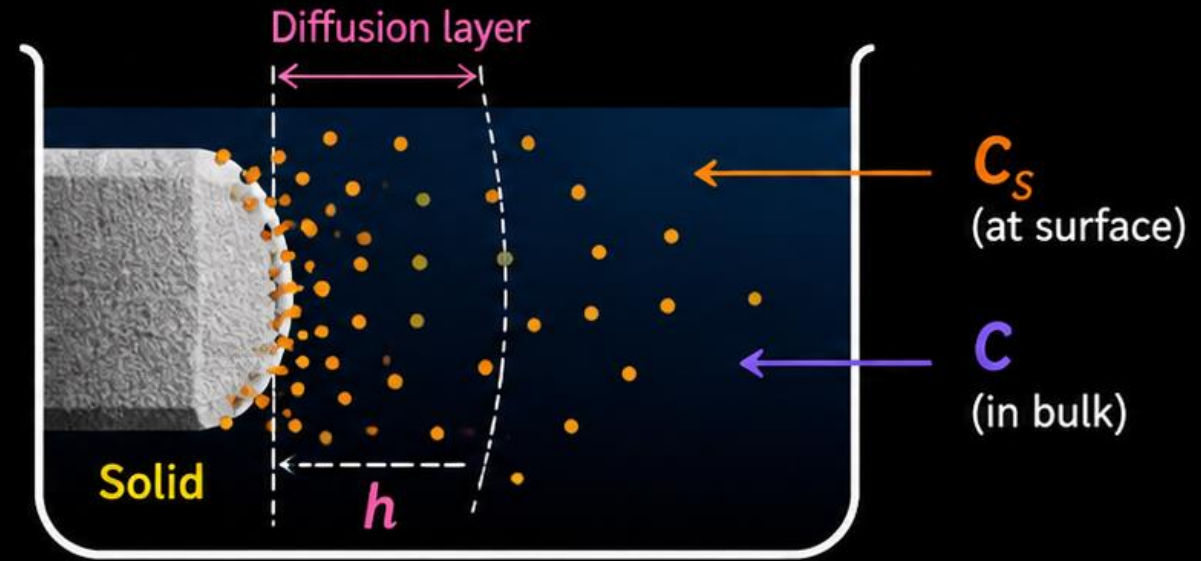
$$\frac{dC}{dt} = \frac{D \cdot A}{h} (C_s - C)$$

- $dC/dt$  : Rate of dissolution  
 $D$  : Diffusion coefficient  
 $A$  : Surface area of solid  
 $h$  : Thickness of diffusion layer  
 $C_s$  : Saturation solubility  
 $C$  : Concentration in bulk solution



**Noyes-Whitney equation** relates the rate of dissolution to physical and concentration factors.

## VISUAL REPRESENTATION



## RATE OF DISSOLUTION $\propto$





43.

**Convective transport, bulk flow or filtration is also known as:**

- A. Passive diffusion**
- B. Active transport**
- C. Pore transport**
- D. Ion-pair transport**



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43.

