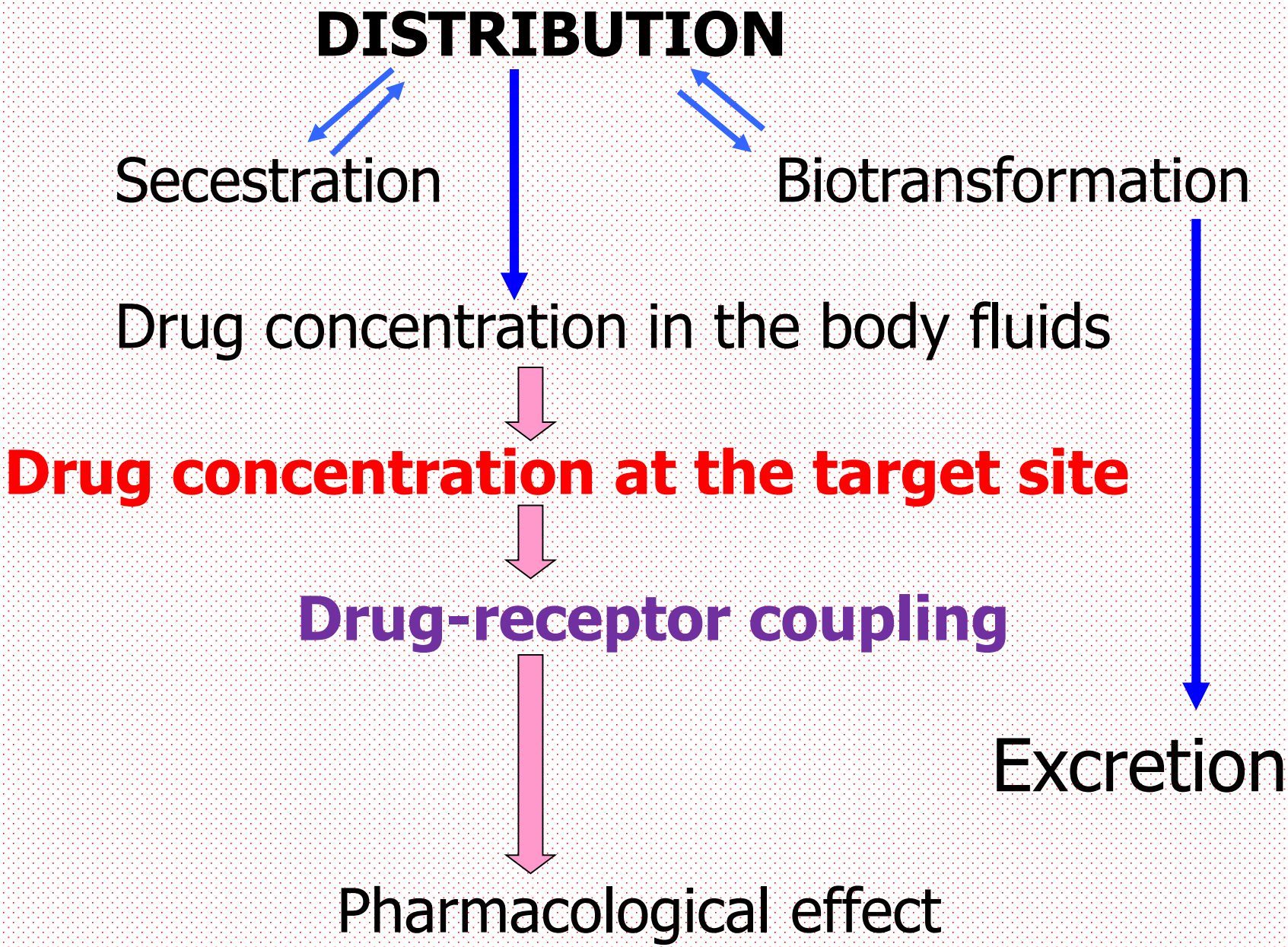
Dose (solid dosage form)

Disintegration
Dissolution

Absorption

Distribution


DISTRIBUTION
Secestration
Biotransformation
Drug concentration in the body fluids
Drug concentration at the target site
Drug-receptor coupling
Excretion
Pharmacological effect

ADME

- Absorption: Transfer of drug from site of administration to systemic circulation.
- Distribution: Transfer of drug from systemic circulation to tissues.
- Metabolism: Alteration of drug to increase excretion from the body.
- Excretion: Drug movement out of the body.

