Pharmacokinetics from medicinal point of view

interphase between organic – pharma

A definition of medicinal chemistry

- A definition of medicinal chemistry was given by a specialized IUPAC commission:
- "Medicinal chemistry concerns with the **discovery (**lead compounds, improvement of potency, selectivity and toxicity**)**, the **development (**improvement of pharmacokinetic properties**)**, the **identification** and the **interpretation** of the mode of action of biologically active compounds at the molecular level.

الكيمياء الدوائية تهتم باكتشاف المركبات الفعّالة حيويًا (المركبات الرائدة، وتحسين الفعالية والانتقائية وتقليل السمية)، وتطويرها (من خلال تحسين الخصائص الحركية الدوائية)، وكذلك تحديد وتفسير آلية عمل هذه المركبات على المستوى الجزيئي.

Definition of Medicinal Chemistry

- Medicinal chemistry is also concerned with the study, identification, and synthesis of the **metabolic products** of these drugs and related compounds. ”
- Drugs – natural and synthetic alike – are chemicals used for medicinal purposes. They interact with complex chemical systems of humans or animals.

Definition of Medicinal Chemistry

- So, it is the science that studies the relationship between the chemical structure of the drug/ molecule with its biological activity.
- In our course, this relationship will be studied from different aspects:

1- Structure-activity relationship (SAR):

a- Topological match (3D structure match)

b- Attraction forces

2- structure-pharmacokinetics relationship:

- Absorption, distribution, metabolism and excretion (ADME)

3- Metabolism

4- Prodrugs

1- Structure-activity relationship (SAR):
- Topological match (3D structure match)
- Attraction forces

Structure activity relationship (SAR)

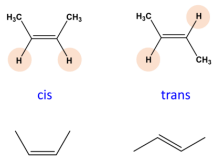
بفسر شو الي بخلي الدوا يرتبط بال receptor
و العوامل اللي تؤثر على هذا الارتباط

1. 3D match: brings the drug closer to the receptor, thus increases attraction forces → Also called: complimintary fit

زي الجبل والوادي — Fits well

a- Optical isomerism — chiral center — steric selective : D-D ✓ L-L ✓ L-D ✗

b- Geometrical isomerism (صفة توزيع بالفراغ)



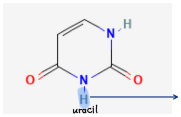
it has to mach so the drugs could bind to there receptors

c- Conformational isomerism (could be active / inactive)

الجزيء نفسه يمكن أن يأخذ أشكالاً مختلفة في الفراغ بدون كسر أي رابطة، فقط عن طريق الدوران حول رابطة أحادية.

مثال : Ach
مرتبط بـ Nicotinic (E) و Muscirinic (S)
how? → by single bond rotation creating diff. conformations

d- isosterism ★ مركبات لها نفس الحجم

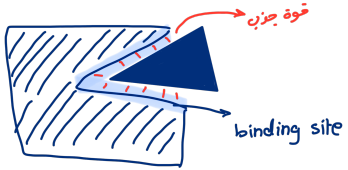


الفلور استبدالها بـ H أو F يغير اشي بالدوا بس الحجم نفس الـsize يعطي دوا اسمو Flurocil ↓ Anticancer