**Convective transport, bulk flow or filtration is also known as:**

**A. Passive diffusion**

**B. Active transport**

**C. Pore transport**

**D. Ion-pair transport**



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# CONVECTIVE TRANSPORT / BULK FLOW / FILTRATION

Also called **pore transport**



## DEFINITION

Drug moves with **water** through tiny aqueous **pores**



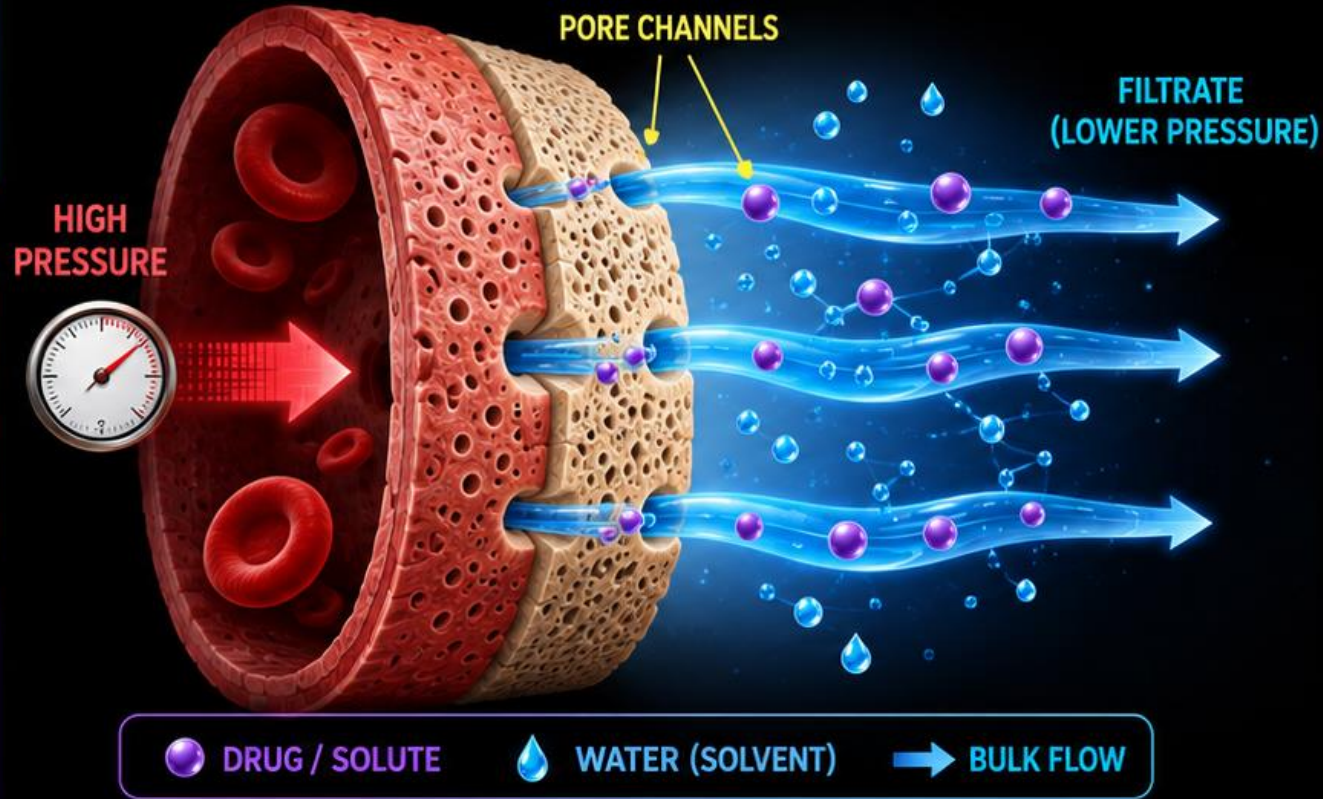
## MECHANISM

- Driven by **pressure gradient**
- Movement of **solute + solvent together**



## IMPORTANT NOTE

Useful for **small, water-soluble** molecules



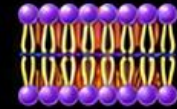
## WHERE SEEN



Capillaries



Renal glomeruli



Some membranes



## MEMORY HOOK

**Pressure** pushes fluid through **pores**



WATER



PRESSURE



PORES



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44.

**The onset of drug action depends on the rate of:**

- A. Drug absorption**
- B. Drug dissociation**
- C. Both A and B**
- D. None of these**



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44.

**The onset of drug action depends on the rate of:**

**A. Drug absorption**

**B. Drug dissociation**

**C. Both A and B**

**D. None of these**



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# Onset of Drug Action



How fast the effect appears

1



Faster  
absorption  
=  
faster onset

2



Dissociation  
controls  
availability  
of free drug

3



Unionized /  
available form  
acts sooner

4



Both  
processes  
can influence  
how quickly  
action starts

5



Key idea:  
onset depends  
on **rate**,  
not just **dose**

Dosage form



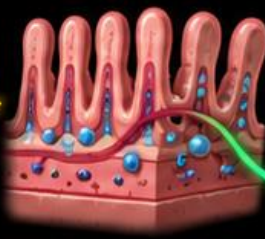
Tablet, capsule,  
solution, injection,  
etc.

Drug release



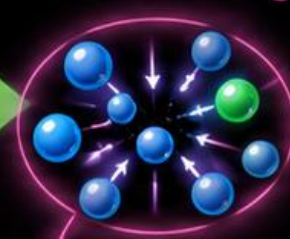
Breaks apart  
and dissolves

Absorption



Passes across  
membrane into  
**blood**

Free /  
available drug



● Ionized / bound  
● Unionized / free  
(active)

Pharmacological  
effect



Binds to receptor  
→ Response  
→ Effect

**ONSET**  
Time to  
begin effect

FACTORS THAT  
AFFECT ONSET



Route



Absorption  
rate



GI motility



Blood flow  
at site



pH &  
lipid solubility



Protein  
binding



First-pass  
metabolism



Formulation  
& particle size



Remember:  
**onset** =  
time to begin effect







45.

**Which one of these is not a theory of drug dissolution?**

- A. Diffusion layer model**
- B. Fick's law of diffusion**
- C. Penetration or surface renewal theory**
- D. Interfacial barrier model**



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45.

**Which one of these is not a theory of drug dissolution?**

**A. Diffusion layer model**

**B. Fick's law of diffusion**

**C. Penetration or surface renewal theory**

**D. Interfacial barrier model**



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# Drug Dissolution: Key Explanation



## 1 CLASSICAL THEORIES

### 1 Diffusion layer model

- ★ A **stagnant** liquid film forms around the drug particle.
- ★ Drug **diffuses** through this layer into bulk fluid.

### 2 Penetration / surface renewal theory

- ★ Fresh liquid continuously contacts the surface.
- ★ Dissolution depends on repeated surface **renewal**.