ABSORPTION
DISTRIBUTION
METABOLISM
ELIMINATION (EXCRETION)

PHARMACOKINETICS

PHARMACOKINETICS

- Pharmacokinetics is a subdivision of pharmacology that studies the processes of absorption, distribution, metabolism and excretion of drugs in the body.

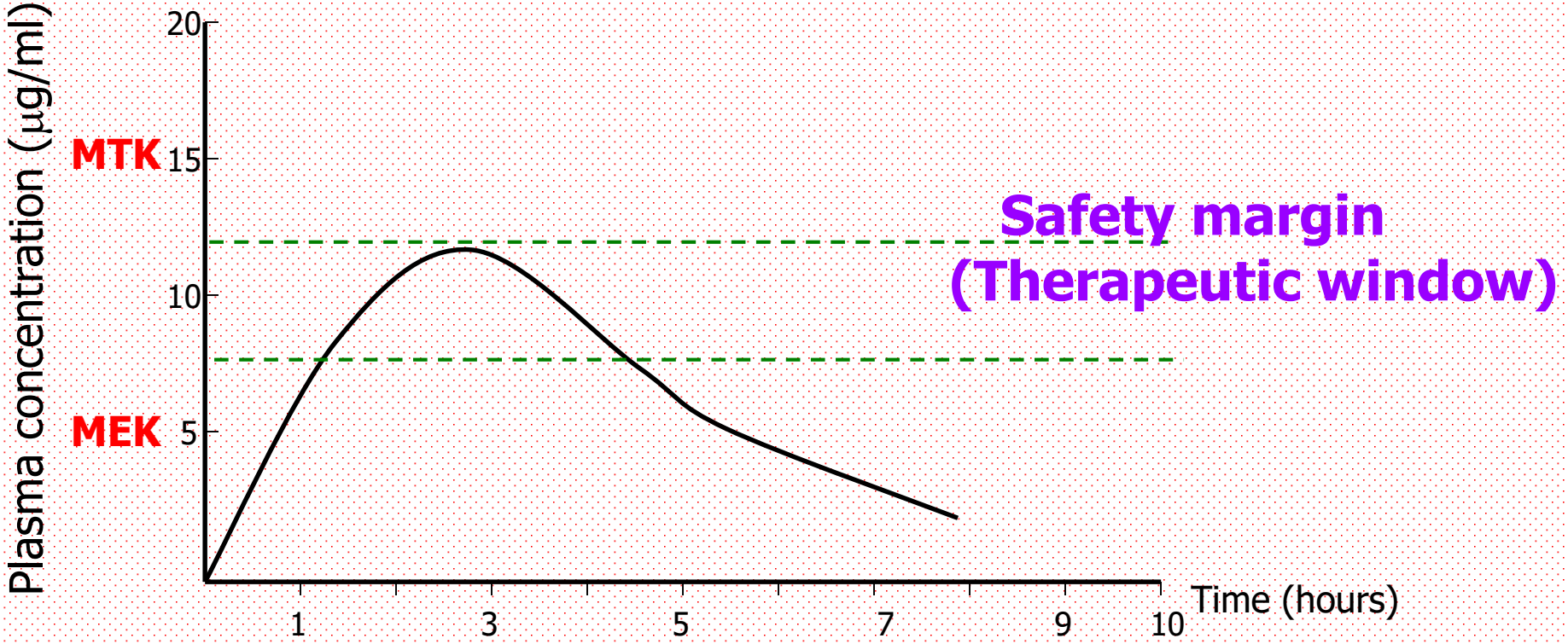
Pharmacokinetics

- How the concentration of drugs in the body changes over time.

