4

Pharmacology

Doctor 2018 | Medicine | JU

◉ Sheet ○ Slides

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Quick revision:

Pharmacokinetics is one of the two main branches in the science of pharmacology. Simply, pharmacokinetics is what the body does to the drug. More specifically, it is the study of the movement of drugs in the body. It is the determination of the fate of the substances administered from an exogenous source to a living organism.

There are four important properties that we must consider in pharmacokinetics as they determine the onset, intensity, and the duration of drug action.

1) Absorption: It is the movement of the drug from the site of administration to the bloodstream (plasma)

2) Distribution: The drug leaves the bloodstream *reversibly* and goes to tissues and cells where the action is done.

3) Metabolism (biotransformation): The drug is metabolized or "changed" in order to be excreted out of the body.

4) Elimination: The drug is eliminated from the body through urine, feces, or bile.

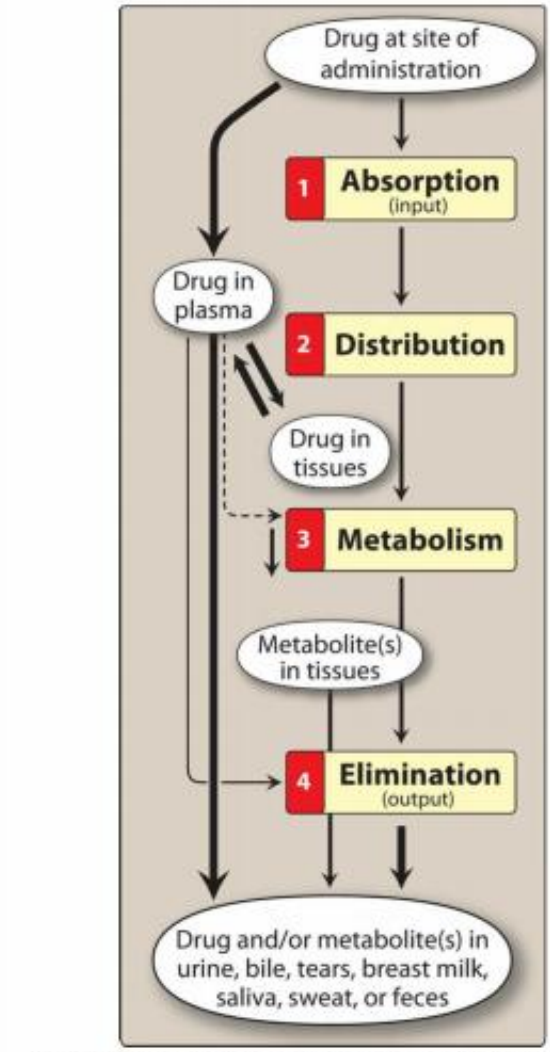


Figure 1.1 Schematic representation of drug absorption, distribution, metabolism, and elimination.

NOTE: Not all absorbed drugs are distributed to the body tissues, as some may undergo immediate biotransformation depending on their route of administration and the chemical properties of the drug.

Question: Is there a linkage between pharmacokinetics and pharmacodynamics? And if so, when does it occur?

Answer: Yes, there is. Pharmacodynamics begins when the drug is **distributed** inside the body tissues.

Routes of administration:

We know that drugs can be administered by various methods, for example, orally taking a drug or by using an intravascular injection. But a common question that arises in one's mind is:

"How do we determine the route of administration for a specific drug?"

Well, silly, we determine the route of administration by properties of the drug. For instance, what is the water or lipid solubility and the ionization of the drug? Another determinant of the suitable route of administration is the therapeutic agents of the drug. Like is the drug desired for a rapid onset? And what is the duration of the treatment? Is it long-term or short term? And finally, Is there a need for restriction of the drug to a local site?