may affect activity but not the drug - binding

2. Attraction forces:

- Electrostatic, Van der Waal, covalent, **H- bonding**

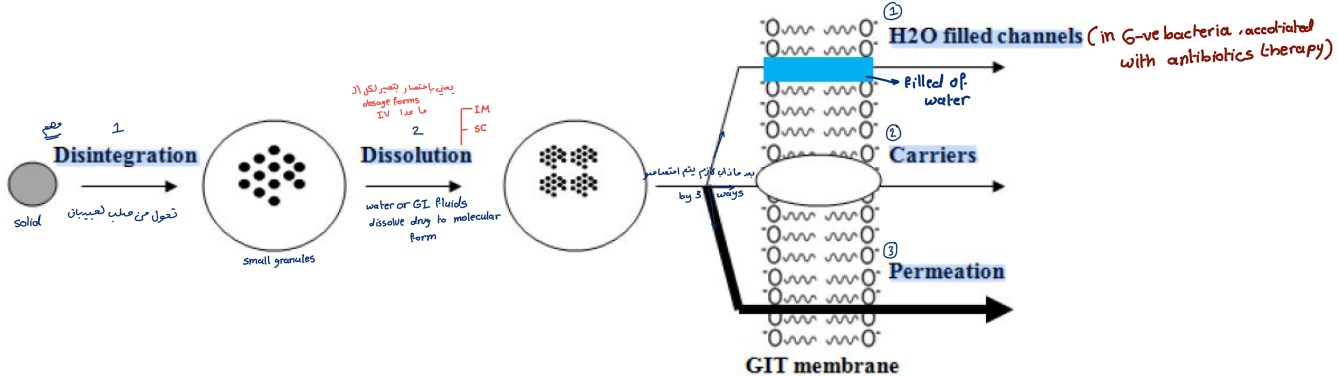


2- structure-pharmacokinetics relationship:
- Absorption, distribution, metabolism and excretion (ADME)

- **Structure - Pharmacokinetics relationship** which means we'll study
- **Structure – Absorption relationship** how do the drugs enter the body?
- **Structure – Distribution relationship** how are the drugs distributed in the body
- **Structure– Metabolism relationship** chemical modification of drugs (breakdown, increase of hydrophilicity to improve clearance)
- **Structure – Elimination relationship** how do the drugs leave the body
- how the chemical structure affect all these pharmacokinetic profiles

Structure - Pharmacokinetics relationships

- **Structure - Absorption relationships**
- in order for a drug to be bioavailable the first condition is to be water soluble, if it doesn't dissolve in water (insoluble) it won't be available for absorption



Routes of GIT penetration

- The drugs penetrate the GIT by 3 routs (H_2O filled channels; Carriers; Permeation):
- **1- Water filled channels** (minor route)
- Are actually integral proteins forming passage filled with water through which a drug molecule can cross, but they have some restrictions:

a. The molecule must be totally water soluble.

b. The molecule must be very small in size (< 4 Angstrom).

EXAMPLE

- The only known drug to cross the membrane through this route is **Li^+ ion** which is used in certain psychotic disorders such as bipolar depression

ليثيوم

- Lithium is approved by the US Food and Drug Administration (FDA) as a prescription medication for bipolar disorder. It helps stabilize patients quickly.

Routes of GIT Penetration

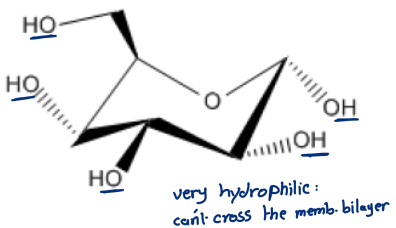
- **2- Carriers** (minor route) for essinsial compounds
- They are integral protein which can carry molecules across the cellular membrane of the GIT.
- Carriers are meant to be used for hydrophilic molecules which are essential for biological activity and don't have the optimal hydrophilic-hydrophobic properties needed to cross the phospholipids bilayer of cellular membranes.

Routes of GIT penetration

2- Carriers (Example)

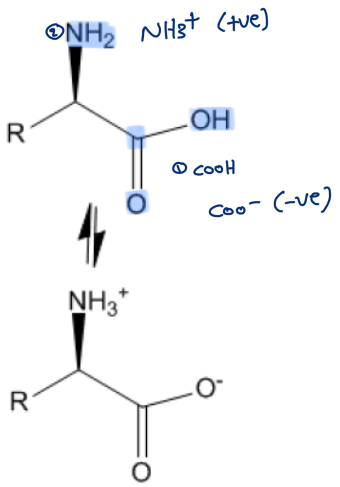
Glucose (α-D-glucose)

Is very essential and is hydrophilic due to the presence of hydroxyl groups in its structure and it can't cross the phospholipid bilayer by simple diffusion, it needs a carrier.



Amino acids

Are essential compounds which contain a carboxyl and an amine group in their structure which are ionized under physiological pH carrying +ve and -ve charges at the same time (zwitterion), so they need carriers.