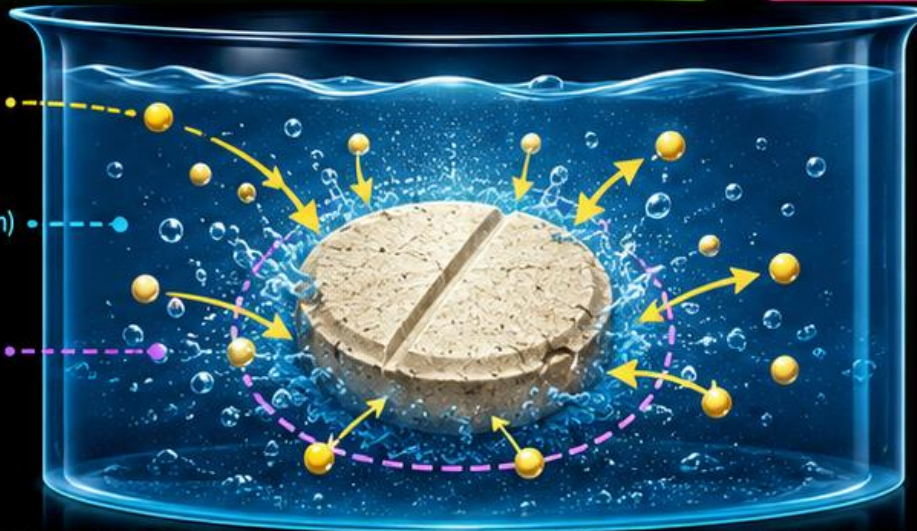
### 3 Interfacial barrier model

- ★ A **barrier** at the solid-liquid interface controls release.
- ★ Interfacial step may **limit** dissolution.

### 2 EXAM POINT

- ★ These 3 are the **classic theories** of drug dissolution.

- Drug molecules
- Bulk fluid (medium)
- Dissolution boundary layer



### 3 FICK'S LAW

- Describes **diffusion** mathematically.
- It supports dissolution concepts, but it is **not** listed as a separate dissolution theory.



SOLID DOSAGE  
FORM



MOLECULES  
LEAVING SURFACE



BULK  
SOLUTION



RENEWAL  
ACTION



INTERFACE  
CONTROL



RATE OF  
DISSOLUTION



TIME  
FACTOR



CLINICAL  
RELEVANCE



46.

**Which type of drugs are absorbed by ion pair transport?**

- A. High lipophilicity**
- B. Oily droplets**
- C. Quaternary ammonium compounds**
- D. All of the above**



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46.

**Which type of drugs are absorbed by ion pair transport?**

A. High lipophilicity

B. Oily droplets

C. Quaternary ammonium compounds

D. All of the above



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# ION PAIR TRANSPORT



1



Highly **ionized** drugs **cannot** cross lipid membrane easily

2



They temporarily bind with an **opposite counter-ion**

3



This forms a **neutral ion pair**

4



Neutral pair becomes more **lipid soluble**

5



The pair **diffuses** across the membrane

6



Inside, the pair **dissociates** and releases the drug

IONIZED DRUG  
(CATIONIC)