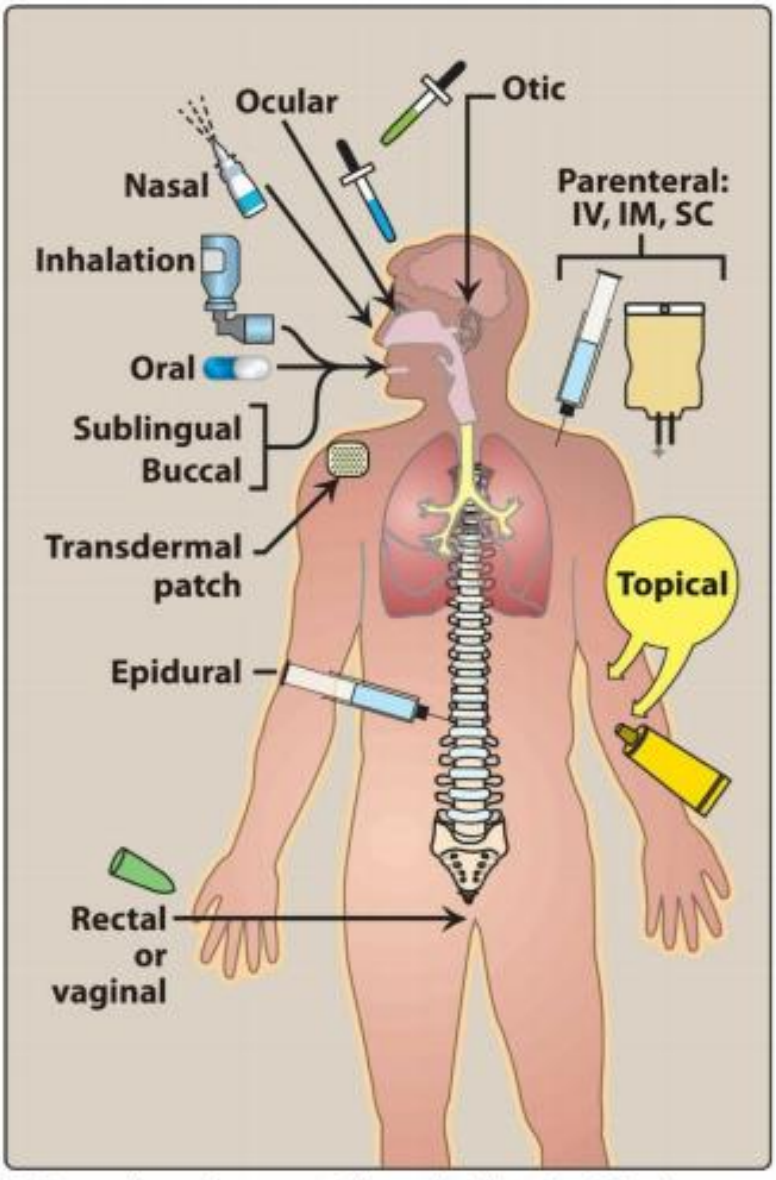


Figure 1.2 Commonly used routes of drug administration. IV = intravenous; IM = intramuscular; SC = subcutaneous.

So, what are some of the common routes used for administrating drugs?

1. Oral:

Oral administration is the most common, convenient, and economical method of drug administration. It is also considered the safest method of all. No physician/specialist/nurse is needed to monitor/perform the drug administration, as it is easily done by the patient compared to injections.
Some drugs in this method have poor absorption and therefore the drug is partially absorbed to the bloodstream and partially metabolized.
Some drugs that are taken orally get digested in the stomach by digestive enzymes due to their chemical structure. (e.g. insulin and most hormone drugs are peptides and will be cleaved by the digestive enzymes in the stomach if taken orally).
Drugs cannot be taken orally if the patient is vomiting or if the drug induces vomiting in the patient or if the patient is unconscious.
[EXTRA INFO]: *drugs that are taken orally can be chemically enveloped (enteric coating) to protect the drug from the stomach acid.*

First Pass Effect,
Also known as the "presystemic metabolism" *is a phenomenon of drug administration whereby the concentration of the drug is greatly reduced before it reaches the systemic circulation. If the drug is highly influenced by the first pass effect, then it is not suitable to be taken orally. Instead, we can take it sublingually. e.g. nitroglycerin*

[EXTRA INFO] INSTRUCTIONS ON HOW TO TAKE A DRUG ORALLY:
1) take the pill in your hands
2) put the pill in your mouth on top of your tongue
3) swallow the pill. If you can't do it, drink water and swallow it while the drug is in your mouth
4) congratulations! You are now a professional oral-drug taker.

