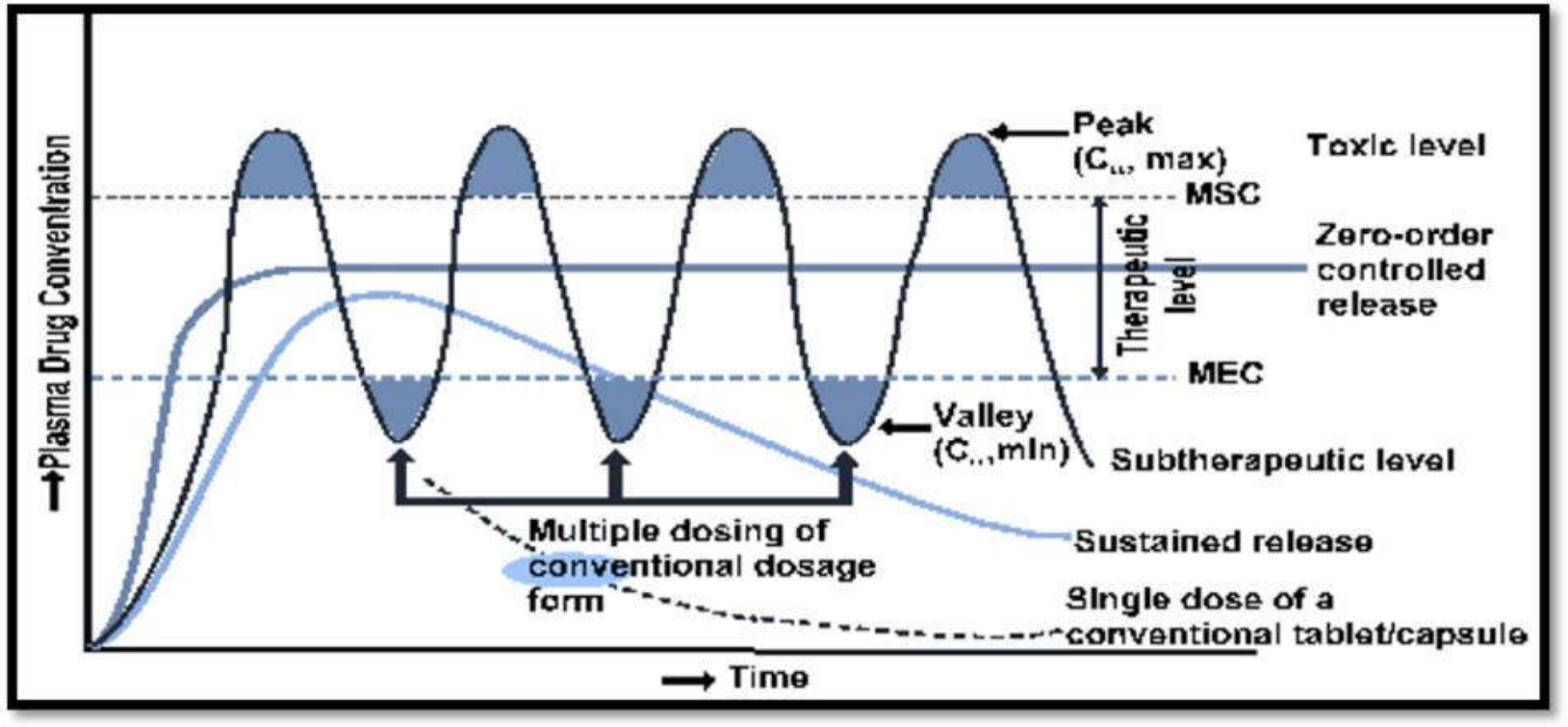
SYSTEMS FOR CONTROLLED DRUG DELIVERY AND DELIVERY MECHANISMS

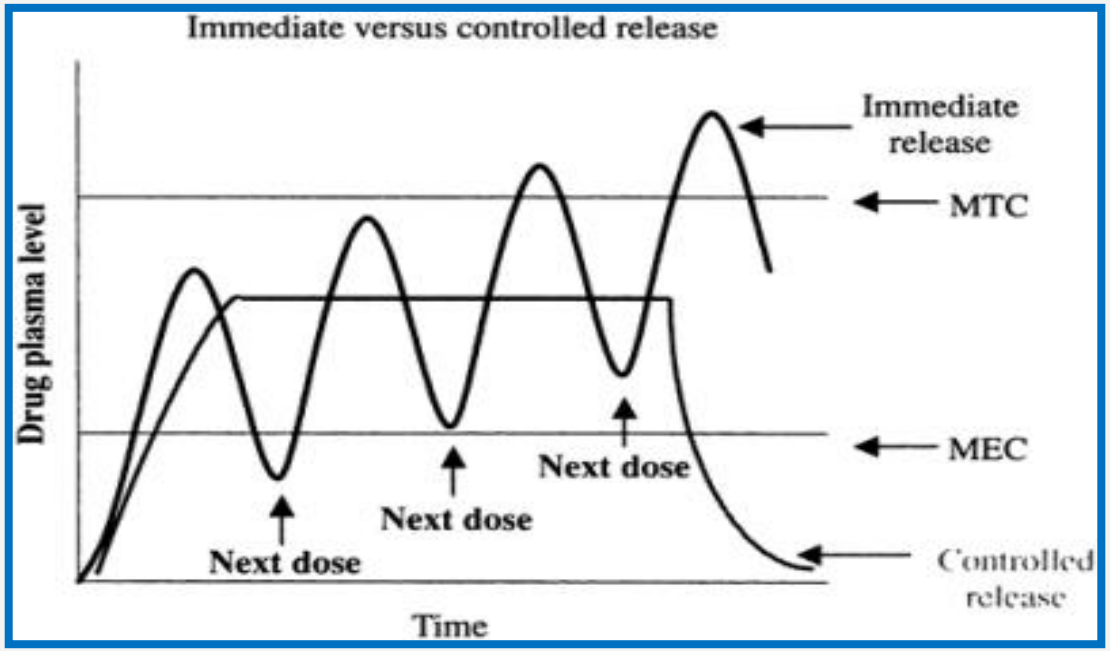
WEEK 6

Conventional dosage forms are designed to release the active agent to ensure immediate and complete systemic absorption.