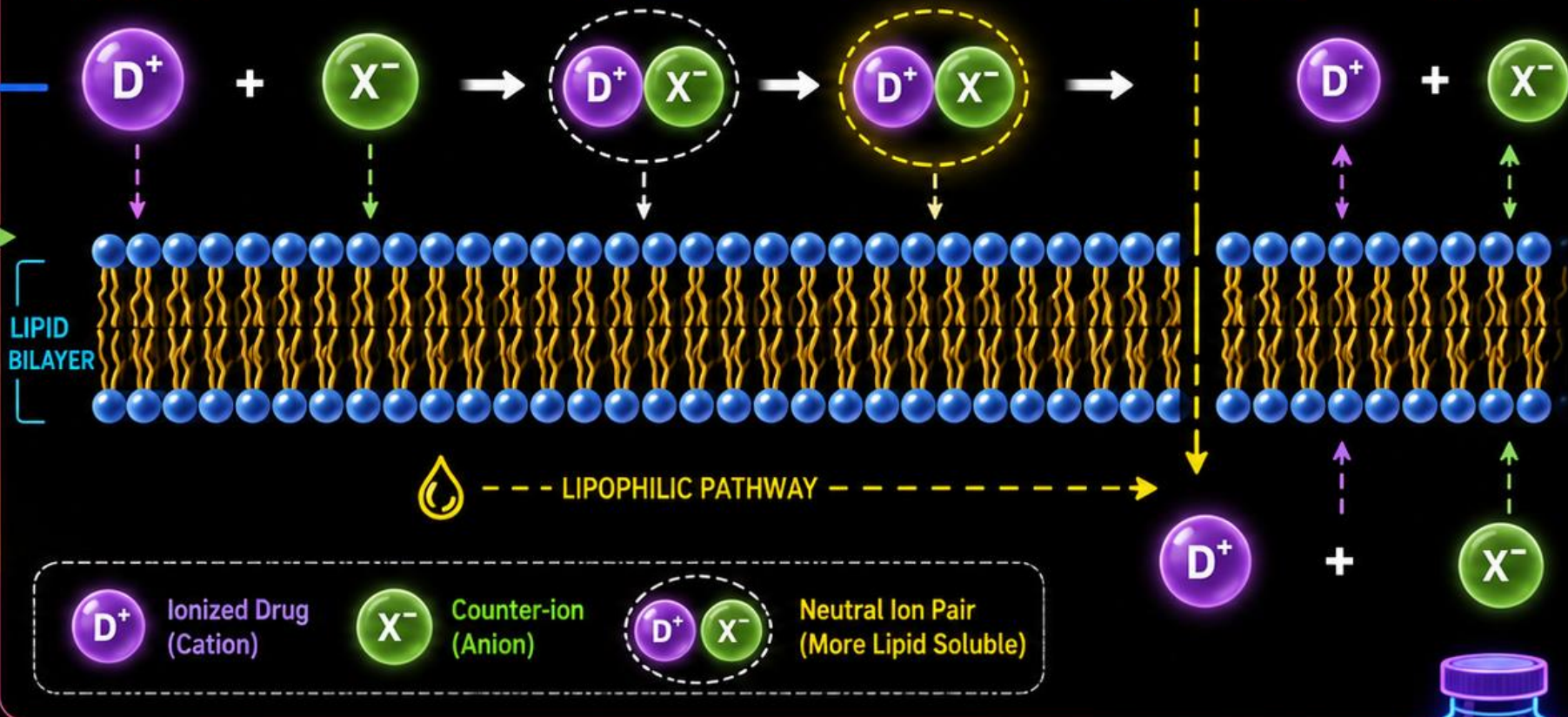
OPPOSITE  
COUNTER-ION

ION PAIR  
(NEUTRAL)

LIPID SOLUBLE  
NEUTRAL PAIR

DIFFUSION ACROSS  
LIPID MEMBRANE

DISSOCIATION  
INSIDE



COMMON IN PERMANENTLY CHARGED DRUGS LIKE QUATERNARY AMMONIUM COMPOUNDS





47.

**In sink condition, passive diffusion follows:**

- A. First order kinetics**
- B. Zero order kinetics**
- C. Mixed order kinetics**
- D. All of the above**



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47.

**In sink condition, passive diffusion follows:**

- A. First order kinetics**
- B. Zero order kinetics**
- C. Mixed order kinetics**
- D. All of the above**



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# PASSIVE DIFFUSION IN SINK CONDITION

1



Sink condition = **receiver side** concentration stays very low

2



Large concentration **gradient** is maintained

3



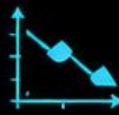
Drug moves from **high** concentration to **low** concentration

