UNIT-I

CONTROLLED DRUG DELIVERY SYSTEM

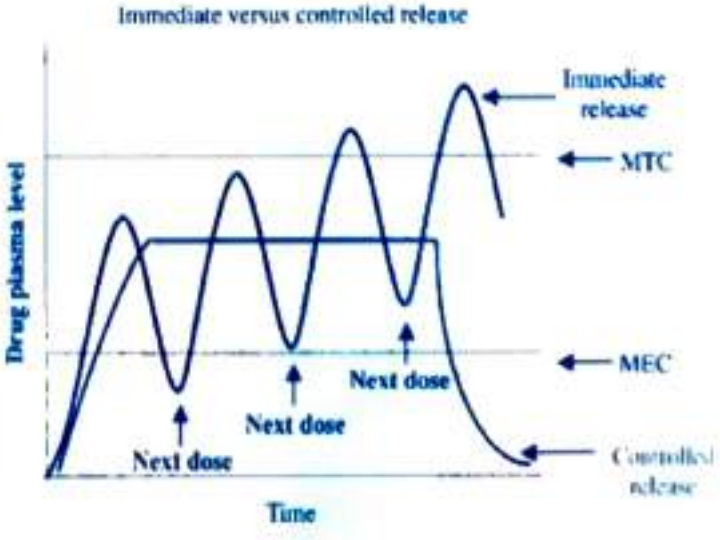
Points to be covered in this topic

- ❑ INTRODUCTION
- ❑ DEFINITIONS
- ❑ RATIONAL
- ❑ ADVANTAGES
- ❑ DISADVANTAGES
- ❑ SELECTION OF DRUG CANDIDATES
- ❑ APPROACHES
- ❑ PHYSIOLOGICAL AND BIOLOGICAL PROPERTIES OF DRUGS

CONTROLLED DRUG DELIVERY SYSTEM

❑ INTRODUCTION

- Every drug molecule needs a **delivery system** to carry the drug to the **site of action upon administration** to the patient.
- Delivery of the drugs can be **achieved using various type of dosage forms like** tablets, capsules, creams, liquids, ointments etc.
- Most of these **conventional drug delivery systems** are known to provide **immediate release** of the drug with little or **no control over delivery rate**
- To achieve & maintain **therapeutically effective plasma conc.**
- Several doses are needed daily which may cause **significant fluctuations in plasma.**
- Because of these fluctuations in plasma levels the **drug level could fall below the MEC.** Such fluctuations result in **unwanted side effects** or lack of intended therapeutic benefit.
- **Sustained-release & controlled release** drug delivery systems can **reduce the undesired fluctuations of drug levels, reduce side effects,** while improving the therapeutic outcome of the drug.
- Controlled drug delivery systems can include the **maintenance of drug levels within a desired range,** the need for fewer administrations, optimal use of the drug in question, and increased patient compliance.



❑ DEFINITIONS

- **CONTROLLED DRUG DELIEVRY SYSTEM:** This drug systems are More advanced & are designed to deliver the drug at specific release rate within a predetermined time period .
- **SUSTAINED-RELEASE DRUG SYSTEM-**This system prolong the duration of action by slowing the release of drug usually at the cost of delayed onset & its pharmacological action.

❑ RATIONAL

- The basic idea behind CDDS concept is to **alter the pharmacokinetics & pharmacodynamics of bioactivities** either by modifying the **molecule structure or physiological parameters**.
- By using NDDS, the primary objective of CRDDS is to **safety & enhance efficacy of drug with improved** patient compliance.

❑ ADVANTAGES

- **Improvement in bioavailability** of some drugs
- **Improved** patient compliance
- **Reduction in drug level fluctuation** in blood
- **Reduction in total drug usage** ,compared to conventional therapy
- **Reduction in drug accumulation** with chronic therapy
- **Reduction in drug toxicity** (local/systemic)
- **Reduction in frequency** of drug administration

❑ DISADVANTAGES

- **Delay** in onset of drug action
- **Possibility of dose dumping** in the case of a poor formulation strategy
- **Increased potential** for first pass metabolism
- Possibility **of less accurate dose adjustment** in some cases
- **Not all drugs are suitable** for formulating into ER dosage form

❑ SELECTION OF DRUG CANDIDATES

Characteristics that may make a drug unsuitable for CDDR

- ✓ Short elimination half-life
- ✓ Long elimination half-life
- ✓ Narrow therapeutic index
- ✓ Poor absorption
- ✓ Active absorption
- ✓ Low or slow absorption
- ✓ Extensive first pass effect

Parameters for drug selection parameter : Preferred value

- **Molecular weight/ size: < 1000**
- **Solubility: > 0.1 µg/ml for pH 1-7.8**
- **Pka Non ionized moiety: > 0.1% at pH 1- 7.8**
- **Apparent partition coefficient: High**
- **Absorption mechanism: Diffusion**
- **General absorbability: From all GI segments**
- **Release: Should not be influenced by pH and enzymes**

❑ APPROACHES TO DESIGN CONTROLLED RELEASE FORMULATIONS

1. **Dissolution controlled release**
   - ✓ Encapsulation Dissolution control
   - ✓ Seed or granule coated
   - ✓ Micro encapsulation
   - ✓ Matrix Dissolution control
2. **Diffusion controlled release**
   - ✓ Reservoir type devices
   - ✓ Matrix type devices
3. **Diffusion and Dissolution controlled systems**
4. **Ion exchange resins**
5. **Osmotically controlled release**

❖ Dissolution controlled release

It is a rate determining step when **liquid is diffusing from solid**. Several theories explain dissolution:

- ✓ Diffusion layer theory,
- ✓ Surface renewal theory,
- ✓ Limited solvation theory.

Noyes Whitney Equation

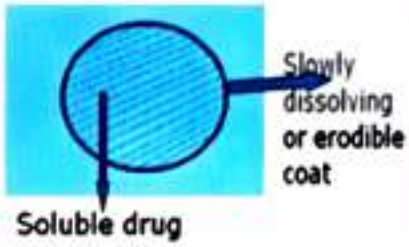
$dc/dt = kD.A\ (Cs - C)$

$dc/dt = D/h\ A.\ (Cs - C)$

dc/dt = Dissolution rate,
K = Dissolution rate constant (1st order),
D = Diffusion coefficient/diffusivity,
Cs = Saturation/maximum drug solubility,
C = Conc. Of drug in bulk solution
Cs-C = Concentration gradient,
h = Thickness of diffusion layer.

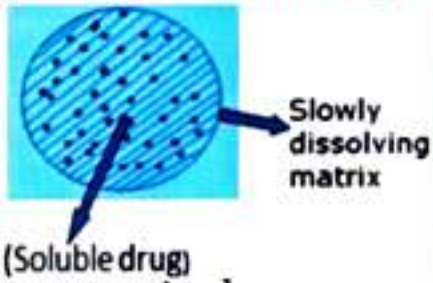
➢ Encapsulated dissolution system

- This is also known as **coating dissolution controlled system.**
- Dissolution rate of coat depends upon **stability & thickness of coating.**
- Controlled release **by decreasing the dissolution rate of drugs** which are highly water soluble can be formulated by preparing appropriate salt.



➢ Matrix dissolution system

- It is also known as **monolithic dissolution controlled system.**
- In this dissolution is controlled by: Altering porosity of tablet, decreasing its wet ability, dissolving at slower rate.
- It follows **first order drug release.**



❖ Diffusion controlled system

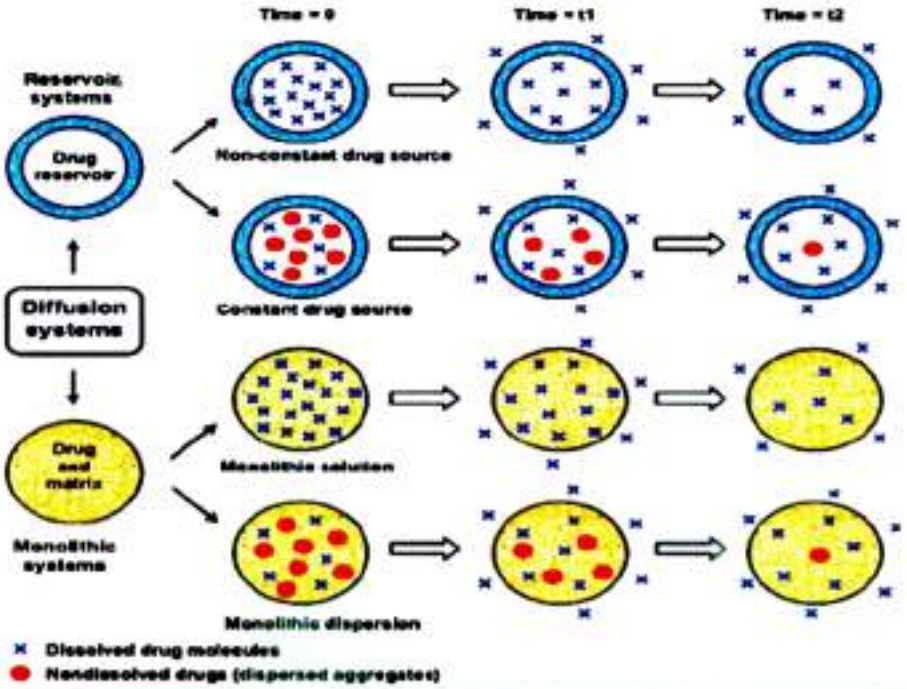
- It is a major process for **absorption** in which no energy required.
- In this drug molecules diffuse from a region of **higher concentration to lower concentration** until equilibrium is attained and it is **directly proportional to the concentration gradient** across the membrane.
- In this system release rate is **determined by its diffusion through a water-insoluble polymer.**

➢ Reservoir diffusion system

- It is also called as **laminated matrix device.**
- It is a hollow system containing **an inner core surrounded by water insoluble membrane** and polymer can be applied by coating or micro encapsulation.
- The Rate controlling mechanism is that drug will partition into membrane and exchange with the fluid surrounding the drug by diffusion. Commonly used polymers are HPC, ethyl cellulose & polyvinyl acetate.
- **Examples: Nico-400, Nitro-Bid.**

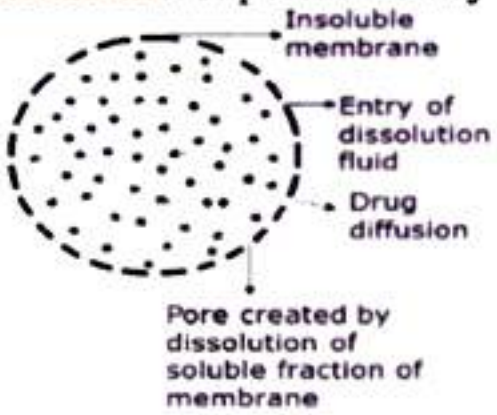
➢ Matrix dissolution system

- **Rigid Matrix Diffusion:** Materials used are insoluble plastics such as PVP.
- **Swellable Matrix Diffusion:** it is also called as **Glassy hydro gels** and popular for sustaining the release of highly water soluble drugs. Materials used are hydrophilic gums.
- Examples:
  - ✓ Natural- Guar gum, Tragacanth.
  - ✓ Semi synthetic -HPMC, CMC, Xanthum gum.
  - ✓ Synthetic -Polyacrilamides.
  - ✓ Examples: Glucotrol XL, Procardia XL



❖ Dissolution & Diffusion Controlled Release system

- In this drug is encased in a **partially soluble membrane** and **pores are created due to dissolution of parts of membrane.** It permits entry of aqueous medium into core & drug is dissolved or diffused out of the system.
- Ex- Ethyl cellulose & PVP mixture dissolves in water & creates pores of insoluble ethyl cellulose

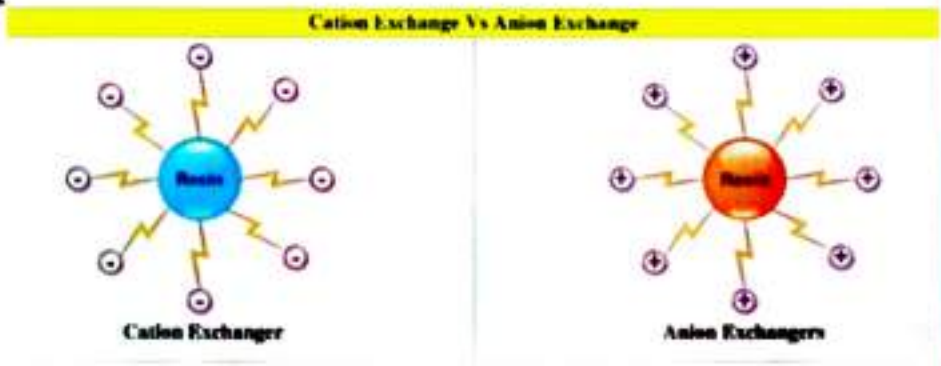


❖ Ion exchange resins controlled release system

- Ion exchange resins are **cross-linked water insoluble polymers** carrying ionizable functional groups.
- These resins are used for **taste masking** and controlled release system. The formulations are developed by **embedding the drug molecules in the ion-exchange resin matrix** and this core is then **coated with a semi permeable coating material** such as Ethyl Cellulose.
- In tablet formulations ion-exchange resins have been used as **disintegrant.**

➢ **Principle:**

- ✓ Is based on preparation of totally **insoluble ionic material**
- ✓ Resins are **insoluble in acidic and alkaline media**
- ✓ They contain **ionizable groups** which exchanged for drug molecules
- ✓ IER are capable of **exchanging positively**
- ✓ **or negatively charged drug** molecules to
- ✓ form insoluble poly salt resinates.



❑ PHYSIOLOGICAL AND BIOLOGICAL PROPERTIES OF DRUGS

❖ Physiological properties

➢ Aqueous Solubility's:

- Weak water soluble drugs are difficult to design the controlled release formulations.
- High aqueous solubility drug show burst release followed by a rapid increment in plasma drug concentration.
- BCS class-III & IV drugs are not a suitable candidate for this type of formulations.

➢ Partition coefficient (P-value):

- P-value denotes the fraction of the drug into oil & aqueous phase that is a significant factor that affects the passive diffusion of the drug across the biological membrane.
- The drugs are having high or low P value not suitable for CR, it should be appropriate to dissolve in both phases.

➢ Drug pKa:

- pKa is the factor that determined the ionization of drug at physiological pH in GIT.
- Generally, the high ionized drugs are poor candidates for CRDDS.

➢ Drug stability:

- Drugs that are stable in acid/base, enzymatic degradation, and other gastric fluids are good candidates for CRDDS.

➢ Molecular size & molecular weight:

- The molecular size & molecular weight are two important factors which affect the molecular diffusibility across a biological membrane.
- The molecular size less than 400D is easily diffuse but greater than 400D create a problem in drug diffusion.

➢ Protein binding:

- The drug-protein complex act as a reservoir in plasma for the drug.
- Drug showing high plasma protein binding are not a good candidate for CRDDS because Protein binding increases the biological half-life.

❖ Biological factors

➢ Absorption:

- The absorption rate should rapid then release rate to prevent the dose dumping.
- The various factors like aqueous solubility, log P, acid hydrolysis, which affect the absorption of drugs.

➢ Biological half-life ($t_{1/2}$):

- Ideally, the drugs having $t_1/2$ 2-3 hrs are a suitable candidate for CRDDS.
- Drugs have t1/2 more than 7-8 hrs not used for controlled release system.

➢ Dose size:

- The CRDDS formulated to eliminate the repetitive dosing, so it must contain the large dose than conventional dosage form.

➢ Therapeutic window:

- The drugs with narrow therapeutic index are not suitable for CRDDS.
- If the delivery system failed to control release, it would cause dose dumping and ultimate toxicity.

➢ Absorption window:

- The drugs which show absorption from the specific segment in GIT, are a poor candidate for CRDDS.
- Drugs which absorbed throughout the GIT are good candidates for controlled release.

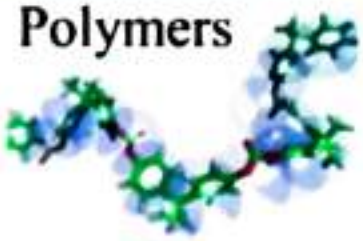
UNIT-I

POLYMERS

Points to be covered in this topic

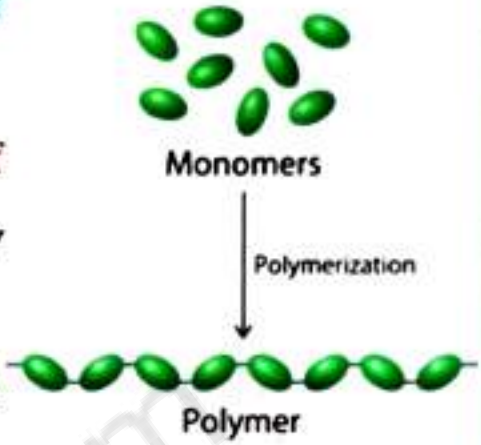
- ❑ INTRODUCTION
- ❑ SIGNIFICANCE
- ❑ CLASSIFICATION
- ❑ PROPERTIES
- ❑ ADVANTAGES OF POLYMERS IN CRDDS
- ❑ APPLICATION OF POLYMERS IN FORMULATION OF CDDS

POLYMERS



❑ INTRODUCTION

- The word "polymer means "many parts.
- A polymer is a large molecule made up of many small repeating units.
- Polymers are considered to be a subset of macromolecules. Macromolecule refers to any large molecule.
- A monomer is a small molecule that combines with other molecules of the same or different types to form a polymer.

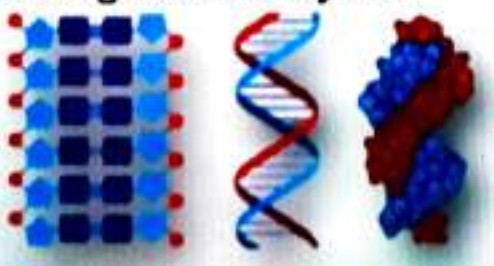


❑ SIGNIFICANCE

- In the field of drug delivery, polymers are becoming increasingly significant.
- Polymers are the major tool for controlling the medication release rate from the formulation.
- Polymers can be used to conceal the flavor of a medicine, improve its stability, and change its release properties.

❑ CLASSIFICATION

- Natural Polymer
- Synthetic Polymers
  - ✓ Biodegradable Polymer
  - ✓ Non-biodegradable Polymer



Natural polymer

❖ Natural Polymer

- ✓ **Protein based polymer** : Collagen ,Albumin ,Gelatin
- ✓ **Polysaccharides**: Alginate, Cyclodextrin, Chitosan, Dextran, Agarose, Hyaluronic acid, Starch,Cellulose

❖ Synthetic Polymers

✓ Biodegradable Polymer

- **Polyester:** Poly lactic acid, Poly glycolic acid, Poly hydroxyl butyrate, Polyester, Polycaprolactone, Poly lactide-co-glycolide (PLGA), Poly diaxonone
- **Polyanhydride:** Poly adepic acid, Poly sebacic acid, Poly terpthalic acid
- **Polyamides**: Poly amino acid, Poly imino carbonate
- **Phosphorous based polymer:** Polyphosphates, Polyphosphonates, Poly Phosphazenes

✓ Non-Biodegradable polymers

- **Cellulose derivative**: Carboxy methyl cellulose, Ethyl cellulose, Cellulose acetate, hydroxylpropyl methyl cellulose.
- **Silicons**: Polydimethyl siloxane, Colloidal silica, Polymethacrylate, Polymethyl methacrylate
- **Others**: Poly vinyl pyrolidine, Ethyl vinyl acetate, Poloxamine etc.

Biodegradable Polymer

- ✓ Natural polymers and their modified derivatives (e.g. starch, cellulose) as well as **synthetic polymers (e.g. polyacrylamides, polyacrylates, and polyethylene glycol)** are utilised in the technology of prolonged release medication formulation.
- ✓ In order to build a good **medication delivery system**, the **polymer matrix** must be chosen carefully.

- ✓ **Degradable polymers** are favoured for medication delivery applications since they **do not require surgical removal.**
- ✓ They disintegrate into smaller, more absorbable molecules, therefore it's crucial to ensure sure the **monomers are not hazardous.**
- ✓ **Polylactide (PLA) and Poly Lactide co Glycolide (PLGA)** are the most commonly utilised polymers for this application.

Biodegradable

- ✓ These polymers have been utilised in biomedical applications for over 20 years and are **biodegradable, biocompatible, and non-toxic.**

Non-Biodegradable Polymers

- ✓ Non-degradable polymers have **the primary disadvantage** of requiring **surgery to remove them from the body** once the medication has been depleted.
- ✓ **As a result, non-biodegradable polymers can only be used if the implant can be easily removed.**

❑ PROPERTIES

- The following properties are used to classify the polymers for medication delivery:
  - ✓ **Source:** A polymer might be **synthetic, natural, or a mix** of two.
  - ✓ **Chemical nature: polyester, polyanhydride, protein-based, cellulose derivatives**, and so on can all be used.
  - ✓ **Backbone stability**: either **biodegradable or non biodegradable** polymers exist.
  - ✓ **Solubility**: The polymer can be either **hydrophilic or hydrophobic** in nature.

- However, each of the above characteristics has its **own set of constraints**, such as the fact that natural polymers, while abundant and biodegradable, are difficult to copy and purify.
- Synthetic polymers have a high **immunogenicity**, which prevents them from being used for lengthy periods of time.

❑ ADVANTAGES OF POLYMERS IN CRDDS

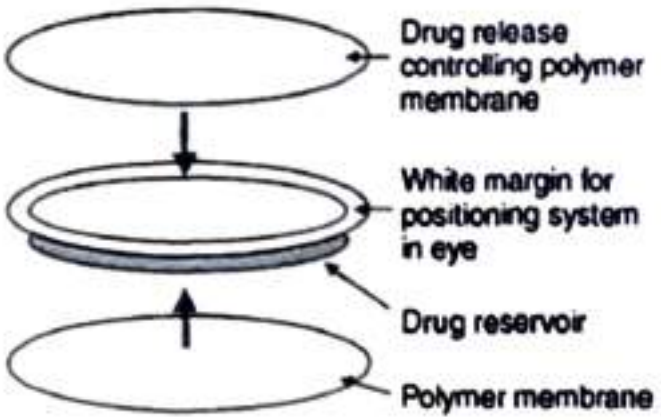
- Polymers are the most promising option for controlled drug administration because of their attractive, flexible features and ease of production at industrial scale, and potential for further modification.
- Polymer therapeutics include linear or branched polymer chains that act as a bioactive molecule, such as polymeric drugs, or as an inert carrier for a drug
- Polymers play an important part in the advancement of drug delivery technology by offering long repetitive dose and coordinated release of medicines.
- There are several advantages to using a polymer as an inert carrier to which a drug can be conjugated.
- Rheumatoid arthritis, diabetes, hepatitis B and C, cancer, and ischemia have all been targeted with polymer conjugates.
- This is a critical for the persistent growth of this field and will continue to harvest accomplishment in the synthesis of novel biopharmaceuticals.

❑ APPLICATION OF POLYMERS IN FORMULATION OF CDDS

❖ The Ocuserts System:

- The use of conventional drug delivery systems, such as drops and ointments, to transport therapeutic agents to the eye for the treatment of eye problems (eg, glaucoma), is an inefficient process.

- The use of polymeric **implants inserted under the lower cul de-sac** of the eye improves the **efficiency** of ocular medication delivery.
- **Pilocarpine** is distributed within an **alginic acid matrix** in this system, which is sandwiched between two polymer layers (ethylene-co-vinyl acetate).



❖ Transdermal Patches:

- Transdermal medication delivery entails the **drug diffusing through the skin and eventually being absorbed into the systemic circulation.**
- The drug delivery system is made up of **many layers**, including a **metallic backing layer** that prevents drug loss by **being resistant to drug diffusion**, a drug containing reservoir, a rate controlling membrane, and an adhesive layer.
- Membrane controlling drug diffusion Adhesive layer. The medicine is dissolved or disseminated in the matrix using solid polymer (acrylate co-polymer).