Mechanisms of Permeation of Drug Molecules

C. The solute carrier families (SLC):

- **They do not bind ATP but use ion gradients for transport energy.**
- **They are important in the transport or the uptake of neurotransmitters across nerve ending membranes.**

* Energy provided not by ATP, but ion concentration gradient
* Energy is released by re-entry of ions into cell
* Mediated by MRP and Na^+ channels

Mechanisms of Permeation of Drug Molecules

4. **Endocytosis and exocytosis:**

- **Endocytosis is responsible for transport of vitamin B_{12} complexed with the intrinsic factor across the wall of the gut into the blood, and iron associated with transferrin into RBCs.**

Active Transport

- **Exocytosis is responsible for secretion of many substances from cells such as neurotransmitters and some hormones.**

Mechanisms of Permeation of Drug Molecules

- ***These principles of permeation of drug molecules apply to drug absorption, distribution and elimination.***
- ***These processes determine how rapidly and for how long the drug will appear in the target organ, the site of action, and organs of elimination.***

Metabolism

Excretion

Drug Disposition:

~~A~~ D M E

absorption

distribution

metabolism

excretion

(Everything except Absorption)

هاي الخلاصة

Barriers Against Drug Permeation & Transport

1. **Tight junctions between endothelial cells and absence of pores.**
2. **The presence of thick basement membrane at which endothelial cells lie.**
3. **The presence of connective tissue cells around endothelial cells (such as astrocytes in the brain).**
4. **The presence of drug export pumps.**
5. **The presence of intracellular and extracellular enzymes that metabolize drugs.**