4



Rate depends on **concentration gradient**

5

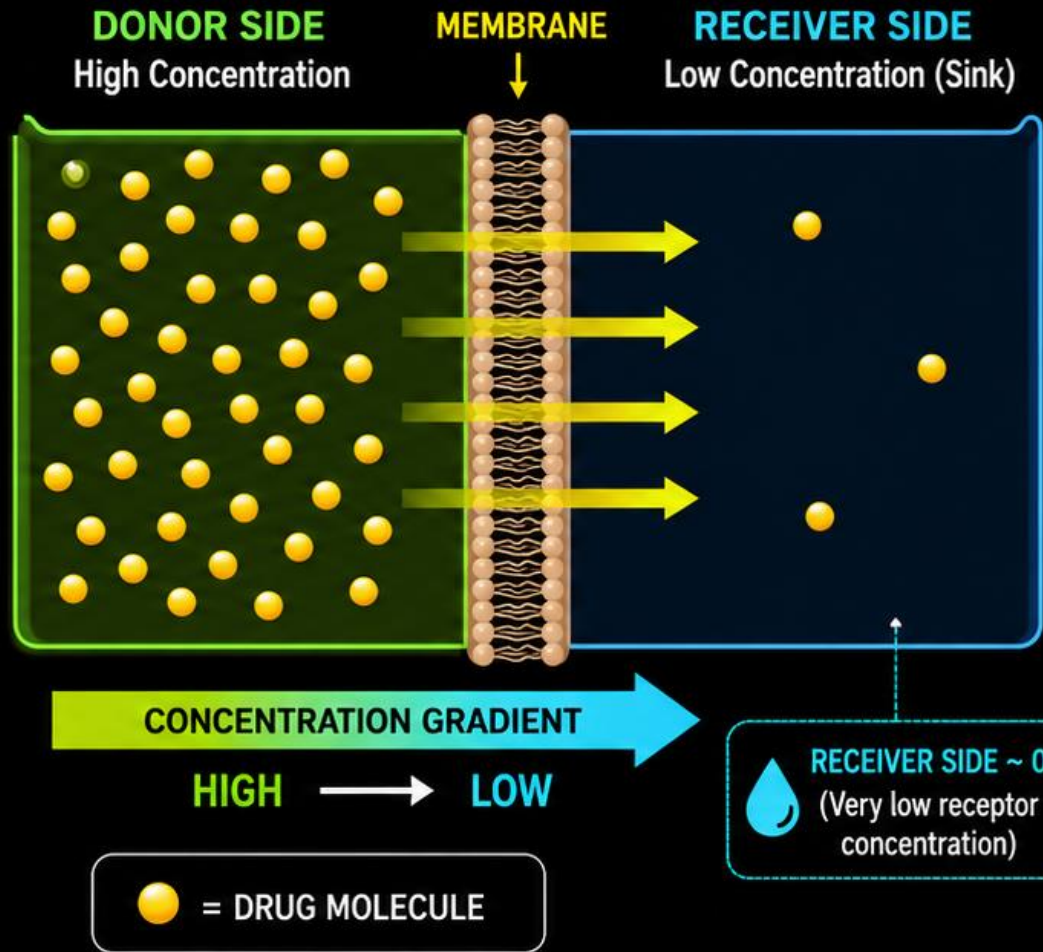


As donor concentration **decreases**, diffusion rate also decreases

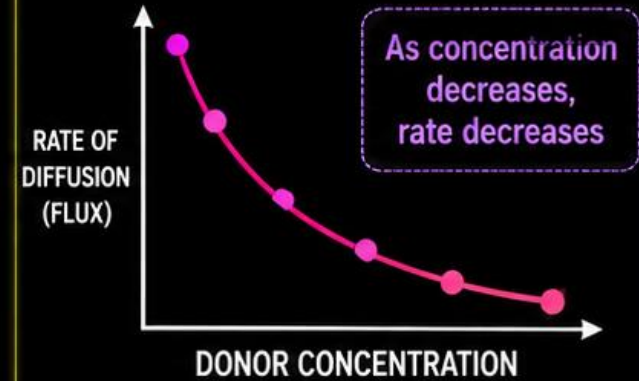
6



Therefore, passive diffusion shows **first-order behavior**



## RATE vs DONOR CONCENTRATION



## KINETICS SUMMARY

Rate  $\propto$  concentration difference

$$\text{Rate} = k (C_{\text{donor}} - C_{\text{receiver}})$$

$C_{\text{donor}}$  = donor concentration

$C_{\text{receiver}} \approx 0$  (sink condition)

$\Rightarrow \text{Rate} \propto C_{\text{donor}}$

★ **FIRST-ORDER BEHAVIOR**



Maintains driving force for diffusion



Ensures continuous drug transfer



Used in in vitro dissolution studies



Achieved by large volume / rapid removal



Ideal for studying intrinsic permeability



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**48. Vitamin B12 is absorbed by:**

- A. Passive diffusion**
- B. Active transport**
- C. Facilitated diffusion**
- D. Pore transport**



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**48. Vitamin B12 is absorbed by:**

**A. Passive diffusion**

**B. Active transport**

**C. Facilitated diffusion**

**D. Pore transport**



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# Vitamin B12 Absorption



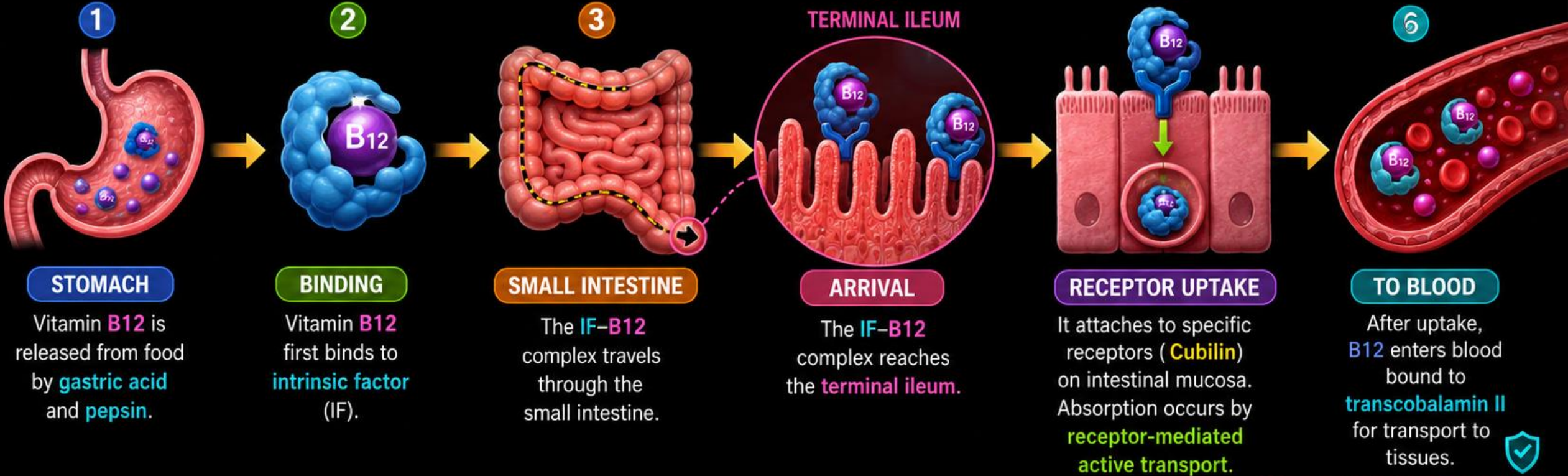
Intrinsic Factor  
(IF)



Vitamin B12  
(Cobalamin)



Absorption occurs  
mainly in the  
**terminal ileum.**



Essential for **DNA synthesis**,  
**RBC formation** &  
**neurologic function**.