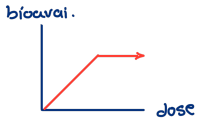


In order for a drug to cross through a carrier, it must be very similar to one of the essential molecules found in nature because those carriers have 3 special characters:

- **a. Very stereoselective:** They can distinguish certain arrangement of atoms in the 3 dimensional space.
- Example: Amino acids in natural are "L" form (= S form), so it will recognize the L form not the D form amino acids.

no Abs.

- **b. Saturable:** They can carry limited number of molecules per unit time, so increasing the dose will increase the bioavailability of a particular molecule up to a certain limit.

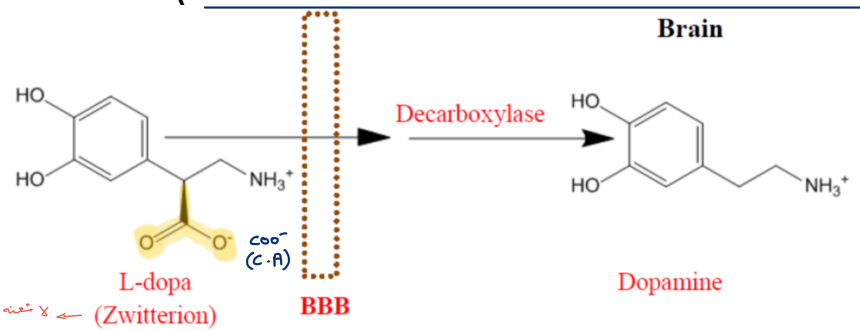


① To overcome this problem in clinical practice those drugs are given in small divided doses instead of single large doses, or using controlled release formulations. ②

- **c. They either use energy or not.**

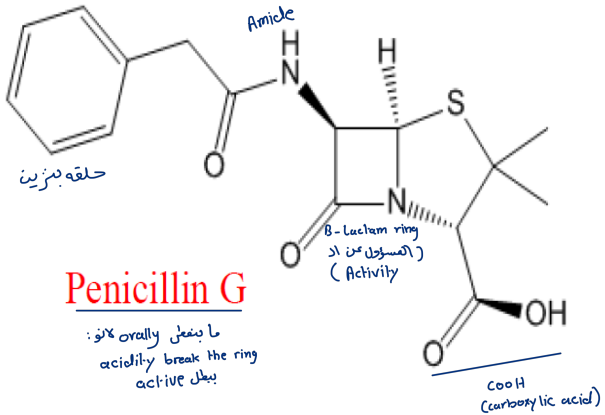
- Facilitated diffusion: transport with the concentration gradient and don't need energy.
- Active transport: against the concentration gradient so it needs energy.

- **EXAMPLE (Important)**
- **L-dopa**
- Parkinson's disease is related to deficiency of dopamine which is an amine (pKa=9.5).
- Under physiological conditions (pH=7.4) which are acidic conditions having enough hydrogen to keep it protonated (+vely charged) so it's difficult to administer dopamine because it can't cross the BBB due to its charge. If dopamine was given orally, it will cause peripheral side effects (hypertension due its adrenergic activity).
- To overcome this problem, we changed dopamine to its corresponding amino acid form L-dopa which is a liable substrate for the amino acids' carriers found on the BBB.
- Inside the brain, L-dopa is converted to dopamine under the action of L-dopa decarboxylase. L-dopa is carried throughout both the BBB and GIT membrane. (BBB is similar to GIT membrane even tighter).