prevent drugs from reaching brain

placenta ⇒ placental barrier

Efflux proteins

in placenta, enzymes metabolize before reaching fetal circulation

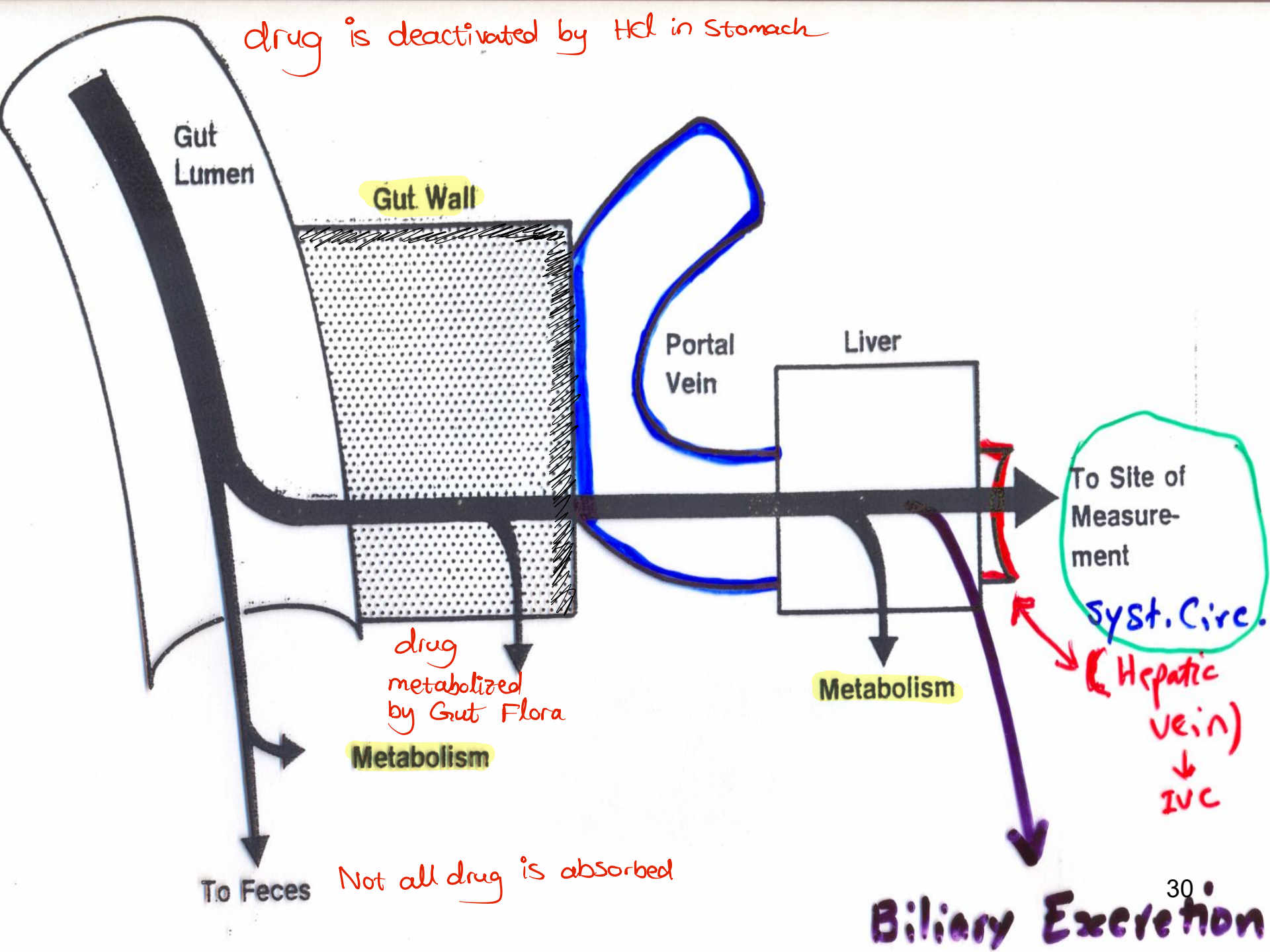
First-Pass Effect

Affects most drugs but not all.

- Drugs absorbed from the GIT must pass through the gut wall and portal vein to the liver before reaching the systemic circulation.
- The drug may be metabolized in the gut wall, portal vein, and the liver prior to entry to the systemic circulation.
- Or, it may get excreted by the liver through bile.

First-Pass Effect

- **This will lead to incomplete delivery of the dose given to the systemic circulation.**
- **This process is called "first-pass effect" or "first-pass metabolism" or "pre-systemic elimination".**


drug is deactivated by HCl in Stomach
Gut Lumen
Gut Wall
Portal Vein
Liver
To Site of Measure-ment
Syst. Circ.
(Hepatic vein)
IVC
drug metabolized by Gut Flora
Metabolism
Metabolism
To Feces
Not all drug is absorbed
Biliary Excretion

First-Pass Effect

Another name : Pre-Systemic Elimination

Applicable only for drugs which experience first pass effect

- **Therapeutic blood concentration may still be reached by using larger dose.**
- **Therefore, the oral dose is usually higher than intravenous dose for such drugs.**
- **Also the concentration of drug metabolites after oral administration will be higher than after intravenous administration (why?).**

(1) Drugs given orally ⟹ All drug passes through liver ⟶ Metabolized

(2) Drugs given Intravenously ⟹ liver acts as any other organ (since [drug] reaching liver is much lower than in oral route, due to it being already absorbed by other tissues)

Drugs which have first-pass effect have very large inter-personal variation

First-Pass Effect

Scarring (Fibrosis)

- **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.**

Scarring ⟶ less Metabolic Enzymes working ⟶ Drugs not metabolized (broken down) ∴ Drugs build up.

Bioavailability

- **It is the fraction of the unchanged active drug reaching the systemic circulation, following drug administration; irrespective of the route.**
- **It is equal to "1" or 100% following intravenous drug administration.**
- **After oral administration, bioavailability may be less than 1, because of:**

explained below.

Bioavailability

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.

Dosage form

↓

Disintegration (Low Intestinal Wall)

↓

Dissolution

↓ ***absorption***

Drug in the systemic circulation

Any problem in Disintegration or Dissolution causes ↓ in bioavailability

Bioavailability

- **The area under the blood concentration *versus* time curve (AUC) is a common measure of the extent of bioavailability.**
- **Causes of reduction of the extent of absorption:**

usually done by computers

Bioavailability

1. **The drug may be too hydrophilic (atenolol), or too lipophilic (acyclovir), to be absorbed easily.** there is such a thing as too hydrophilic & too hydrophobic
- **Too hydrophilic drugs can NOT cross lipid membranes easily.**
- **Too lipophilic drugs are NOT water soluble enough to reach the membrane (to cross the water layer adjacent to the cell).**

Bioavailability

2. **Drugs may NOT be absorbed because of the presence of a reverse transporter (P-glycoprotein) that pumps the drug out of the gut wall cells back into the gut lumen.**