A tiny amount may diffuse **passively** at **very high doses** ( $\approx 1\%$  of an oral dose).







49.

**Sabin polio vaccine is absorbed by:**

- A. Passive diffusion**
- B. Phagocytosis**
- C. Pinocytosis**
- D. Pore transport**



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49.

**Sabin polio vaccine is absorbed by:**

A. Passive diffusion

B. Phagocytosis

**C. Pinocytosis**

D. Pore transport



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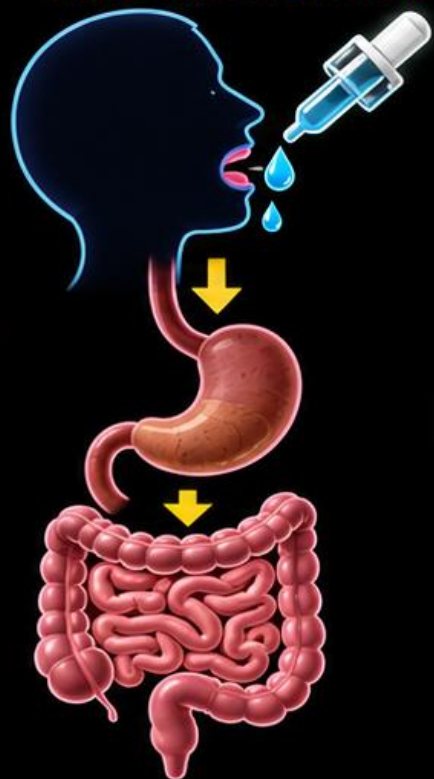


# Sabin Vaccine – Uptake Mechanism



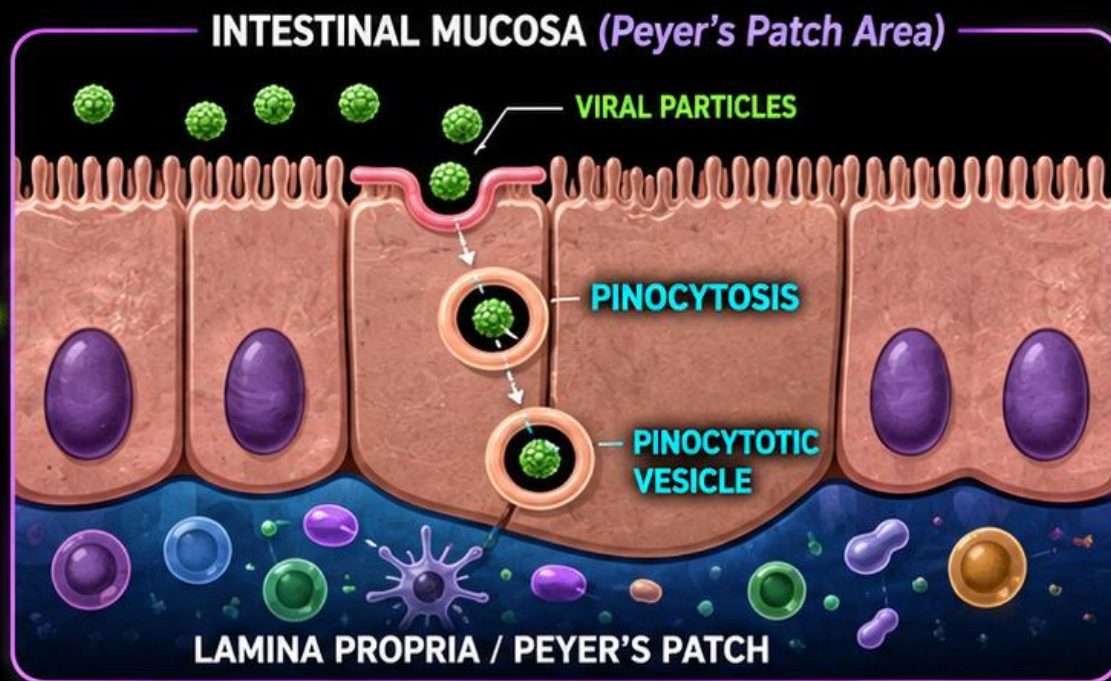
Oral *live attenuated* polio vaccine

ORAL VACCINE DROPS



REACHES INTESTINE

Taken up by **PINOCYTOSIS**



GUT IMMUNITY



1 Given orally → reaches intestine



2 Intestinal mucosal cells take up viral particles



3 Pinocytosis = cell drinking of fluid / tiny particles



4 Then stimulates gut immunity



5 Helps local IgA protection



**MEMORY LINE:** Biological particles / vaccines can enter by **vesicular uptake**





50.

**The main mechanism of absorption of most drugs in the GI tract is:**

- A. Active transport**
- B. Filtration**
- C. Endocytosis and exocytosis**
- D. Passive diffusion**



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50.

