للوصول الى guidance الفارما و تفاريغ المادة كاملة :

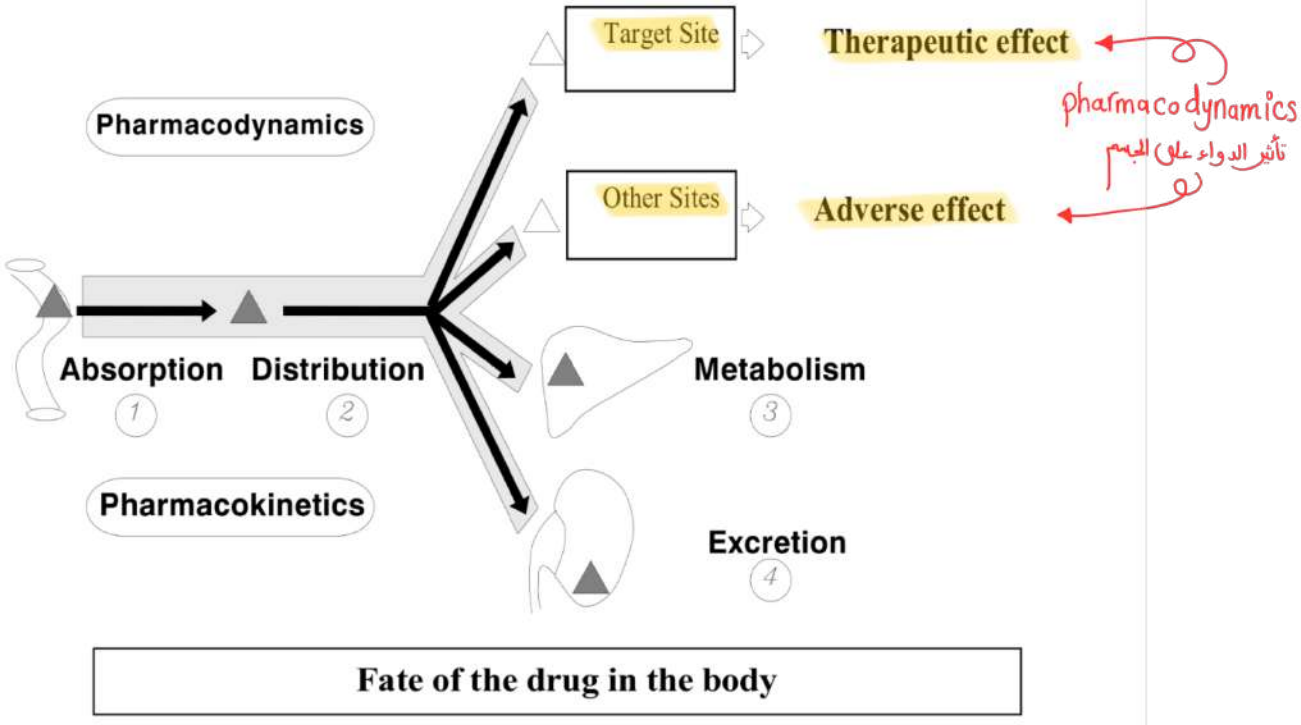
كل اعمال الفريق العلمي تنشر على قناة التيليغرام

تجدون في guidance مادة الفارما على موقع النادي :

PHARMACOKINETICS

What body does to a drug

The term pharmacokinetics denotes the quantitative studying of drug **A**bsorption, **D**istribution, **M**etabolism and **E**xcretion **(ADME)** and their mathematical relationship.



Fate of the drug in the body

Absorption: Describes how the drug moves from the site of administration to the site of action.

Distribution: Describes the journey of the drug through the bloodstream to various tissues of the body.

Metabolism: Describes the process that breaks down the drug.

Excretion: Describes the removal of the drug from the body.