However, some problems arise with the frequent and repeated administration of such dosage forms:

- the concentration of the active substance may fall below the effective level or
- rise above the toxic level and consequently increase the side effects or their severity.

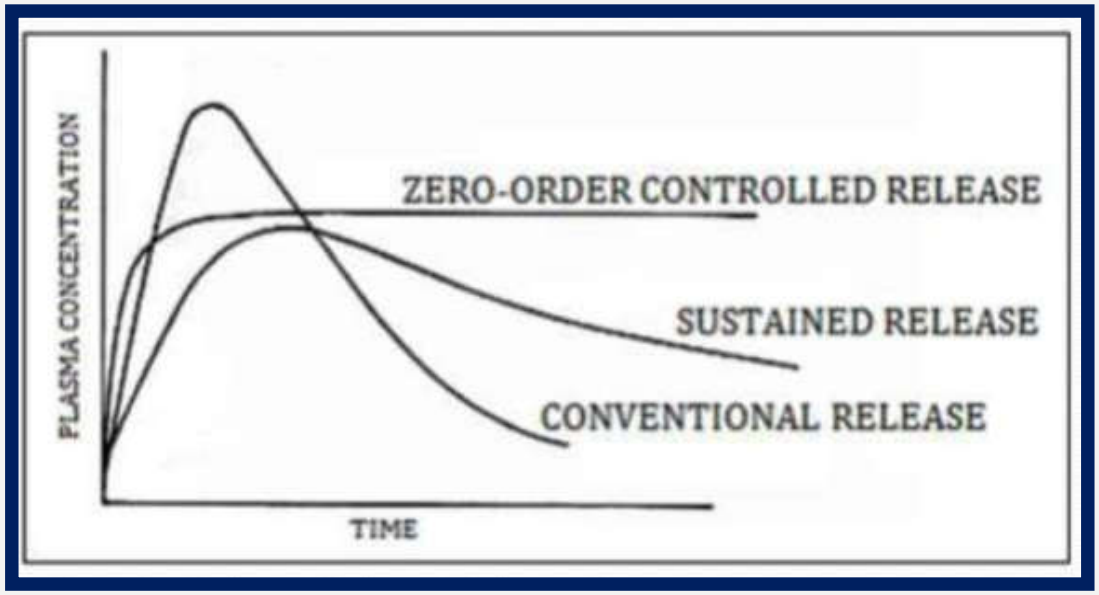


These problems can be overcomed by systems which prolong the systemic absorption and biological activity of the active agents by releasing the active agent over a longer period of time than the immediate release dosage forms.

Controlled drug delivery systems deliver the **drug** at a predetermined rate, for locally or systemically, for a specified period of time.

Controlled drug delivery systems provide modified drug release.

Modified release dosage forms; forms administered by the same route with conventional dosage forms such as solutions, ointments, tablets or capsules but release the active agent at different sites and / or rates than



Therminology

Due to the varying release characteristics, a number of different expressions are used to describe controlled release systems, and different types of classifications are found based on different references.

According to EP 2005, drug release systems are classified as follows:

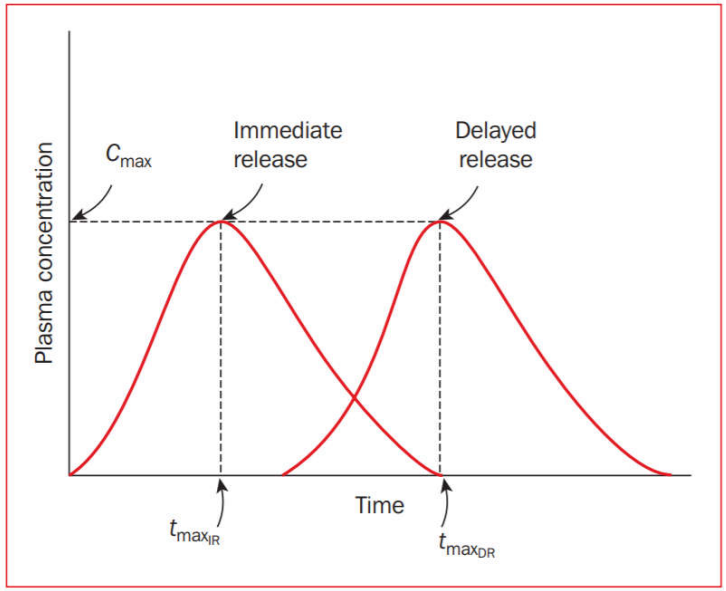
1. Conventional release dosage forms / Immediate release dosage forms
2. Modified release dosage forms
3. Pulsatile release dosage forms
4. Delayed release dosage forms / Gastro-resistant preparations
5. Prolonged release dosage forms / Extended release dosage forms

In USP 27, Modified Release Systems are grouped under two main groups.

1. Delayed release systems
2. Extended/prolonged release systems
   a) Controlled release systems
   b) Sustained release systems

Delayed release: Delayed-release dosage forms can be defined as systems which are formulated to release the active ingredient at a time other than immediately after administration. Delayed release from oral dosage forms can control where the drug is released, e.g. when the dosage form reaches the small intestine (enteric-coated dosage forms) or the colon (colon-specific dosage forms).

Figure 1.3 Idealised plasma concentration versus time profile of a delayed-release oral dosage form compared to an immediate-release dosage form. T_{maxIR} is the time for maximum plasma concentration of the drug released from an immediate-release dosage form and T_{maxDR} is the time for maximum plasma concentration of the drug released from a delayed-release dosage form.



Extended release: Extended-release systems allow for the drug to be released over prolonged time periods. By extending the release profile of a drug, the frequency of dosing can be reduced.(min 2 doses).

Extended release can be achieved using sustained- or controlled-release dosage forms.

Controlled release systems; release rate can be adjusted in advance and drug release fits zero degree kinetics.

Can maintain the plasma or tissue levels of the active substance for a much longer period than conventional dosage forms. However, since the system can be affected by the ambient conditions, it is difficult to determine the release mechanism in advance. In general, drug release fits first order kinetics.

Pulsatile release dosage forms; **modified release systems in which the active agent is released consecutively.**

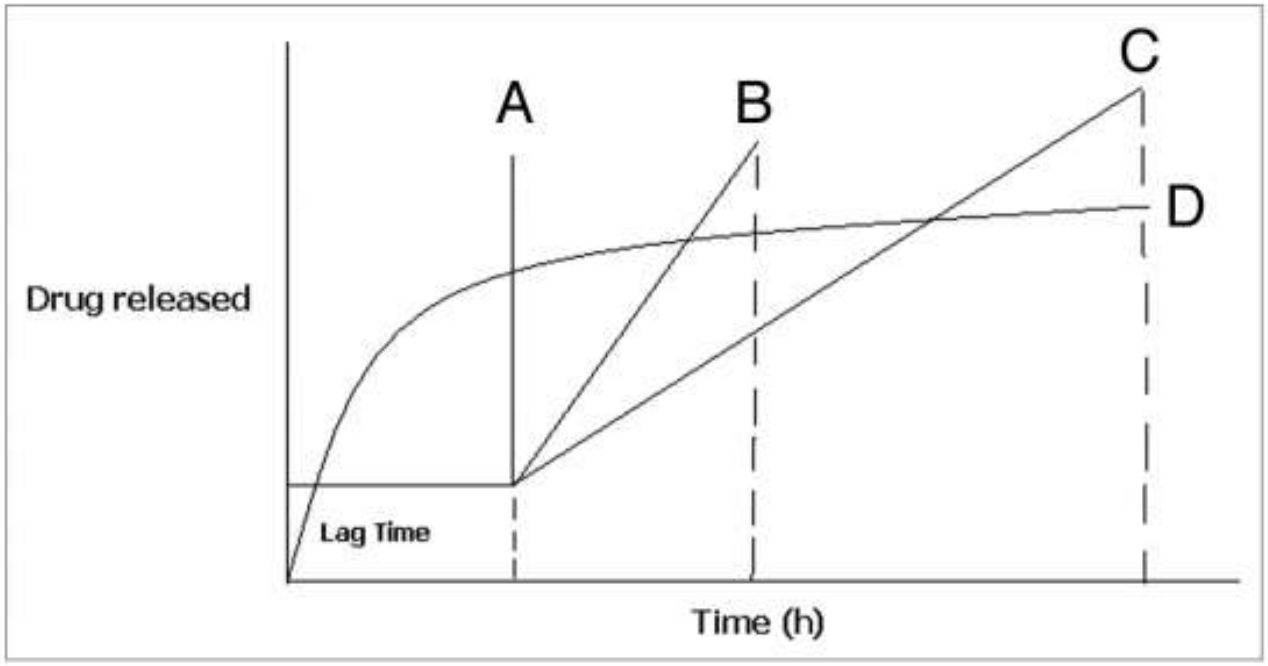


Figure 1. Schematic representation of different drug delivery systems, with (A) sigmoidal release after lag time, (B) delayed release after lag time, (C) sustained release after lag time and (D) extended release without lag time.

Differences between sustained release and controlled release

SUSTAINED RELEASE	CONTROLLED RELEASE
Provide long-term treatment	Provide a constant drug concentration in the blood / tissue.
do not release drug by zero order kinetics Generally drug release is close to first-order kinetics,	Zero order release kinetic Drug release rate and time can be adjusted
Generally do not contain mechanisms leading drug targetting to the site of action	They enable the localization of the active agent in the site of action.

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.

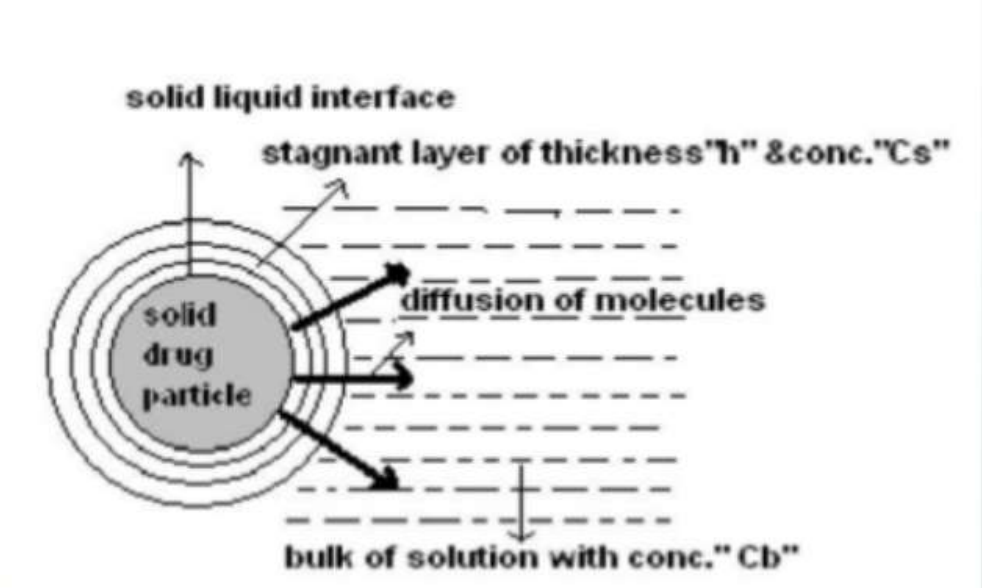
- **Active substances with good water solubility (especially regardless of pH) are good candidates**

- **$ka < kr_0$ ⟶ 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.

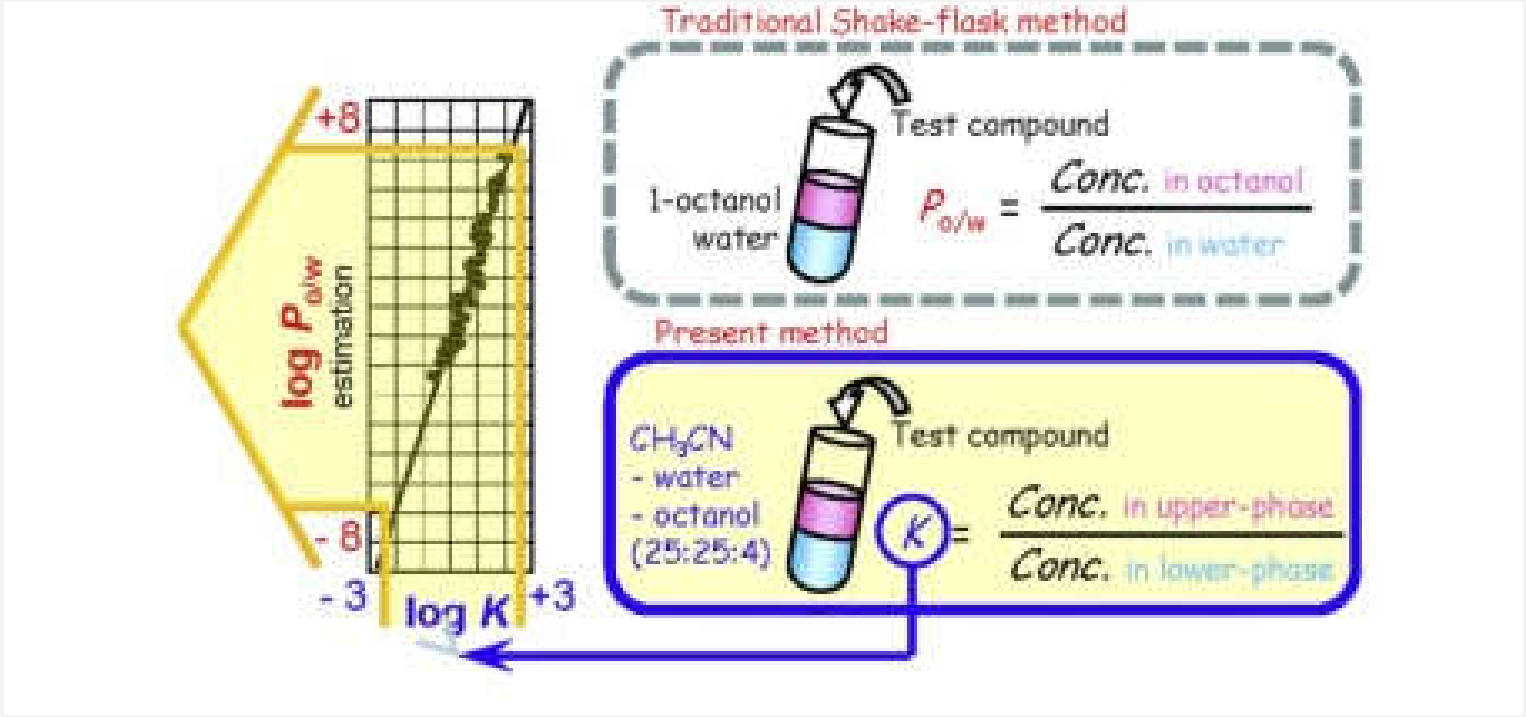
- **Since the membranes are in lipid structure, the oil / water partition coefficient (K) has an important role in determining the penetration of the active substances.**

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.**

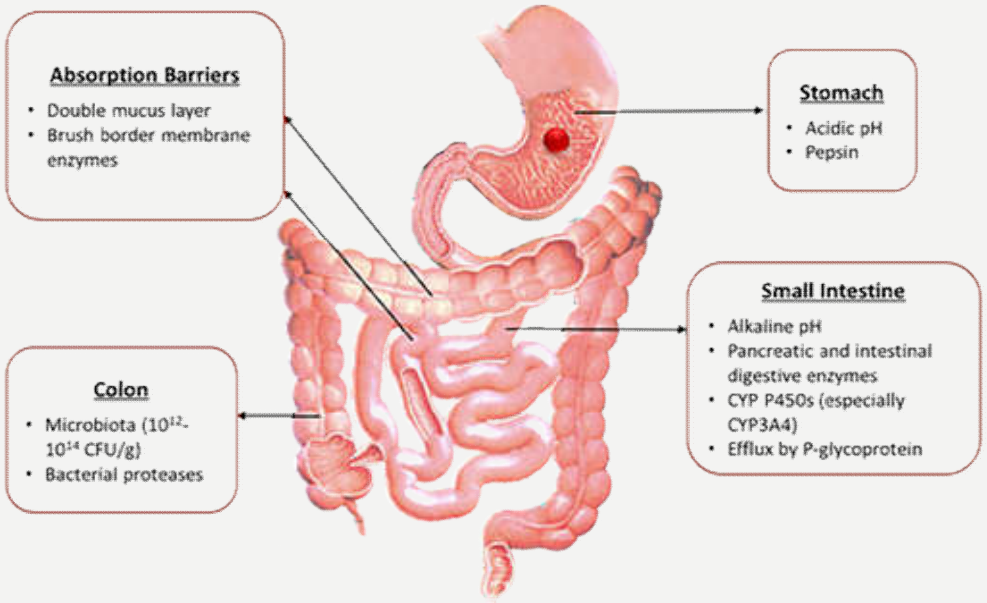
- **Partition coefficients below the optimum value result in reduced lipid solubility and remain localized within the first aqueous phase it comes into contact with.**

- **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.**

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.**

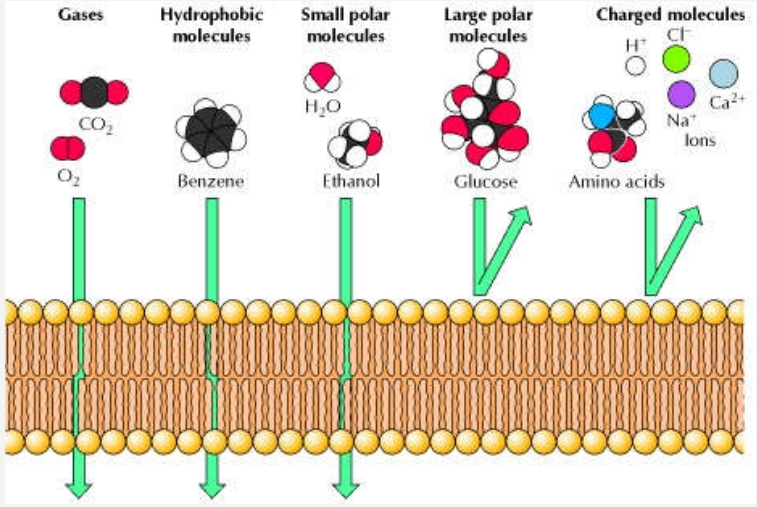
Physicochemical

- 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.

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

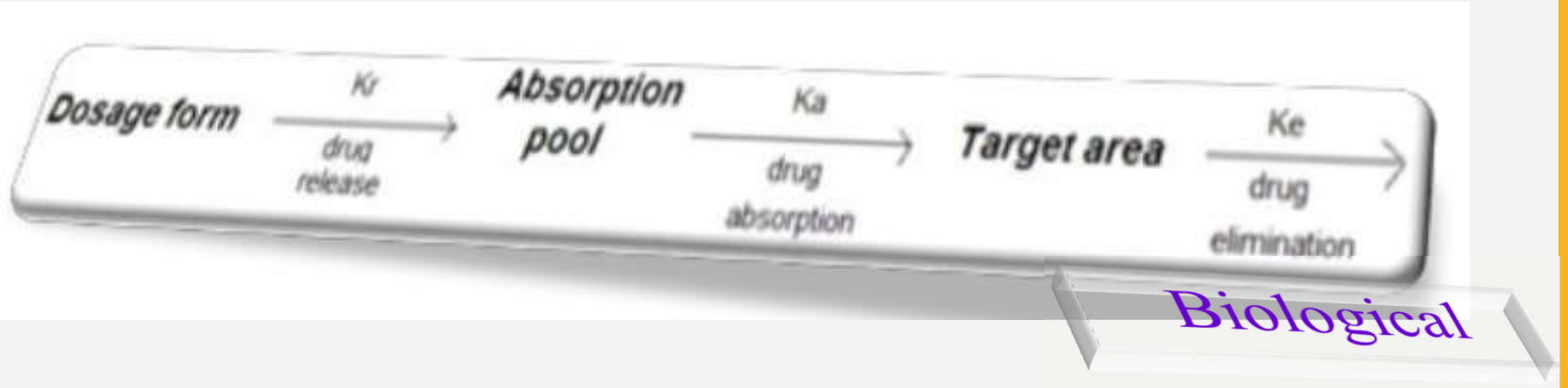
Biological

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.**

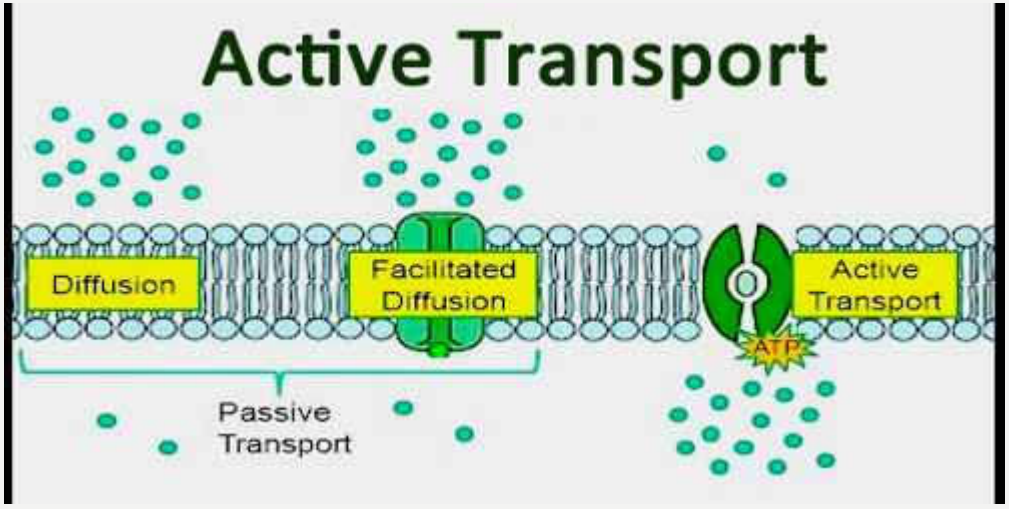
Biological

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.

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.**

Biological

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.**

Biological

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.**

Polymers are compounds with high molecular masses formed by monomers.
poly: 'many'
meros: 'units or parts' in Greek.

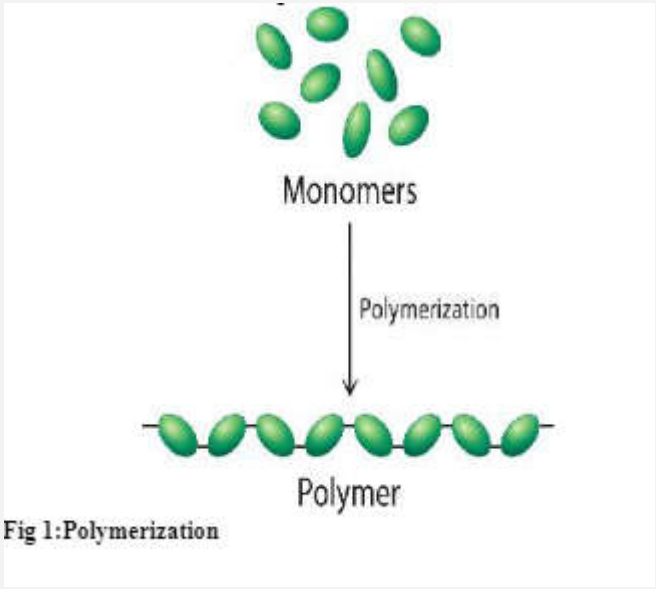
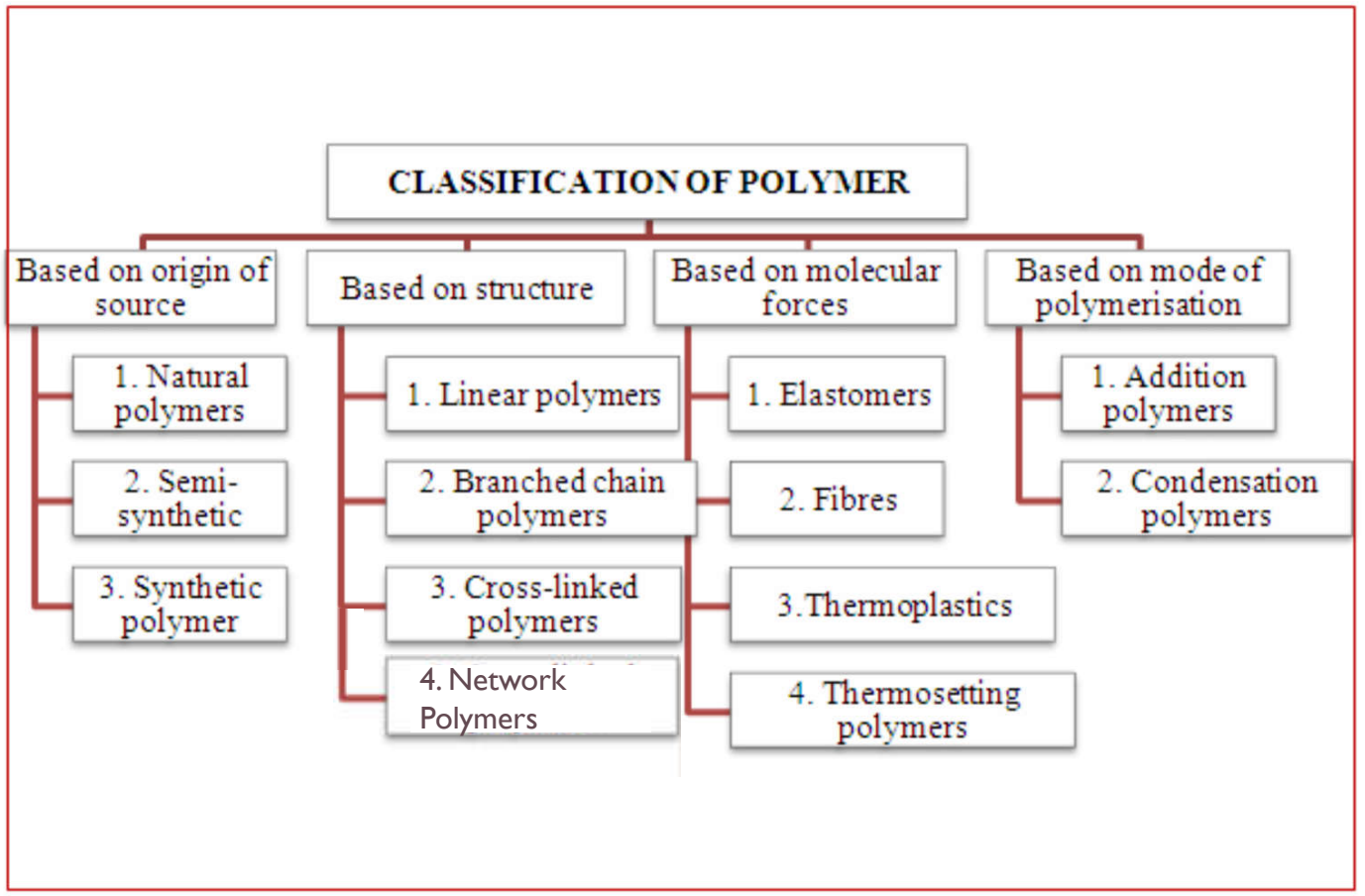


Fig 1:Polymerization

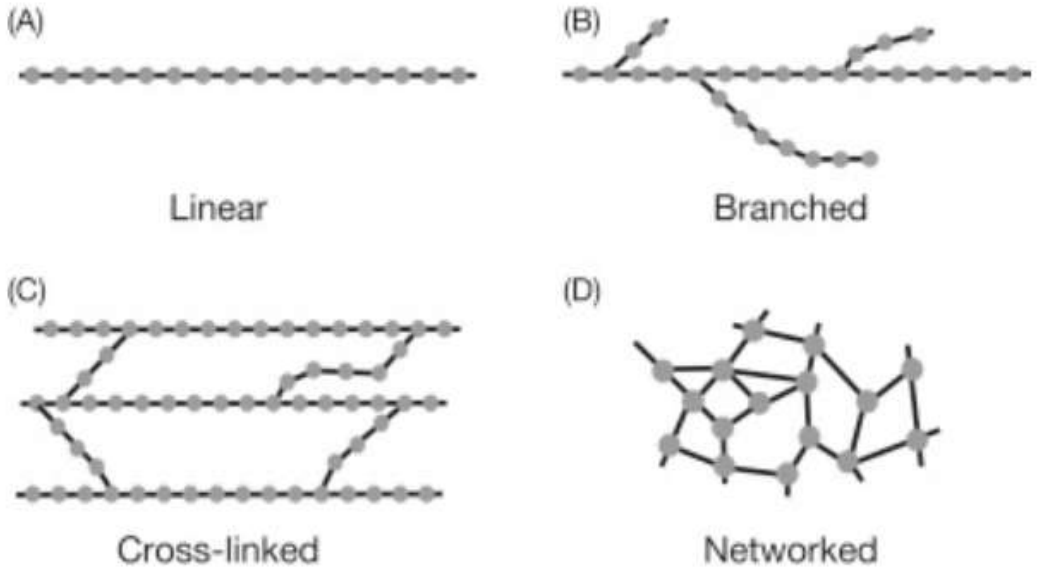
Polymer, any of a class of natural or synthetic substances composed of very large molecules, called macromolecules, that are multiples of simpler chemical units called monomers. Polymers make up many of the materials in living organisms, including, for example, proteins, cellulose, and nucleic acids.



Polymers

- Biodegradable
- NonBiodegradable

POLYMER CHAIN STRUCTURE



Linear polymers, the monomers are joined together in a linear manner, branched polymers, some monomers are joined as branches on the polymer backbone.

If the monomer units are joined in multiple chains and form interconnections between chains, cross-linked polymers are made. When a cross-linked polymer includes plentiful interconnections between chains in 3D, a network polymer is formed

Thermoplastic polymers can be thermally softened or plasticized repeatedly. (polyolefins, nylons and linear polyesters)

For thermosetting polymers, in the product manufacture process, chemical changes occur upon heating of this type of polymers and convert them into an infusible mass. The curing or setting process leads to growth and cross-linking of chain molecules, producing giant molecules. After product manufacture, thermosetting polymers cannot be re-melted. (resins, urea, diene rubbers and phenolic)

Polymer Synthesis

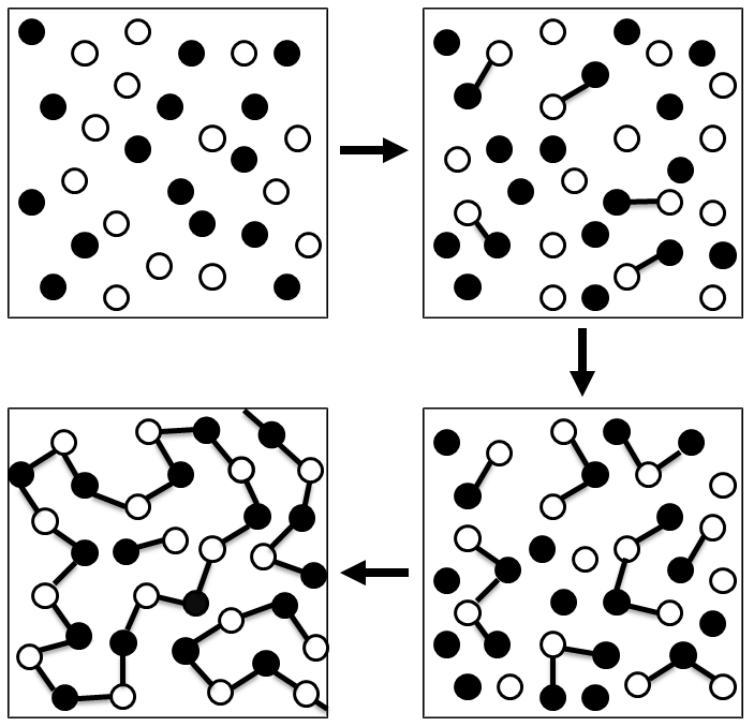
- Step-growth polymerization or condensation polymerization
- Addition polymerization or chain reaction polymerization
- Ring opening polymerization

If polymerization involves multiple types of monomers, copolymerization takes place, forming copolymers.

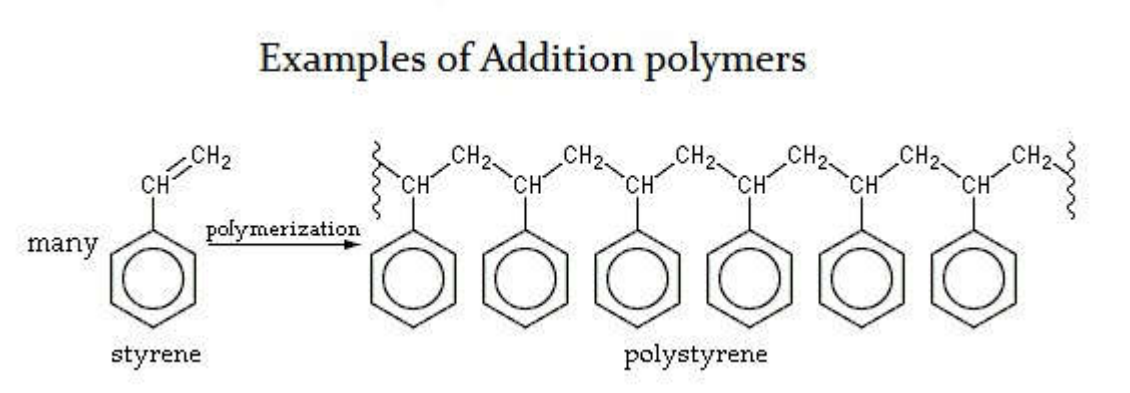
Step-growth polymerization, or condensation polymerization

The polymerization reaction occurs between the functional groups of molecules. Small molecules such as water are eliminated by the chemical reaction in step-growth polymerization (polyesters and nylons)

In step-growth polymerization, one or more types of monomers can be involved, and each monomer should have at least two sites for bonding. For polymerization with more than one type of monomers, for example, involving A and B monomers, A–B stepgrowth polymerization or A–A/B–B step-growth polymerization can occur.