2. Intravenous Injections:

One of the main advantages of taking a drug through an injection is the immediate effect. Useful in case of allergy attacks.

It immediately enters the systemic circulation and there is no loss of the drug as it does not get presystemically metabolized. Therefore, drugs that were unable to be taken orally due to their chemical structures, can be taken intravenously. (e.g. hormones)

We should not give large doses at once in a bolus injection as it may lead to severe adverse effects. Instead, we titrate the drug and give the required dose in a spaced time period.

NOTE: we do not give a large dose of a drug intramuscularly as the size of the muscle is relatively small compared to the volume of the bloodstream.

Intravenous injections are the fastest of all injection methods.

One of the disadvantages of injections is that it must be administered by a specialist or a nurse and it is inconvenient.

3. Transdermal patches:

It helps avoid the problem that occurs in oral administration. Examples of transdermal patches include nicotine and progesterone contraceptive patches.

The patch gives a sustained, continuous administration of the drug, over a long period of time.

This method of administration is painless and bypasses the first-pass effect.

The drug has to be lipophilic in order to be absorbed by the plasma membrane of the cell.

One of the disadvantages is allergies.

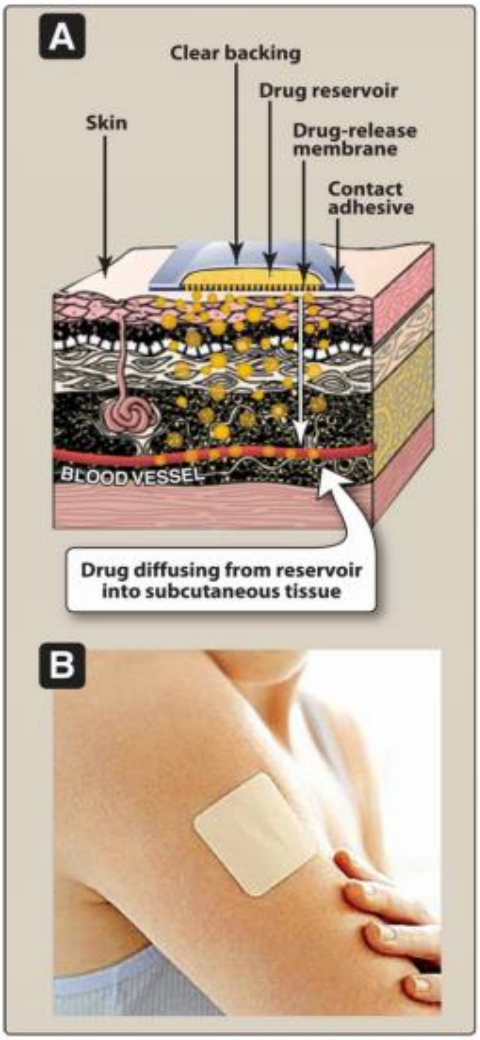


Figure 1.4 A. Schematic representation of a transdermal patch. **B.** Transdermal nicotine patch applied to the arm.

4. Rectal:

One problem with the rectal method is that the absorption is not very controlled as it is erratic and variable. It bypasses the first-pass effect partially, because some blood vessels in the rectum do not go to the portal vein directly. Very useful with children. 😈

5. Inhalation:

Absorption is rapid and can have immediate effects.
Most common example are general inhalation anesthetics.