**The main mechanism of absorption of most drugs in the GI tract is:**

- A. Active transport**
- B. Filtration**
- C. Endocytosis and exocytosis**
- D. Passive diffusion**



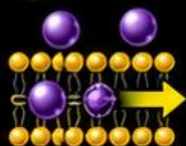
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# GI ABSORPTION: KEY MECHANISM

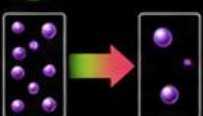


1



Most drugs cross the GI membrane by **SIMPLE MEMBRANE DIFFUSION**.

2



Movement is from **HIGHER** concentration in **LUMEN** to **LOWER** concentration in **BLOOD**.

3

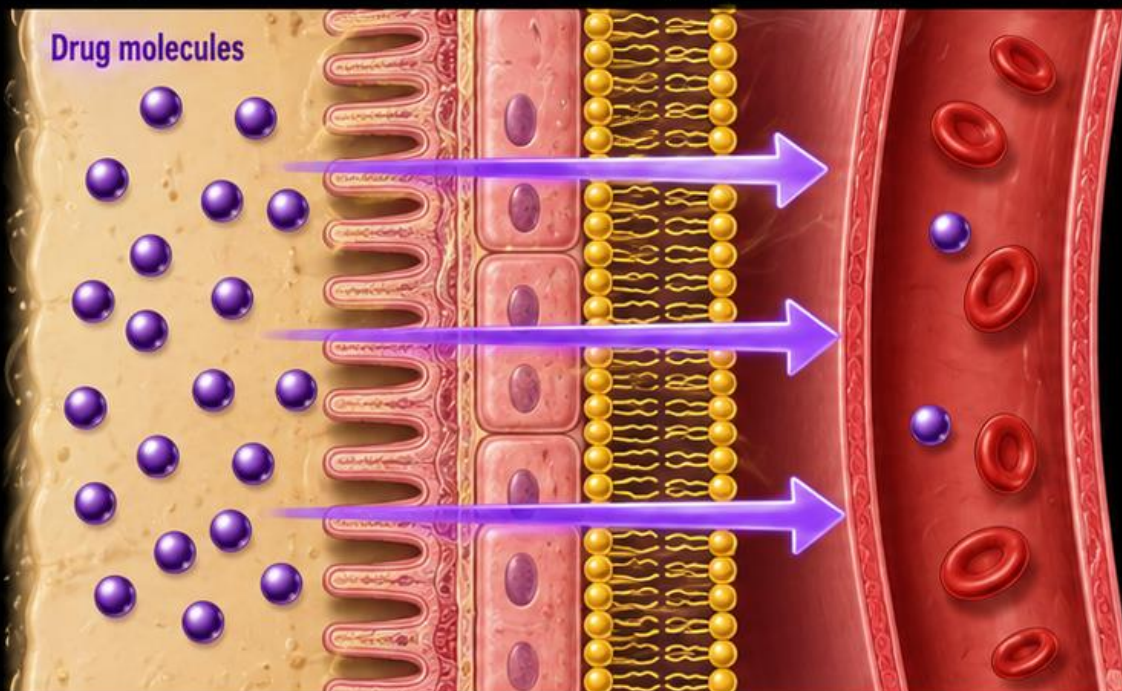


No **ENERGY (ATP)** needed.

**LUMEN**  
(Higher concentration)

**MEMBRANE**  
(Lipid bilayer)

**BLOOD**  
(Lower concentration)



Drug  
(**Unionized**)



Passive Diffusion  
(Down Gradient)



Lipid Bilayer  
(Cell Membrane)

4



No **CARRIER** required.

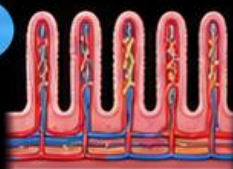
5



**UNIONIZED**

Best for **LIPID-SOLUBLE, UNIONIZED** molecules.

6



Large **INTESTINAL SURFACE AREA** helps absorption.

7



**pH** and **pKa** influence how much drug stays **UNIONIZED**.



**THINK:**



**DOWN GRADIENT**

+



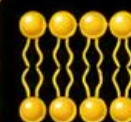
**NO ENERGY**

+



**NO CARRIER**

+



**LIPID MEMBRANE PASSAGE**





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THANK  
YOU!



