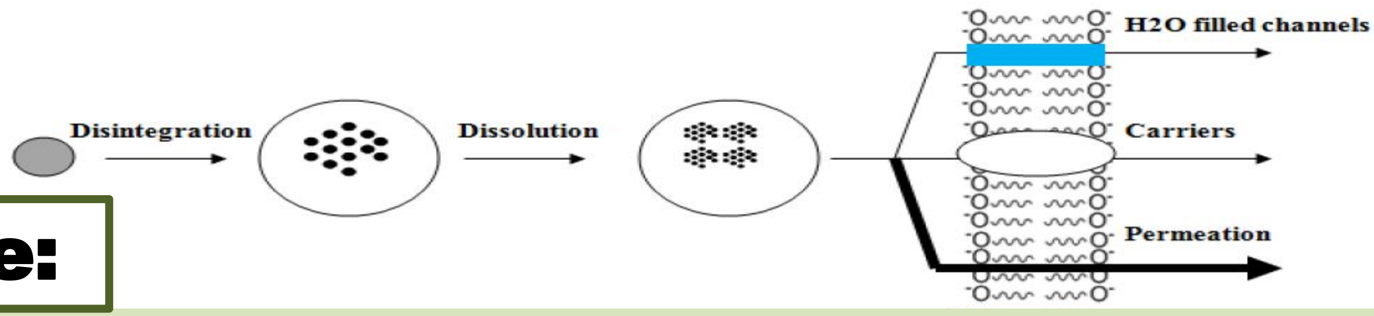
Structure - Pharmacokinetics relationships

- **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



Slide note:

*When a patient takes an oral medication it would be solid dosage form, suspension or other liquid dosage forms like solutions.
*If we start with the solid dosage form, the tablet first undergo disintegration in GIT to smaller particles called granules forming a suspension, followed by dissolution forming a solution in which each drug molecule is separated by water molecules, then follows penetration in which the molecules cross the GIT membrane to the plasma.
*Dissolution is the first step of absorption.So, 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
- Lithium is approved by the US Food and Drug Administration (FDA) as a prescription medication for bipolar disorder. It helps stabilize patients quickly.desaqwxy g

Slide note:

*This route is minor in humans, but is a major route of transport in certain bacteria especially G-ve bacteria in which its outermembrane contains water filled channels that are larger in size and tend to allow hydrophilic molecules to cross through. When we talk about antibacterial agents you'll notice that the more hydrophilic they are, the broader their spectrum is.

*EXAMPLE

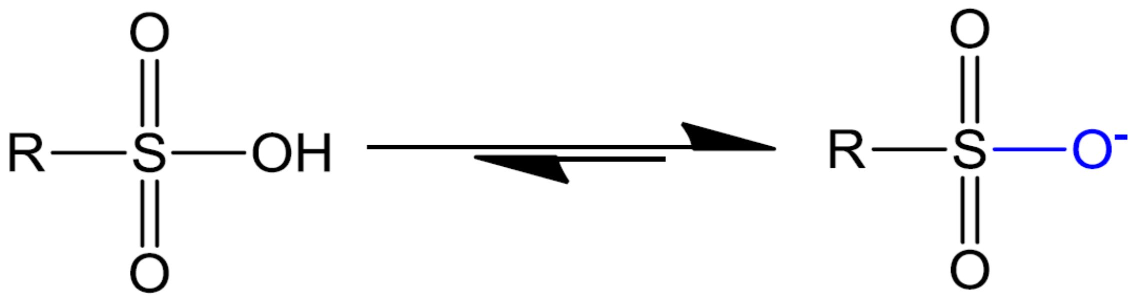
Penicillin G was first discovered followed by discovery of broader spectrum activity penicillin's like Ampicillin and Amoxicillin which are more hydrophilic

- **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).**

Slide note:

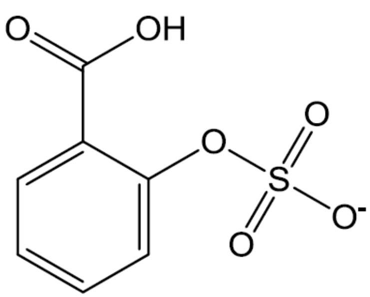
When pH is lower than pKa of a base, then the conditions are acidic to this particular base... So it's ionized. When pH is higher than pKa of a base, then the conditions are basic to this particular base... so
it's unionized Opposite apply for acids

- **Salicylic acid is the active form of Aspirin (acetylsalicylic acid), salicylic acid is absorbed through the GIT; if I want to treat a local inflammatory condition in the GIT such as Crohn's disease or ulcerative colitis, we can attach a sulfonic acid group to salicylic acid forming sulfosalicylic acid which is not absorbed orally and treat inflammation of the GIT in a local sense minimizing side effects.**