Summary of basically everything said so far and more: (look at slides for better quality)

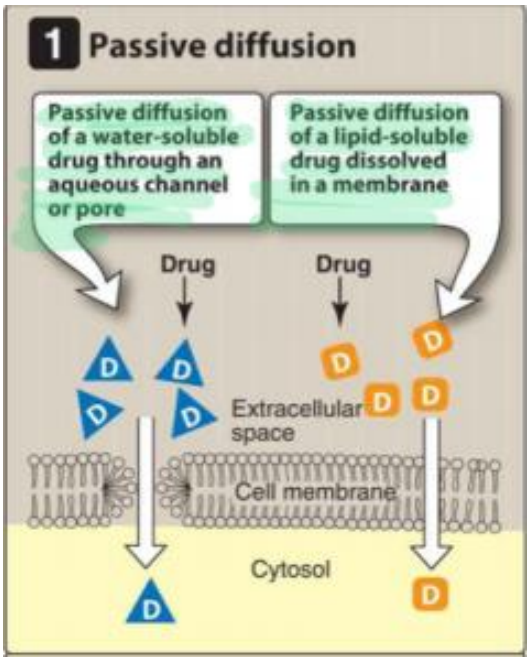
ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
Oral	• Variable; affected by many factors	• Safest and most common, convenient, and economical route of administration	• Limited absorption of some drugs • Food may affect absorption • Patient compliance is necessary • Drugs may be metabolized before systemic absorption	• *Acetaminophen* tablets • *Amoxicillin* suspension
Sublingual	• Depends on the drug: Few drugs (for example, *nitroglycerin*) have rapid, direct systemic absorption Most drugs erratically or incompletely absorbed	• Bypasses first-pass effect • Bypasses destruction by stomach acid • Drug stability maintained because the pH of saliva relatively neutral • May cause immediate pharmacological effects	• Limited to certain types of drugs • Limited to drugs that can be taken in small doses • May lose part of the drug dose if swallowed	• *Nitroglycerin* • *Buprenorphine*
Intravenous	• Absorption not required	• Can have immediate effects • Ideal if dosed in large volumes • Suitable for irritating substances and complex mixtures • Valuable in emergency situations • Dosage titration permissible • Ideal for high molecular weight proteins and peptide drugs	• Unsuitable for oily substances • Bolus injection may result in adverse effects • Most substances must be slowly injected • Strict aseptic techniques needed	• *Vancomycin* • *Heparin*
Intramuscular	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable if drug volume is moderate • Suitable for oily vehicles and certain irritating substances • Preferable to intravenous if patient must self-administer	• Affects certain lab tests (creatine kinase) • Can be painful • Can cause intramuscular hemorrhage (precluded during anticoagulation therapy)	• *Haloperidol* • *Depot medroxyprogesterone*
Subcutaneous	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable for slow-release drugs • Ideal for some poorly soluble suspensions	• Pain or necrosis if drug is irritating • Unsuitable for drugs administered in large volumes	• *Epinephrine* • *Insulin* • *Heparin*
Inhalation	• Systemic absorption may occur; this is not always desirable	• Absorption is rapid; can have immediate effects • Ideal for gases • Effective for patients with respiratory problems • Dose can be titrated • Localized effect to target lungs; lower doses used compared to that with oral or parenteral administration • Fewer systemic side effects	• Most addictive route (drug can enter the brain quickly) • Patient may have difficulty regulating dose • Some patients may have difficulty using inhalers	• *Albuterol* • *Fluticasone*
Topical	• Variable; affected by skin condition, area of skin, and other factors	• Suitable when local effect of drug is desired • May be used for skin, eye, intravaginal, and intranasal products • Minimizes systemic absorption • Easy for patient	• Some systemic absorption can occur • Unsuitable for drugs with high molecular weight or poor lipid solubility	• *Clotrimazole* cream • *Hydrocortisone* cream • *Timolol* eye drops
Transdermal (patch)	• Slow and sustained	• Bypasses the first-pass effect • Convenient and painless • Ideal for drugs that are lipophilic and have poor oral bioavailability • Ideal for drugs that are quickly eliminated from the body	• Some patients are allergic to patches, which can cause irritation • Drug must be highly lipophilic • May cause delayed delivery of drug to pharmacological site of action • Limited to drugs that can be taken in small daily doses	• *Nitroglycerin* • *Nicotine* • *Scopolamine*
Rectal	• Erratic and variable	• Partially bypasses first-pass effect • Bypasses destruction by stomach acid • Ideal if drug causes vomiting • Ideal in patients who are vomiting, or comatose	• Drugs may irritate the rectal mucosa • Not a well-accepted route	• *Bisacodyl* • *Promethazine*

Mechanisms of drug absorption in the gastrointestinal tract:

The rate and extent of absorption for a drug depends the environment where the drug is absorbed, the chemical characteristics of the drug, and the used route for administration.

