تفريغ بيوفارما

اسم الموضوع: نهاية شابتر الabsorption و بداية شابتر الdistribution

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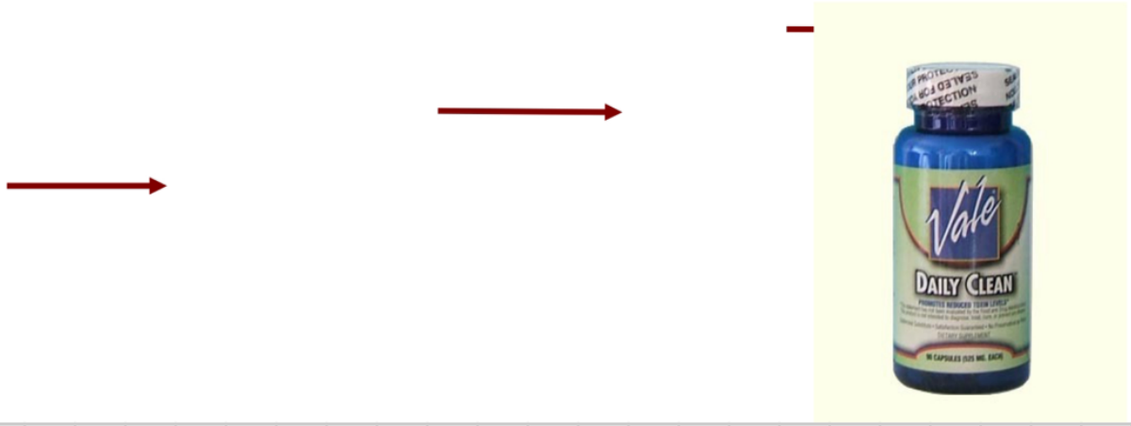
لجان الدفعات

F- Adsorption

- Certain insoluble susbstances may adsorbed co-administrated drugs leading to poor absorption.
- Charcoal (antidote in drug intoxication).
- Kaolin (antidiarrhoeal mixtures)
- Talc (in tablets as glidant)



- ال charcoal مناخدو لما يكون في intoxication من دوا معين و هي بتمنع امتصاص الادوية لأنه على سطحه عملية adsorption الي دمصاص

- kaolin هاد لما كانوا بيستخدموا anti bacterial drug اللي كانت فعّالة برا الجسم ، لما اعطوها جوا الجسم قتلت البكتيريا و لكن خلت ال diarrhea بشخالة فكانت تطلع مواد exotoxins من البكتيريا لبرا وتربط على جدار الامعاء و تضلها تعمل diarrhea فكانت الطريقة عشان اتخلص من هاي الـ exotoxins انه اعملها adsorption على سطح ال kaolin وهي كمان ادوية ممكن ترتبط على kaolin ، اذا الشخص بياخد anti diarrheal drug و اخد معه اي دوا تاني ممكن يصير له adsorption

III Formulation Factors Affecting Oral Absorption

- The role of the drug formulation in the delivery of drug to the site of action should not be ignored.

- Since a drug must be in solution to be absorbed efficiently from the G-I tract, you may expect the bioavailability of a drug to decrease in the order solution > suspension > capsule > tablet > coated tablet.

A. *Solution dosage forms:*

- In most cases absorption from an oral solution is rapid and complete, compared with administration in any other oral dosage form.

- different dosage forms:-
ما عندي مشكلة solution ①
فيه لأنه ما فيها
dissolution state
يعني على طول بصير
absorption

III Formulation Factors Affecting Oral Absorption

- Some drugs which are poorly soluble in water may be:

1- dissolved in mixed water/alcohol or glycerol solvents (cosolvency),

2- given in the form of a salt (in case of acidic drugs)

3- ~~An oily~~ emulsion or soft gelatin capsules have been used for ~~some~~ compounds with lower aqueous solubility to produce improved bioavailability.

disintegration فش capsule ②
dissolution بس في خطوة
- لو كانت الكبسولة للكبير
و بدي اعطيه للصغير ليس
ما بدوب بالمي فصعب احضره
على شكل solution
الحل :-
- ممكن اعمله على شكل
suspension
- عشان احضره عشكل
سبستخدم solution
co-solvent قبل الكحول
و ال glycerol
- ممكن احضره على شكل salt
لأنه ال dissolution تبعه
احسن

III Formulation Factors Affecting Oral Absorption

B. Suspension dosage forms:

- A well formulated suspension is second to a solution in terms of superior bioavailability.

