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ADME Distribution

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Distribution

توزيع الدواء في الجسم
من الدم إلى
سائر أعضاء الجسم

- Once a drug is absorbed, it is subsequently distributed around the blood supply and to tissues and cells.

- Distribution is the process by which a drug reversibly leaves the blood stream and enters the interstitial or cellular fluid of the body. Intestinal fluid, intracellular fluid, and transcellular fluid are 16%, 35%, and 2% of the body mass, respectively. Meanwhile, plasma is 5% of body mass and fat is 20%.
- All of the fluid in the body (total body ^{fluid} water) in which a drug can be dissolved may be roughly divided into three compartments: intravascular (blood plasma found within blood vessels); interstitial/tissue (fluid surrounding cells); and intracellular (fluid within cells, i.e., cytosol).

3

2

جسم
سائل
Fluid

1

- The distribution of a drug into these compartments is dictated by its physical and chemical properties. Compounds distribute differentially within body and PPB may limit distribution.
- Most noticeably, lipophilic compounds may accumulate in fatty tissues. For instance, thiopental, ethers, and minocycline tend to collect in adipose tissues.
- Additional examples of tissue storage include:
 - Iodine in thyroid gland;
 - Calcium, tetracyclines in bones and teeth;
 - Digoxin (to muscle proteins) in heart and skeletal muscles;
 - Chloroquine, tetracyclines, and digoxin in liver;
 - Tetracyclines and digoxin in kidney;
 - Chlorpromazine, isoniazid, and acetazolamide in the brain;
 - Ephedrine and atropine (to melanin) in iris.

قد يشار بعض الأحيان
الوعين
(صيلة صفتهم)

* التي يتركز فيها ويرجع الدماء في الـ Physicochemical Properties (تركزوا عليها)

* إذا تفرغت الخلايا أكثر فاد V_d لا يكون عالي
دس إذا بالبلازما فيكون V_d قليل

- Overall, volume of distribution (V_d) of a drug is determined by its partitioning across various membranes; binding to tissue components; binding to blood components; and physiological volumes. Apparent volume of distribution (V_d) is a primary PK parameter and could be greater than 10,000 L.
- The larger the volume of distribution, the more likely that the drug is found in the tissues of the body. In contrast, the smaller is the volume of distribution, the more likely is the drug confined to the circulatory system.

يمكن يتلغ أكثر من 10 آلاف

وسبب الخصائص الفيزيوكيميائية بتتغير كثير
منظار 3 أمثال الأدوية

Compounds	V_d (L/kg)	V_d (L)
① Acidic	<0.4	<28
② Neutral	0.4-1.0	28-70
③ Basic	>1.0	>70

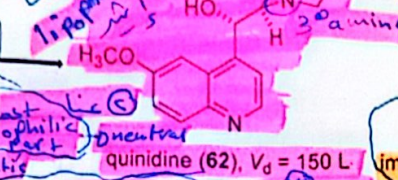
القيم الأول إذا السوا بعض في البلازما
مع يكون V_d قليل

القيم الثاني الأدوية التي تكون V_d متوسط

القيم الثالث القاعدية يكون V_d يكون عالي > 70

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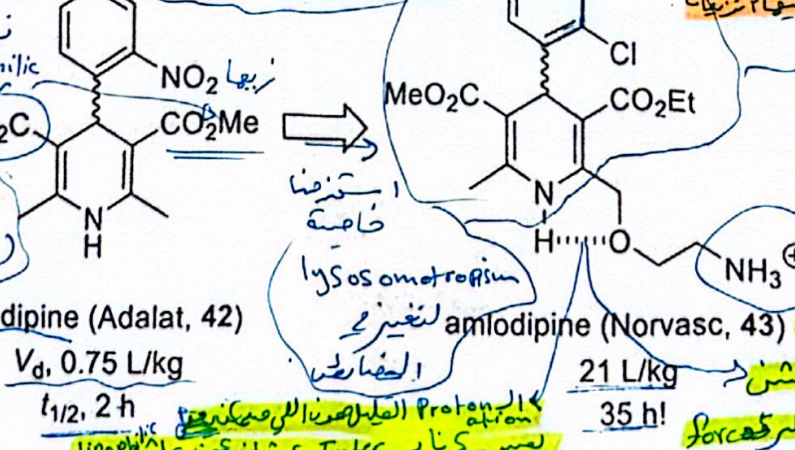
The presence of basic amines normally leads to increase of tissue affinity, thus boosts the V_d value



Lysosomotropism:
 lipophilic amines ($\log P > 1$) and amphiphilic drugs (cationic amphiphilic drugs) with ionizable amines ($pK_a > 6$) can accumulate in lysosomes.