We will be briefly discussing the ways of which a drug can enter a cell.

1) Passive diffusion:



The driving force for passive diffusion is the concentration gradient across a membrane separating two body compartments. We need to have a difference in the concentrations between the site of administration (GI system) where the concentration should be high, and the bloodstream, where the concentration is low.

Not all drugs diffuse by this method, and it depends on some characteristics of the drug, such as its **degree of lipophilicity** (the higher the lipophilicity the easier it gets diffused passively).

Molecular weight of the drug plays an important role in whether or not it will be absorbed using passive diffusion. (The lower the molecular weight the easier it is to get passively diffused), so the drug has to be small in size.

>> Perfect drug characteristics for passive diffusion: ***small molecular weight and high lipophilicity****.*

>> Some of the features of passive diffusion is that there is **low structural specificity (Compatibility) for all molecules**. Meaning that any molecule, as long as it has acceptable characteristics (not a specific drug), can use this method to enter the cell.

>> Passive diffusion is also characterized by **not having a carrier**. It does not require energy (ATP).

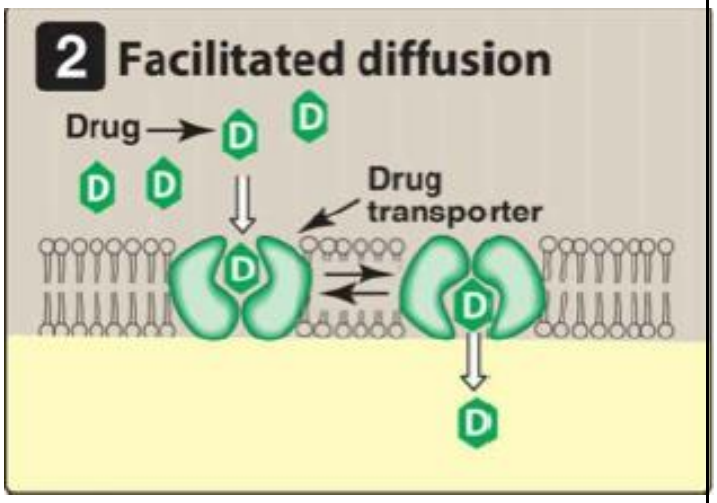
And because there are no carriers used in this method, it is **not saturable** (does not have a limit), as long as the concentration gradient is available.

>> Water can also diffuse passively across the plasma membrane using *aqueous channels* found on the membrane.

Lipid-soluble drugs move readily across most biological membranes due to their solubility in the membrane lipid bilayers.
Water-soluble drugs penetrate the cell membrane through aqueous channels or pores.

2) Facilitated diffusion:

In facilitated diffusion, drug molecules can enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules.



The carrier protein undergoes conformational changes to allow the entry of molecule inside the cell. There has to be **structural compatibility** between the carrier protein and the shape of drug. Also, the drug should not be too polar.

The driving force in facilitated diffusion is the same as in passive diffusion, which is **the concentration gradient, so it does not require energy.** However, unlike passive diffusion, facilitated diffusion is **saturable**. Meaning that there is an **upper limit** of how many molecules can enter the cell at the same time. (so, once all carriers are used even there're more and more of the drug, the increased number of drug will not be upload to carriers because they're saturated, and this is limited by the concentration of carriers in plasma membrane.)