- A suspension of a finely divided powder will maximize the potential for rapid dissolution.
- A good correlation can be seen for particle size and absorption rate.

- The addition of a surface active agent will improve the absorption of very fine particle size suspensions.

كل ما suspension ③
كان ال particle size
كل ما كان الاضطراب نتجه
احسن وكل ما كانت ال
bioavailability افضل
و ال surfactants ك
emulsifying agent
بلعب دور كمان

III Formulation Factors Affecting Oral Absorption

C. Capsule dosage forms:

- The hard gelatin shell should disrupt rapidly and allow the contents to be mixed with the G-I tract contents.

- If a drug is hydrophobic a dispersing agent should be added to the capsule formulation. These diluents will work to disperse the powder, minimize aggregation and maximize the surface area of the powder.

- Tightly packed capsules may have reduced dissolution and bioavailability.

مشكلة ال capsule
انها tightly packed
ممكن البودرة تطلع بشكل
ابطأ وممكن يأثر عال
dissolution

III Formulation Factors Affecting Oral Absorption

- The tablet is the most commonly used oral dosage form.
- It is also quite complex in nature.

1-Ingredients

Drug : may be poorly soluble, hydrophobic

Lubricant : usually quite hydrophobic

Granulating agent : tends to stick the ingredients together

Filler: may interact with the drug, etc., should be water soluble

Wetting agent: helps the penetration of water into the tablet

Disintegration agent: helps to break the tablet apart

في Tablet ④ بجدين disintegration و dissolution

- الاشياء الثانية الموجودة مع البودرة
  ① الدوا نفسه
  ② lubricant
  ③ granulating agent
  ④ filler اللي هو diluent مثل اللاكتوز و ال starch وبزيد حجم ال tablet
  ⑤ wetting agent
  ⑥ disintegration agent
  هاي الاشياء اذا كان واحد منهم بطيء محناها رح يأثر عال dissolution وال absorption وال bioavailability

Distribution

Drug distribution: means the reversible transfer of drug from one location to another within the body.

- The distribution of drugs in the body depends on:

1- their lipophilicity

2- protein binding.

Low plasma binding or high tissue binding or high lipophilicity usually means an extensive tissue distribution.

- عملية ال distribution هي عملية reversible
- مجرد ما الدوا يمارله absorption راح ال blood vessels و الخطوة اللي بعدها حسب ال lipophilicity و اذا في اله protein binding و حسب ال size ال molecule
- اذا ال plasma binding كان قليل معناها انتشاره اعلى و اذا كان عالي مرح يضل بالدم

Distribution

- In pharmacokinetics, the distribution is described by the parameter V, the apparent volume of distribution.

- At equilibrium, V will theoretically not be lower than 7 L in a 70-kg person, but it has no upper limit.

- ال distribution من ناحية pharmacokinetics فحكي عن parameter اللي هو volume of distribution و هو بتفاوت من شخص لشخص بس معقول اقل من 7 اللي هو ال volume تبع الدم بس ال upper limit هو ما اله limit يعني خير محدود يعني اذا ال distribution عالي جدًا ممكن يوصل المالانهاية

Drug distribution patterns

-The extent to which a drug distributes affects the half-life of the drug and the fluctuation of the concentration at steady state.

Distribution can be thought of as following one of four types of patterns:

1-The drug may remain largely within the vascular system. Mannitol and plasma substitutes such as dextran are examples of this type, but drugs which are strongly bound to plasma protein may also approach this pattern.