Aliphatic
 tertiary amine
 Basic
 Protonation
 binding site

(3) V_d عالية جداً؟
 Amine
 Phospholipid
 lysosomes

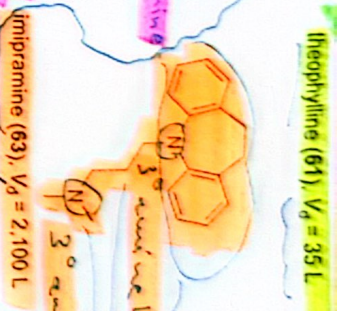
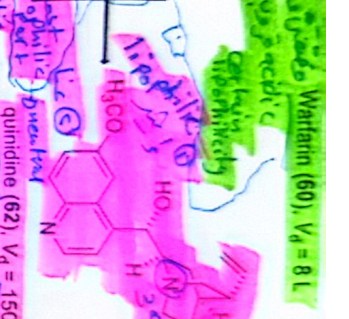


- First-generation calcium channel blocker
- Neutral drug with a moderate V_d of 0.75 L/kg
- Has a short half-life of 2 h, thus has to be taken three times a day.
- Third-generation calcium channel blocker
- Has a basic primary amine sidechain (lysosomotropism)
- Has a very high V_d of 21 L/kg
- Has a half-life of 35 h (once daily regimen).

(3) V_d عالية جداً؟
 Protonation
 trapped inside cell

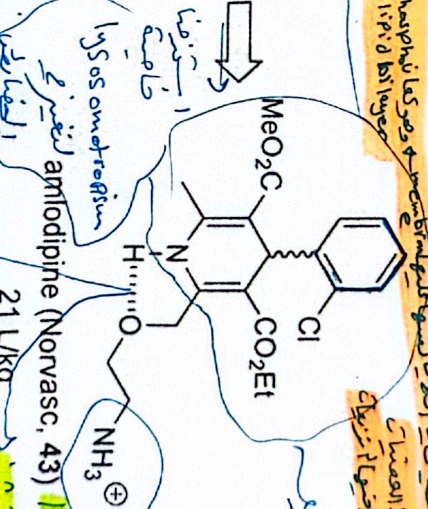
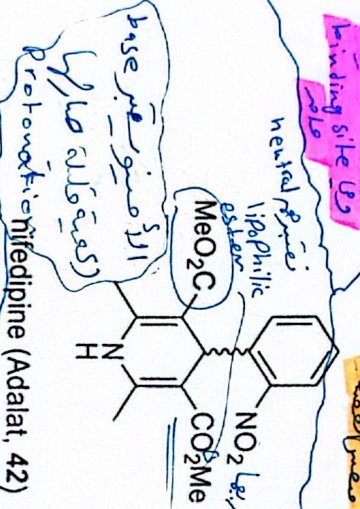
Volume of distribution (Vd) is a pharmacokinetic parameter that indicates the extent to which a drug is distributed throughout the body. It is defined as the volume of fluid in which the total amount of drug would have to be dissolved to give the same concentration as in the plasma.

The presence of basic amines normally leads to increase of tissue affinity, thus boosts the V_d value.



Lysosomotropism: Amphiphilic amines ($\log P > 1$) and amphiphilic drugs (cationic amphiphilic drugs) with ionizable amines ($pK_a > 6$) can accumulate in lysosomes.

Protonation: The presence of basic amines normally leads to increase of tissue affinity, thus boosts the V_d value.



- First-generation calcium channel blocker
- Neutral drug with a moderate V_d of 0.75 L/kg
- Has a short half-life of 2 h, thus has to be taken three times a day.

- Third-generation calcium channel blocker
- Has a basic primary amine sidechain (lysosomotropism)
- Has a half-life of 35 h (once daily regimen).

Protonation: The presence of basic amines normally leads to increase of tissue affinity, thus boosts the V_d value.

acidic pH / almost neutral

Handwritten notes at the top right of the page, including the name 'Dawood' and some illegible scribbles.