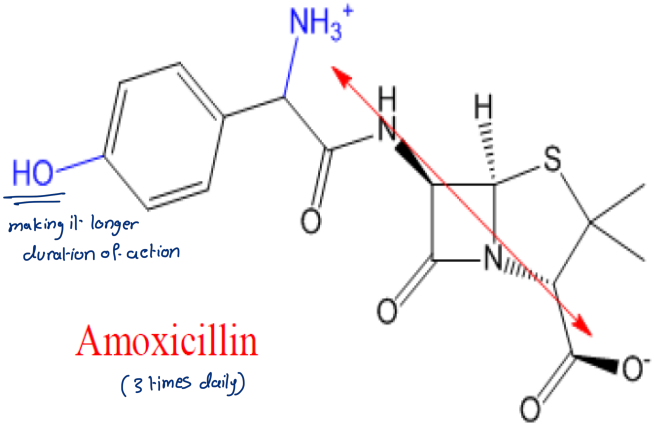
2- Carriers: Example

- **Penicillin's**
- 1st discovered is **Penicillin G** which is orally inactive, but when converted to **Ampicillin**
- the carboxylic acid (pKa= 3) is ionized to carboxylate which is -vely charged and the amine +vely charged through GIT (pH= 1-8).
- Ampicillin structure is similar to dipeptides, making it a good candidate to be carried across the GIT by carriers originally found to carry di- and tri-peptides formed by protein break down.
- Ampicillin bioavailability can reach a maximum of only 60-66% because the carriers are saturable.



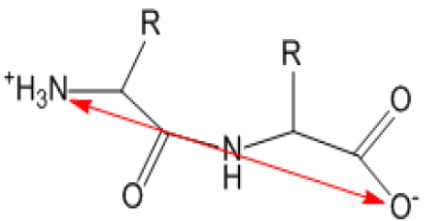
Penicillin G

ما بنعطي orally عشان:
acidity break the ring
بيبطل active

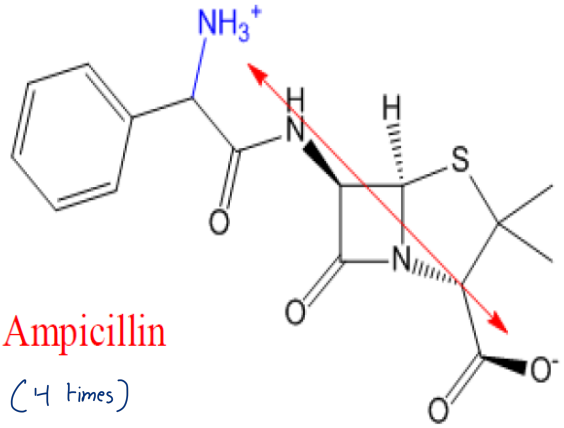


Amoxicillin

(3 times daily)

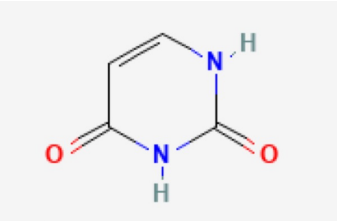


Dipeptides



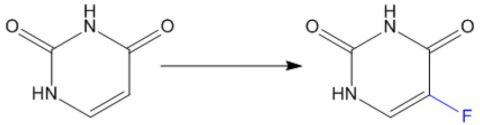
Ampicillin

(4 times)



2- Carriers: Example

- Other EXAMPLES on drugs that cross through carriers are a group of anticancer drugs called **Antimetabolites** which are compounds very similar to natural metabolites.
- **Uracil** is a nitrogenous base that gets incorporated into RNA by being converted to nucleoside (+Ribose sugar) then to nucleotide (+Phosphate).
- If we make isosteric replacement of a hydrogen H by flour F (size wise) we produce **Fluorouracil** which can compete with uracil carriers therefore blocking its absorption to cells and blocking RNA production killing the cell, so it's used as an anticancer agent.



3. **Permeation** by partitioning (major) The 3rd route of absorption

- Permeation is to cross the membrane by dissolving in the phospholipid bilayer in a process called **partitioning**.
- If a drug has optimal hydrophilic/hydrophobic properties, then the drug can partition itself and dissolve in both phases (water and oil) to certain limit. After dissolving in water outside the cell it starts to partition in both phases, and then after saturating the oil phase (phospholipid bilayer)
- it starts to partition toward the other water phase inside the cell.