Elimination: metabolism + excretion

When you either swallow a tablet or apply a cream on your skin the first thing that takes place is ABSORPTION through the skin or stomach , then it gets into your bloodstream …

And then it get DISTRIBUTED into the fluids outside and inside the cells

these cells could be at the target site -> therapeutic effect التأثير العلاجي للدواء

Or other sites -> adverse effect or side effect الأعراض الجانبية أو السلبية للدواء

So once the drug gets distributed all over the body the body started METABOLISING it, basically modifying the drugs so that it's easy to excrete

This is primarily done by liver , but it can also be done by other tissues

The last step is EXCRETION in bile, urine, feces

هاد الشغل ما بصير بالترتيب... يعني مو كل الجزيئات بعد ما صارلها distribution بتروح على الliver وتعمل metabolism
وبعدين تروح على ال kidney وتعمل excretion... الموضوع انه الدواء صار بالدم ف بنفس الوقت في جزء من الدواء بروح على ال liver وبيعمل metabolism وفي جزء اخر بروح على ال kidney وبيعمل excretion فهي العمليات بتصير مع بعض ع اجزاء
يعني كل جزء بحقق شروط معينة بيقدر يدخل المرحلة التانية وبكون في جزء غيره بلش بمرحلة غير وهكذا

ABSORPTION OF DRUGS

❖ **Definition:** absorption is the passage of drug from the site of administration to the systemic circulation.

ال absorption هو الفاصل بين ال local effect وال systemic effect
لو الدواء انتقل من مكان الي وضعته او مكان الي حصله admministration وراح لل circulation وهيك بكون صار absorptiom وهيك صار systemic لكن لو ما صارله passage
وضل بيشتغل ع نفس المكان الي انا حطيته فيه هيك صار local

❖ **Methods of transport across cell membranes:**

بدون أي واسطة **1- Passive transport:**

أهم طريقة يتم فيها النقل

a. **Simple (lipid) diffusion:** the **lipid soluble** drugs can easily cross lipid membranes along concentration gradient with no energy.

b. **Aqueous diffusion (filtration):** the **water soluble** drugs can pass only through water filled **pores or channels**.

proteins ←

بتحتاج واسطة **2- Carrier-mediated transport:** the drug passes across cell membrane by specialized carrier molecules (which are sites for saturation & competition):

a. **Facilitated diffusion**: as simple diffusion but with aid of carrier. e.g. glucose uptake ↑ →↓

b. **Active transport**: the drug is carried against concentration gradient by energy. e.g. Na/K pump ↓ → ↑

example

ال saturation يعني الدواء اله capacity معينة على الامتصاص والباقي ما بتمتصه

For example, when we talk about the excretion :

If the patient took diuretics (مدرات البول الي بتزيد urine volume)

The diuretics need a carrier to enter the kidney and this carrier also carries the uronic acid to remove it out of the body

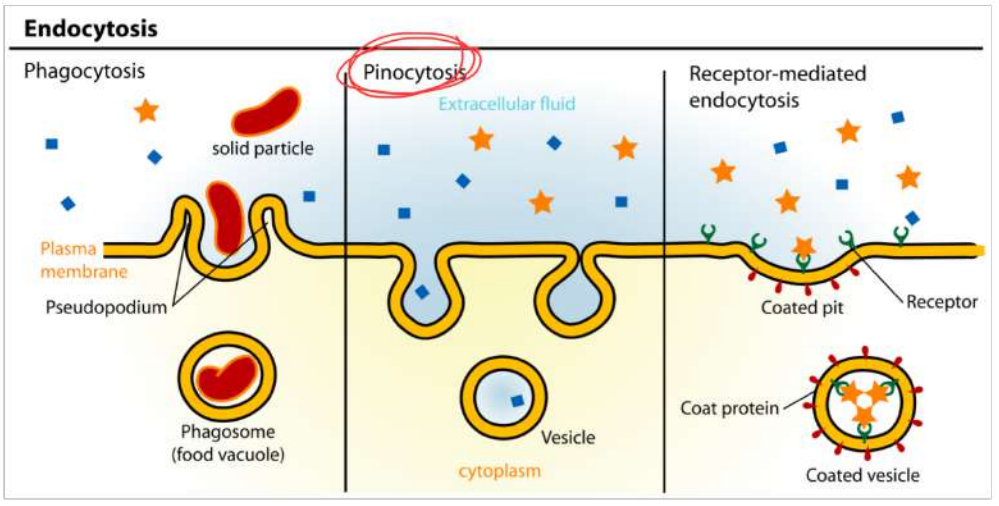
There is a competition between diuretics and uronic acids, which one will enter the kidney?