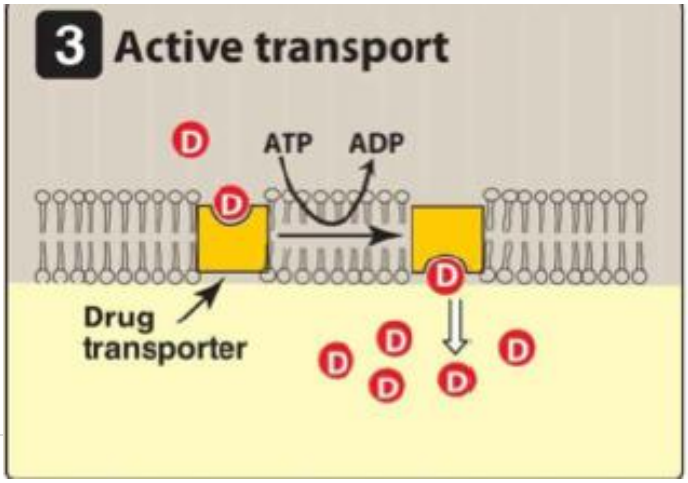
Fun fact:
Diabetic patients are given drugs that inhibit kidney proteins (CGLT) that reabsorbs glucose from the urine back to the bloodstream. it's the newest drug in treatment of diabetes.

>> May be inhibited by compounds that compete for the carrier. Using this feature, we can target these carrier proteins for drug therapy.

e.g. *glucose transport* (GLUT transporter)

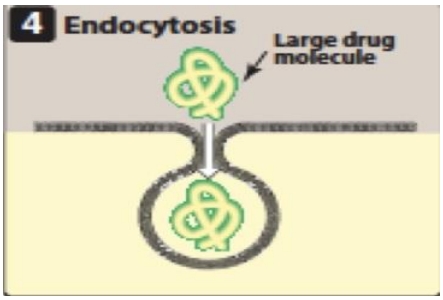
3) Active transport

In this mode, we also use a carrier protein. However, unlike facilitated diffusion, active transport is the transport of molecule



AGAINST their concentration gradient (uphill). This means that it will require energy provided by the hydrolysis of ATP in order to accomplish this.
>> Complementarity between the drug molecule and the carrier protein is a must (selective) .
>> It is a saturable mechanism .
>> protein carrier can be inhibited by other co-transported substances.
e.g. *Sodium-Potassium pump* (like in the heart), so when we have a problem in sodium-potassium pump and I inhibit it using certain substances (inhibitors) ,, I would solve the electron gradient ,, like in heart , there are inhibitors for this pump that are used to treat some conditions (heart failure).

4) Endocytosis & exocytosis:



This type of absorption is used to transport drugs of exceptionally large size across the cell membrane.
In endocytosis, engulfment of a drug by the cell membrane and transport in the cell by pinching off the drug-filled vesicle. **Exocytosis** is the reverse of endocytosis (The molecule vesicle binds to the plasma membrane and leaves the cell).
>> *Vitamin B12* is absorbed by endocytosis from the GI tract.
>> *Norepinephrine* (neurotransmitter) leaves the nerve terminals through exocytosis.
>> We can use a drug that inhibits exocytosis of norepinephrine if the patient requires that, and so inhibiting the function.

> *In case to treat depression, patient is given **serotonin** hormone that is present in the brain , so when serotonin binds to its receptor , that will make the mood well ,,, so one way to treat depression is to prevent reuptake or reabsorption of serotonin to the nerve terminal , by inhibiting a transporter that reuptake it >> so ,, serotonin will be presented in nerve endings where can interact with the receptor and making you feeling good and happy .*

>> These mechanisms are not specific for the GIT, as they can be utilized between any two body compartments with a membrane in between, like between the blood and diff. tissue.

Absorption:

>> A drug is absorbed means that the drug got the blood stream not in the tissue where will be work in.

NOTE: IV administration will give **100%** absorption. However, all other routes will give **lower** absorption due to the first-pass effect.