- Determining the dosage scheme which is required for the patients.

Therapeutic Range

•Medicines are expected to be above a certain threshold level in order to be able to see the expected effects of the tissues in which they are active.



Optimal treatment will be enabled, if the concentration of the drug remains within the "therapeutic range".

Absorption of the Drugs

Sites of absorption through the GI tract

- Mouth
- Stomach
- Small intestine
- Large intestine

Absorption of the Drugs

Biological Membranes

- Membranes are formed in the structure of lipoproteins consisting of two rows of molecules.
- It has a porous structure.
- Permeability of membrane is selective. It is a semi-permeable membrane.

TRANSPORT MECHANISMS

- Passive Diffusion
- Active Transport
- Facilitated Diffusion
- Endocytosis

Passive Diffusion (Passive Transport)

- Passive transport is a movement of ions and other atomic or molecular substances across cell membranes without need of energy input.
- Passive diffusion does not require an energy source.
- Molecules move from high concentration to low concentration until equilibrium is reached.

- This mechanism is responsible for the passage of many lipid-soluble compounds through the membranes.
- The passage of the substances through the membranes is achieved by the differences in the density between the sides.

FACILITATED DIFFUSION

- Carrier-mediated transport from higher to lower concentration without energy and translocation of the substrates in the direction of electrochemical gradient.
- The substrate is transported only in the direction of the concentration gradient, not against the concentration gradient.

ACTIVE TRANSPORT

- The drugs move across from lower concentration to higher concentration via carriers or transporters.
- Active transport is an energy dependent process.
- Depending on the driving force, the active transport is subdivided into primary or secondary active transport.

ENDOCYTOSIS

- It is a biomechanical process.
- Large molecules and colloid particles such as lipid soluble vitamins (A, D, E, K), lipids and fatty acids are carried by this process.

FACTORS AFFECTING ABSORPTION

1- PHYSICOCHEMICAL FACTORS RELATED TO DRUGS

Molecular size

- In general, small molecule compounds pass membranes more easily.

Particle size

- When the solid drug particles are small, the total surface area of the drug in the media fluids is large, thus the dissolution rate is accelerated.

Lipid solubility of the molecule

- When the solubility of the non-ionized form of the drug molecule in the lipids is high, it passes easily the biological membranes in lipid structure.

- The degree of lipophilicity of the drug is expressed by the oil / water partition coefficient (O / W).
- When the lipophilicity of the drug is high, oil/water partition coefficient is also high.

- If oil/water partition coefficient of the active substance is low, the drug can be prepared as a pro-drug with greater lipid solubility when new drug is being developed.

Pro-Drug

- A chemically modified form of a drug that is prepared for preventing it from breaking down in the gastro-intestinal tract, and also increasing the solubility and thus absorption
- Pro-drugs do not have pharmacological effects outside the body.

Pro-Drug

- Chloramphenicol palmitate is a prodrug which is designed to mask the unpleasant taste of chloramphenicol.

Chloramphenicol palmitate → Chloramphenicol

Ionisation of drugs

- Most of the drugs have weak acidic or weak basic structure as chemically so they possess chemical groups that is ionisable.

- The dissociation constant (pKa) of the drug and pH of the medium determines the ratio of ionised/non-ionised form of the drug in the liquid milieu.

Ionisation of drugs

Ionisation of the weak base:

$R\text{-}NH_2 + H^+ \leftrightarrow \mathbf{R\text{-}NH_3}$

Ionisation of the weak acid:

$\mathbf{R\text{-}COOH} \leftrightarrow R\text{-}COO^- + H^+$

- Ionisation is important for the absorption of drugs from the membranes.
- Drugs can pass through the membranes in a non-ionized form.

- The drugs in the weak acidic character are more non-ionized form in acidic environment and are more easily absorbed.
- The drugs in the weak basic character are more ionized form in acidic environment and their absorption are very poor.