If the carriers pass the diuretics to the kidney, the uronic acid won't enter the kidney and they will return to the blood and then to the joints

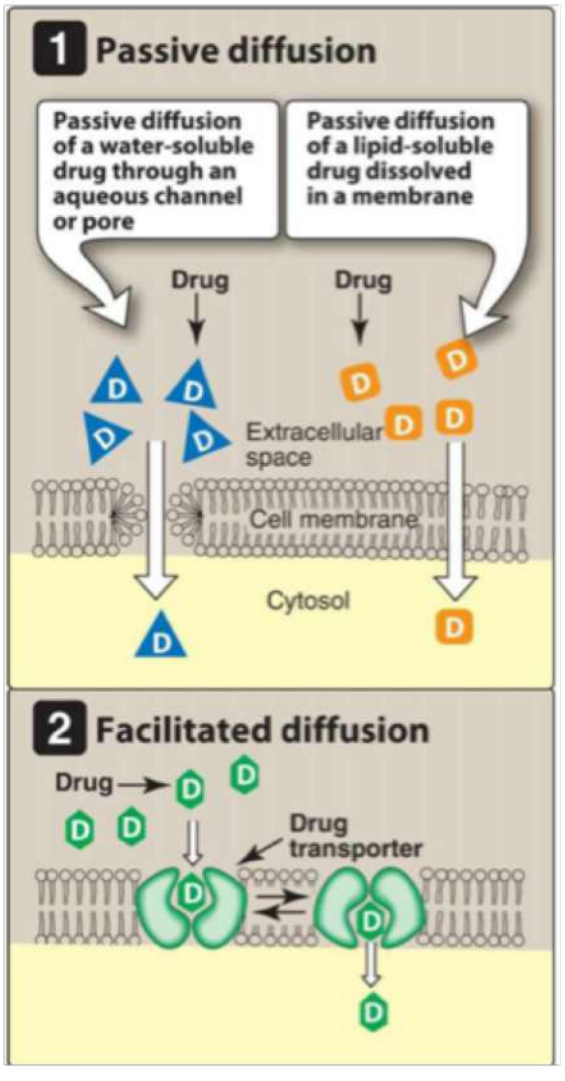
If the uronic acid is accumulated in the joints that could cause—

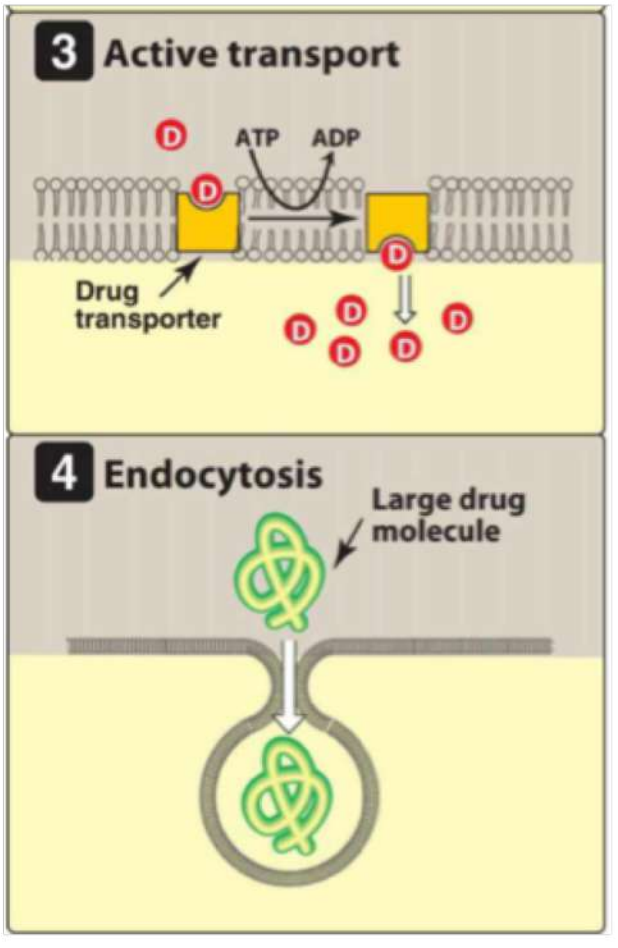
> GOUT النقرص

3- Endocytosis (pinocytosis): it occurs in cases of large molecule by invagination of part of cell membrane and engulfing the drug molecule. Energy is needed. e.g. absorption of vit.B12 & intrinsic factor in terminal ileum.