Factors influencing absorption:

There are some factors that determine the rate of absorption and are related to the drug itself, such as its chemical and physical properties, solubility, and ionization. And there are some factors that are related to the environment, such as:

>> PH :

(PH of the environment will affect the absorption of the drug)

Remember that the pH of the stomach is **acidic (- PH ,, $+H^+$)** . Whereas the pH of the intestine is **basic (alkaline), (+PH ,, $-H^+$) .**

 # The percentage of ionized form of the drug in relation to non-ionized determines how much the drug is gonna be absorbed .

>> A drug passes through membranes more readily if not charged. (it is easier to pass through the membrane if it is neutral and not charged)

Therefore, the weak acid is preferred to pass in its protonated form (HA), whereas the weak base is preferred to pass in its unprotonated form, AKA its conjugate base form (B).

Most drugs are either weak acids or weak bases.

pKa is the measure of the acidity of a compound.

>> *Weak acidic drugs are absorbed faster and more completely in the stomach (acidic environment).*

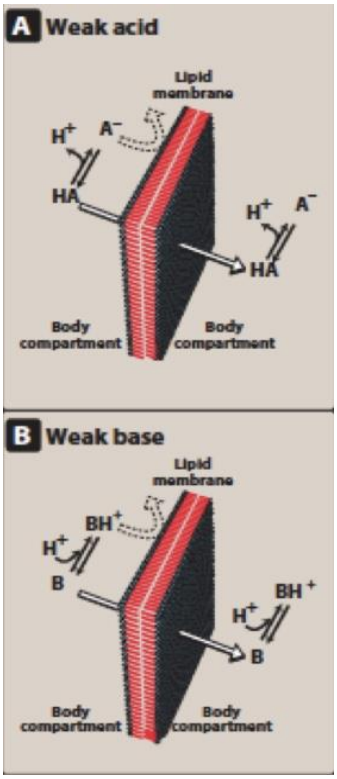
>> Weak basic drugs are absorbed faster and more completely in the intestines (alkaline environment) .

HA ⟷ $H^+ + A^-$ ***,,, acidic drugs (HA) release a proton (H^+) , causing a charged anion (A^-) ,, so there's equilibrium between weak acid and its conjugate base . when a drug is a weak acid , in stomach → the concentration of H^+ is high → so the rxn will drive to the reverse direction (to the left) → so , more weak acid will be available (HA) and the uncharged form (HA) will get transferred through the membrane → so , the absorption will be higher in acidic environment . but in intestine (basic environment) → [H^+] is low → so there will be dissociation of the acidic drug (HA) → more (A^-) and its charged so,it will not be absorbed in a high rate in intestine just like in stomach .***

And the same as basic drugs that favors the basic (alkaline) environment in intestine .

$BH^+ \longleftrightarrow B + H^+$

>> Therefore the effective concentration of the permeable form of each drug as its absorption site is determined by the relative concentrations of the charged and uncharged forms.



$$pH = pK_a + \log \frac{[\text{nonprotonated species}]}{[\text{protonated species}]}$$

For acids: $pH = pK_a + \log \frac{[A^-]}{[HA]}$

For bases: $pH = pK_a + \log \frac{[B]}{[BH^+]}$

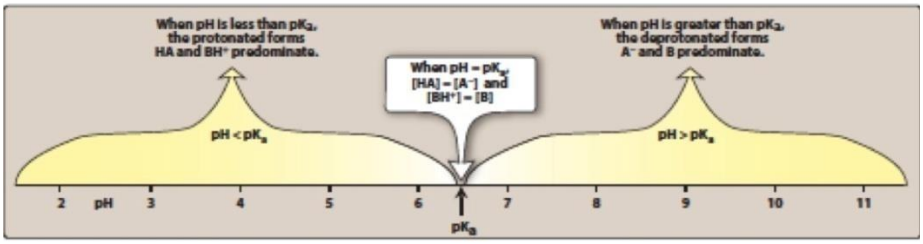


Figure 1.8
The distribution of a drug between its ionized and nonionized forms depends on the ambient pH and pK_a of the drug. For illustrative purposes, the drug has been assigned a pK_a of 6.5.