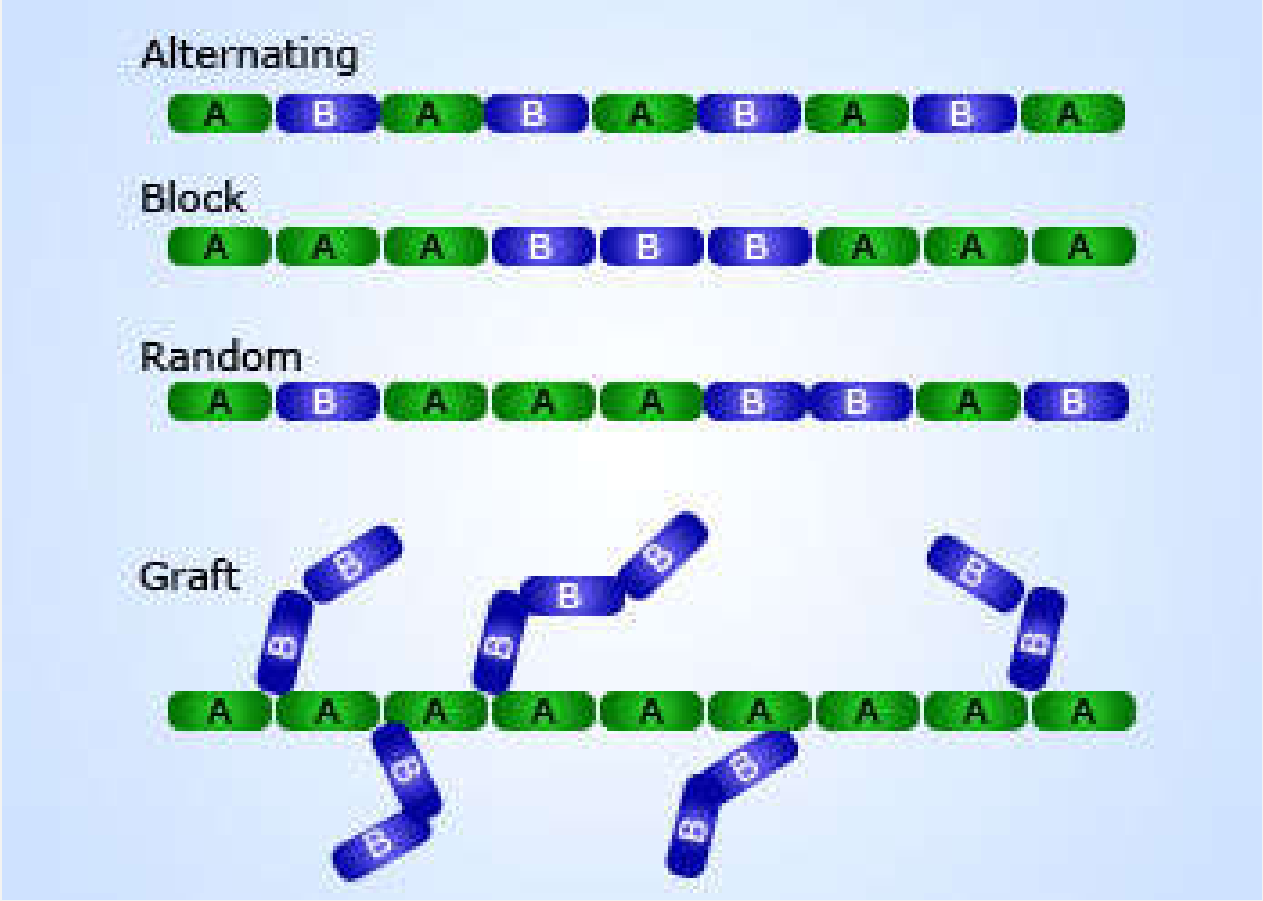


Addition polymerization or chain reaction polymerization, requires the monomers to have at least one double bond. In addition polymerization, no molecule is eliminated and no by-product is generated. The molecular weight of the formed polymer is exactly the same as the sum of all monomers included in the polymerization. A chain reaction links monomers together by rearranging the bonds with each monomer.



Copolymerization

Copolymerization is the polymerization using two or more types of monomers and produces copolymers.



Polymers • Biodegradable

Biodegradable polymers are one group of polymeric materials. The molecular chains of the polymers can be broken down either through hydrolytic degradation or by enzymatic means.

The degradation of the polymer results in the formation of natural byproducts such as oxygen, nitrogen, carbon dioxide, water, biomass, and inorganic salts.

Biodegradable polymers can be divided into water-soluble and water insoluble polymers

- Polyesters and polyester derivatives
- Polylactones
- Poly(amino acids)
- Polyphosphazenes
- Poly(orthoesters)
- Polyanhydrides

The use of biodegradable polymers offers several advantages over other materials.

- the ability to tailor
- the mechanical properties,
- the degradation rates
- the ability to be formed into various shapes. reduces the need for subsequent surgical removal, saving time and money.

Disadvantages:

- degradation products be problematic.

Eg: degradation products of PLA and PGA were highly toxic if they accumulated.

- complicated and expensive to synthesise and process

Factors influencing biodegradation of polymers

- Chemical structure and composition
- Physico-chemical factors (ion exchange, ionic strength, pH)
- Physical factors (shape, size, chain defects)
- Morphology (amorphous, semicrystalline, crystalline, microstructure,residual stress)
- Mechanism of degradation (enzymatic, hydrolysis, microbial)
- Molecular-weight distribution
- Processing conditions and sterilization process
- Annealing and storage history
- Route of administration and site of action

The most widely used synthetic biodegradable polymers belong to the polyester family, such as Poly Lactic Acid (PLA) and Poly Glycolic Acid (PGA) and their copolymers, such as PGLA. They have been extensively studied and reported in the literature and have many applications including resorbable sutures, surgical fixation devices and drug delivery devices.

Table 2.5 Drug release devices made from degradable aliphatic polyesters and copolymers

Delivery system	Material composition	Product name	Therapeutic	Type of drug: indications
Microsphere	PLA	Lupron Depot	Leuprolide acetate	Peptide hormone: cancer and Alzheimer's
	PLGA	Eligard	Leuprolide acetate	Peptide hormone: Cancer and Alzheimer's
		Decapeptyl	Synthetic hormone	Synthetic hormone: reproduction
		Risperdal Consta	Risperidone	Peptide: schizophrenia
		Trelstar LA	Triptorelin pamoate	Peptide hormone: prostate cancer
	PLGA-glucose	Sandostatin LAR	Octreotide	Peptide: anti-growth hormone
Implant	PCL	Capronor	Levonorgestrel	Contraceptive
	PLGA	Durin	Leuprolide	Peptide hormone: cancer and Alzheimer's
		Zoladex	Goserelin acetate	Peptide hormone: prostate/breast cancer
Gel	PLGA-PEG	Oncogel	Paclitaxel	Anti-cancer

PLA, poly(lactic acid); *PLGA*, poly(lactide-co-glycolide); *PCL*, poly(ε-caprolactone); *PEG*, polyethylene glycol.

Polymers

- NonBiodegradable

- Poly (ethylene-co-vinyl acetate)
- Polysiloxanes (silicones)
- polyurethanes
- polythene