Efflux of drug

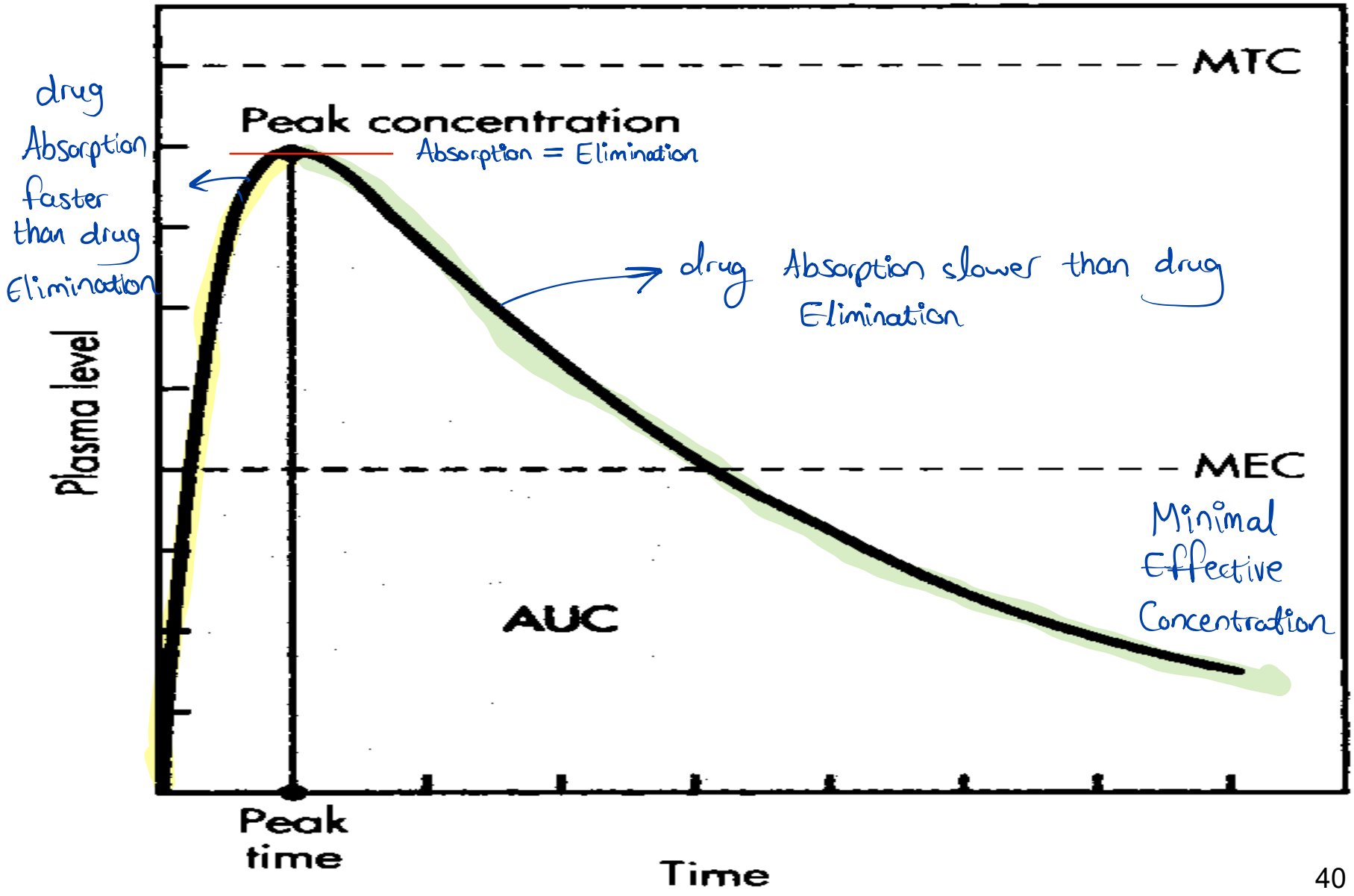
Bioavailability

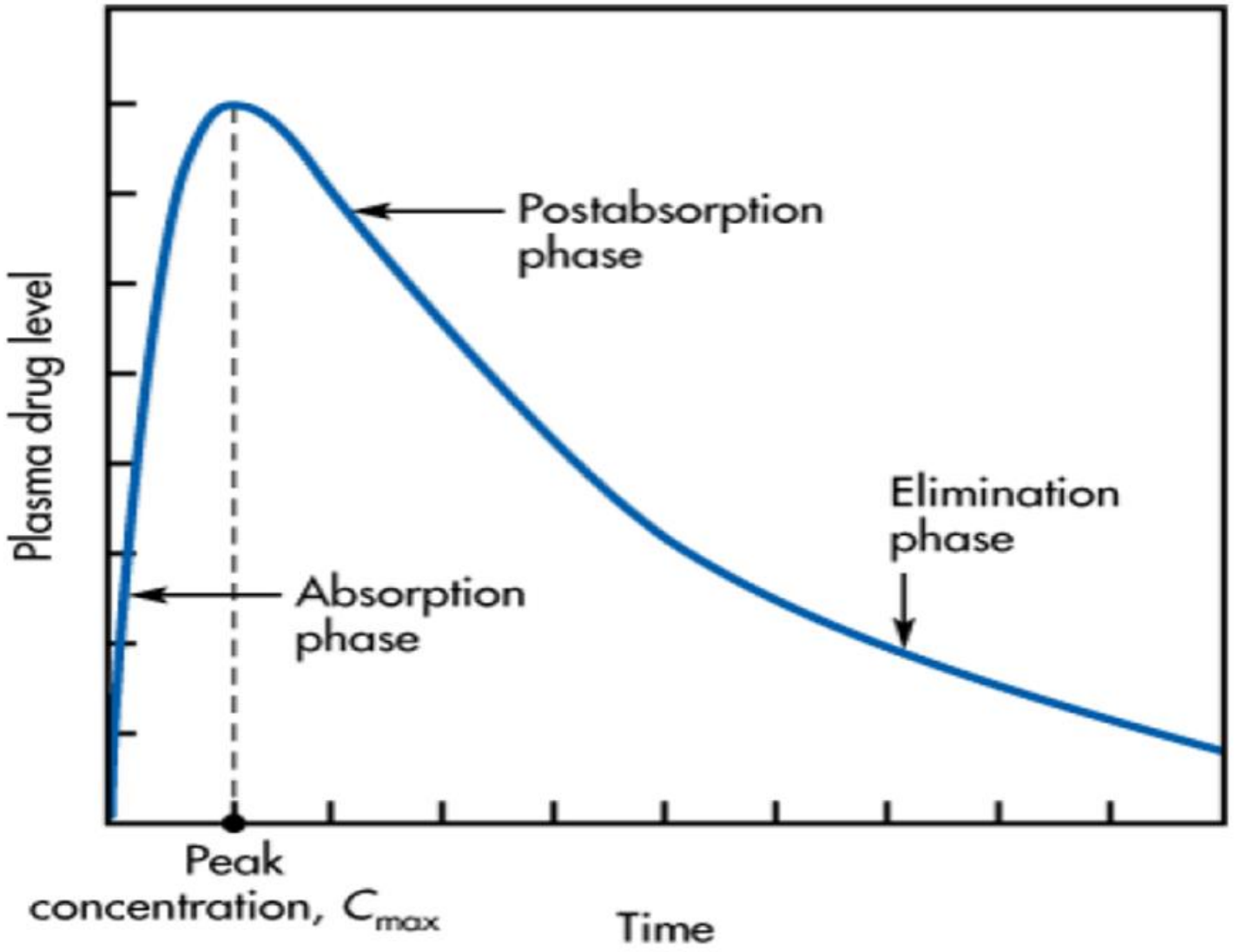
- **Inhibition of the reverse transporter by the use of some drugs and grapefruit juice, may be associated with substantial increase in drug absorption and thus bioavailability.**
- **Grapefruit juice also inhibits presystemic elimination of some drugs, and thus, increases their bioavailability.**

Dangerous in patients taking many meds ⟹ why?

as it inhibits Reverse Transporter (P-glycoprotein)

↑ absorption ↑ toxicity


MTC
drug Absorption faster than drug Elimination
Peak concentration
Absorption = Elimination
drug Absorption slower than drug Elimination
Plasma level
MEC
Minimal Effective Concentration
AUC
Peak time
Time



Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

Effect of First-Pass Effect on bioavailability

- **The effect of first-pass hepatic elimination on bioavailability is expressed as the extraction ratio (ER):**
- **Bioavailability (F) = 1-ER.**
- **If absorption is not complete, bioavailability (F) can be predicted from the extent of absorption (f) and ER.**

$$F = (f) \,.\, (1 - ER)$$

$$F = f \times (1 - ER)$$

Effect of First-Pass Effect on bioavailability

- **A drug like morphine is completely absorbed but its ER is 0.67, so its bioavailability is 33%.**
- **Drugs with high extraction ratio exhibit interindividual differences in bioavailability and drug concentration, because of differences among individuals in hepatic blood flow and hepatic drug metabolism.**

Avg. → high interpersonal variation

↑ ER ⇒ Alter Dose

Bioequivalence

- **This term is used to compare the rate and extent of absorption of different formulations (or dosage forms) of the same active drug.**
- **The extent of absorption is measured by AUC, and the rate is assessed by C_{max} (peak concentration) and T_{max} (time to peak concentration).**