- different patterns في للمركبات
- السوائل و المي ممكن تكون بين الخلايا فال distribution ممكن يضل بال blood vessels وممكن اذا حجمه صغير وال lipophilicity عالي الاقته بالمي بين الخلايا وممكن يدخل عال intracellular fluid وممكن يصير له accumulation in certain organs مخصوص اكتر من نوع ال distribution

كمان مثال : Sorbitol وممكن اعطيه IV للناس اللي بصير عندهم Acute renal fail او بعطوهم mannitol وهو عبارة عن سكر وبس يروح عالكلى بتكسر كله و يضل نازل عال urine

بس بال blood vessels

Drug distribution patterns

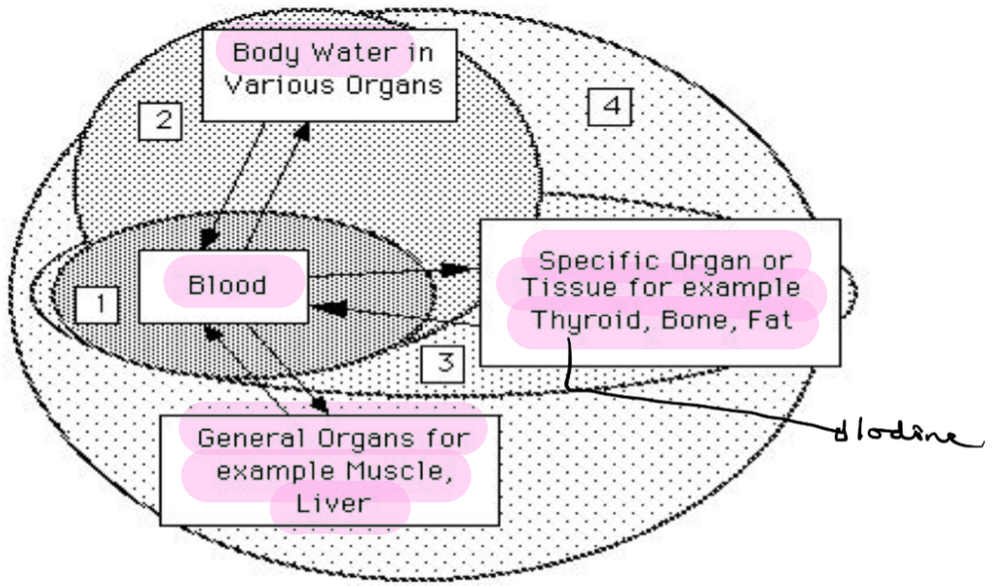


Diagram Representing Various Volumes Distribution Patterns

- لما كلها تتركز في organs بحيث معناته ال volume of distribution الها عالية و اللي بس تبقالها بالدم بكون ال volume of distribution الها قليل

Drug distribution patterns

2- Some low molecular weight water soluble compounds such as ethanol and a few sulfonamides become uniformly distributed throughout the body water.

- اذا كان المركب حجم صغير و hydrophilic يروح عال extra cellular fluid فرح يكون الـ Volume of distribution اعلى من 7

Drug distribution patterns

3- A few drugs are concentrated specifically in one or more tissues that may or may not be the site of action.

concentrated in certain organs

Iodine is concentrated by the thyroid gland.

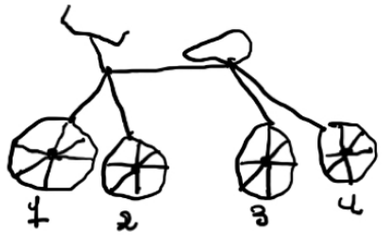
The antimalarial drug chloroquine may be present in the liver at concentrations 1000 times those present in plasma.

Drug distribution patterns

Tetracycline is almost irreversibly bound to bone and developing teeth.

Consequently tetracyclines should only be given to young children or infants in extreme conditions as it can cause discoloration and mottling of the developing second set of teeth.

Another type of specific concentration may occur with highly lipid soluble compounds which distribute into fat tissue.



tetracycline

اذا كان الطفل عمره ١٢ سنة او ٨ سنين يمكن تصير اسنانه تتغير كتير و ما يرجع irreversible

Drug distribution patterns

4- Most drugs exhibit a non-uniform distribution in the body with variations that are largely determined by the ability to pass through membranes and their lipid/water solubility.

