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**.

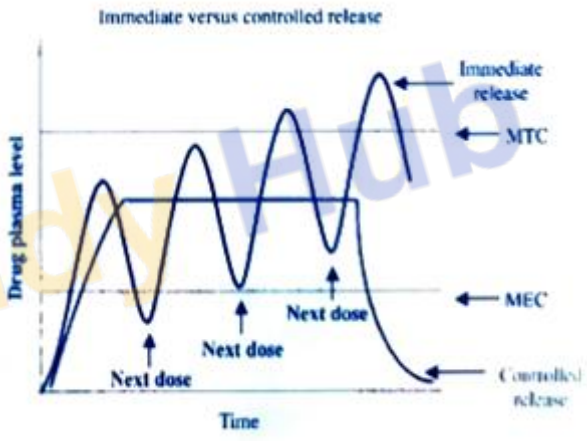
• To achieve & maintain **therapeutically effective plasma concentration**.

• 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 DELIVERY 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**

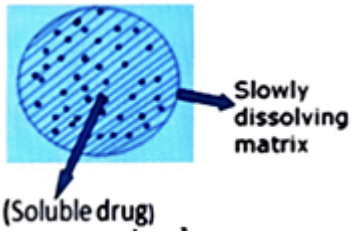
• In this dissolution is controlled by:

– 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

• Drug molecules diffuse from a region of **higher concentration to lower concentration** until equilibrium is attained

• Release rate is directly proportional to the **concentration gradient across the membrane**

• Release rate is determined by diffusion through a **water-insoluble polymer**

❖ RESERVOIR DIFFUSION SYSTEM

• Also called **laminated matrix device**

• Hollow system containing an **inner core surrounded by water insoluble membrane**

• Polymer can be applied by coating or micro-encapsulation

• Drug partitions into membrane and exchanges with surrounding fluid by diffusion

• Common polymers: **HPC**, **ethyl cellulose**, **polyvinyl acetate**

Examples:

• Nico-400

• Nitro-Bid

❖ MATRIX DIFFUSION SYSTEM

Rigid Matrix Diffusion

• Materials used: insoluble plastics such as **PVP**

Swellable Matrix Diffusion

• Also called **glassy hydro gels**

• Popular for sustaining release of highly water soluble drugs

• Materials used: hydrophilic gums

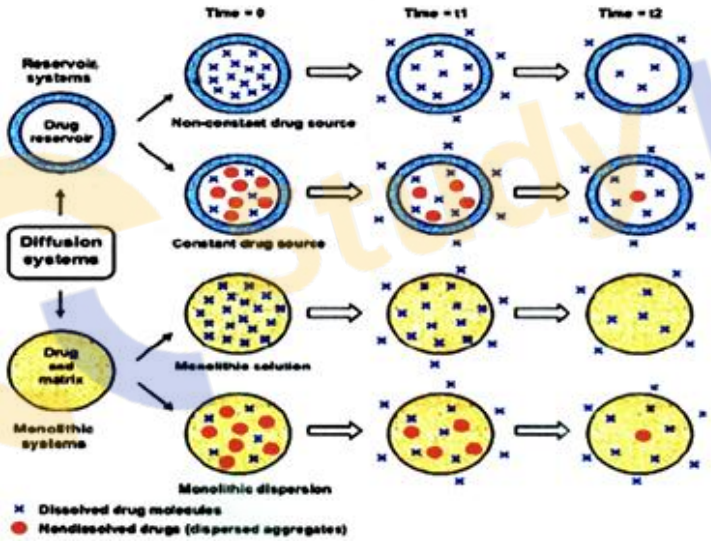
Examples:

✓ Natural – Guar gum, Tragacanth

✓ Semi-synthetic – HPMC, CMC, Xanthan gum

✓ Synthetic – Polyacrylamides

✓ Drug examples – Glucotrol XL, Procardia XL



❖ DISSOLUTION & DIFFUSION CONTROLLED RELEASE SYSTEM

• Drug is encased in a **partially soluble membrane**

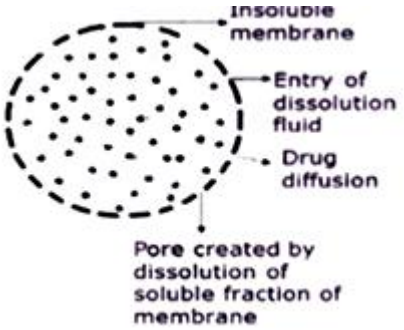
• Pores are created due to dissolution of parts of membrane

• Permits entry of aqueous medium into core

• Drug is dissolved or diffused out of system

Example:

• Ethyl cellulose & PVP mixture dissolves in water and 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

• Used for **taste masking** and controlled release system

• Drug molecules are embedded in ion-exchange resin matrix

• Core is coated with **semi-permeable coating** such as Ethyl Cellulose

• In tablet formulations, ion-exchange resins are used as **disintegrant**

Principle

✓ Based on preparation of totally insoluble ionic material

✓ Resins are insoluble in **acidic and alkaline media**

✓ Contain ionizable groups which exchange with drug molecules

✓ IER are capable of exchanging **positively** **or negatively charged drug molecules**

✓ Form insoluble poly-salt resinates

❖ PHYSIOLOGICAL AND BIOLOGICAL PROPERTIES OF DRUGS

Physiological Properties

Aqueous Solubility

• Weak water soluble drugs are difficult to design controlled release formulations

• High aqueous solubility drugs show **burst release** followed by rapid increase in plasma drug concentration

• BCS class-III & IV drugs are **not suitable candidates** for this type of formulation

Partition Coefficient (P-value)

• Denotes fraction of drug into oil & aqueous phase

• Significant factor affecting passive diffusion across biological membrane

• Drugs with very high or very low P-value are **not suitable**

• Should dissolve in both phases

Drug pKa

• Determines ionization of drug at physiological pH in GIT

• Highly ionized drugs are **poor candidates for CRDDS**

Drug Stability

• Drugs stable in acid/base, enzymatic degradation, and gastric fluids are good candidates for CRDDS

Molecular Size & Molecular Weight

• Important factors affecting molecular diffusibility across biological membrane

• Molecular size < **400D** diffuses easily

• Molecular size > **400D** creates diffusion problems

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 $t_{1/2}$ 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.

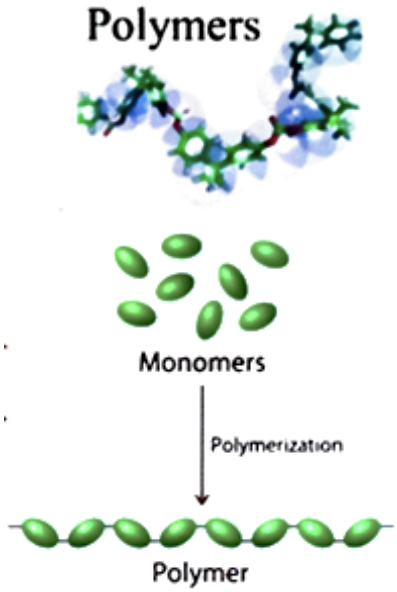
UNIT–I POLYMERS (PART - 2)

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

✓ 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 dioxanone

• Polyanhydride: Poly adipic acid, Poly sebacic acid, Poly terphthalic 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, hydroxypropyl methyl cellulose

• Silicons: Polydimethyl siloxane, Colloidal silica, Polymethacrylate, Polymethyl methacrylate

• Others: Poly vinyl pyrrolidine, Ethyl vinyl acetate, Poloxamine etc.

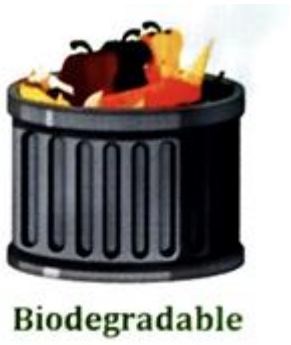
Biodegradable Polymer

✓ 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.

✓ 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**.

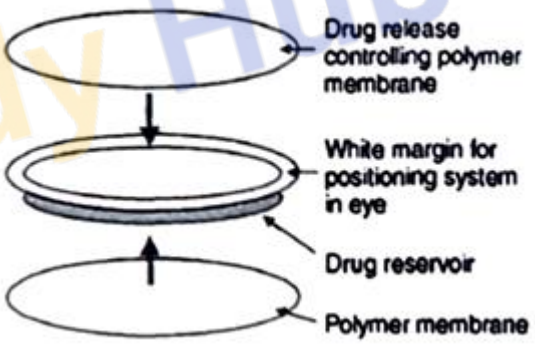
APPLICATION OF POLYMERS IN FORMULATION OF CDDS

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)**.