3. **Permeation** by partitioning (major)

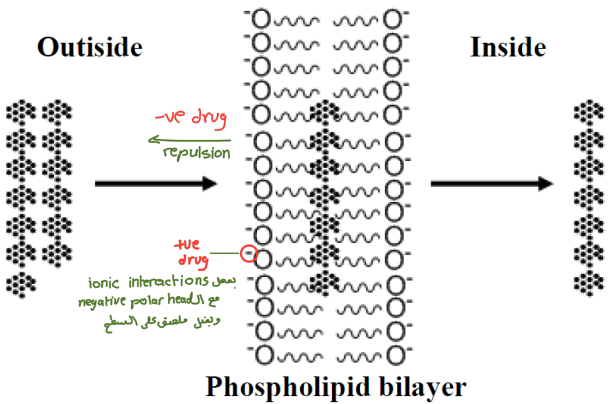
In order for partitioning to occur, 2 conditions must exist:

a. The drug must be unionized

If it was ionized: the +vely charged drug will be adsorbed to the -vely charged phospholipid bilayer heads; while repulsion between -vely charged drugs and the –vely charged phospholipid bilayer heads. Also the charge will make the drug hydrophilic therefore insoluble in the lipid bilayer.

b. The drug must have optimal Hydrophilic/Hydrophobic properties

In order to get partitioned between water and fatty layers.



Drug ionization very important

- **Drug ionization**
- We can classify the drugs found in pharmacopeia according to ionization to 3 classes:
- 1. Strong acids and bases.
- 2. Weak acids and bases.
- 3. Intermediate acids and bases.

pH < pKa : union.
pH > pKa : ion.

- **Strong acids and bases**
- **Strong acids...**
- Their **pKa is 2 or less**, and the stomach pH= 1-3 while intestine pH= 7-8; the pH through all the GIT is higher than the pKa which represents basic conditions for this strong acid shifting the equilibrium toward A- side, therefore it will be ionized through all the GIT and its ionization accounts for high hydrophilicity making it unavailable for absorption through oral route.

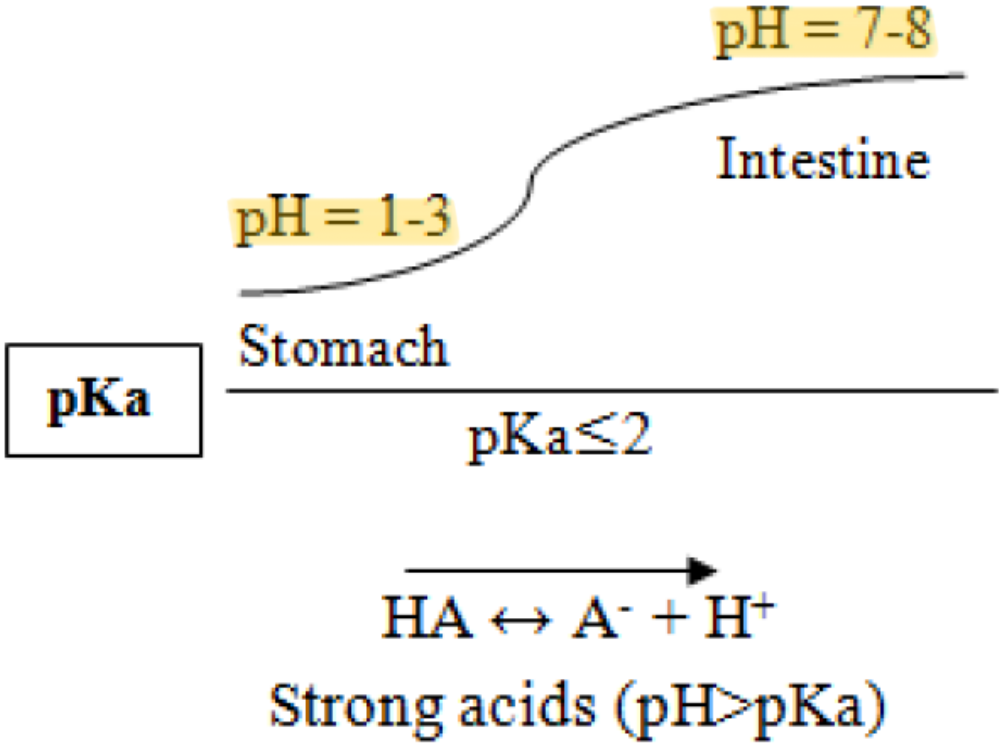
- **EXAMPLES**
- **Sulfonic acid group** pKa<1 so it's always ionized and we expect the drug carrying sulfonic acid group to be totally ionized through the GIT therefore orally unavailable.