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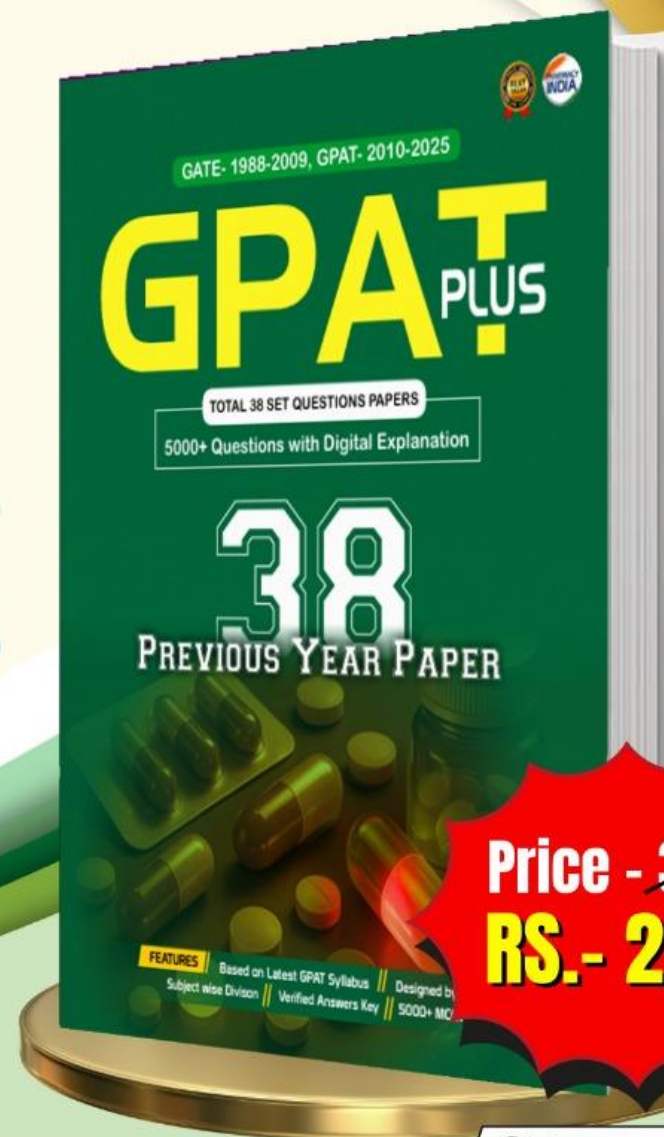
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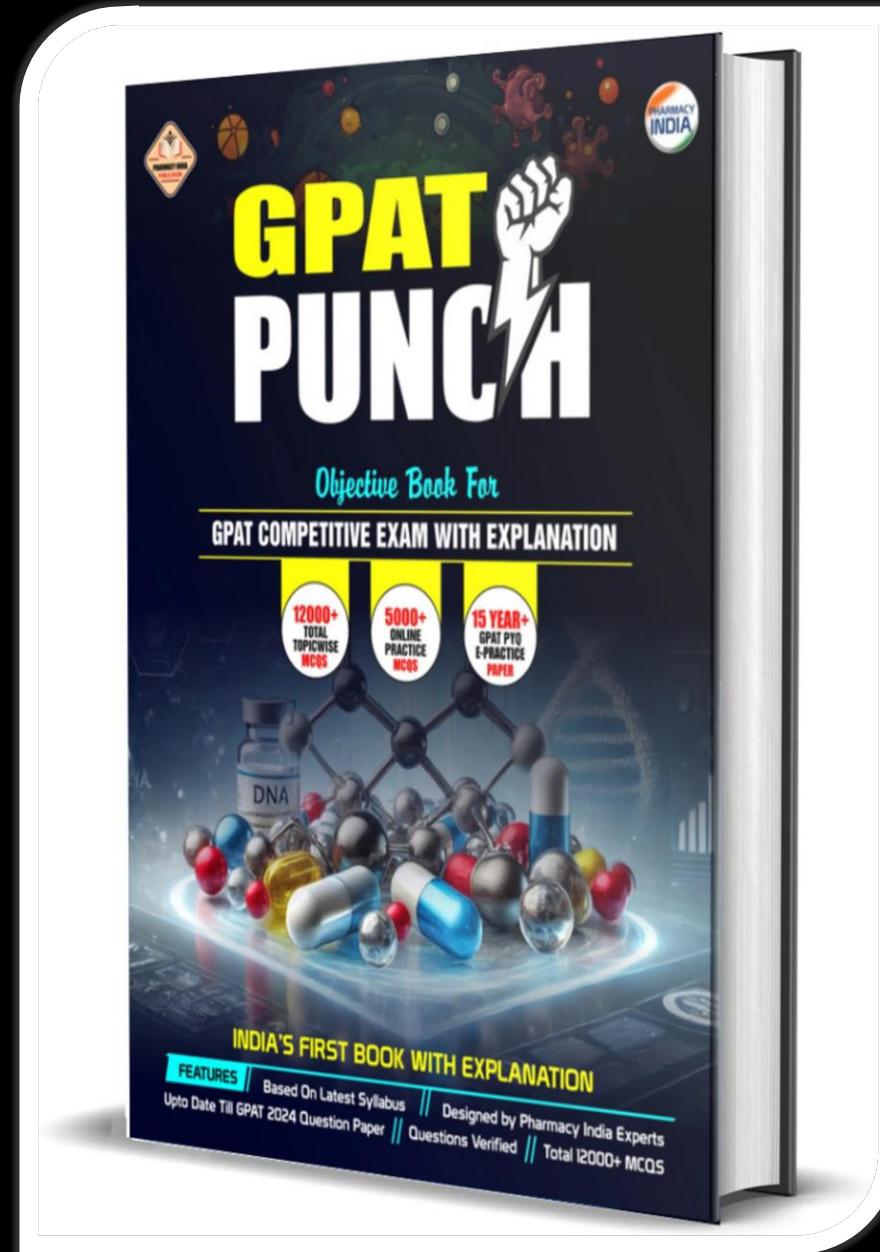
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