Vitamin B12 binds to the protein in the foods we eat. In the stomach, hydrochloric acid and enzymes unbind vitamin B12 into its free form. From there, vitamin B12 combines with a protein called intrinsic factor so that it can be absorbed further down in the small intestine.
This mix of vitamin B12 and intrinsic factor is then absorbed into the body in part of the gut called the distal ileum. Pernicious anaemia causes your immune system to attack the cells in your stomach that produce the intrinsic factor, which means your body is unable to absorb vitamin B12.





❖ Factors affecting drug absorption:

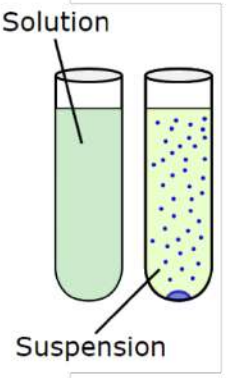
→ related to drug
→ related to patient

A. Factors related to drug:

1. Molecular size: small molecules are absorbed than large molecules

2. Pharmaceutical preparations

- **Dosage form:** - solutions are better absorbed than suspensions



مثل الكبسولة
بتتكون من طبقات وكل طبقة الها الفترة الزمنية للامتصاص مختلفة
- sustained-release preparations are slow in absorption

- **Rates of disintegration & dissolution:**

Rapid with paracetamol and slow with digoxin

Panadol
→ heart failure

Rate of disintegration : proportional to the number of atoms and the activity measured in terms of atoms per unit time

Rate of dissolution : measure of how fast a solute dissolves in a solvent

3. Lipid and water solubility:

- Drug must be water soluble as well as lipid soluble

لما نحكي عن water solubilty لازم نحط بعين الاعتبار the size of molecules
لو كان حجم جزيئات الدواء كبير ، ما حيدخل الخلية 👌.

- ***More lipid solubility → high lipid/water partition coefficient → better absorption***

From the book :

Very hydrophilic drugs are poorly absorbed because of the inability to cross lipid rich cell membranes.(they pass through aquaporin (عددها قليل))

Drugs that are extremely lipophilic are also poorly absorbed, because they are insoluble in aqueous body fluids (interstitial fluids, cytoplasm) therefore they cannot gain access to the surface of cells.

For a drug to be readily absorbed, it must be largely lipophilic, yet have some solubility in aqueous solutions. This is one reason why many drugs are either weak acids or weak bases.

توضيح للي بنحكي فيه (مهم حتى لو الدكتور ما وضحه) :

أول شي لازم تكونوا عارفين انه كلما زادت الlipid solubility كل ما زاد الvolume of distribution يعني كل ما زاد توزع و انتشار الدواء بين cells و tissues لغاية ما نوصل لحد معين بكون فيه الدواء ما اله water solubility كفاية لتخليه يوصل الخلية عبر السوائل الي حولها او يعبر بالسيتوبلازم

لهيك الideal drugs صفاتهم :

1- lipophilic to pass through the cell membrane easily

2- hydrophilic to reach the target tissue and to pass through the cytoplam

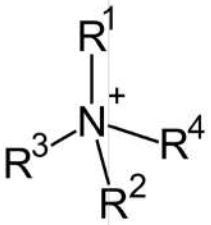
↑ hydrophilic			↑ lipophilic
Water	Water > lipid	Water < lipid	lipid
more absorbed	poorly absorbed	more absorbed	poorly absorbed

4. Ionization: - *Ionized (polar or charged) forms are poorly absorbed*

- *Unionized (non-polar or non-charged) forms are more absorbed*

e.g. - Quaternary ammonium compounds: always ionized → poor absorption

- Tertiary amines (physostigmine): always unionized → better absorption



The coefficient of drugs : the ability to pass the cell membrane.

The ionized or charged drug -> low coefficient -> poorly absorbed.

The unionized drug -> high coefficient -> better absorbed

Some drugs are both ionized and unionized ..