>> *Intestine* is the best place to absorb drugs because it has much larger surface area due to brush border microvilli & it's a highly vascularized area .

>> The ratio between the 2 forms is , in turn , determined by the PH at the site of absorption and by the strength of the weak acid or base , which is represented by the ionization constant (PKa) → it is a measure of the strength of the interaction of a compound with a proton .

>> Distribution equilibrium is achieved when the permeable form of a drug achieves an equal concentration in all body water spaces .

>> Blood flow to the absorption site :

The intestines receive much more blood flow than the stomach , so absorption from the intestine is favored over the stomach .

Any condition that will alter blood supply to certain organ , it can alter the absorption of the drug to that organ . for example ; in case of pregnancy (a physiological condition) → decrease in blood supply in GIT , because most of blood supply is going to growing fetus . so pregnant women may have problems in GI system .

>>Total Surface Area available for Absorption :

With a surface rich in brush borders containing microvilli , the intestine has a surface area about 1000 fold that of the stomach , making absorption of the drug across the intestine more efficient .

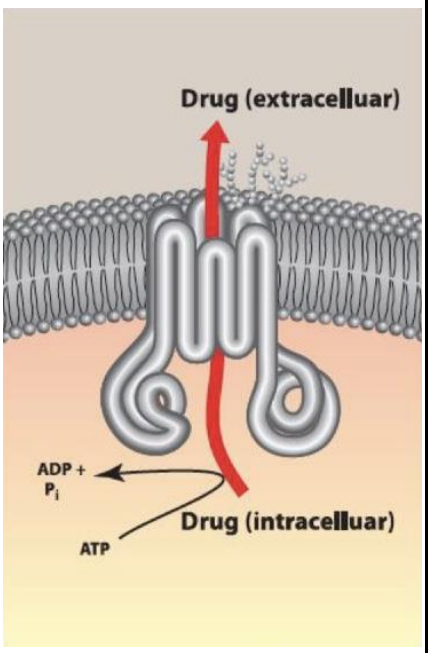
>> Contact time at the absorption surface :

If the drug moves through the GI tract very quickly , as can happen with severe diarrhea , it is not well absorbed . **(** a patient that has diarrhea ,, contact time of substance in GI system will be low , because of fast emptying of intestine content containing the drug → so , decreasing the absorption of the drug **)** .
Anything that delays the transport of the drug from the stomach to the intestine → delays the rate of absorption of the drug .
The presence of food in the stomach both **dilutes** the drug and slows gastric emptying . a drug taken with a meal is generally absorbed more slowly .
(a patient takes a drug in empty stomach and another that takes the same drug in the same amount with food → so concentration of the drug in the 1st patient will be high in stomach compared with the 2nd one that has dilution of concentration of the drug in his stomach [volume is high and low con.] → sometimes the drug is transported with facilitated diffusion that depends on concentration gradient → low con. Of the drug → low con. Gradient → low absorption of the drug in specific place **).**

>> Expression of P-glycoprotein :

P-glycoprotein is transmembrane transporter protein responsible for transporting various molecules including drugs across cell membranes .
(it takes the drug from the blood to the lumen of intestine , so it prevents the entry of materials from outside the body to the blood stream in away to protect) .
When intestine has high expression of P-glycoprotein → less absorption of the drug .
so , The expression level of P-glycoprotein will affect the absorption of the drug .
Where : liver , kidneys , placenta , intestines and brain capillaries .
involved in transportation of drugs from tissue to blood , pumps drugs out of the cell .

The blood barrier protects brain from outside materials or poisons ,, so , if we have highly expressed of P-glycoprotein in Blood Brain Barrier → it will take the drug and kick it out ,, so P-glycoprotein is beneficial in most cases to protect the CNS and Brain (normal defense mechanism) .



Associated with multi drug resistance.
(in microorganisms ,, there's expression of P-glycoprotein → so, when antibiotic enters the bacteria → P-glycoprotein will kick it out) .
Example ,, a drug resistance in cancer cells that tend to protect itself .

That's all folks!