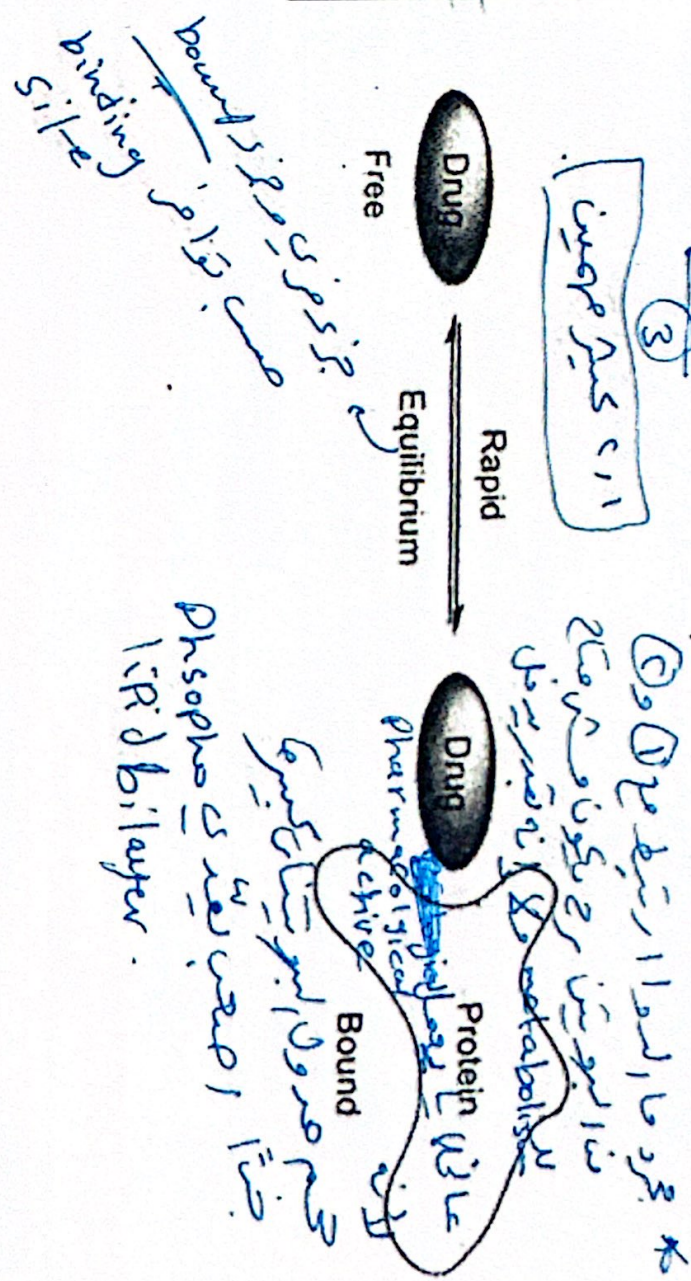
Plasma Protein Binding

PPB (Plasma Protein Binding) ...

• Drugs can bind to protein macromolecules in the blood, a phenomenon known as plasma-protein binding (PPB).

• The protein-bound form of the drug must dissociate from the protein in order to be useful because only unbound compound is available for distribution into tissues. There are three types of plasma proteins: human serum albumin (HSA) and α -1 acid glycoprotein (AAG) are the two more abundant proteins; whereas the third plasma protein, lipoprotein, is of less importance for PPB.

NOTE:
 Drug bound to albumin is also not available for metabolism in hepatocytes nor for renal elimination. The complex is large and cannot penetrate the cell membrane of hepatocytes.



Clinical implications of drugs' PPB

تأثير الدواء في الجسم يعتمد على نسبة الدواء الحرة في الدم

1. There is an equilibration between the PPB fraction of the drug and the free molecules of the drug. The PPB fraction is not available for action.



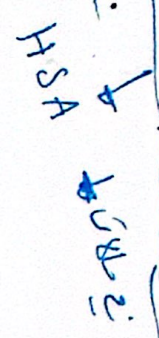
2. The drugs with high physicochemical affinity for plasma proteins (e.g., aspirin, sulfonamides, chloramphenicol) can replace the other drugs (e.g., warfarin) or endogenous compounds (bilirubin) with lower affinity.

3. High degree of protein binding makes the drug long-acting, because bound fraction is not available for metabolism, unless it is actively excreted by the liver or kidney tubules.

