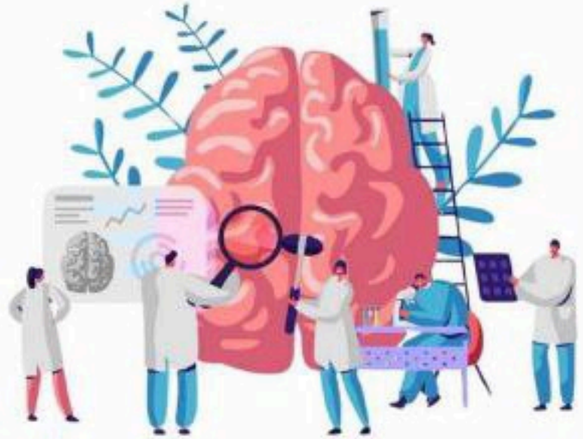


تفريغ لحاينتك

محاضرة: *Pharmacokinetic of drug absorption / lec 9*

الصيدلاني\ة: *Alaa Otoum*

لجان الدُّفعات

Soul Academy

Pharmacokinetic of drug absorption

PK theory lec.9

Sites of Drug Administration

- Sites of drug administration are classified into:
  - Intravascular routes in blood vessel.
  - 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. Rate of bioavailability considered instantaneous.	Drug is given for immediate effect.	Increased chance for adverse reaction. Possible anaphylaxis. → allergic shock. * لازم يكون الدواء homogenous مافي suspended & oil
Intravenous infusion (IV inf)	Complete (100%) systemic drug absorption. Rate of drug absorption controlled by infusion rate.	Plasma drug levels more precisely controlled. May inject large fluid volumes. ← لأنه الinfusion بستغرق فترة أطول فبالتالي الأدوية رح تدخل براحتها. May use drugs with poor lipid solubility and/or irritating drugs.	Requires skill in insertion of infusion set. Tissue damage at site of injection (infiltration, necrosis, or sterile abscess).
Intramuscular injection (IM) * الsolution إذا كان oily نقدر أعطيه على شكل IM	Rapid from aqueous solution. Slow absorption from nonaqueous (oil) solutions.	Easier to inject than intravenous injection. Larger volumes may be used compared to subcutaneous solutions.	Irritating drugs may be very painful. Different rates of absorption depending on muscle group injected and blood flow.
Subcutaneous injection (SC)	Prompt from aqueous solution. Slow absorption from repository formulations.	Generally, used for insulin injection.	Rate of drug absorption depends on blood flow and injection volume.

* من ناحية سرعة وصول الدواء للsystemic circulation
SC << IM << IV

الدكتورة بس ركزت على ٤ أنواع اللي عليهم البوكس الأحمر.

Route	Bioavailability (F)	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. كل حسب نوع الدواء.	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.	* غير مناسب في حالات vomiting, emergency diarrhea. * والأدوية المتأثرة بـ pH.
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.
	Total dose absorbed is variable.		May stimulate cough reflex. Some drug may be swallowed.

Extravascular Routes of administration

- 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

- 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:

← مثلاً: A^-

→ يعني مثلاً لو عندي acidic drug معين شحنة سالبة لما يدخل الـ stomach رح يرتبط مع H^+ فيتكون عندي HA يعني الشكل بسهولة بإمكانه تعبر lipid bilayers.

* بينما لو كان مثلاً BH⁺ مادة ما رح يقدر يعبر الـ stomach بده يوصل الـ intestine والي basic (OH) ويدخل عندي B فيقدر يعبر.

  - the physicochemical properties of the drug

* يعني مثلاً drug – drug interaction
drug – food interaction

  - the dosage form used

← أغلب الأدوية تتأثر بشكل سلبي امتصاصها بسبب الأكل.

