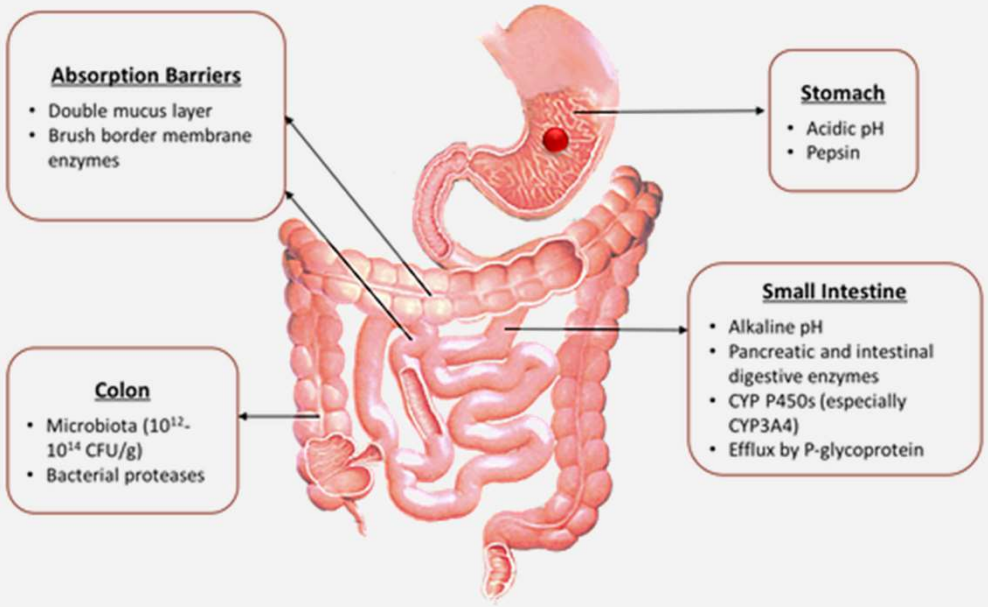
WEEK 3

Stability

- **Active agents in solid form are degraded more slowly than liquid forms such as suspensions or solutions.**



Physicochemical

- **The active substances having stability problems in any part of the GIS are less suitable for the preparation of controlled release preparations.**

- **The active substances can be protected against enzymatic degradation by entrapping them in the polymeric matrix.**

Physicochemical

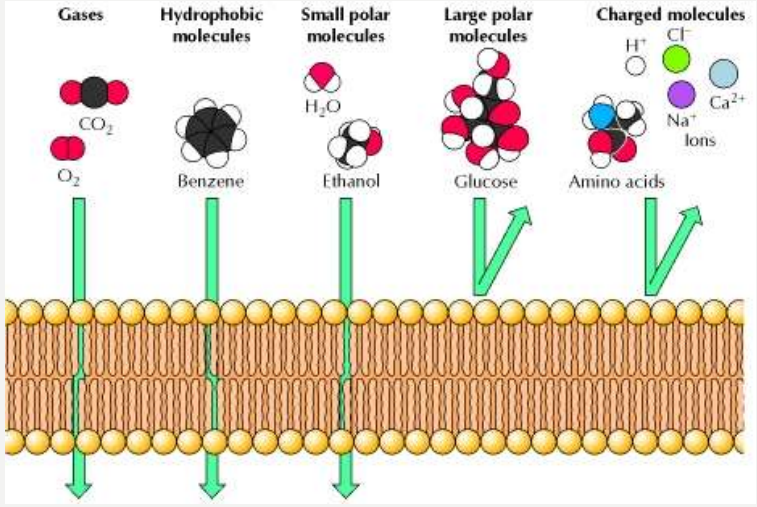
- If the stability of the active substance varies depending on the pH, it is not appropriate to formulate it in a controlled release manner. The pH of the gastrointestinal tract is in the range of 1.2-7.5, and each time the active ingredient is released from the dosage form, it will pass through this channel and be inactive at the pH that it has bad stability.

Physicochemical

Molecular weight and ability to diffuse

- **The ability of an active agent to diffuse from a polymer is defined as the diffusion coefficient (D) of that active agent and is a function of the molecular weight.**

- **The D value refers to the size and shape of the active agent and the gaps that it diffuses.**



- **The passage of drugs with high molecular through biological membranes via diffusion mechanism is very hard.**

Physicochemical

Dose

- For active substances with a high conventional dose, the sustained effective dose may be too high to be practically administered.

- Active substances with an oral dose of over 500 mg are not suitable candidates for the design of controlled release systems.

- The larger the dose size, the greater the fluctuations in the blood profile.

Physicochemical

Absorption

- **For efficent treatment: after administration the drug must first be absorbed from the biological membranes.**

- **The absorption properties of the active agent can significantly affect the design of CDDSs.**

- **In conventional dosage forms, the rate determining step is ka (absorption rate constant). The unit is h^{-1}.**

ka

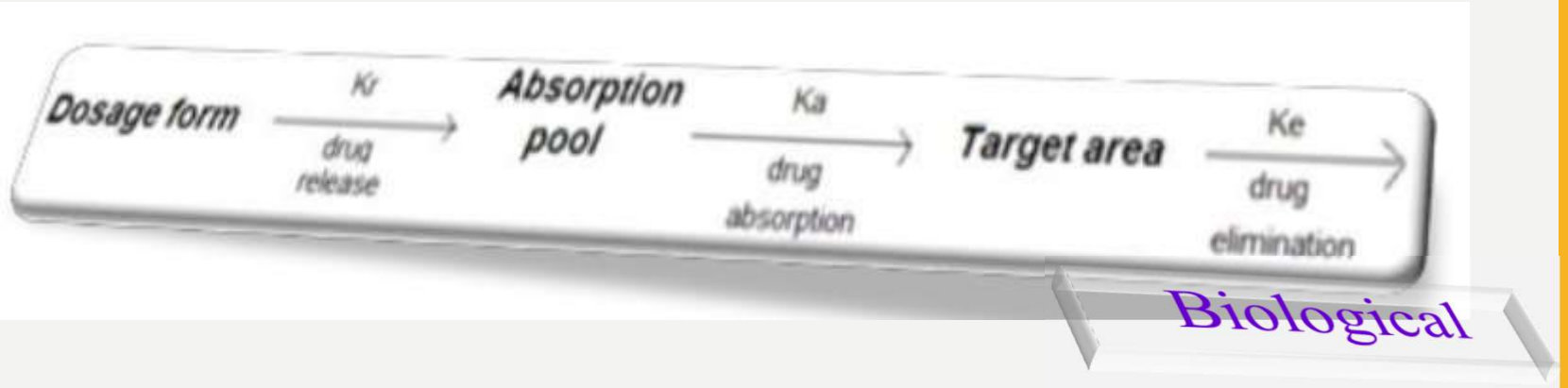
Biological

Absorption

- In controlled release systems, the rate determining step is kr0, ie the rate of release of the active agent from the dosage form.

- In all sustained release preparations, the absorption rate constant must be greater than kr0.

$$kr_0 << ka$$



Absorption

- **Active substances with an absorption rate constant (ka) of less than 0.25 / hour are suitable candidates for the preparation of sustained-acting dosage forms.**

$$kr_0 << ka$$

- **Constant and uniform absorption rate is prefered. Absorption should not increase with the dose.**

- **Absorption properties of the active agent must be the same in all regions of the GIS.**

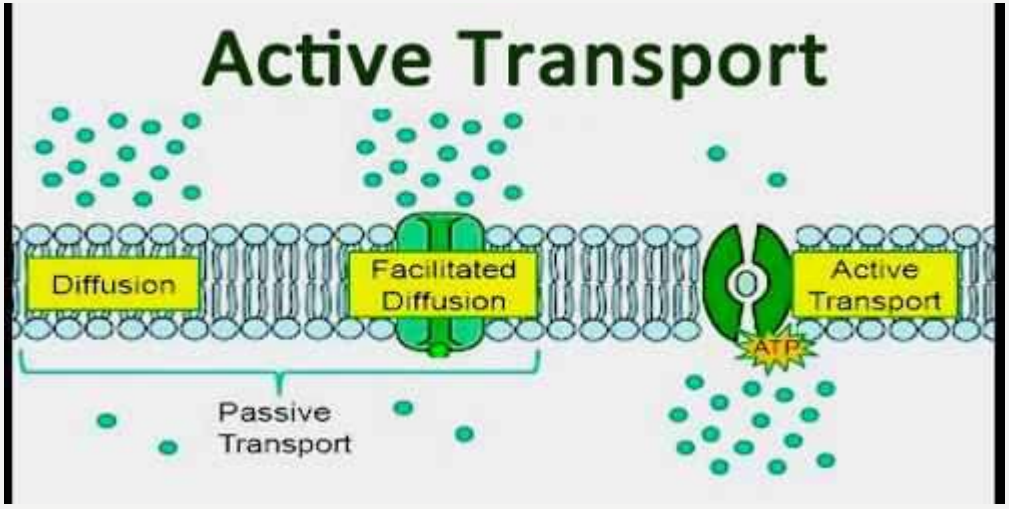
Biological

Absorption pathways of active substances:

- Passive diffusion (suitable)

- Active transport (not suitable)

- Facilitated diffusion



Distribution

Two important parameters used to define the distribution properties of drugs in the body;

- **Visible distribution volume (Vd)**
- Ratio of drug concentration in tissues to drug concentration in plasma **Relative distribution ratio (T / P)**

Vd is an approximate proportional constant calculated by the ratio of the concentration of drug in the blood to the amount of drug in the body.

$$Vd = Dose / C_0$$

C_0 = initial drug concentration in the blood after IV injection

$$V_{ss} = (1+K12/K21)/V1$$

Where:

V1= volume of central compartment

K12= rate constant for distribution of drug from central to peripheral

K21= rate constant for distribution of drug from peripheral to central

V_{ss}= estimation of extent of distribution in the body

- ✓ **Vss is used to express binding in the body.**
- ✓ **As the binding to plasma proteins increases, Vss decreases.**
- ✓ **As tissue binding increases,Vss increases.**
- ✓ **If the active substance binds to both proteins and tissue,Vss is equal to the volume of fluid in the body.**

Biological

The T / P ratio is used to calculate the amount of drug in the body to avoid confusion caused by the apparent dispersion volume.

The amount of drug in the body can be calculated by the T / P ratio.

$$T/P = k_{12} (k_{21}-\beta)$$

β = elimination rate constant
T= Drug amount in periferic tissues
P= Amount of drug in the central compartment (blood)
k_{12}= Distribution rate constant from the central compartment to the peripheral compartment
k_{21}= Distribution rate constant from peripheral compartment to central compartment

Vd and T/P schould be small.

Biological

❖ The tissues that the active substance reaches are examined in 3 sections:

❖ 1. Tissues with high blood supply (heart, lung, liver): In these tissues, the balance of drug concentration between plasma concentration and tissue is established within a few minutes.

❖ 2. Tissues with low blood supply (muscle, skin)

❖ 3. tissues with negligible blood supply (hair, nails)

❖ If the blood supply level of a tissue is too high, the distribution of the drug in the tissue and central circulation reaches the equilibrium very easily.

❖Drugs are divided into 3 groups according to their distribution volume:

❖1. Drugs that bind to body tissues at low levels: If the drug does not enter to the tissues and usually prefer to be in the bloodstream, its blood concentration is always high. As C_0 will increase, the Vd value is numerically very small.

❖If a drug highly binds to plasma proteins, which means it is not free the blood, the amount of drug in the blood is still high. Because it remains in the blood circulation.

Biological

If the drug stays in the circulation and highly binds to plasma proteins Vd value remains between 5-10 l/kg. Drugs commonly bind to albumin. If the drug is permanently bound to albumin, it always remains in the blood. Blood concentration is high.

2. Drugs that bind to body tissues: C_0 is low if the drug tends to bind to tissues too much. Because it quickly goes to the tissue. Since the blood concentration is low, the Vd value is also quite high (25 liters / kg).

3. Drugs that do not bind to tissues and proteins: If the drug binds to neither tissue nor plasma proteins, but only remains in the blood, the dispersion volume of the drug is equal to the plasma volume and cannot exceed 60% of body weight.

In this case;

Controlled release preparation is not recommended if an active substance binds too much to plasma proteins.

Metabolization

- **Especially in enzyme rich tissues (such as liver), drugs are metabolized to active / inactive forms.**
- **In general, controlled release preparations of drugs which do not have a high metabolic rate can be prepared.**
- **Controlled release preparations of substances that are highly metabolized, show complex metabolization, increase / decrease enzyme synthesis, and metabolites are difficult to prepare.**

Elimination

- The majority of drugs and their metabolites are eliminated from the kidneys. Although saliva, sweat and faeces are elimination pathways, the drugs are eliminated in urine at the rate of 99%.
- The capillary pores of the glomeruli allow the passage of many drug molecules, while not permeating blood cells and plasma proteins. The transition from blood to nephron takes place by passive diffusion. So «glomerular filtration is a selective event with passive diffusion».

Biological

Elimination

- When the active substance and metabolites in the blood pass to the glomeruli, a drug bound to the protein cannot pass and therefore the residence time in the blood is prolonged.

- Up to 180 liters of protein-free filtrate pass through the glomeruli daily. However, the volume of excreted urine is about 1.5 liters. The remaining filtrate is reabsorbed.

- Active substances with a high oil / water distribution coefficient can be reabsorbed without excretion in the urine by the passive tubular reabsorption mechanism.

Biological

Elimination

- **So the main events in the kidneys:**
- **1. Glomerular filtration**
- **2. Active tubular secretion involving carrier molecules**
- **3. Passive tubular reabsorption**

- **Renal clearance** describes the volume of plasma completely cleared of a substance by the kidneys per unit time

$$Cl_R = \frac{\text{Rate of urinary excretion}}{\text{Plasma drug concentration}}$$

Biological

- **Renal clearance refers only to excretion from the kidneys. That is, if the drug is excreted completely and only from the kidneys in the organism, excretion occurs according to renal clearance and excretion occurs in proportion to the RCL.**

Excretion rate (dx / dt) = Elimination rate constant (k) X Drug amount in the body (x)

- **The elimination rate is proportional to $t_{1/2}$ since elimination of the drug in the body is carried out according to the first degree kinetics.**

- As a result;

- The half-life of a drug in the body is proportional to the renal clearance value of that drug. The less the drug is excreted from the organism, the lower the new renal clearance, the higher the $t_{1/2}$ value, ie the longer it remains in the organism.

- In this way, the dosing intervals of the drugs are determined by determining the half-life.

Binding to proteins

- The active substances bind to plasma proteins such as albumin, which results in increased blood residence times.
- The drug-protein complex can act as a depot in the circulation.
- The main forces that bind the active substance to proteins are Van der Waals forces, Hydrogen bonds and Electrostatic forces.
- Charged compounds tend to bind to proteins more than uncharged ones.

Biological

❖**The high binding of the active substance to plasma proteins results in a long elimination half-life.**

❖**Ex: Amitriptyline, diazepam and diazepoxide bind to plasma proteins at a level of 95% .**

Biological

Biological Half-Life

- ☆ **Active substances with very low half-lives ($t_{1/2}$ <2 hours) and high doses are not suitable for controlled release.**
- ☆ **Drugs with $t_{1/2}$ of 4-6 hours and an initial dose of 125-325 mg are suitable for controlled release.**
- ☆ **The active agents with very long half-life already act as controlled release systems.**

Therapeutic Index

Increased blood concentration increases the potential for side effects.

Therapeutic index (TI) = Toxic dose (LD50) / Effective dose (ED50)

Ti ↑ Safety ↑

Ti ≥ 10 suitable for CDDs

Ti< 2 not suitable for CDDs

Biological

Active Substances Suitable for Control Release

- Not having a very short (<2 hour) or very (>8 hour) long half-life,
- Water solubility higher than 0.1 mg / ml,
- Partition coefficient is around 1,
- The dissociation constant is pKa > 2.5 for weak acids and pKa <11 for weak bases,
- If the oral dosage is less than 500 mg,
- Having a high therapeutic index,
- Active substances used for the treatment of chronic diseases rather than acute treatment.

Unsuitable Active Ingredients

- ☹ Has short biological half-life (<2 hours) (eg Penicillin, Furosemide),
- ☹ Has a very long biological half-life (> 12 hours) (eg Diazepam, Phenytoin),
- ☹ Requires a high treatment dose (> 1 g) (eg sulfonamides),
- ☹ It has a narrow therapeutic index (eg Digitoxin),
- ☹ Low absorption rate or absorbed in a specific area of the GIS,

- ☹ slow and low solubility (<0.1 mg / ml),
- ☹ There is no correlation between pharmacological effect and blood concentration (compatible with nonlinear pharmacokinetics),
- ☹ Active substances that undergo the first pass effect in liver
- ☹ Active substances that bind highly to plasma proteins,
- ☹ Active substances that accumulate in the body and have undesirable side effects. Ex. phenobarbital
- ☹ Active substances that require precise dosage titration for each individual. Ex. Warfarin, Digitoxin.