4. Generally expressed bound plasma concentrations of the drug refer to bound as well as free drug.

5. In hypoalbuminemia, binding may be reduced and high concentration of free drug may be attained.

high affinity
bilirubin
HSA
drug
metabolism



Human serum albumin (HSA)

بلازما، بروتين الجلبان البشري

- Human serum albumin ((HAS): 6700 Dalton), the most abundant protein in human blood plasma, has more than six distinctive binding sites including two for long-chain fatty acids, one for bilirubin; and two for acidic drugs.
- On the other hand, AAG has only one selective site for basic drugs.
- Acidic drugs in particular, bind to serum albumin and tend to have higher PPB than neutral/basic drugs (low Vd).
- Meanwhile, bases bind to AAG.
- Serum albumin binding increases as log P increases. In other words, hydrophobic drugs bind more strongly to serum albumin than hydrophilic drugs

مواقع ارتباط الحمضية
مواقع ارتباط القاعدية

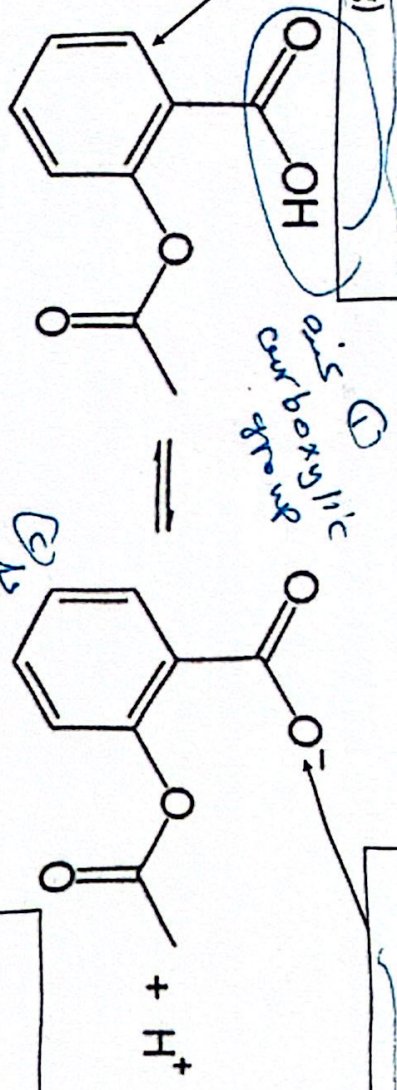
Hydrophobic Vd → AAG
مواقع ارتباط AAG
مواقع ارتباط HSA

مواقع ارتباط HSA
مواقع ارتباط AAG

Example 1: Aspirin

اسپیرین
HSA (Albumin)

1) Aromatic ring will bind to other aromatic rings found in aromatic amino acids in albumin (by π stacking)



2) >80% will bind to the positively charged arginine and lysine in albumin

H-bond forming groups

Aspirin at pH 7.4 will be in the ionized form (negatively charged)

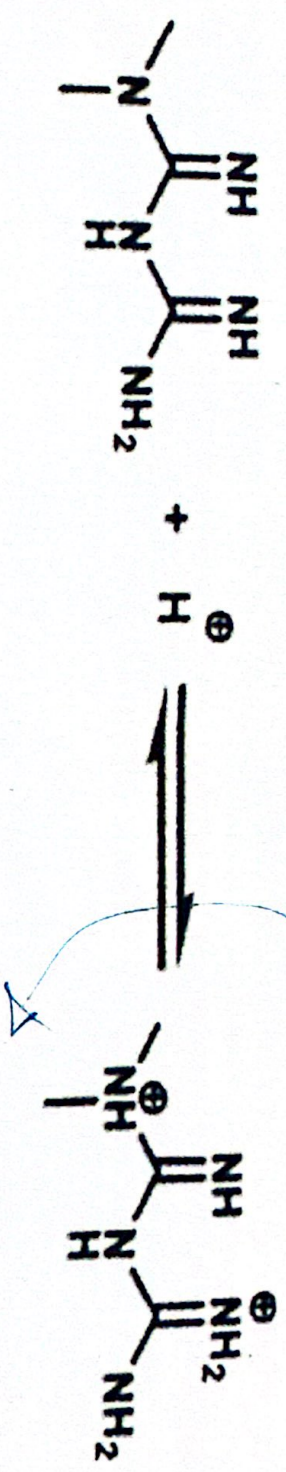
95% is bound to albumin
1.5 Free
100% bound

Free
السيكل صير صوا

Example 2: Metformin

Basic drug

وهي ترتبط الى BSA
البروتينات ويكون
كثير صوفين



Weak binding of metformin to BSA was governed by hydrogen bonds and van der Waals forces