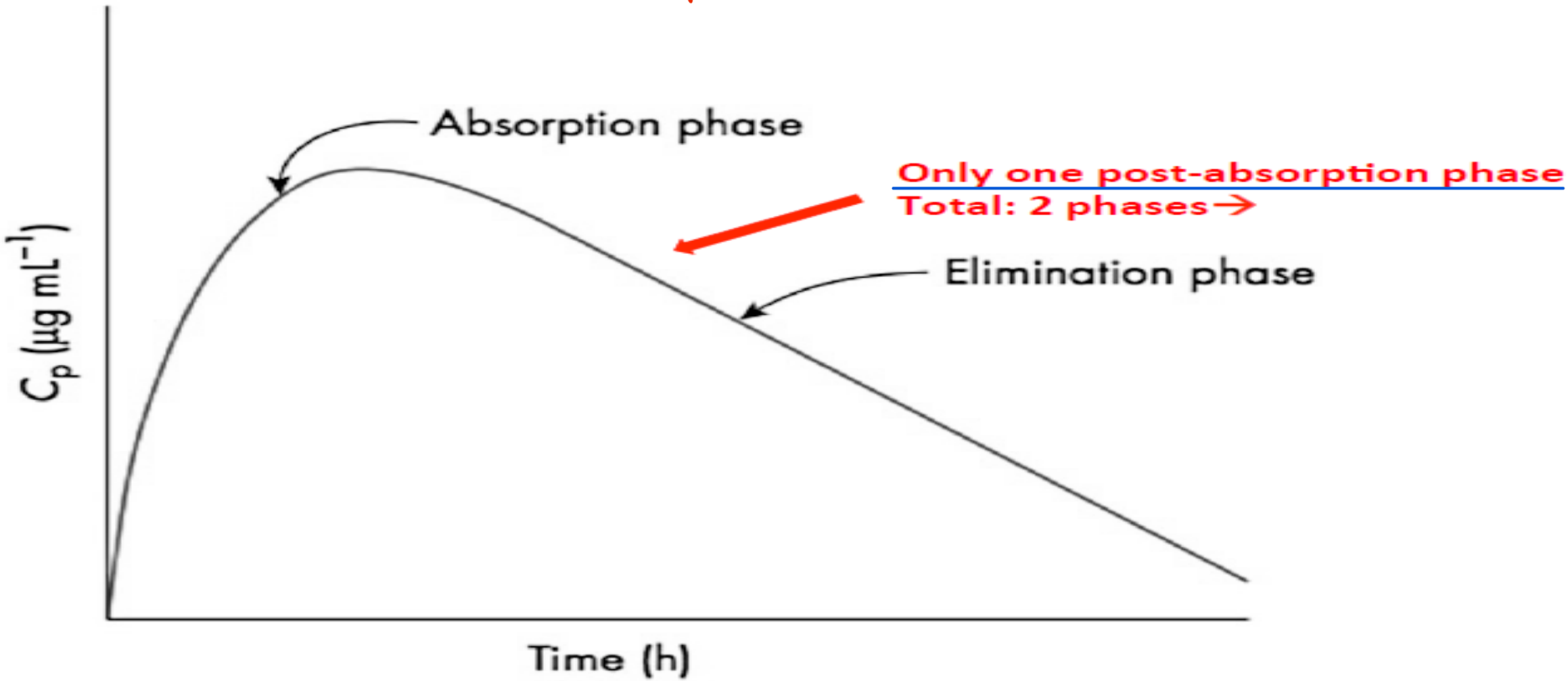
  - the anatomy and physiology of the absorption site

← مثلاً الـ intestine الها large surface area مقارنة بغيرها فـ تعتبر best absorption site مقارنة بـ stomach

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)