☆ معلومة

سحب الإلكترونات من مجموعة الهيدروكسيل (–OH) يزيد من قابليتها لفقدان البروتون (+H) لأنّه يجعل رابطة O–H أكثر قطبية ويُثبّت الشحنة السالبة الناتجة بعد نزع البروتون.

1# Strong acids...

gives proton



Summary examples on strong acids expected to be orally not available

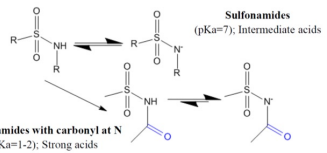
c

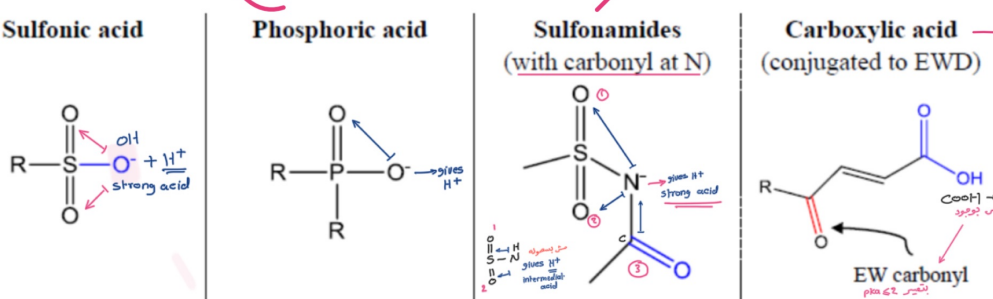
- Another example on strong acidic groups which if found in drugs they make them orally unavailable is **phosphoric acid**;.

a

- Another group is **sulfonamids** which is per say an intermediate acid **pKa=7**, but if we attach an extra carbonyl to its nitrogen it becomes strong acid **pKa=1-2**.

sulfonamide with the carbonyl at the N is nearly as strong as the sulfonic acid with a pKa=1-2; therefore, its **orally unavailable**.





d

- **Carboxylic acid** is another group to discuss, even though it's solely intermediate acid with **pKa=3-4.5** but if it was conjugated to an electron withdrawing group like carbonyl it will become a strong acid.

b

An example is **Saccharine** produced as Na-Saccharine which is a diabetic sweetening agent; diabetic patient can feel its sweetness without concerning about elevating blood sugar levels because it's eliminated through the fecal system without being absorbed.

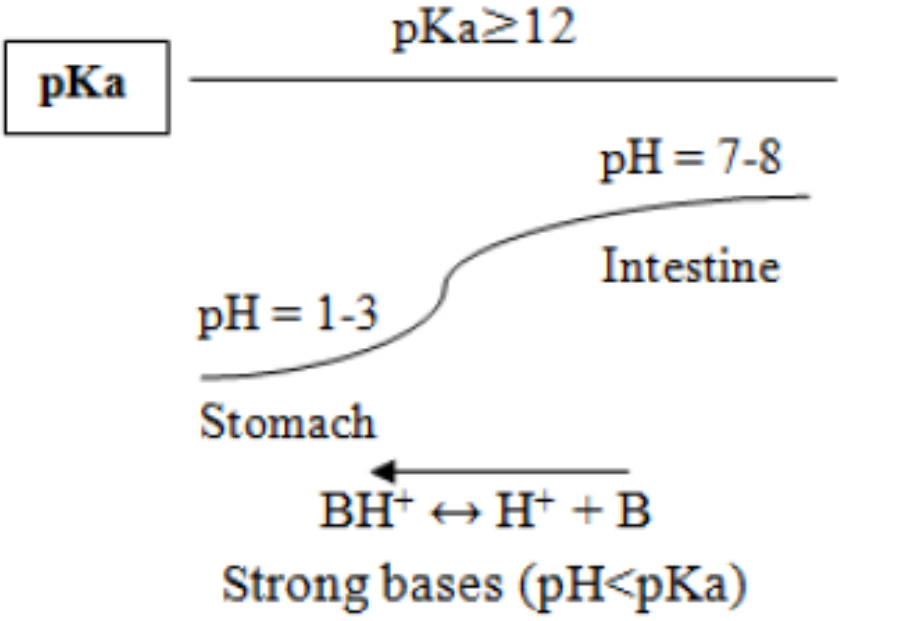
2# Strong Bases...