Sulfonic acid

Sulfosalicylic acid



Slide note:

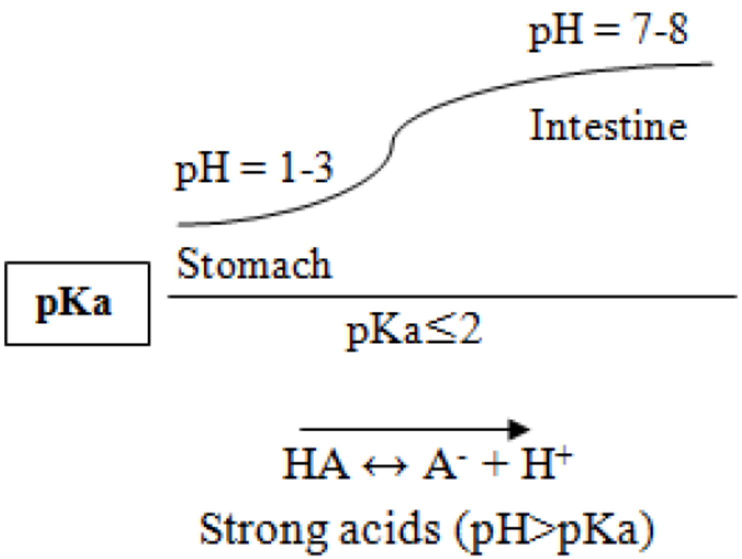
*How to judge an acid being strong or not? by looking at its conjugate base and its ability to stabilize the -ve charge, ↑Stable conjugate base ↑Strength of the acid.
Let's take sulfonic acid as an example, it is a strong acid because the negative charge is stabilized by 2 electron withdrawing oxygen, so the Sulfur become very deficient in electrons carrying a strong partial +ve charge; this partial +ve charge will attract the -ve charge of the ionized oxygen stabilizing it.

Strong acids...

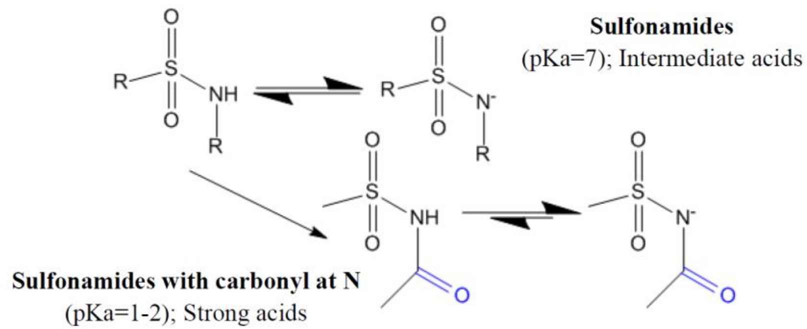
Slide note:

To refresh your memories What does pKa mean?
HA ↔ A- + H+
If you take an acid HA and put it in water it will be ionized to its conjugate base A- and H+ in an equilibrium manner expressed by an equilibrium constant Ka.
Ka =
and by using Henderson hasselbalch equation we can construct the value of the ionization constant pKa tells how acidic a compound is.
pH = pKa - log

- For acids, ↓pKa ↑Acidity.
- For bases,



- 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**.



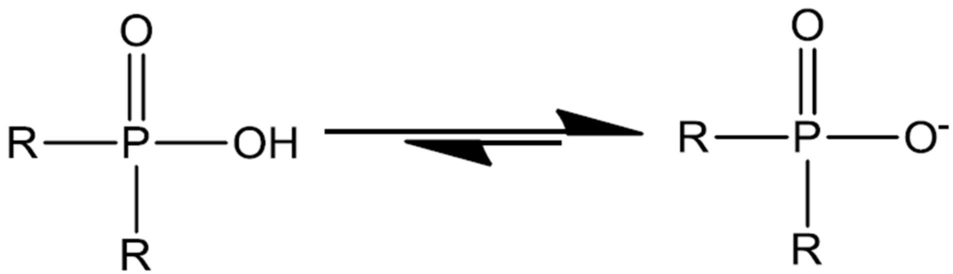
Slide note:

Same applies for sulfonamides, when the N loses its H, it's left with -ve charge forming sulfonamidate; as the N is less electronegative than O so it's less withdrawing therefore less happy to have -ve charge; less able to stabilize the negative charge like the oxygen of the sulfonic acid; and the less stable the conjugate base, the weaker the acid is. That's why sulfonic acid is stronger acid than sulfonamide.