Concentration of drugs

- The concentration at which the drug is applied affects the rate of absorption.
- Absorption is accelerated as the dissolved drug concentration increases *(Fick's Law).*

Salts

- The solubility of the salts of the compounds is often different from that of the main compound.

- Sodium and potassium salts of weak acids and salts formed by weak bases with HCl and other strong acids are generally more soluble and absorbed faster than main compound.

- Naproxen – Naproxen sodium
- Diclofenac – Diclofenac potassium
- Irinotecan – Irinotecan HCl

FACTORS RELATED TO THE PHARMACEUTICAL FORM

- Bioavailability of oral dosage forms:

solution> emulsion> suspension> capsule> tablet> coated tablet

PHYSIOLOGICAL FACTORS RELATED TO THE APPLICATION AREA

Surface area where the medicine is applied

- The absorption rate of drugs increases as the surface area where the drug is applied is increased if the drug is absorbed by passive diffusion *(Fick's Law)*.
- The drugs are mostly absorbed from the intestine as compared to stomach since the total surface area of the intestine is higher than stomach.

Permeability of the membrane

- If the permeability of the membrane is higher, than e diffusion is faster.
- The skin has limited permeability because of stratum corneum layer, but drugs pass through the mucous membranes very rapidly.

Blood flow at the site of application

- When the blood flow is fast, the absorbed drug rapidly pass to the circulation and is so quickly removed from the area.

- The concentration difference on both sides of the membrane remains high until significant portion of the drug is absorbed.

- Absorption accelerates!

Blood flow at the site of application

- When the tissue blood flow decreases in the cases of shock, edema, vascular occlusion and congestive heart failure, the absorption of the drugs also decreases.
- While local anesthetics are injected into the tissue, vasoconstrictor agent is added into the solution.
- Ultracaine® D-S amp.
  Articain 40 mg + epinephrine 0.006 mg / 1 ml

Structure of the gastrointestinal tract

- In practice it is assumed that there is no absorption from the stomach.

  The reasons for this are:

- Narrow mucosal surface area
- Transit time of the drugs are short (~1 hour).
- Alcohol and salicylates may be absorbed if they remanin long enough in the stomach.

Structure of the gastrointestinal tract

- The most important part of the drug absorption is the small intestine.
- The absorption area is very wide due to the villus on the surface (~ 200 m^2).
- There are active transport mechanisms for the absorption of drugs.
- Transit time is long (~ 4-5 hours).

Structure of the gastrointestinal tract

- In practice it is assumed that there is no absorption from the large intestine.
- Due to the small amount of mucosal folds, the surface area is reduced.
- Only the drugs which are absorbed after hydrolysis by intestinal bacteria such as sulfasalazine are absorbed sufficiently.

pH of the gastrointestinal tract

- pH
  Stomach: 1-2
  Small intestine: 5-7
  Large intestine: 7-8

- In particular, pH is important for the drugs in solid pharmaceutical form since they need to be disintegrated and dissolved in the milieu prior to absorption.

Gastric emptying

- Conditions that accelerate gastric emptying, also accelerate the absorption, while retardation decreases absorption.

- Drugs which are disrupted in the stomach acid environment, are not required to remain in the stomach for a long time.

Factors Affecting Stomach Emptying

- Fatty foods↓
- Foods with high viscosity ↓
- Mental depression ↓
- Severe pain ↓
- Stomach ulcer↓
- Pyloric stenosis ↓
- Crohn's disease ↓
- Hypothyroidism ↓
- Anticholinergics ↓
- Opioid analgesics ↓
- Prokinetic drugs ↑
- Hyperthyroidism ↑
- Anxiety ↑

Motility of the gastrointestinal tract

- In the case of constipation, the peristaltic movements of the gut and amount of fluid decrease. This may cause reduction in the absorption.

- In the case of diarrhea, the passage of the drugs in the intestine increase and thus bioavailability of drugs may decrease.

Effect of nutrients on drug absorption

- In general, the foods affect drug absorption negatively in the gut.