علاقتها
علاقتها

Example 3: Thyroxine

98%
بمرتبط
H-Salts

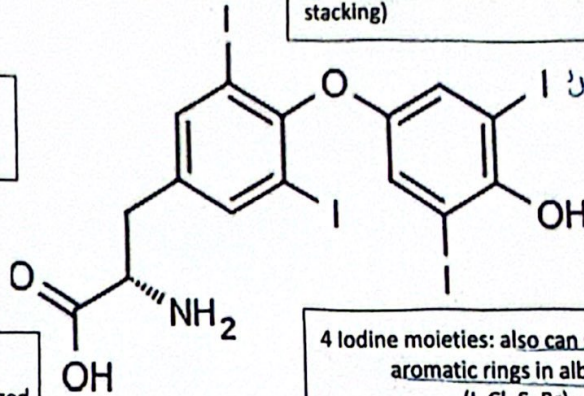
Aromatic ring will bind to aromatic rings found in albumin (by π stacking)

H-bond forming groups

هو عند كاربوكسيل
أسيد متروپ

Zwitterion at pH 7.4
-ve charge will bind to +vely charged binding pocket in albumin

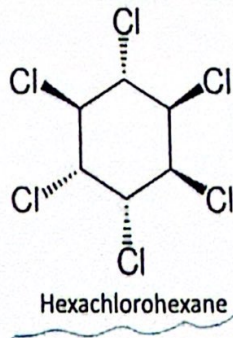
4 Iodine moieties: also can stack against aromatic rings in albumin (I, Cl, S, Br)



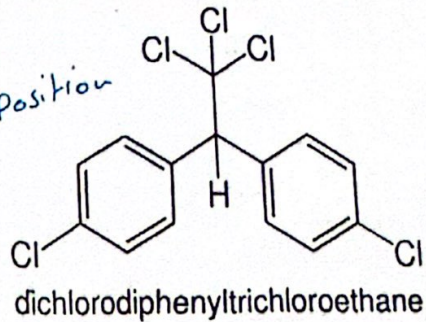
Thyroxine is more than 98% bound to albumin

Fat Deposition

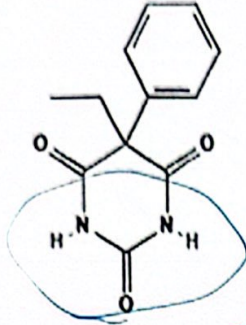
- Lipophilic drugs and multi-halogenated drugs tend to deposit in fats
- 20-30% of human weight is fat فكثير ادمية صيرت على علم
- Drugs deposit in fat are biologically inactive, neither metabolised nor renally eliminated.
- Fat deposition caused sustained release of the drug.



سبب
Fat Deposition



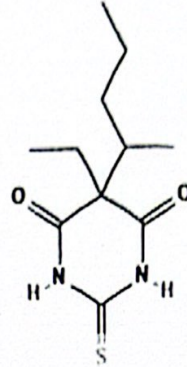
Example



Phenobarbital
Onset of action: 1.5hr
t1/2 = 8 hr

بعض
certain
hydrophilicity

* يمكنه يوصل
البرون



Thiopental

Onset of action: 5 min

t1/2 : 2 days

Quickly cross the BBB and deposit in the body fat

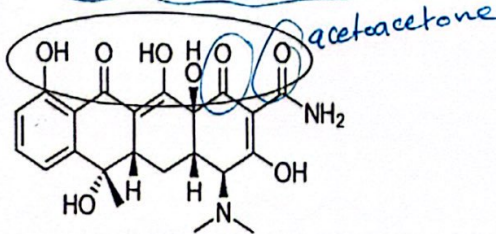
أسرع
أكثر
على
membrane

بسبب زيادة
الليبوليتي

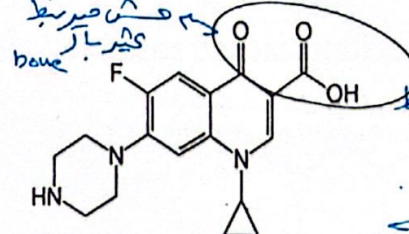
بدلوا ال (O) اللي بتعطي
lipophilicity
hydro
philicity

Bone Adsorption

- Any drug contains acetoacetic acid or acetoacetone group will form a complex with metals in bones
- Bone deposits remain for a long time (sometimes for a life time)
- Drugs chelate to bones are biologically inactive, neither metabolised nor renally eliminated.



Tetracycline
4 acetoacetic acid groups



Ciprofloxacin

بن
اشوف هار
التركيب
يعرف
على
الاسنان

بعض
البرون
اللي بتعطي
الليبوليتي

8)