contain N not O

gives lone pair of electrons

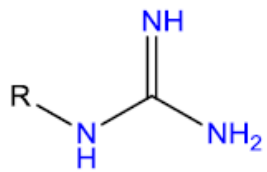
- Strong bases have high **pKa 12**
- in GIT (pH=1-8), the conditions are continuously acidic and the reaction is shifted toward BH+, as previously said, in order for a compound to be absorbed it has to be unionized but strong bases are permanently +vely ionized through GIT.

Absorption of strong bases

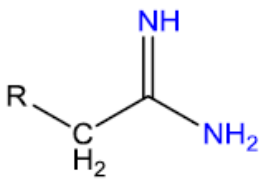


- There are some functional groups if found in a chemical structure they indicate that this structure is permanently (بشكل دائم) +vely charged during passage of GIT; most important ones are:
- **Guanidine** and **Amidine** both with pKa 12.

Guanidine



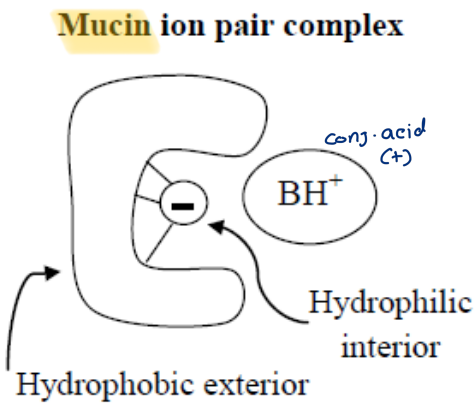
Amidine



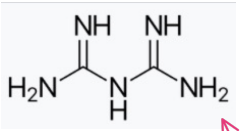
- So, both Guanidine and Amidine if they were found in a chemical structure we can conclude that this structure is permanently cationic (+vely charged) through all the GIT, therefore we expect them to be not available for absorption **BUT** that's not the case,
- **Strong bases actually are of poor bioavailability,** unlike strong acids which are completely not available for absorption This poor bioavailability of strong bases is due to the presence of **Mucin** which is a hydrophobic protein produced by GIT cells bearing a -ve charge on its interior while its exterior is hydrophobic therefore it's able to form complexes with the +vely charged bases forming **ion-pair complexes** protecting them from water and they're hydrophobic enough to cross the GIT cellular membrane.

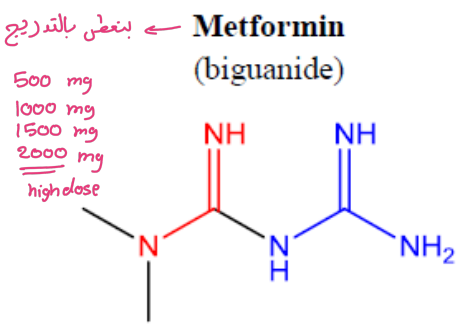
What applies to strong bases applies for quaternary ammonium salts; they're permanently ionized however because of the presence of mucin we do have some bioavailability however it's not more than 40%.

up to 40%. cause: this process depends on
1. inter individual variation
2. time variation
3. Amount of Mucin



- **EXAMPLES**
- **Metformin** (diabetic medication) Its trade name is Glucophage ® ; it has biguanide groups in its structure so it's a strong base with pKa 12 yet it's administered orally!
- It is given in high doses and the physician needs time adjusting the dose for a particular patient due to its **erratic** bioavailability as the presence of biguanide groups make it permanently ionized and permanently +vely charged as well as variation in the amount of mucin among individuals





The proton in strong bases rotate among the basic groups and so called **tautomerism** which is best drawn as below structure: