WEEK 2

Advantages

- ☺ **Since a sustained and stable blood drug concentration is provided, fluctuations in plasma concentration are reduced and a uniform therapeutic response is obtained.**
- ☺ **They reduce the frequency of dosing and decrease the number of missing doses.**
- ☺ **The patient compliance is increased.**
- ☺ **Shorten the patient care period.**
- ☺ **Reduce local and systemic side effects.**
- ☺ **İmprove the treatment efficacy. A uniform therapeutic response is obtained.**

- ☺ **They provide maximum bioavailability with minimum dose.**
- ☺ **Since the concentration of active substance in the blood is constant, the accumulation of the active substance in the body is prevented.**
- ☺ **A constant blood concentration ensures that the desired effect is achieved and this effect remains constant for the desired duration.**
- ☺ **The active substance molecules are encapsulated in a polymer suitable for sustained release to protect against enzymatic inactivation or bacterial decomposition.**
- ☺ **They can be used to target the drug to specific tissues.**

- ☺ **Side effects due to the high drug concentration (especially in the gastrointestinal tract) are reduced.**
- ☺ **Due to the constant drug concentration, the risk of side effects is minimized.**
- ☺ **It is ensured that short-acting drugs are administered at longer dosage intervals.**
- ☺ **They provide cheaper treatment. They are economical in terms of preventing drug losses, but are expensive systems due to their preparation technologies and excipients used.**

Disadvantages

- ☹ Administration of controlled release medication does not permit the prompt termination of therapy.
- ☹ Flexibility in adjustment of dosage regimen is limited.
- ☹ Controlled release forms are designed for normal population i.e. on the basis of average drug biologic half lives.
- ☹ The implants must be sterile and the implantation and removal of the implants takes place through surgery.
- ☹ Economic factors must also be assessed, since more costly process and equipment are involved in manufacturing of many controlled release dosage forms.

- ☹ **The main limiting parameter in the preparation of such systems is the dose of the active substance. It is particularly difficult to prepare high-dose active substances in this form.**

- ☹ **A controlled release dosage form of every active agent cannot be prepared. Physicochemical and biological properties of the active substance are very important.**

DESIGN OF CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

- **Should release the active substance at the predetermined rate for the required period of time.**
- **Localized drug activity should be provided after implantation of the implants to the target region.**
- **Drug targetting should be provided. Drug carriers are used for this purpose.**

What are the factors that should be considered in the desing of CDDs?

Biological properties of the active agent	*Physicochemical properties of the active agent*
Absorption	**Dose**
Distribution	**Partition coefficient**
Metabolism	**MW**
Elimination	**Aqueous solubility and pKa**
Biological half life	**Stability**
Side effects	
Therapeutic index	
Protein binding	
First pass effect	
Role in the disease	

Solubility and pKa (dissociation constant)

Physicochemical

Aqueous solubility:

The active substance to be absorbed must first dissolve in the aqueous phase in the region of application and then pass through the biological membrane.

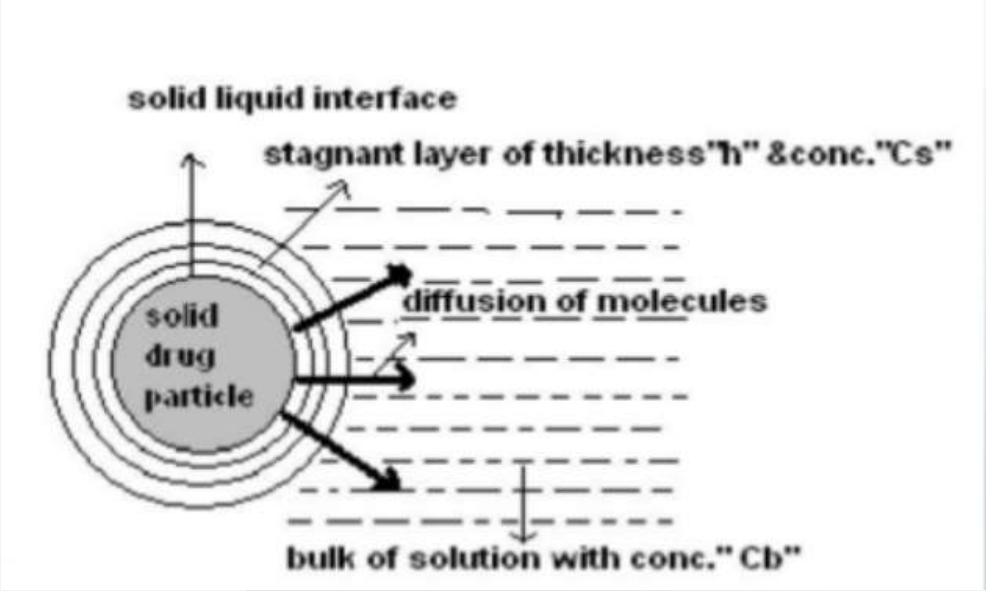
- **Active substances with good water solubility (especially regardless of pH) are good candidates**

- **$ka < kr_0$ ⟶ Conventional dossage forms**

«**absorption** of drug across a biological membrane is the rate-limiting step in delivery of the drug to its target area.»

- **$ka >> kr_0$ ⟶ CDDSs**

«**release** of drug from the dosage form is the rate limiting step»



NOYES AND WHITNEY EQUATION

The rate of change in concentration of dissolved material with time it directly proportional to the concentration difference between the two sides of diffusion layer

$$\text{i.e.} \quad \frac{dc}{dt} = k\,(C_s - C_b)$$

Where, dc/dt - Dissolution rate of drug.

k - Rate constant

Cs - Concentration of solution at solid surface

Cь - Bulk of the solution

- **Drug release is directly proportional to drug solubility**
- **Solubility in water shoul be > 0.1 mg/ml**
- **If the drug has low water solubility: its dissolution is slow**

  -thus have oral bioavailability problems.
- **Active substances with very high water solubility are not also good candidates for sustained release drug forms.**

Physicochemical

pKa

An acid dissociation constant, Ka, (also known as acidity constant, or acid-ionization constant) is a quantitative measure of the strength of an acid in solution.

pK_a is the negative base-10 logarithm of K_a of a solution.

- **Since the most of the active agents are weak acids or weak bases, the presence or absence of charge on the molecule is important to determine their ability to pass through membranes and hence their dissolution properties.**

Physicochemical

- **The solubility of weak acids and weak bases in water depends on the pKa value of the compound and the pH of the medium.**

Weak Acids;

$$St = So(1+Ka\backslash[H\ ] = So(1+10pH-pKa)$$

St – Total solubility of the weak acid

So – Solubility of the non-ionized form

Ka – Acid dissociation constant

H - Hydrogen ion concentration

- **In stomach weak acidic drugs are in non-ionized form and are more easily absorbed.**

Weak Bases;

$$S_t = S_o(1+[H\ ] \backslash Ka) = S_o(1+pKa-pH)$$

St - Total solubility of the free and conjugated form of the weak base.

So– Solubility of the free base.

- Since weak bases are in ionized form in the stomach, their absorption in this medium is weak.

Partition Coefficient

- A drug has to pass through various biological membranes between the time it is administered to the body and its removal from the body.