- Most drugs are either weak acids or weak bases.
- Acidic drugs (HA) release an H+ producing a charged anion (A-):

$$HA \rightleftarrows H^+ + A^-$$

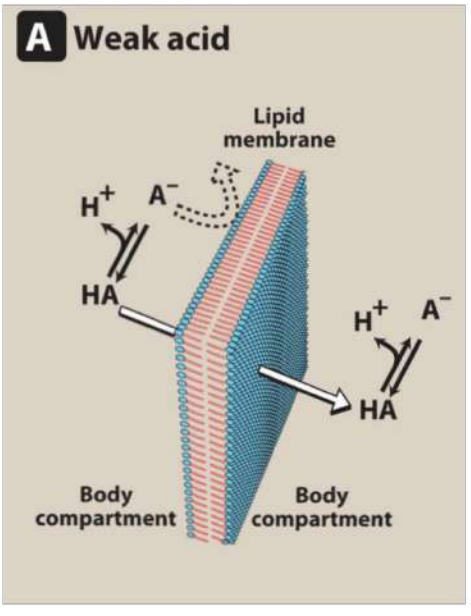
يتم امتصاصه

- Weak bases (BH+) can also release an H+ producing the uncharged base (B):

$$BH^+ \rightleftarrows B + H^+$$

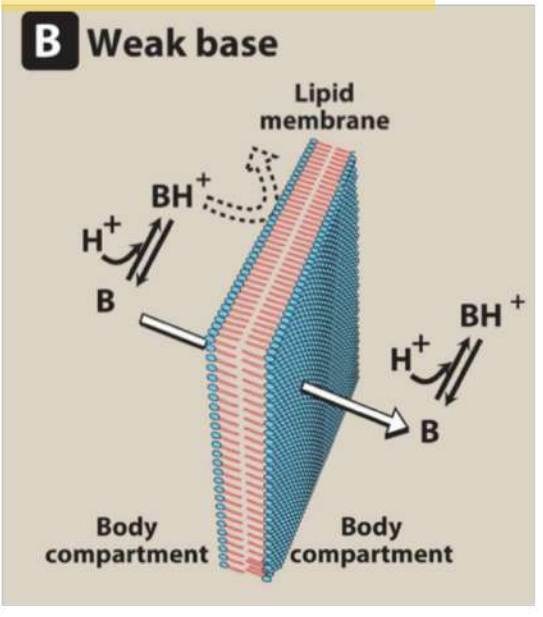
يتم امتصاصه

The Reactions are REVERSIBLE



for a weak acid, the uncharged, protonated HA can permeate through membranes, and A– cannot.

Unionized = protonated



For a weak base, the uncharged form B penetrates through the cell membrane, but the protonated form BH+ does not.

Unionized = non protonated

❖ Ionization depend on pH of the medium ① and pKa of the drug ② (pKa is a measure of the strength of the interaction of a compound with a proton).

❖ **The lower the pKa** of a drug, **the more acidic** is the drug. Conversely, **the higher the pKa, the more basic** is the drug.

Acidic media -> Unionized molecules -> high absorbtion

And if we put this acid in an alkaline -> the acidity will decrease -> Ionized molecules -> low absorbtion

Basal media -> Ionized molecules -> low absorbtion

And if we put this base in an alkaline -> the Ph will decrease -> Unionized molecules -> high absorbtion

لما يكون ال drug شبه ال media حيزيد ال absorbtion و لو انعكس حيقل

❖ Relation between pH of the medium and pKa of the drug is presented by **(Henderson-Hasselbach equation):**

important

The pKa of a drug is that point at which the compound is 50% ionized

The Pka is a measure of the relative strength (degree of ionization) of a weak acid and base (بعبر عن قوة ارتباط الهيدرجين بالدواء)

If Pka is low -> weak bonds -> release a proton -> ionization -> low absorbtion

If Pka is high -> strong bonds -> oxidation -> unionization -> high absorbtion

The lower the pKa of a drug, the more acidic it is.

the higher the pKa, the more basic is the drug.

$$pka = pH + \log \frac{\text{concentration of protonated}}{\text{concentration of nonprotonated}}$$

® If the drug is weak Acid :

$$pka = pH + \log \frac{\text{concentration of Unionized acid}}{\text{concentration of ionized acid}}$$

protonated

IMPORTANT

® If the drug is weak base:

$$pKa = pH + \log \frac{\text{concentration of the ionizd base}}{\text{concentration of unionized base}}$$

protonated

- **pKa of a drug:** is the **pH** at which **50%** of the drug molecules exist in the **ionized** form and **50%** in the **unionized** form.

When the [ionized] = [unionized] the Pka will = Ph , why ?

If we devide [ionized] to the [unionized] and they were equal,

the answer is 1

Log 1 = 0

So the Pka = Ph in this example

و بهالحالة بكون نص الدواء ionized و نصه الثاني unionized