But if we attach another withdrawing group (carbonyl) to the N of sulfonamide, the O of the carbonyl will withdraw electrons from the N which further stabilize its -ve charge making this

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

Phosphoric acid



Slide note:

the O of the phosphorous oxide withdraw electrons which makes the O of the hydroxyl tend to lose a proton H+ producing a permanent –ve charge through the GIT which is stabilized by the withdrawing effect of the phosphorous oxide

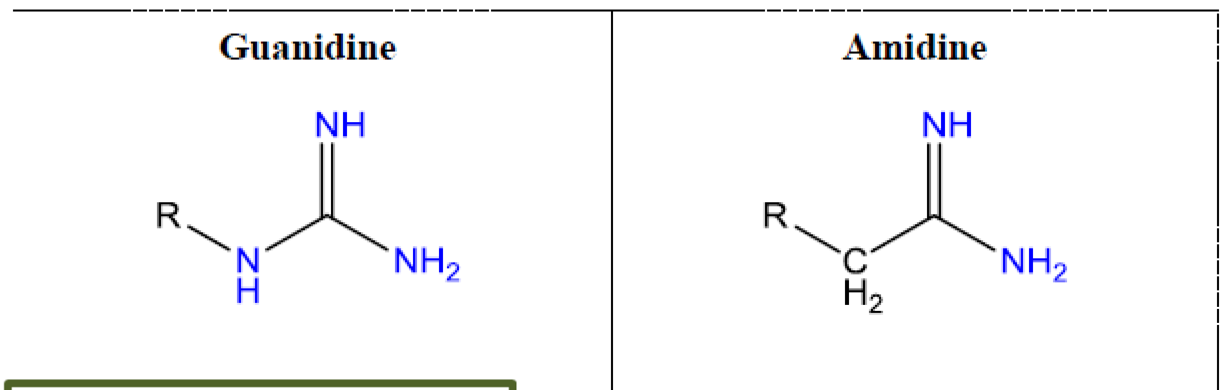
Strong Bases…

- 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.

Slide note:

مرة تانية حط حالك محل الدواء إزا كان الدوا قاعدة قوية جدا
Strong bases have high pKa 12رح يشوف الدنيا كلها
حامضية يعني فائض بال +Hيعني رح يتحول ل +BHيعني
رح يكون متأين طول الوقت

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



Slide note:

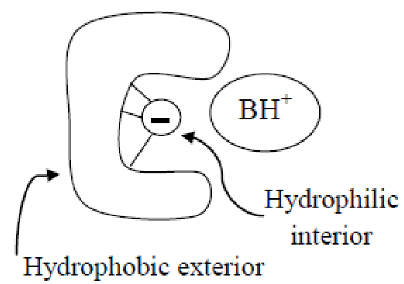
*Regarding Guanidine structure, the N is not very electronegative therefore the presence of N in a structure will make it basic because N has pair of unshared
electrons which don't mind giving it to a proton; what if there are 3 conjugated N in the same structure like Guanidine?! it will be strongly basic, in fact
*Guanidine is quite the most basic group you can find in a chemical structure used as a
drug!. Follow Guanidine in strength is Amidine, it has 2 conjugated N in its structure.

- 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.

Slide note:

This poor bioavailability can approach a maximum of 40% which means if you give a dose of 500mg, only 40% of this dose is bioavailable; also this 40% is highly variable due to inter-individual variation and time variation in the same individual in the amount
of mucin; therefore this bioavailability is described as erratic.
*To summarize, strong bases are generally of poor bioavailability not zero bioavailability
like strong acids, reaching a maximum of 40%, however this bioavailability is highly variable due to interindividual variation and time variation in the same individual in the amount of mucin.

Mucin ion pair complex



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%.

Weak acids

- There **pKa is 12 or more**, which means in the GIT (pH= 1-8) the
- conditions are constantly acidic shifting equilibrium toward HA, therefore weak acids are permanently unionized across GIT so they've well bioavailability not necessarily excellent but they're better candidate to be absorbed orally because there are other important factors controlling bioavailability we mentioned, and we'll discuss in more details later.
- such as optimal hydrophilic/hydrophobic properties represented by **lipinski's rule of 5**. (we will discuss it later)

- For example, if the compound is unionized and highly insoluble in water for some reason it won't be bioavailable, therefore we should keep in mind to check on all the factors to judge bioavailability.

Slide note:

الأحماض الضعيفة pKa is 12 or more
يعني رح يشوف الدنيا حامضية وفائض من
ال +H يعني رح يضل HA وما رح يتبرع
بال +H للوسط المحيط لأنه بكل بساطة المحيط
مش بحاجة هو عنده فائض ولن يحدث التأين