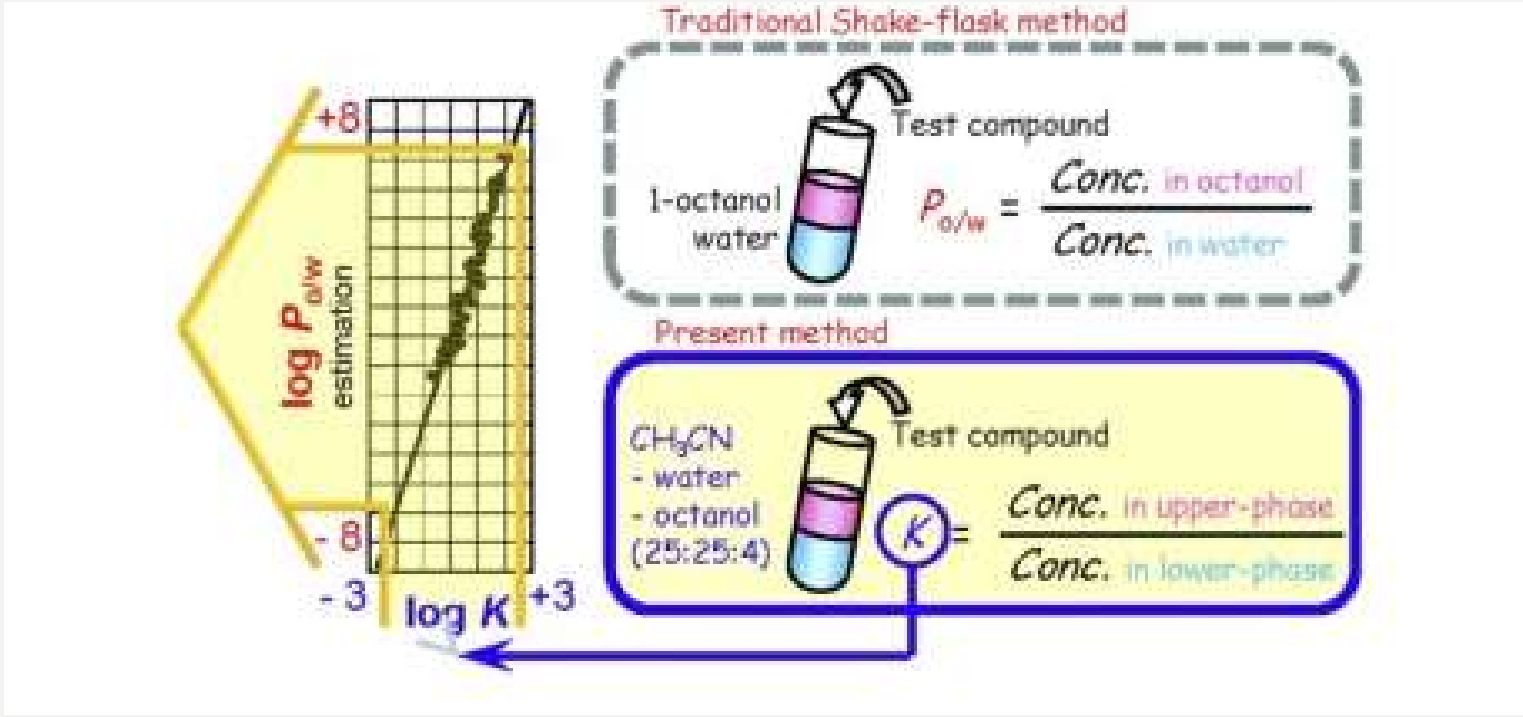
- **Since the membranes are in lipid structure, the oil / water partition coefficient (K) has an important role in determining the penetration of the active substances.**

K=Co/Cs

Co = Equilibrium concentration in the oily phase.

Cs = equilibrium concentration in aqueous phase.

Physicochemical



Physicochemical

- **Active substances with very high partition coefficients are highly soluble in oil and tend to remain there for a long time : so they can easily penetrate through the membranes.**

- **Active substances with low partition coefficients have low bioavailability.**

- **Active agents have an optimum partition coefficient in which they pass effectively through the membranes and exhibit high activity.**

- **Partition coefficients below the optimum value result in reduced lipid solubility and remain localized within the first aqueous phase it comes into contact with.**

- **For the agents with partition coefficients above the optimum value the solubility in water is poor. However, since the solubility in fat increases, the active substance will not be outside the lipid membrane.**

- **As a general evaluation limit, the Partition Coefficient should be close to 1.**