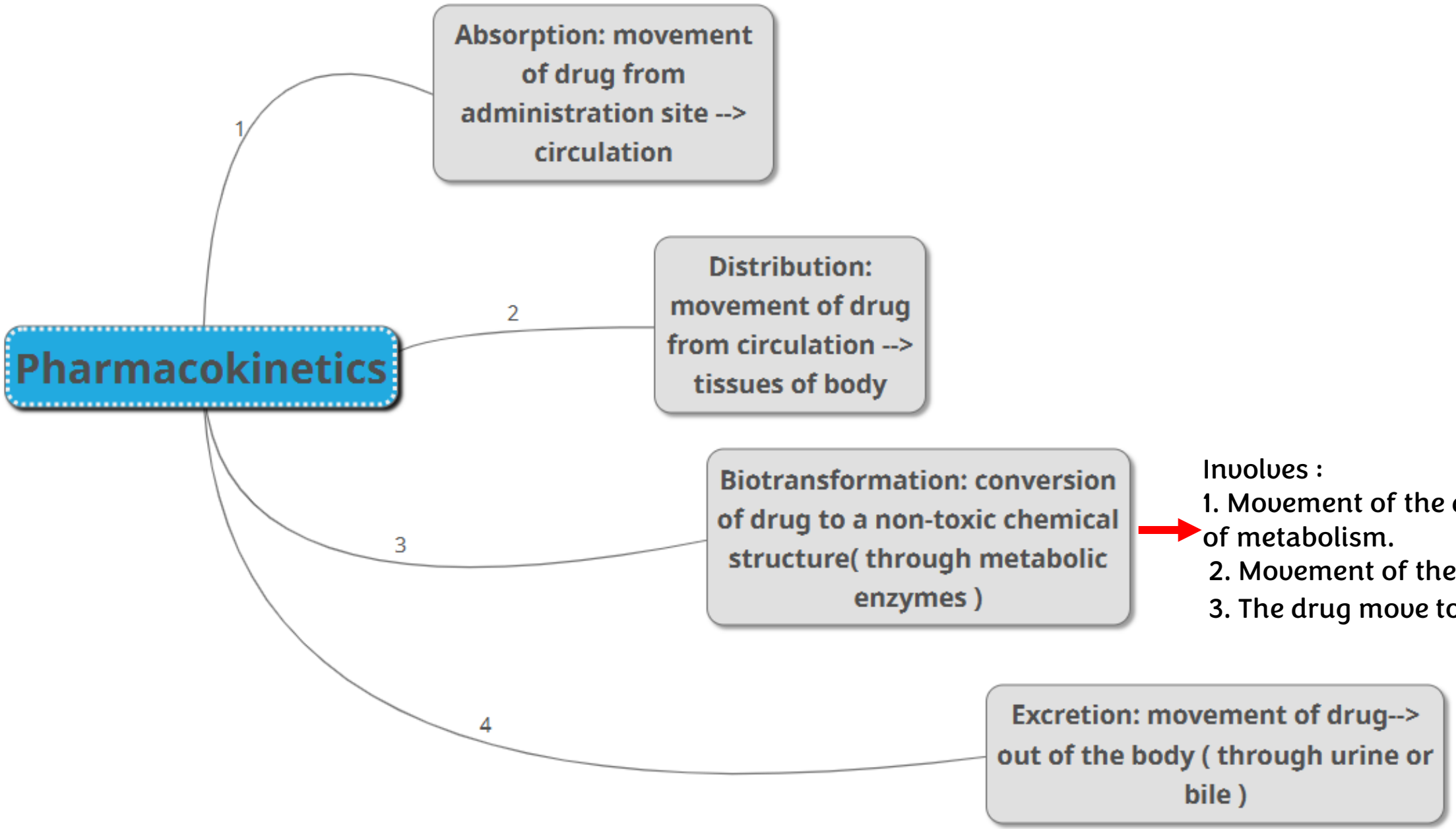
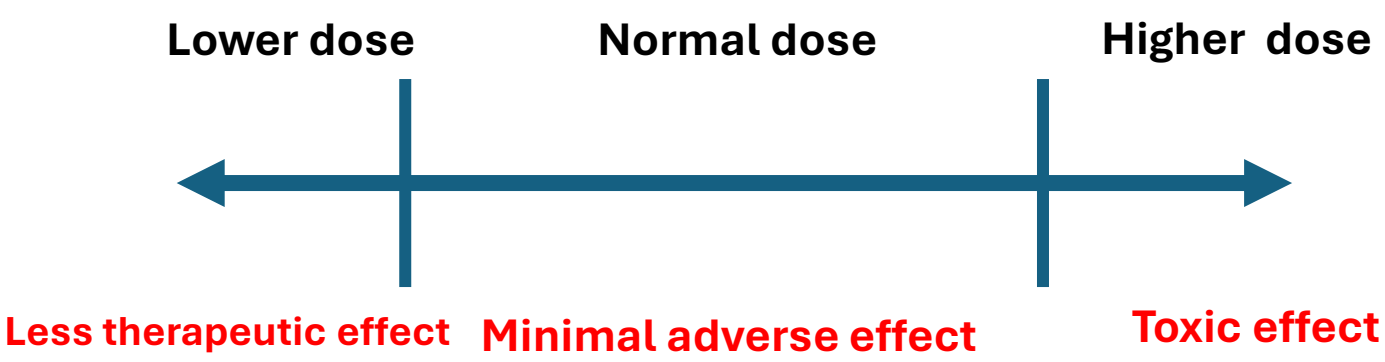
Pharmacolgy lec2+lec3 summary

Done by : Abd AL Rahman Musa

وَتَوَكَّلْ عَلَى الْحَيِّ الَّذِي لَا يَمُوتُ وَسَبِّحْ بِحَمْدِهِ ۚ
وَكَفَىٰ بِهِ بِذُنُوبِ عِبَادِهِ خَبِيرًا


Pharmacokinetics
1
Absorption: movement of drug from administration site --> circulation
2
Distribution: movement of drug from circulation --> tissues of body
3
Biotransformation: conversion of drug to a non-toxic chemical structure(through metabolic enzymes)
Involves :
1. Movement of the drug to the site of metabolism.
2. Movement of the cofactors.
3. The drug move to the enzyme.
4
Excretion: movement of drug--> out of the body (through urine or bile)



Fick's Law of Diffusion: (flux of molecules across the membrane)

$$\frac{(C1-C2)^* (\text{Area} \times \text{Permeability coefficient})}{\text{Thickness}}$$

Henderson-Hasselbalch Equation:

$$\text{Log} \frac{(\text{protonated})}{(\text{unprotonated})} = \text{pka-ph}$$

Examples on this equation can be found on page 18 at modified slides

- Notes regarding the lecture :

- Side effects : can be positive or negative
- Adverse effects : negative effects
- Therapeutic effect: the desired effect (benefit from the drug)

- The drug dose written on the prescription is the **population dose not the individual dose**

- The concentration of the drug at site of action is proportional to drug concentration in the blood (not necessary the same)

- Oral drugs have high absorption rate --> due to the large surface area of the intestine

- The lower the pH relative to the pKa ,the greater will be the fraction of the drug in the protonated form (so we can regulate the ph at specific organs in order to control a specific dose and reabsorption rate)

Drug type	weak acid	weak base
Definition :	neutral molecule that can form an anion(reversible)	neutral molecule that can form a cation (reversible)
Ionized form specs :	1) Negative 2) Water soluble 3) Non-lipid soluble 4) Unprotonated	1) Positive 2) Water soluble 3) Non-lipid soluble 4) Protonated
Acidic medium behavior	More formation of the neutral form (the lipid soluble one)	More formation of the ionized form (the non-lipid soluble)
Alkaline medium behavior	More formation of Ionized (not lipid soluble)	More formation of neutral (lipid soluble)
Excretion rate	Faster in alkaline urine(through NaHCO3) *because it will be ionized and can't pass the membrane of renal tubules - reabsorption- ,so excretion rate increases*	Faster in acidic urine (through ascorbic acid (vitamin C or NH4Cl-not good for liver failure patient - *because it will be ionized and can't pass the membrane of renal tubules - reabsorption- , so excretion rate increases*

Mechanism of Permeation of Drug	Lipid diffusion (Passive diffusion)	Aqueous diffusion	Special carriers (carrier-mediated transport): *check next slide*	Endocytosis and exocytosis
Simplified explanation :	Diffusion of the drug through the membrane	Through aqueous pores	Carrier proteins that transport important substances (peptides, amino acids, glucose…)	Endocytosis→ transport of (vitamin B12-intrinsic factor) across the wall of the gut into the blood + transport of (iron –transferrin) into developing RBCs. Exocytosis : secretion of substances from cells such as neurotransmitters and some hormones.
Permeation factors:	The more lipid soluble the better the permeation of the drug (must be sufficiently water soluble to reach the membrane)	If the drug is charged, its flux is influenced by electrical fields	-	-
Follows the concentration gradient ?	Yes	Yes	Not necessary	Not related
Extra info :	The most important mechanism.	Drugs bound to plasma proteins do not permeate aqueous pores *(because they are larger than the diameter of the pores)*	• The drug movement is driven by active transport or facilitated diffusion • Selective, saturable and inhibitable.	Exocrine secretions, some endocrine secretions, large hormones, & proteins are released by exocytosis

- Note: When we say permeation of drug molecules it means that we are taking about (ADME) not just absorption

Special carriers type :	ATP-binding cassette (ABC) family	The multidrug-resistance associated protein (MRP) transporters	The solute carrier families (SLC)
Type/ ATP dependent :	Efflux pumps **uses ATP**	Another subgroup of the ABC family that **requires ATP**	Facilitated diffusion that uses ion gradients (**not ATP)** for transport.
Function:	Prevents drug entry by transporting drugs out of cells, contributing to drug resistance.	Helps remove drugs and metabolites via bile (for larger molecules) or urine.	Assists in moving neurotransmitters across nerve membranes, helping in neural signaling.
Example :	**P-glycoprotein (MDR1) – found in bacteria also-**	-	In nerve endings, neurotransmitters like catecholamines are reabsorbed through SLCs after signaling.
Extra info :	-	**Cancer Resistance**: These transporters can block drugs from reaching cancer cells, reducing their effectiveness in treatment.	-

Barriers Against Drug Permeation & Transport

Tight junctions +absence of pores

↓

Between endothelial cells

↓

No diffusion occurs across the membrane

Thick basement membrane

↓

Beneath he endothelial cells

↓

Hinders the passage of drugs

Connective tissue

↓

Around the endothelial cells

↓

Hinders the passage of drugs
Example: astrocytes in the brain

Drug export pumps

↓

present in the brain's choroid plexus+ intestine+ other organs

↓

When the drug enter the cell it expels it through efflux mechanisms

Intracellular and extracellular enzymes

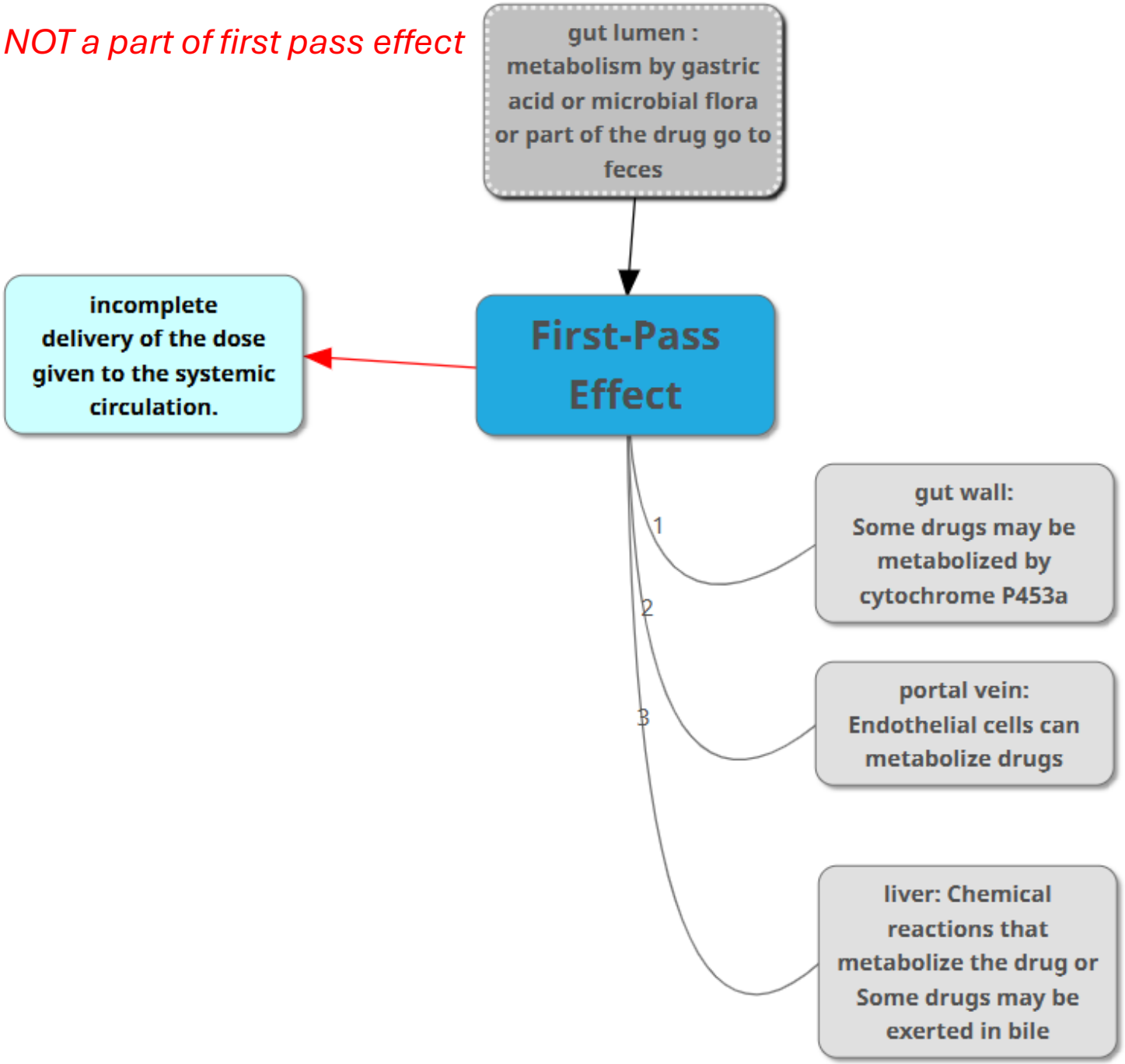
↓

metabolize drugs

↓

These 3 are all crucial factors in maintaining the integrity of the blood-brain barrier (BBB)

NOT a part of first pass effect



Notes regarding the lecture :

- Other names for first pass effect
- 1)first-pass metabolism --> When referring to first pass metabolism we are excluding excretion (because it's only metabolized)
- 2) pre-systemic elimination --> not including metabolism by microbial flora

- The oral dose is usually higher than intravenous dose for drugs due to first pass effect

- Oral and IV drug administration produce different metabolites. Orally, the drug passes through the intestines and liver, leading to unique metabolites. With IV, the drug enters the bloodstream directly, resulting in different metabolite concentrations.

- If the patient is having liver cirrhosis and there is shunting of blood by-passing the portal circulation giving a larger dose orally will lead to substantial increases in concentration of the drug and drug toxicity

- How can we compensate the loss from the first pass effect ?
- 1) Increasing the oral dose
- 2) Give the drug through IV.

Bioavailability:

It is the fraction of the unchanged active drug reaching the systemic circulation

It is equal to “1” or 100% following intravenous drug administration.

After oral administration, bioavailability may be less than 1, because of

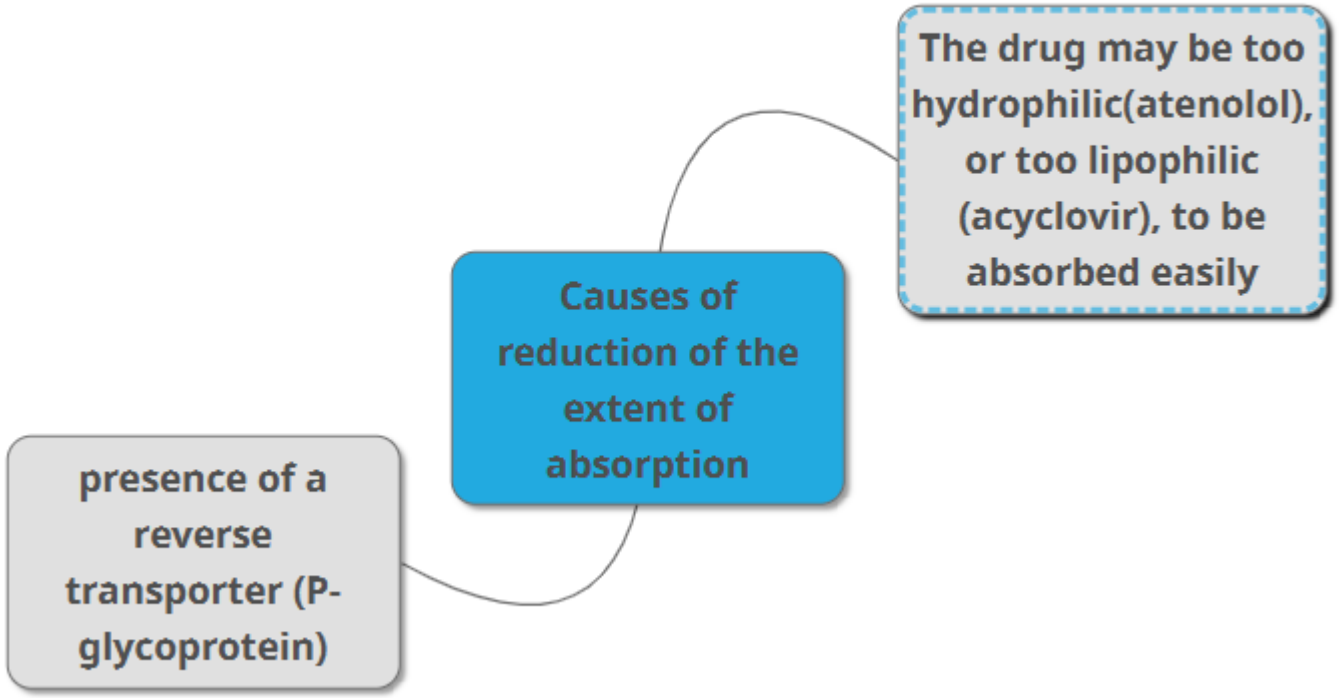
: 1. First-pass effect.
2. Incomplete absorption.
3. Incomplete disintegration and dissolution. →
4. Destruction of drug within GIT lumen by gastric acid, bacteria, ..etc.
5. Faulty manufacturing of the dosage form.
6. Enterhepatic cycling.

1.Disintegration: The solid dosage form (like tablets) breaks down into smaller particles in the intestine. If this doesn’t occur, bioavailability is reduced.

2.Dissolution: The disintegrated particles dissolve in solution, making them ready for absorption.

3.Absorption: The dissolved drug is absorbed into systemic circulation.

Note: *Liquid formulations (like syrups or suspensions) bypass disintegration and dissolution, as they are already in solution and ready for absorption*.



- **Grapefruit juice** may inhibits the reverse transporter and inhibits presystemic elimination of some drugs --> increases drug's bioavailability.

Effect of First-Pass Effect on bioavailability

Bioavailability (F) = 1-ER

Or

F =(f) . (1- ER)

f: fraction absorbed (not always the absorption is complete)

example :

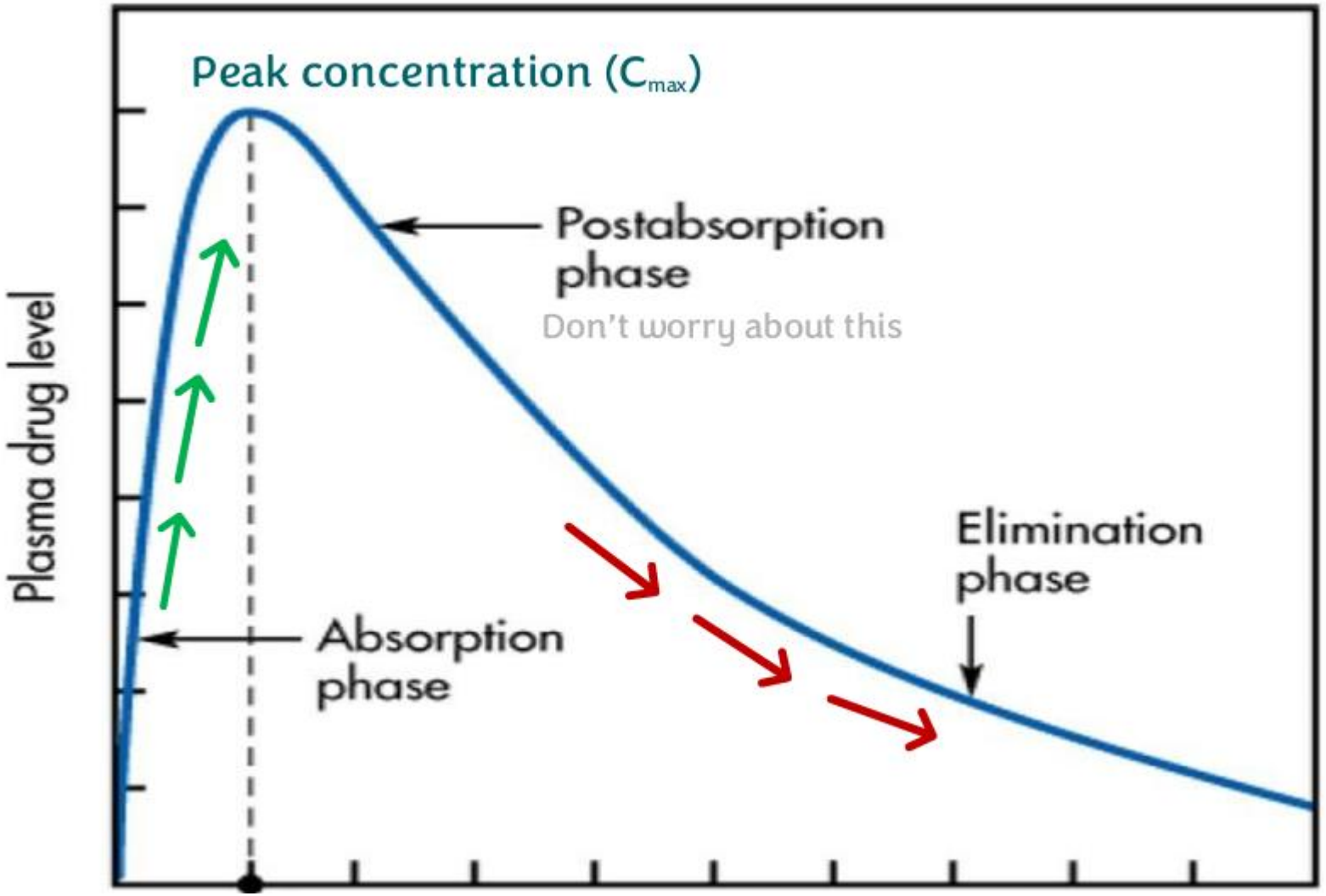
Morphine is completely absorbed but its ER is 0.67, F = 1 – 0.67 = 0.33 = 33%

Bioavailability isn't constant due to differences among individuals in

1) Hepatic drug flow

2Hepatic drug metabolism (difference in enzymes)

Absorption phase
absorption rate is faster than elimination rate.



Elimination phase
Elimination rate is faster than absorption rate

- Peak concentration is when Absorption rate = Elimination rate
- The peak concentration of the dose should be between MTC & MEC
- above MTC = Toxic reaction, Below MEC = no therapeutic effect
- Alternative drugs can differ in the time taken to reach the peak

For more information refer to slide 23,24 of modified slides (lec-3)