PHARMACOKINETICS

Saef dawwas

Pharmacokinetic of drug absorption

PK theory lec.9

العَوة الي بتدخل الدوا للجسم

بتتبع first order elimination

وكمان بتمثل ال elimination من ال gi (للتبسيط*) باتجاه الدم

بزيد

بقل

rate in − rate out = (rate ك) التغييرات الي طارت على الدوا من الدم

بتضل صيغ حتى كمية الدوا كلها تصير بالدم

$k_a * X_{gi}$ $k_\beta * X_\beta * F$

بطلع B: blood

بدخل a: elimation from gi

بنسميها absorption ال gi

بعديز

بدو يطلع

فال elimination بزيد

F: bioavaibiLity

Sites of Drug Administration

- Sites of drug administration are classified into:
  - Intravascular routes
  - Extravascular routes
- Intravascular administration can be either intravenous or intra-arterial

1. No absorption phase
2. Immediate onset of action
3. The entire administered dose is available to produce pharmacological effects

Route	Bioavailability	Advantages	Disadvantages
Parenteral Routes			
Intravenous bolus (IV)	Complete (100%) systemic drug absorption.	Drug is given for immediate effect.	Increased chance for adverse reaction.
	Rate of bioavailability considered instantaneous.		Possible anaphylaxis.
Intravenous infusion (IV inf)	Complete (100%) systemic drug absorption.	Plasma drug levels more precisely controlled.	Requires skill in insertion of infusion set.
	Rate of drug absorption controlled by infusion rate.	May inject large fluid volumes.	Tissue damage at site of injection (infiltration, necrosis, or sterile abscess).
		May use drugs with poor lipid solubility and/or irritating drugs.	
Intramuscular injection (IM)	Rapid from aqueous solution.	Easier to inject than intravenous injection.	Irritating drugs may be very painful.
	Slow absorption from nonaqueous (oil) solutions.	Larger volumes may be used compared to subcutaneous solutions.	Different rates of absorption depending on muscle group injected and blood flow.
Subcutaneous injection (SC)	Prompt from aqueous solution.	Generally, used for insulin injection.	Rate of drug absorption depends on blood flow and injection volume.
	Slow absorption from repository formulations.		

Route	Bioavailability	Advantages	Disadvantages
Enteral Routes			
Buccal or sublingual (SL)	Rapid absorption from lipid-soluble drugs.	No "first-pass" effects.	Some drugs may be swallowed. Not for most drugs or drugs with high doses.
Oral (PO)	Absorption may vary.	Safest and easiest route of drug administration.	Some drugs may have erratic absorption, be unstable in the gastointestinal tract, or be metabolized by liver prior to systemic absorption.
	Generally, slower absorption rate compared to IV bolus or IM injection.	May use immediate-release and modified-release drug products.	
Rectal (PR)	Absorption may vary from suppository.	Useful when patient cannot swallow medication.	Absorption may be erratic.
	More reliable absorption from enema (solution).	Used for local and systemic effects.	Suppository may migrate to different position. Some patient discomfort.
Other Routes			
Transdermal	Slow absorption, rate may vary.	Transdermal delivery system (patch) is easy to use.	Some irritation by patch or drug.
	Increased absorption with occlusive dressing.	Used for lipid-soluble drugs with low dose and low MW.	Permeability of skin variable with condition, anatomic site, age, and gender. Type of cream or ointment base affects drug release and absorption.
Inhalation and intranasal	Rapid absorption.	May be used for local or systemic effects.	Particle size of drug determines anatomic placement in respiratory tract. May stimulate cough reflex.
	Total dose absorbed is variable.		Some drug may be swallowed.

يتكون كمية اقل من [100%]

~~bioavability~~ variation بكمية الدوا اللي بتوصل لأختلاف الـ

Extravascular Routes of administration

tablet < susp < soln

- Oral administration
  (tablet, capsule, suspension, etc.)
- Intramuscular administration (soln. and susp.)
- Subcutaneous administration (soln. and susp.)
- Sublingual or buccal administration (tablet)
- Rectal administration (suppository and enema)
- Transdermal drug delivery systems (patch)
- Inhalation (metered dose inhaler)

Pharmacokinetics of Oral Drug Absorption

الدوا لازم يوصل الدم بس بحتاج بال oral اكتر من خطوة مش زي ال IV (بوصل مباشرة)

- In oral route, systemic drug absorption from the site of administration is an additional step compared to i.v. route
- The systemic drug absorption from the gastrointestinal (GI) tract or from any other extravascular site is dependent on many factors including:
  - the physicochemical properties of the drug
  - the dosage form used
  - the anatomy and physiology of the absorption site

أماكن امتصاص الدوا من مكان E.V الوحدات

الـ intestin الأمتصاص احسن من الـ stomach لانو فيه microvilli فبتزيد الـ surface area

Extravascular Routes of administration

1. An absorption phase is present
2. The onset of action is determined by different physiological variables; such as:
   - Drug formulation
   - Type of dosage form
   - Route of administration
   - Physicochemical properties of drugs, etc.
3. The entire administered dose of a drug may **not** always reach the systemic circulation (i.e. incomplete absorption)

بتختلف حسب الدوا والـ route وطبيعة الجسم

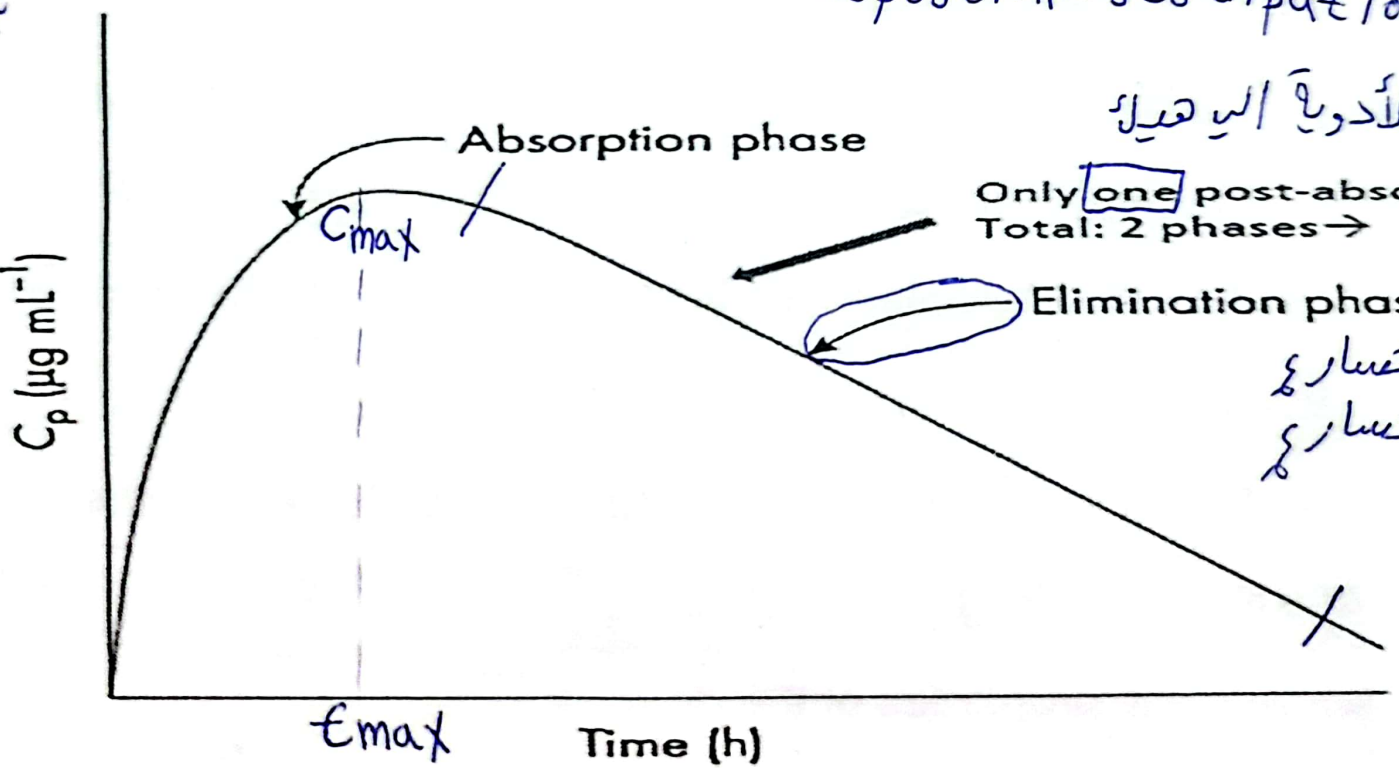
مش الدوا كامل بيوصل بيكون اقل من 100٪

زاد التوزع بقل الامتصاص للدم لأنو بصير يروح على الأنسجة

depostion = destripation + elimination

احنا بنهتم بالأدوية البرهيلة

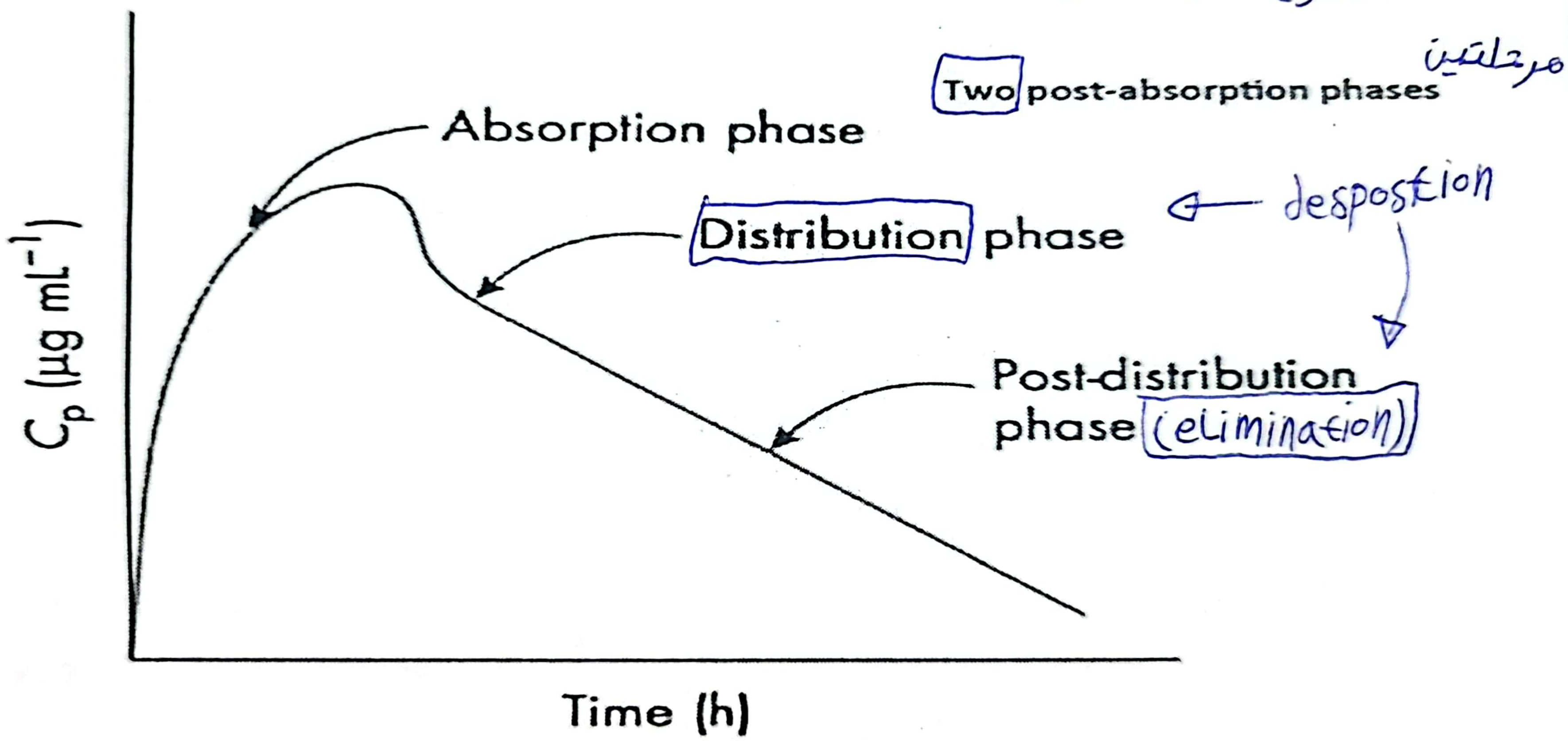
oral route



بطلع بشكل متسارع
وبنزل بشكل متسارع
(exponential)

A typical Cp vs. time profile following the extravascular administration (drug is **rapidly** distributed in the body)→ which means?

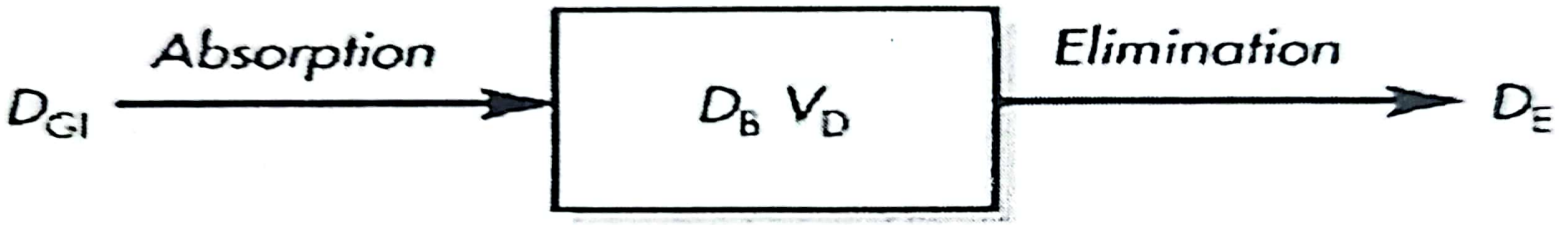
الأدوية اللي بتكون زي هيك بكون الها Vd بطيء وقليل

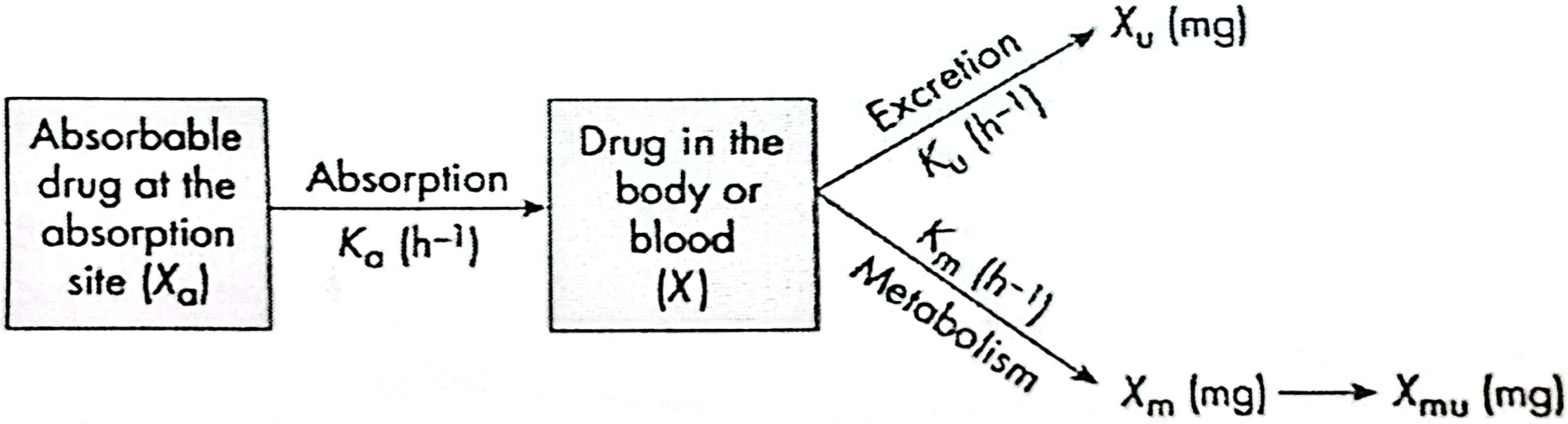


S.L

A typical Cp vs. time profile following the extravascular administration
(drug is **slowly** distributed in the body)→ which means?

بطيء من عنا هون
accumilation





Absorption model

at Least 10%

1. The amount (e.g. mg) of unchanged drug and/or metabolite(s) can be measured in urine

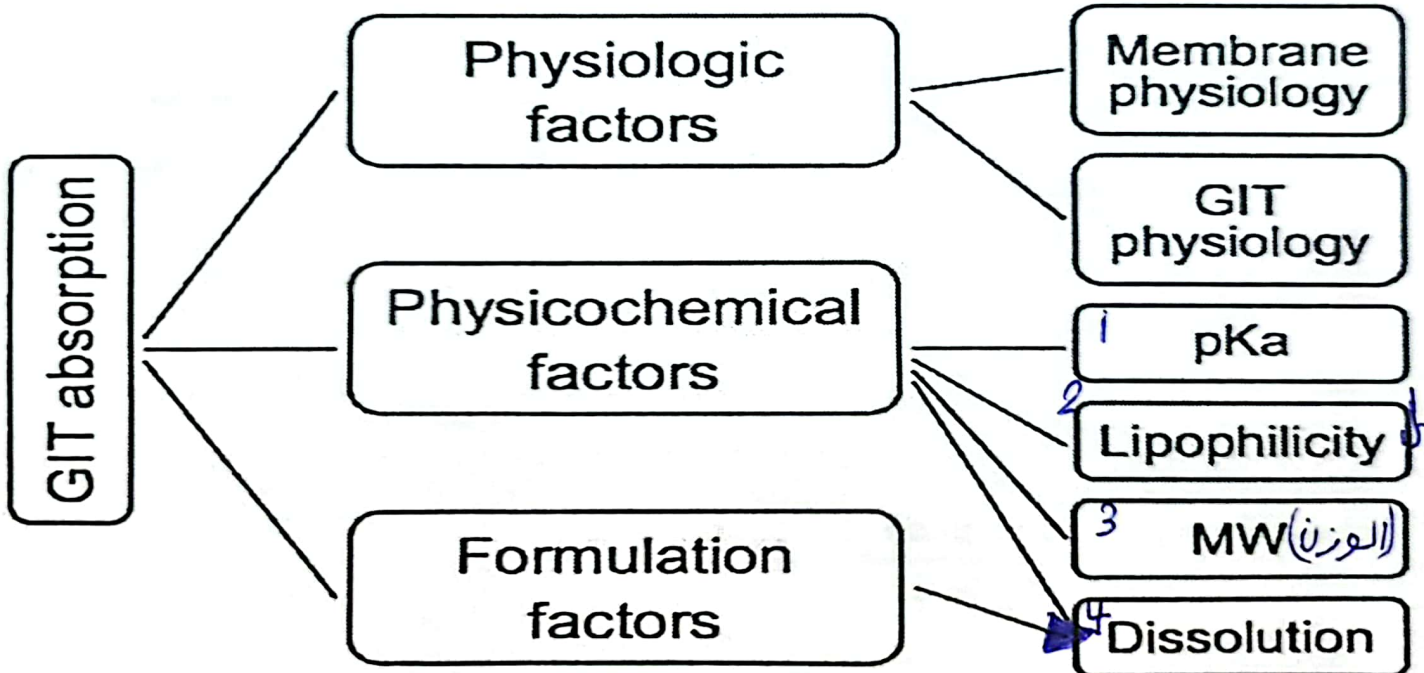
زي مابنحسبوا بال IV بنقدر برضوا بال oral

2. Drug and metabolite(s) in the body (blood, plasma or serum) are measured in concentration units (e.g. mg/mL)

ما بنحسب mg بال blood لأنو مابنقدر نتنبأ بالكمية

3. Direct measurement of drug at the site of administration is impractical → it can be assessed indirectly

Factors affecting GIT absorption



زادت امتصاص أفضل

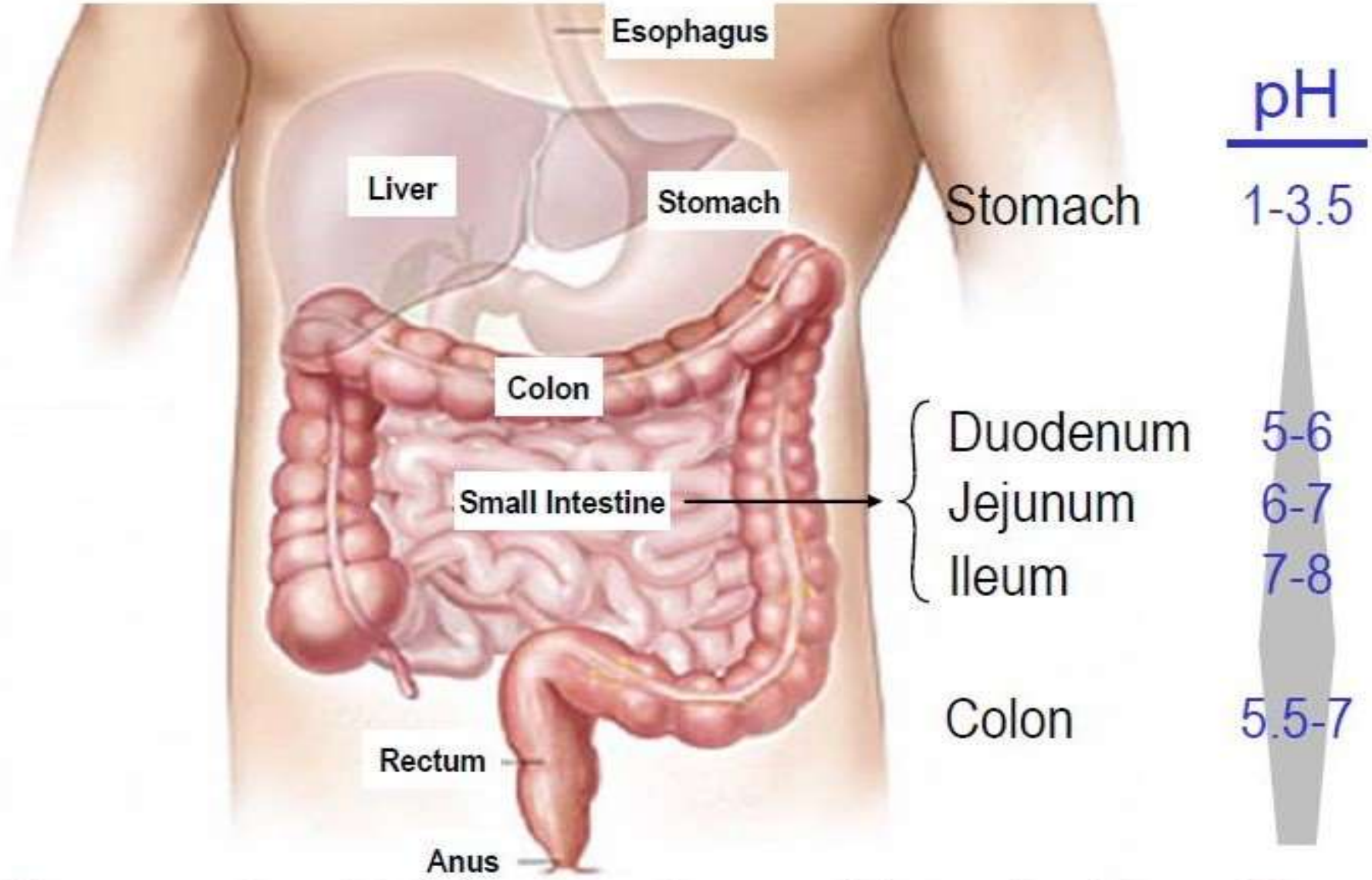
قل " " أقل

يختلف بأختلاف الوزن وباختلاف التركيبة

يصير متبلبا

disintegration

(بمعنى تفتت*)


Esophagus
Liver
Stomach
Colon
Small Intestine
Rectum
Anus
pH
Stomach 1-3.5
Duodenum 5-6
Jejunum 6-7
Ileum 7-8
Colon 5.5-7

Important features of the stomach

high acidity

1. **The stomach contents are in pH range of 1–3.5**; with a pH of 1–2.5 being the most commonly observed
2. The squeezing action of the stomach produces a mild but thorough agitation of the gastric contents.

(بتضر حركة المعدة / التركيبة)

3. A dosage form (tablet, capsule, etc.) may remain in the stomach for approximately **0.5–2 h prior to moving** to the duodenum

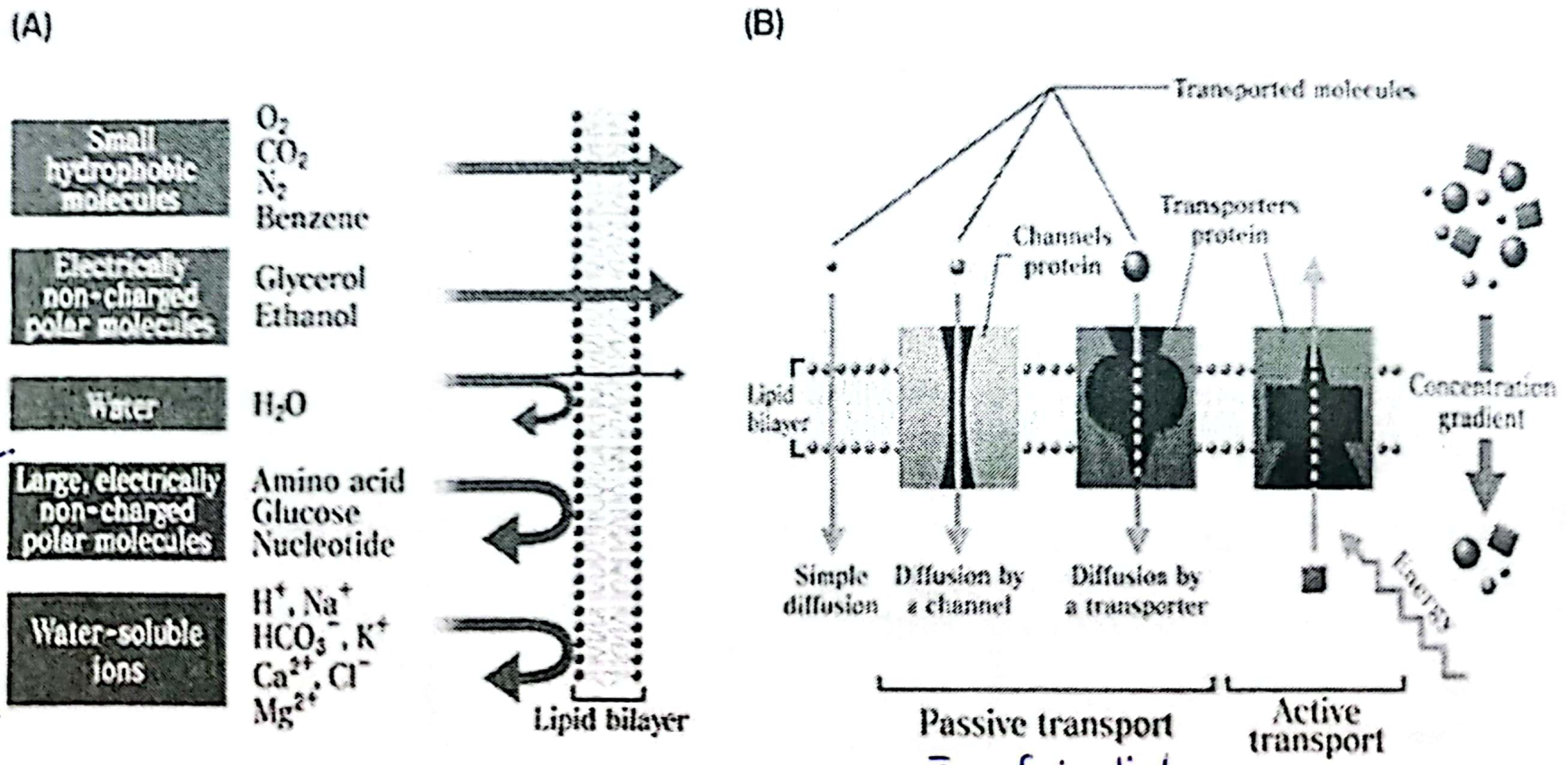
الوقت لتفضي المعد

This gastric emptying of drug may be affected by:

- **Fed vs. fasted state**: transfer is rapid on the fasting stomach and very slow if taken with heavy high fat meal
- Type of food
- Volume of liquid
- Viscosity and temperature

انواع المواد صغيرة و hydrophobic بتمر وامتصاصها اسهل

"lipid bilayer theory" and "fluid mosaic model"



ما يمر

اغلب الأدوية
بتمر عن طريقها
بتعتمد على فرق
التركيز من أعلى لأقل

Transport across the membranes

1) Passive transport

- Most drugs cross biologic membranes by passive diffusion
- Driving force: Concentration gradient (Down-hill)
- The rate of the drug movement per unit cross-sectional area is called flux (J) → $\mathbf{J} = \frac{dM}{dt \times A}$
- The rate of transport of drug across the membrane can be described by Fick's first law of diffusion

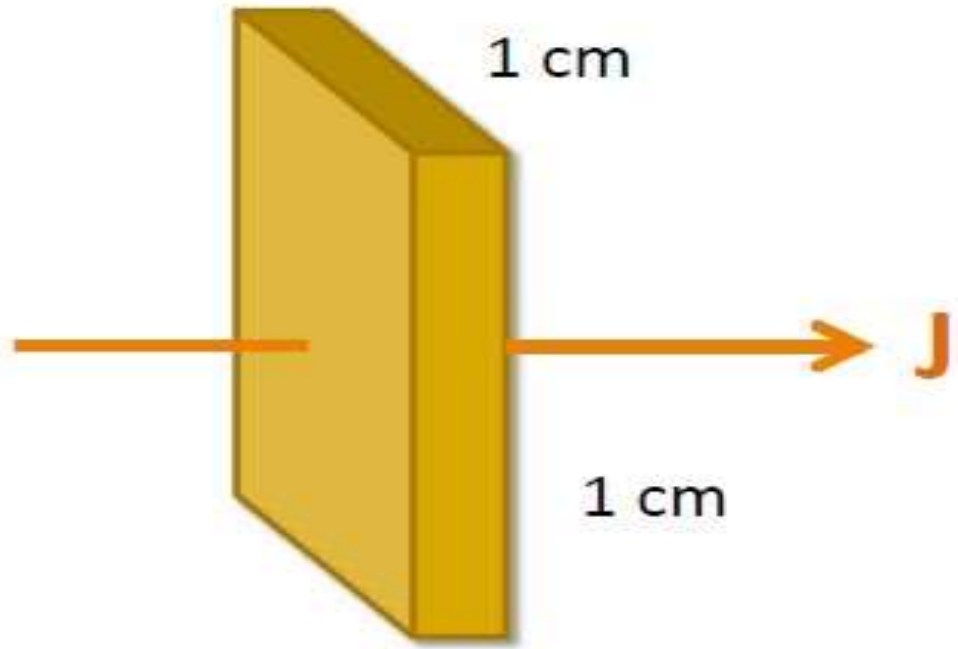
Diffusion equation: Flux, J

Definition of the flux (J): the rate of a solute flowing per unit cross-sectional area

$$\mathbf{J} = \frac{dM}{dt \times A}$$

M: Mass of solute
A: Cross- sectional area

Unit: mass/time/area (e.g. g/s/cm^2)



Fick's first law states that flux (J) is proportional to the change in mass (dM) over the surface area (A) and time (dt)

توزع الدوا بين الـ phases الـ o والـ aqs بعتمد على الـ lipophilicity

- The drug will partition itself between the aqueous phase (in the donor; GI lumen) and receptor (circulation) sides and the lipophilic phase (in the membrane)
- This partitioning depends on the drug's lipophilicity
- Partition coefficient (K) = $[drug]_o/[drug]_{aqs}$

Then,

$$J = D \times K \times \frac{C_1 - C_2}{h}$$

- **J:** flux → J = (dM/dt)/A
- **dM/dt:** Rate of diffusion
- كل ما زاد دوا احسن
  - **A:** Surface area of the membrane
  - **D:** The diffusion coefficient of the drug
  - **K:** Lipid-water partition coefficient of the drug
- **C_1-C_2:** Concentration difference, in our case is C_{GI}-C_p which is difference between the concentrations of drug in the gastrointestinal tract and in the plasma
- **h:** Membrane thickness

زاد فرق التركيز امتصاص اعلى

الأمتصاص بكون حظي

Factors affecting diffusion rate at different sites:

	D	A	h (as a barrier)
Pulmonary		100 m^2	0.2-50 µm
Nasal		160 cm^2	4-6 µm
Gastrointestinal		200 m^2	0.2-3.0 mm
Rectal		300 cm^2	~ 3 mm
Buccal		100 cm^2	0.1-0.8 mm
Transdermal		1-2 m^2	4-6 mm

diffusion coefficient
surface area
thickness

Transport across the membranes

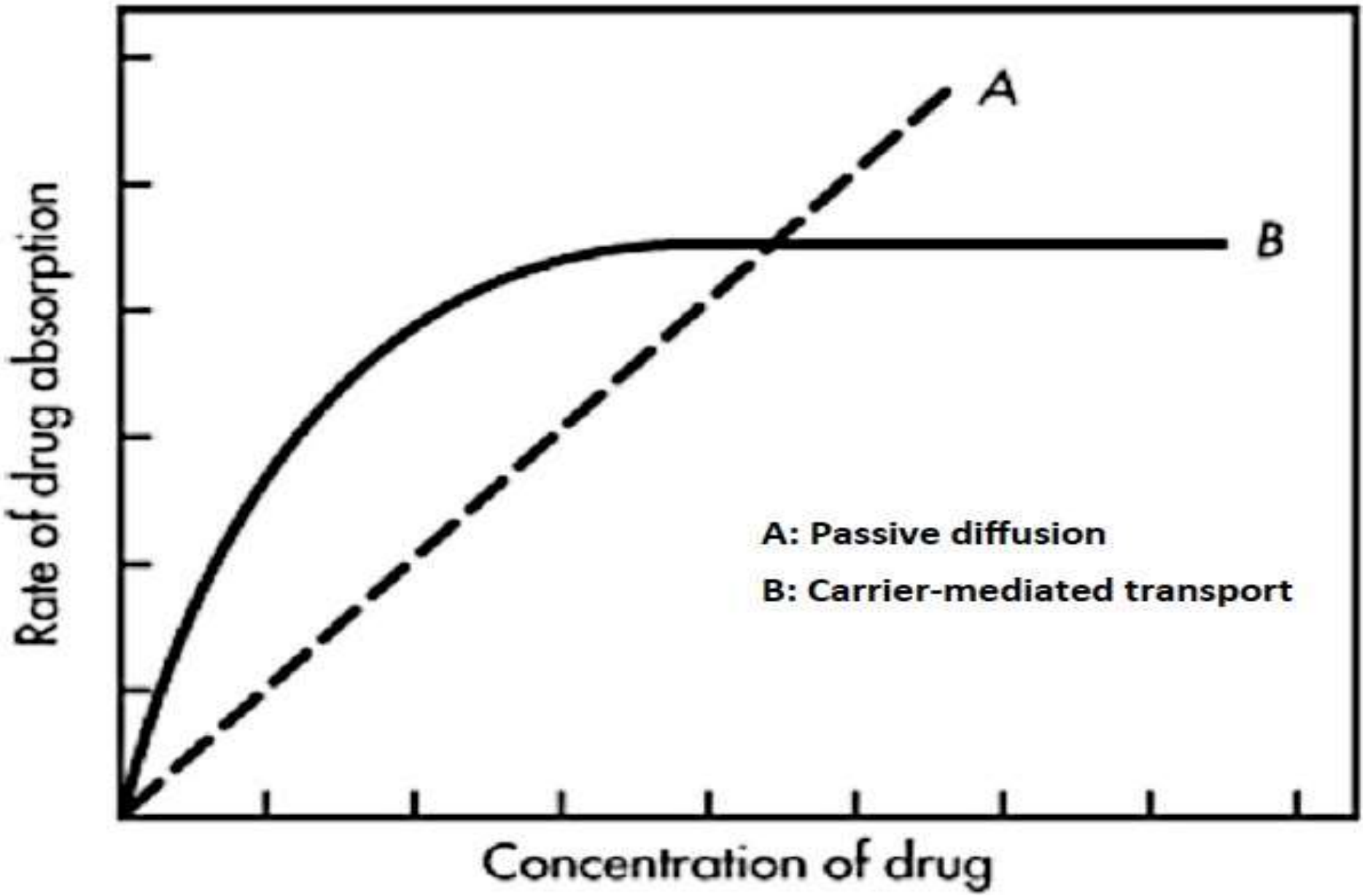
2) Carrier mediated

(i) Active transport

- Requires energy ATP
- The process can be saturated تتشبع
- Transport can proceed against a concentration gradient
- Competitive inhibition is possible Specific carriers لأنو عنا

Active transport obeys laws of saturation (Michaelis–Menten kinetics)→ i.e. the rate of absorption, unlike that of passive diffusion, is **not directly proportional** to the drug concentration in large doses non-Linear

عنا نواقل محددة بتتشبع


Rate of drug absorption
A
B
A: Passive diffusion
B: Carrier-mediated transport
Concentration of drug

آخر سلايد بالمحاضرة

بالتوفيق للجميع

Artery Academy