- Fasting condition: 30 min before meal (breakfast/lunch/dinner) or 2h after meal
- Fed condition: Taking drugs just after meal or during meal.

Effect of nutrients on drug absorption

- If drug cause irritation in the digestive tract, it should be taken together with nutrients.
- The drugs should be taken with one glass of water.

Nutrients,

- Delay stomach emptying.
- Increase the pH of the stomach.
- Increase or decrease the secretion of the stomach.

Effect of nutrients on drug absorption

- Taking tetracycline together with milk or dairy products prevents the absorption of the drug by chelating with calcium ion.
- Foods reduces the effects of some antibiotics such as Ampicillin
  Erithromycine
  Rifampicin

FIRST PASS EFFECT (Presystemic Elimination)

- **First-pass effect** or also known as **first-pass metabolism** or **presystemic elimination** is when an administered drug passes the intestinal wall and enters the liver and undergoes extensive biotransformation and thus decreasing the concentration rapidly before it reaches its target.
  - First-pass metabolism within the gut wall
  - Presystemic drug metabolism in the liver

Factors that play a role in the first pass effect

- Acidic milieu and enzymes in the gastrointestinal lumen
- Gut microbial flora
- Passing through intestinal wall (metabolism and secretion)
- Passing through liver

Insulin

- Insulin which is in the structure of the polypeptide breaks down in the intestine with the effect of proteolytic enzymes and therefore insulin and other polypeptide hormones are not used orally.

Acidic milieu of the stomach

Some drugs are unstable in the stomach (acidic)

- Penicillin G
- Methicillin
- Piperacillin
- Levodopa (increased destruction when gastric emptying is delayed)

- Drug metabolizing enzymes in the GI tract.
- Drug efflux proteins in the GI tract.

Enzymatic metabolism in the intestine

Some drugs are metabolized by the drug metabolizing enzymes during the absorption and lose their effects.

- Morphine
- Terbutaline
- Isoproterenol
- Contraceptive steroids

- Some drugs are thrown into the lumen through the efflux proteins and their bioavailability decrease.
- Digoxin
- Verapamil
- Talinolol
- Paclitaxel
- Dexamethasone
- Grepafloxacine

Propranolol (beta receptor blocker)

- Absorption : close to 100 %
- Bioavailability : 10 %

- Parenteral dose : 1-3 mg
- Oral dose : 20-40 mg

Generally, highly lipophilic drugs undergo a high rate of first pass effect.

- Propranolol
- Isosorbide dinitrate
- Sex hormones
- Opioids (Morphine)
- Lidocaine
- Tricyclic antidepressants (Amitriptyline)

First pass effect in liver

- Some of these drugs are only used parenterally.
- Oral dosage can be adjusted.
- The compounds administered in the form of **Pro-drug** may be activated during the first pass or may be converted into an active metabolite of the active drug.

- Prednison → Prednisolon
- Primidone → Phenobarbital

ENTEROHEPATIC CIRCULATION

- **Enterohepatic circulation** involves substances that are metabolized or non-metabolized in the liver, excreted into the bile, and passed into the intestinal lumen; there they are reabsorbed across the intestinal mucosa and returned to the liver via portal **circulation**.
- This cycling continues to decrease gradually until the drug is completely excreted from the body.

ENTEROHEPATIC CIRCULATION

- Enterohepatic recycling (EHR) is a feedback mechanism resulting from the combined roles of the liver and intestine.
- EHR begins with drug absorption across the intestine into the portal circulation, followed by uptake into the hepatocytes.
- Next, drug and or conjugated metabolites are secreted into the bile and returned to the intestine, where drug can be reabsorbed into the circulation, in some cases after deconjugation in the GI tract.
- A number of drugs are secreted by the liver into bile, and are therefore capable of undergoing enterohepatic recycling. These include antibiotics, NSAIDS, hormones, opioids, digoxin, and warfarin.

Drugs go to enterohepatic circulation

- Chlorpromazine
- Carbamazepine
- Steroid hormones
- Morphine
- Digitoxin
- Cephalosporins