The highest concentrations are often present in the kidney, liver, and intestine usually reflecting the amount of drug being excreted.

- يمكن الدوا يتوزع بطريقة مش منتظمة ويمكن يروح للـ kidney او الـ liver

Drug distribution patterns

- Apparent volume of distribution (V) is a useful indicator of the type of pattern that characterizes a particular drug.
- A value of V in the region of 3-5 liter (in an adult) would be compatible with pattern 1. This is approximately the volume of plasma.
- Pattern two would be expected to produce a V value of 30 to 50 liter, corresponding to total body water.
- Agents or drugs exhibiting pattern 3 would exhibit very large values of V. Chloroquine has a V value of approximately 115 L/ kg .
- Drugs following pattern 4 may have a V value within a wide range of values.

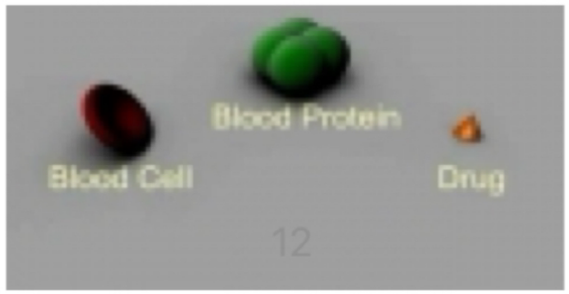
- متحدد عن خلاله ال pattern اللي بتبع الـ الدوا
- ال Volume of distribution → 3.5 L هو البلازما بدون ال RBCs
- 30 → 50 هاد ال pattern التاني
- ال pattern التالت 115 L/kg ⇐
- ال pattern الرابع بوصل إلى ما لا نهاية

Drug distribution patterns

Volumes of body fluids	
Fluid substances	**Volume (liter)**
Extracellular Fluid	19
Plasma	3
Interstitial fluids	16
Intracellular fluids	23
Total body water	42

Factors affecting drug distribution

Factors Affecting Distribution	
A- Rate of distribution	**B- Extent of Distribution**
1. Membrane permeability 2. Blood perfusion	1. Lipid Solubility 2. pH – pKa 3. Plasma protein binding 4. Tissue drug binding



- الاشياء اللي بتأثر على ال drug distribution هي ال rate و ال quantity او ال extent

membrane permeability ①
هل هاد الدوا بمر او لا ؟

Blood perfusion ②
هل هاد الorgan بيجيه دم بكميات كبيرة ولا اقل وكما كانت الكميات اعلى بتكون ال distribution اكبر

lipid solubility ①
lipophilic كلما كان اكتر كلما كان ال volume of distribution اقل اله

pH – pKa ②
unionized كلما كان بال form كلما كان ما كان ال distribution اله اعلى

plasma protein bind ③
حجمه albumin ال كبير بالتالي بضل بالدم فكلما كان الدوا protein binding ال اله عالي مثل ال sulfonylurea ، warfarin distribution ال صعول اليهم قليل لأنهم بضلوا بالدم

Factors affecting drug distribution

A. Rate of distribution

1. Membrane permeability:

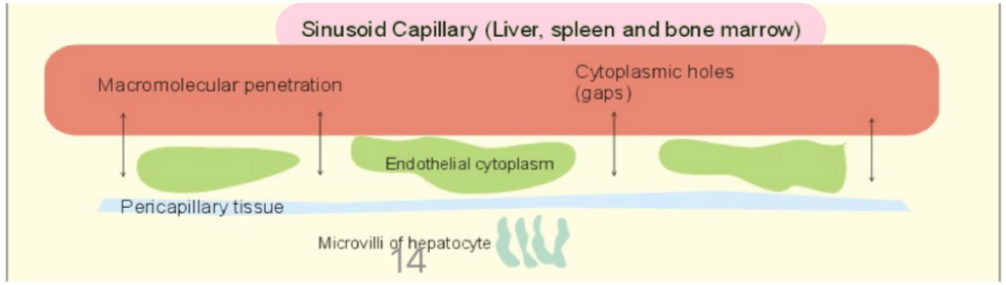
- Capillary walls are quite permeable.
- Lipid soluble drugs pass through very rapidly.
- Water soluble compounds penetrate more slowly at a rate more dependent on their size.
- Low molecular weight drugs pass through by simple diffusion. For compounds with molecular diameter above 100 Å transfer is slow.
- For drugs which can be ionized the drug's pKa and the pH of the blood will have a large effect on the transfer rate across the capillary membrane.