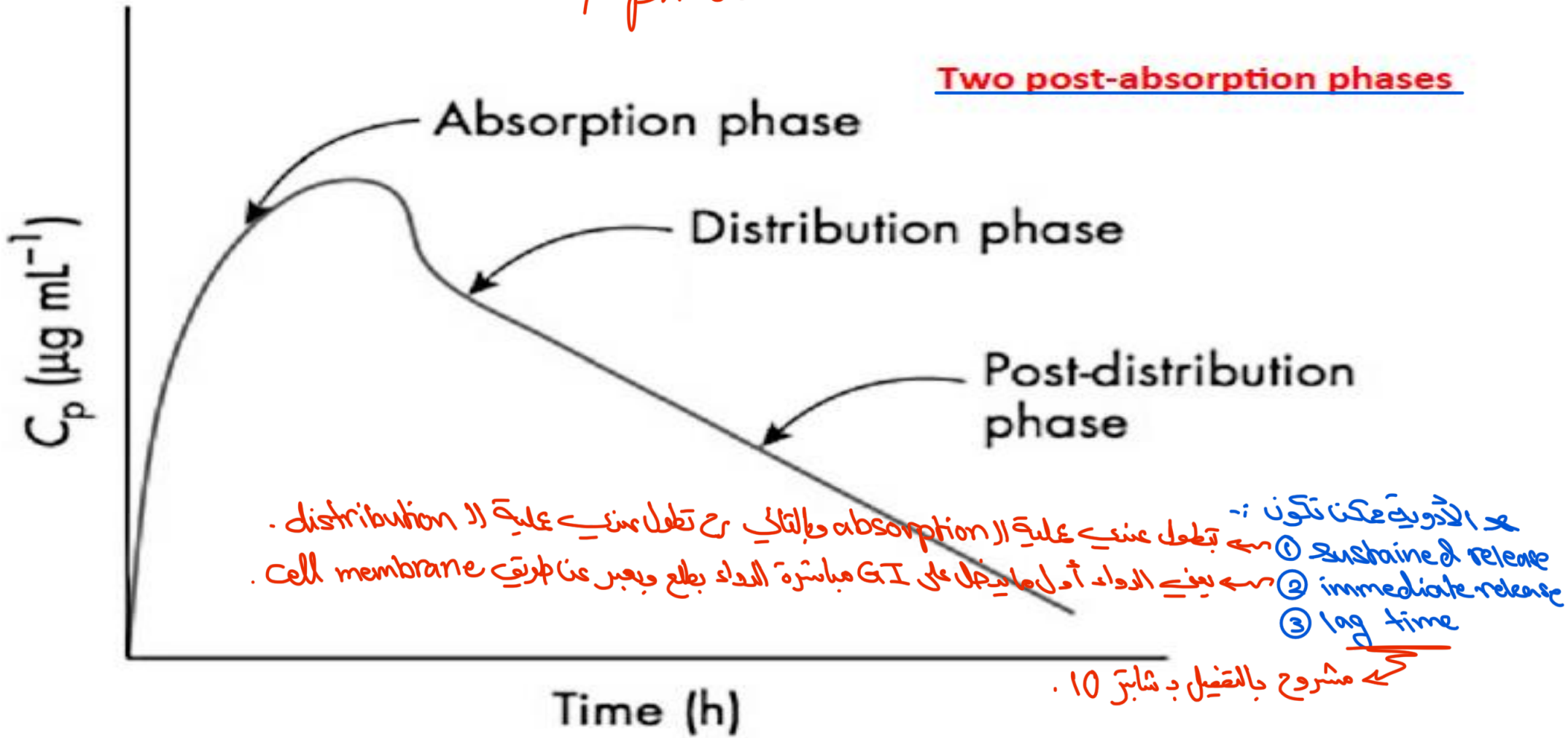
3 phase



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

يعني مثلا الأدوية اللي تكون lipophilicity فيها عالية فـ بتذوب بسرعة فـ ما بتكون بحاجة تمر بال distribution phase

4 phase

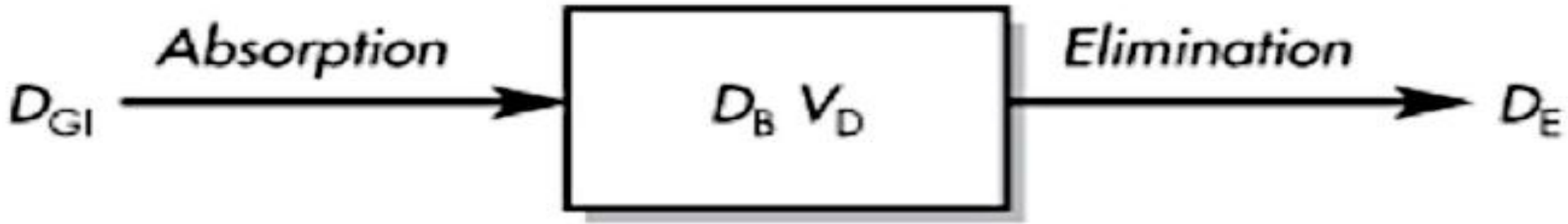


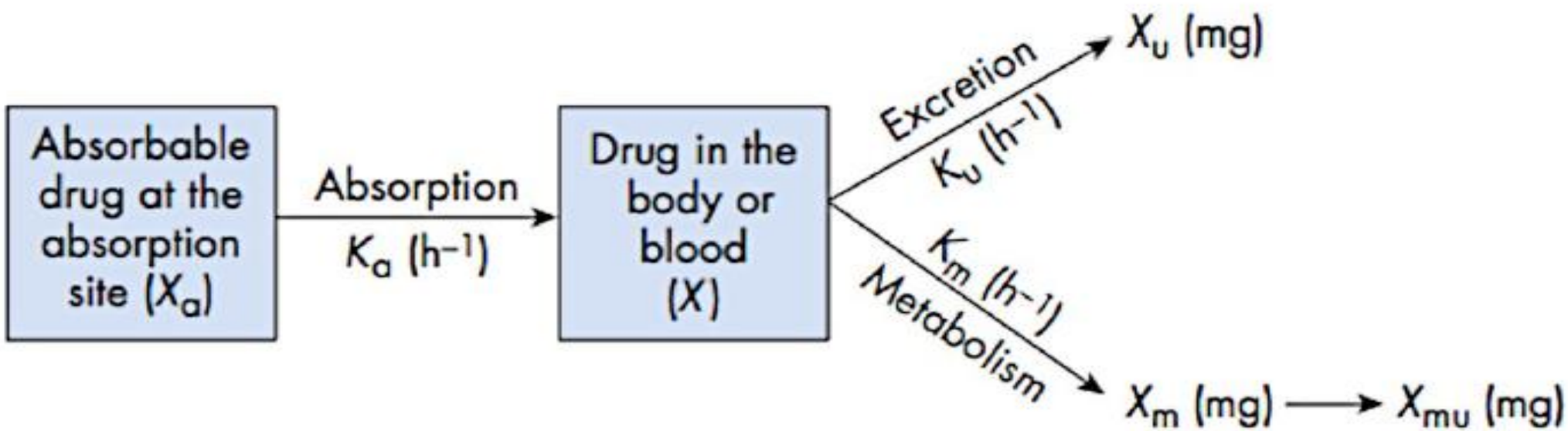
ع الأدوية ممكن تكون :-
① Sustained release
② immediate release
③ lag time
مشروح بالتفصيل بـ شابتر ١٥ .

بعد ما بتطلع عنده عملية الـ absorption وبالتالي رح تطلع عنده عملية الـ distribution .
يعني الدواء أول ما يدخل على GI مباشرة الدواء بطلع وبعبر عن طريق cell membrane .

S.L

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

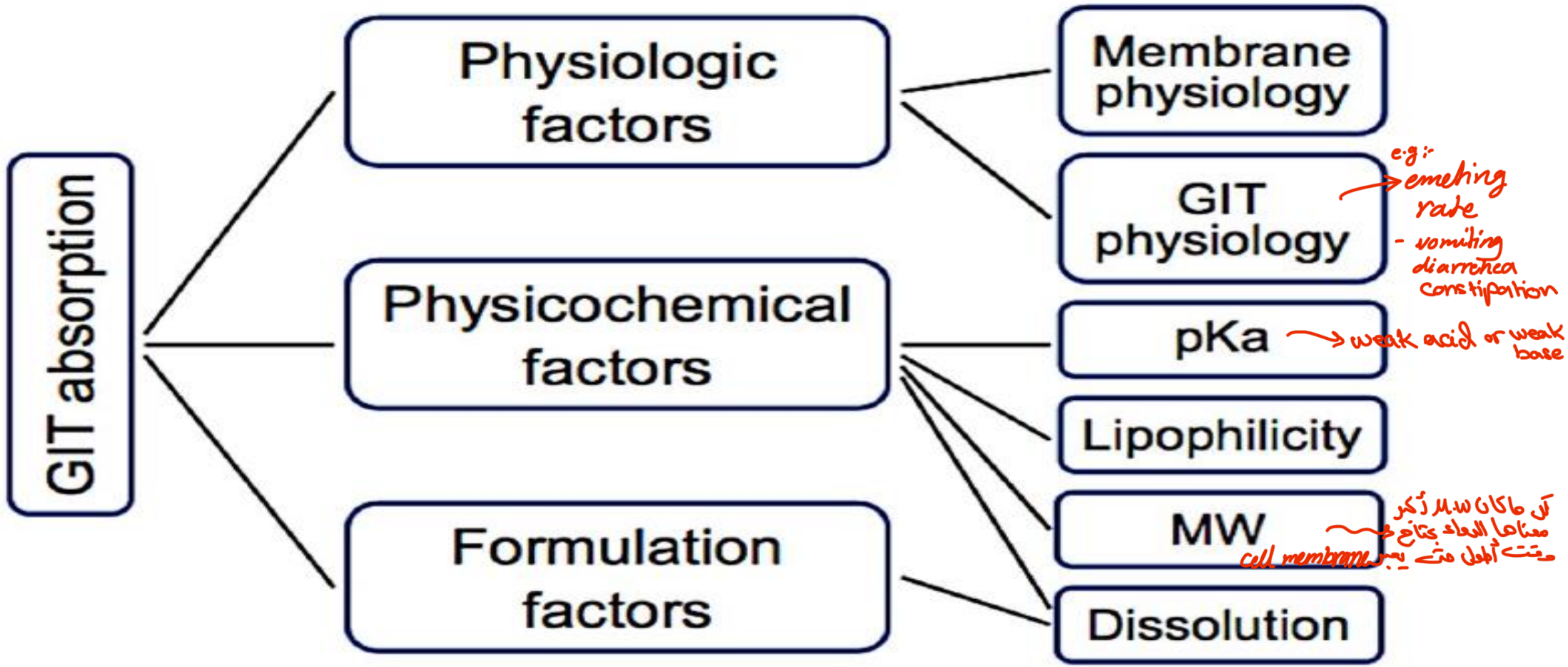

Absorption
Elimination
D_{GI}
D_B V_D
D_E

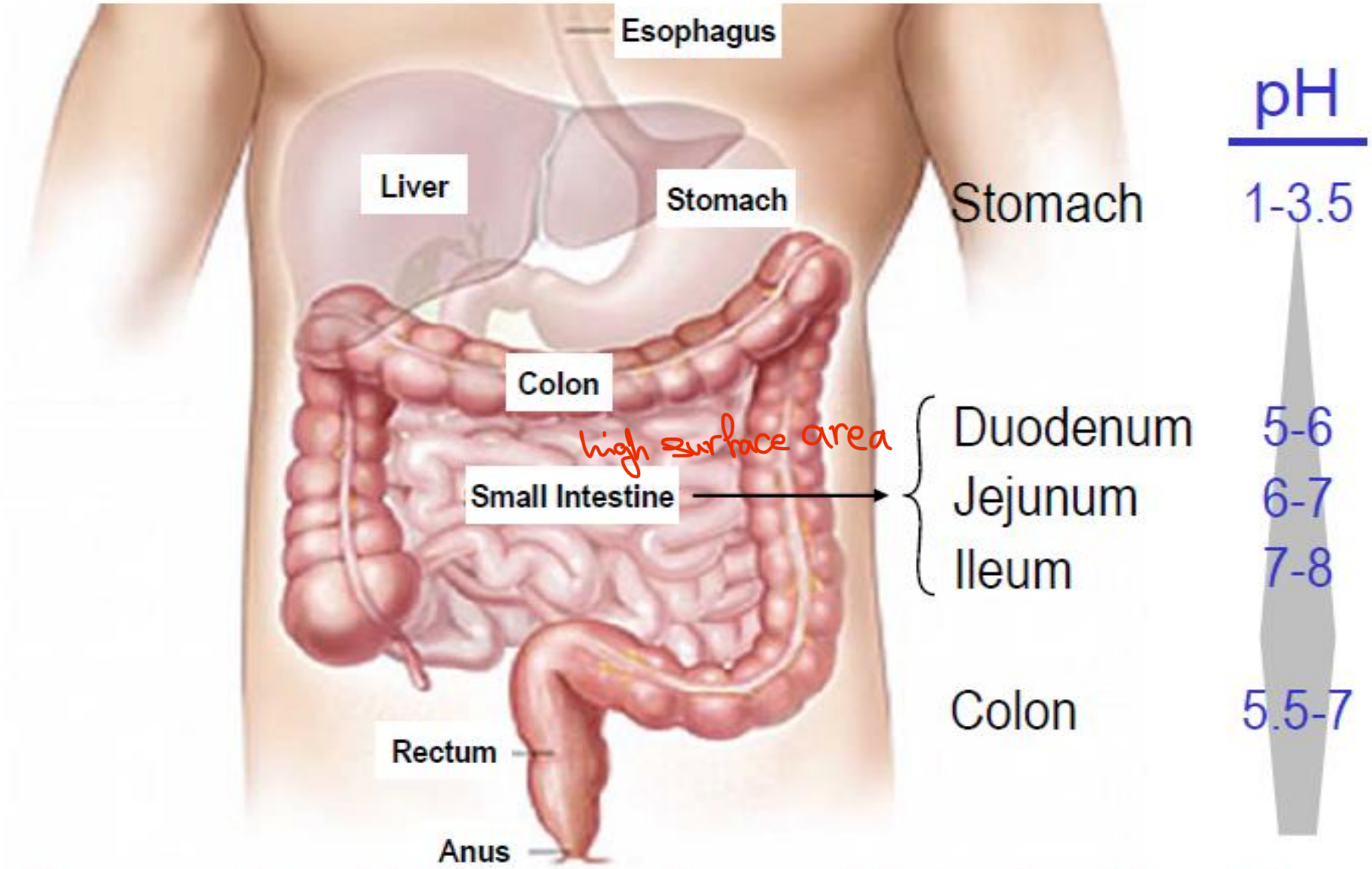

Absorbable drug at the absorption site (X_a)
Absorption
K_a (h^{-1})
Drug in the body or blood (X)
Excretion
K_u (h^{-1})
X_u (mg)
K_m (h^{-1})
Metabolism
X_m (mg)
X_{mu} (mg)

Absorption model

1. The amount (e.g. mg) of unchanged drug and/or metabolite(s) can be measured in urine
2. Drug and metabolite(s) in the body (blood, plasma or serum) are measured in concentration units (e.g. mg/mL)
3. Direct measurement of drug at the site of administration is impractical → it can be assessed indirectly

Factors affecting GIT absorption




Esophagus
Liver
Stomach
Colon
high surface area
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

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

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

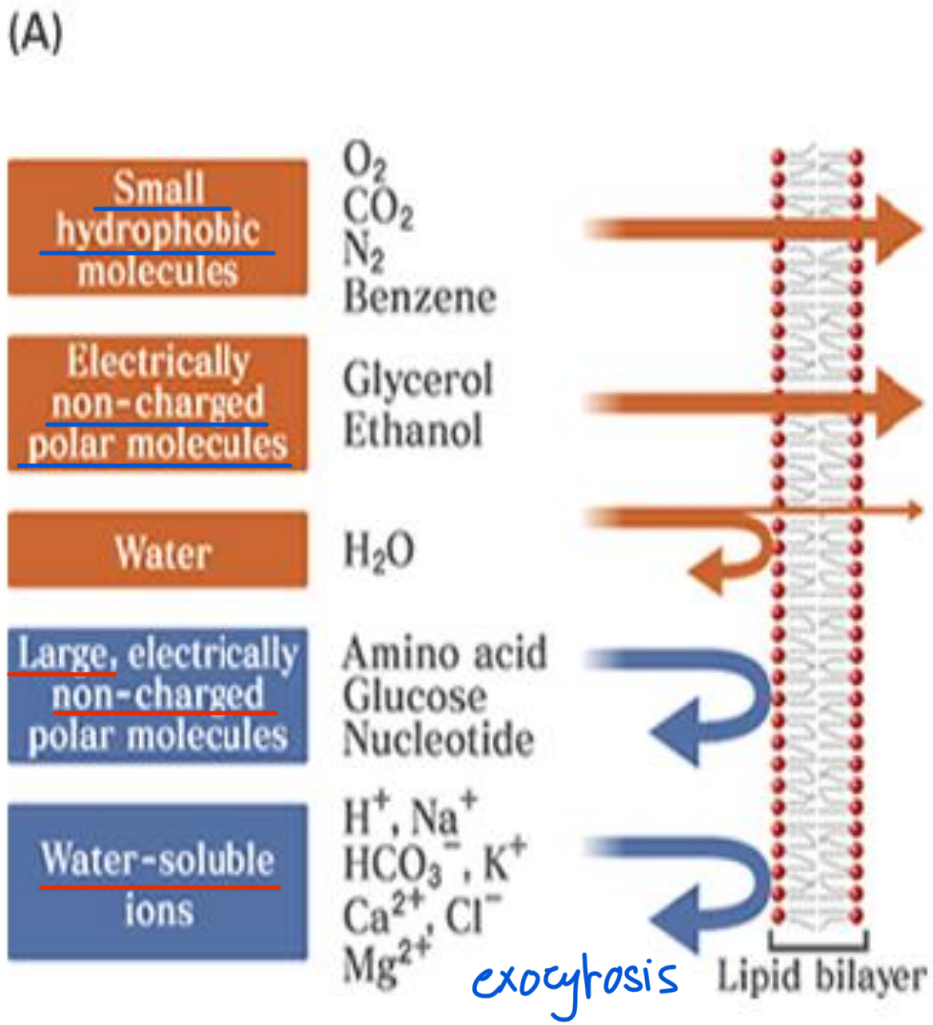
Important features of the duodenum

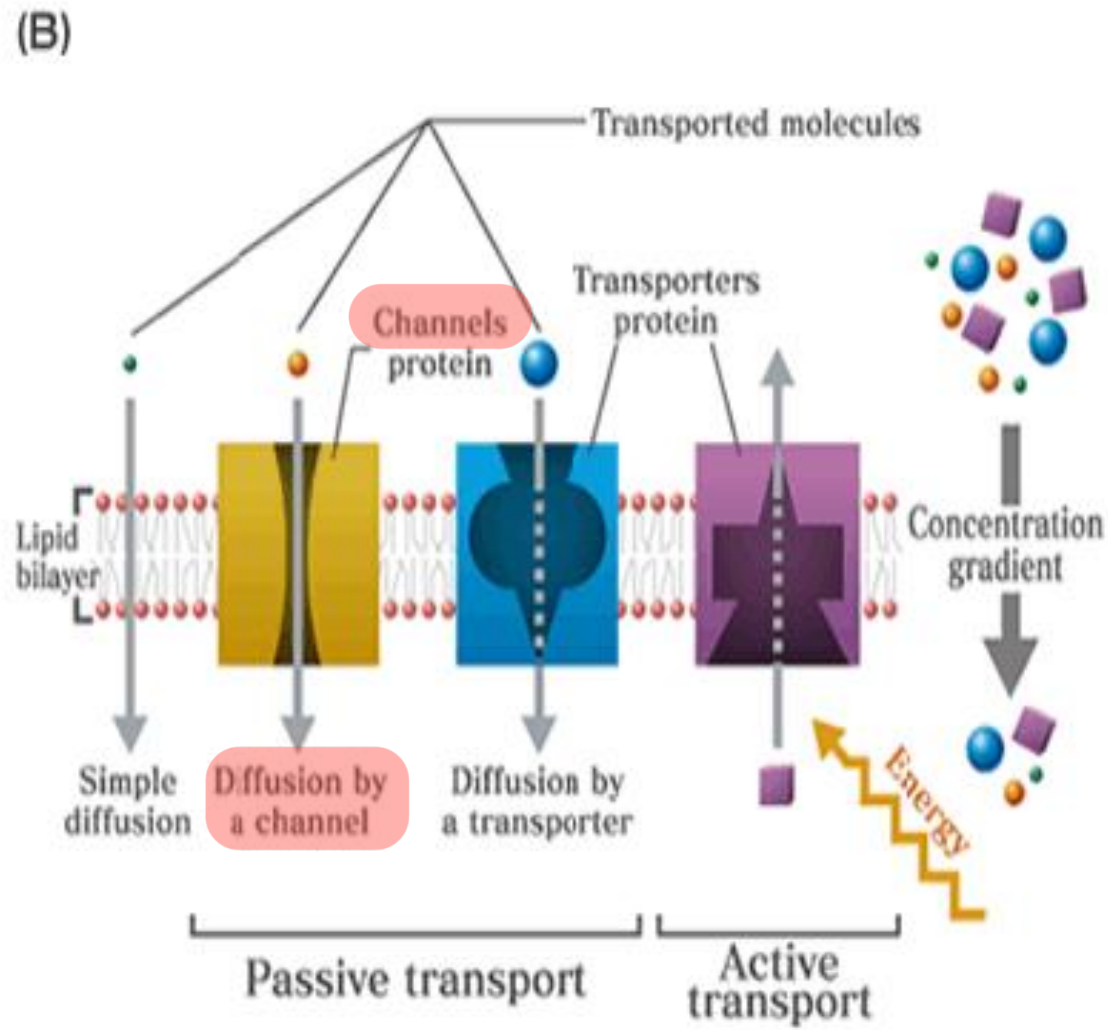
1. In the duodenum, drugs are subjected to a **drastic change of pH (pH range 5–7)**
2. Drugs will encounter **additional enzymes** that were not present earlier in the stomach
3. **The duodenum, jejunum and upper region of ileum** provide **the most efficient areas** in the GIT for drug absorption

- Surface area of the stomach vs. small intestine?

أكيد الـ intestine الها surface area أكبر، والامتصاص عندها أفضل.

"lipid bilayer theory" and "fluid mosaic model"





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

من التركيز العالي إلى التركيز القليل .

معكوس الـ surface area هو نفس مبدأ الـ thickness في كل ما كان الـ cross section area أكبر كل ما كان سرعة الدواء أبطأ .

كي تعبر المادة مع الوقت والتي تتناسب عكسياً بحيث كل ما كانت الـ cross section area أكبر كل ما كانت الـ rate of diffusion أبطأ .

Diffusion equation: Flux, J

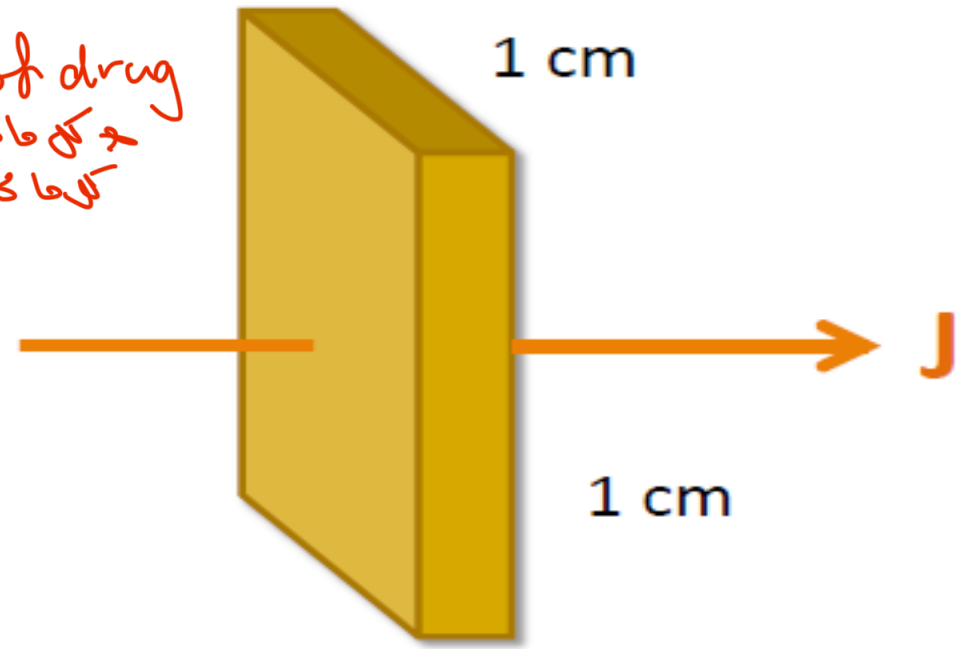
Definition of the flux (J): the rate of a solute flowing per unit cross-sectional area

rate of diffusion

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

→ difference of conc of drug

* كل ما كان فرق الـ conc أعلى
كلما كانت سرعة الـ diffusion أعلى



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)