- water soluble compounds بتعقد على الحجم ، اذا حجمها صغير بتمرق من pores صغيرة موجودة بال cappillaries واذا حجمها كبير ما حتمرق بالمرة

Factors affecting drug distribution

- There are two deviations to the typical capillary structure which result in variation from normal drug tissue permeability.

i) Permeability is greatly increased in the renal capillaries by pores in the membrane of the endothelial cells, and in specialized hepatic capillaries, known as sinusoids which may lack a complete lining. This results in more extension distribution of many drugs out of the capillary bed.

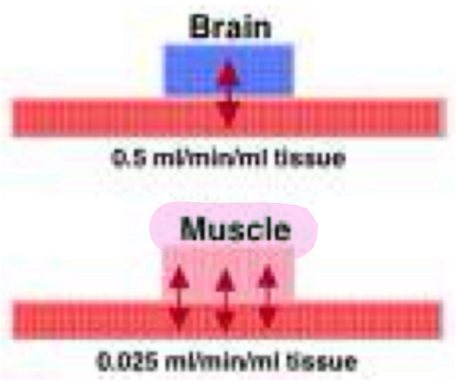


- ال permeability بتزيد بال capillaries تاعت liver أو spleen ال bone marrow أو
و العكس لل Blood brain barrier
و الفتحات تاعت ال liver, spleen, bone marrow
أكبر فالدورة بتمر بسهولة

Factors affecting drug distribution

2. Blood perfusion rate:

- The rate at which blood perfuses to different organs varies widely:



Blood Perfusion Rate		
Organ	Perfusion Rate (mL/min/mL of tissue)	Percent of cardiac output (CO)
Bone	0.02	5
Brain	0.5 - 0.55	14 - 15
Fat	0.01 - 0.03	2 - 4
Heart	0.6 - 0.7	4
Kidneys	4.0 - 4.5	22 - 24
Liver	0.8 - 0.95	25 - 27

- Vital organs:
Brain, kidney, heart
الهم perfusion ال يعتبر عالي

- perfusion rate ال قليل للعضلات لأنه حجمها كبير

Factors affecting drug distribution

- The rate at which a drug reaches different organs and tissues will depend on the blood flow to those regions.

- Equilibration is rapidly achieved with heart, lungs, liver, kidneys and brain where blood flow is high.

- Skin, bone, and depot fat equilibrate much more slowly.

equilibration • يعني الدوا دخل ، distribution صار له الل liver رح يكون خروجه من ال liver سهل يعني كلما كان دخوله أسهل رح يكون خروجه أسهل

Factors affecting drug distribution

B. Extent of Distribution

1.Lipid Solubility:

- Lipid solubility will affect the ability of the drug to bind to plasma proteins and to cross lipid membrane barriers.

- Very high lipid solubility can result in a drug partitioning into highly vascular lipid-rich areas. Subsequently these drugs slowly redistribute into body fat where they may remain for long periods of time.

• بقدرش احكي انه اذا الدوا معناته lipophilic ال volume distribution اله عالي لأنه كمان ال lipophilic ال protein binding اله عالي

Factors affecting drug distribution

2. Effects of pH:

- The rate of movement of a drug out of circulation will depend on its degree of ionization and therefore its pKa.
- Changes in pH occurring in disease may also affect drug distribution. For example, blood becomes more acidic if respiration is inadequate.

3.Plasma protein binding:

- Extensive plasma protein binding will cause more drug to stay in the central blood compartment. Therefore drugs which bind strongly to plasma protein tend to have lower volumes of distribution. (↑ protein binding = ↓ V)