- 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
- **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

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

Transport across the membranes

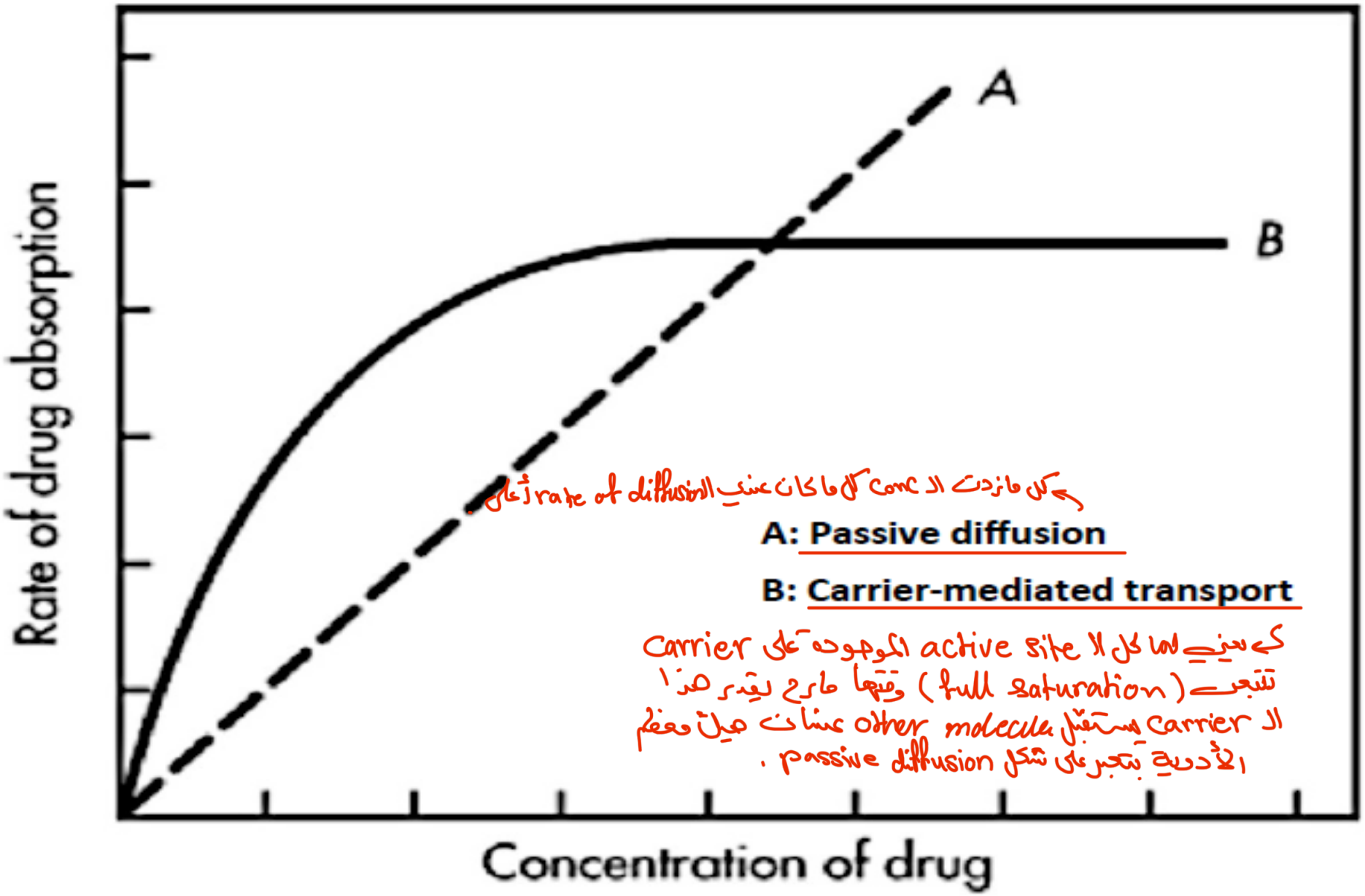
2) Carrier mediated

(i) Active transport

- Requires energy
- The process can be saturated
- Transport can proceed against a concentration gradient
- Competitive inhibition is possible

مشروح في الرسمة ←

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



كل ما زدت الـ conc كل ما كان عندي الـ rate of diffusion أعلى

كمعنى لما كل الـ active site الموجوده على الـ carrier تتشبع (full saturation) وقتها مارح يقدر هذا الـ carrier يستقبل other molecule عشان هيك معظم الأدوية بتتجرعلى شكل passive diffusion .