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Review on Control Drug Delivery System

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ABSTRACT

Controlled drug delivery systems have been developed to improve the next staging of the drug in the body. They can play a significant role in a targeted drug delivery system in organ or tissue. In the Controlled drug delivery system, more than one mechanism may be involved at different stages of drug pharmacokinetics and pharmacodynamics profiling. Some drug delivery systems have been formulated and are being investigated. These types of the system had some advantage over traditional drug delivery system, including a short time of drug release protection of breakable drugs and increased patient comfort and compliance.

INTRODUCTION

Controlled drug delivery systems can include the maintenance of drug levels within the desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance. While these advantages can be significant, the potential disadvantages cannot be ignored like the possible toxicity or non-biocompatibility of the materials used, undesirable by-products of degradation, any surgery required to implant or remove the system, the chance of patient discomfort from the delivery device, and the higher cost of controlled-release systems compared with traditional pharmaceutical formulations. The ideal drug delivery system should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize. The goal of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. With traditional drug delivery systems, the drug level in the blood follows the in which the level rises after each administration of the drug and then decreases until the next administration. [1]

HISTORY

The drug delivery field has advanced for more than 60 years. Two generations have passed since the introduction of the first controlled drug delivery system in the early 1950s. The technologies developed since the early 1950s until 2010, and the technologies necessary for treating various diseases in the next 30 years. The progress made during the last 60 years is divided into two generations: the first generation (1G) and the second generation (2G). During the 1G drug delivery, the main focus was to develop oral and transdermal formulations. During this time, the four main controlled release technologies were established: dissolution, diffusion, osmosis, and ion-exchange. With the technologies firmly established during the 1G, attention during the 2G was focused on the development of more advanced drug delivery systems, such as zero-order drug release systems and environment-sensitive delivery systems using smart polymers and hydrogels. Development of self-regulated insulin has been one of the active research areas, but it turns out to be much more difficult than simply responding to the changes in the blood glucose concentration. Insulin delivery with on-off capability has to be precise in quantity and time. This is very difficult to achieve with the technologies available today. Part of the 2G drug delivery was focused on developing injectable depot formulations for peptide delivery for weeks and months. To date,

only about a dozen of such products are available, and this number is minuscule when compared with thousands of successful oral formulations. The last 10 years of the 2G was consumed by developing nanotechnology-based formulations. [2]

CLASSIFICATION OF CONTROLLED RELEASE SYSTEM

The controlled release system divided into the following major classes based on release Pattern.

(1) Rate pre-programmed drug delivery system

(2) Activated modulated drug delivery system

(3) Feedback regulated drug delivery system

(4) Site targeting drug delivery system

(1) Rate pre-programmed drug delivery system:

In this, the release of drug molecules from the delivery system is pre-planed with a particular flow rate profile of the medicine. The system controls the molecular diffusion of drug molecules in or across the barrier medium within or surrounding the delivery system.

A. Polymer membrane permeation controlled system :

In this system, the drug is completely or partially encapsulated in a drug reservoir cubicle whose drug-releasing surface is covered by flow rate controlling polymeric membrane. In the drug reservoir, the drug can be solid or dispersion of solid drug particle or concentrated drug solution in a liquid or a solid type dispersion medium. The polymeric membrane may be made-up of the fabricated form of a homogeneous or heterogeneous non-porous or partial microporous or semipermeable membrane.

B. Polymer matrix diffusion-controlled system :

In this drug, the reservoir is prepared by the homogeneously dispersing drug particles in the rate-controlling hydrophilic or lipophilic polymer matrix. The resultant medicated polymer matrix provides the medicated disk with a defined surface area and controlled thickness.

C. Micro reservoir partition controlled system :

The drug reservoirs are a suspension of the solid particles in the aqueous solution of the water-miscible polymer. The micro-dispersion partition controlled system is prepared by applying high dispersion techniques. In short reservoir and matrix dispersion forms micro-reservoir.

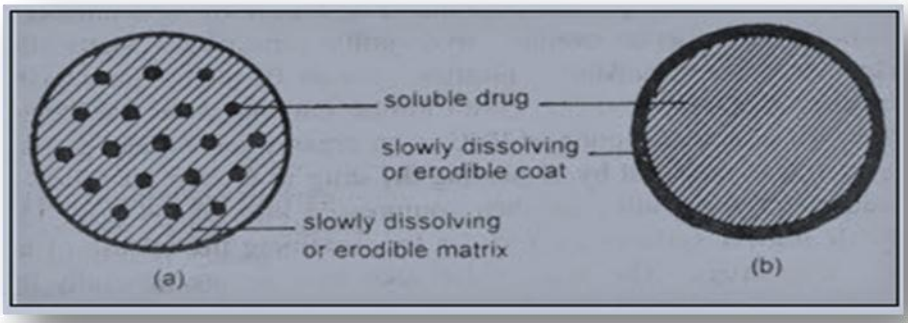


Figure No. 1: Matrix and membrane type delivery systems

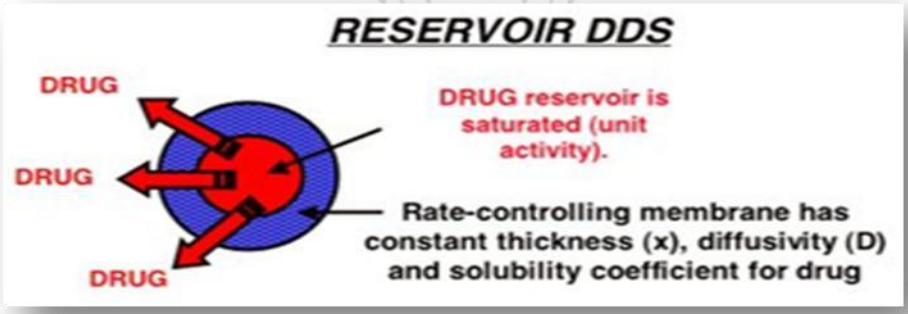


Figure No. 2: Reservoir type drug delivery system

(2) Activated modulated drug delivery system

In this, the release of drugs from the delivery system is controlled or activated by some physical, chemical and biological processes or by any supplied external energy source. Drug release controlled by the energy input or any applied process. This activation process can be classified into the following categories.

Activation by physical process

a) Osmotic pressure activated the system

In this osmotic pressure is used as the driving force for the release of drug in a controlled manner.

b) Hydrodynamic pressure activated the system

This drug is placed into the collapsible impermeable container which contains liquid drugs and forms a drug reservoir compartment. It is present inside the rigid shape cover.

c) Vapour pressured activated system

In this, a liquid exists in equilibrium with its vapor phase and pressure of the independent volume of fluid. One device is used for pressure control delivery, the device consists of two chambers, one contains the drug solution and second with a vaporizable fluid such as fluorocarbon. After shooting of drug, volatile liquid vaporizes at the body temperature and creates a vapor pressure that compresses the below chamber, which releases the drug in a controlled way.

d) Mechanically activated system

In this, a storage place or drug reservoir equipped with a mechanically activated pumping system. A controlled amount drug is delivered into the body cavity, such as nose or mouth, through a spray system which works on mechanically drug delivery pumping system. The spray volume of the delivered drug is fixed in each pumped spray. Ex metered-dose nebulizer for the luteinizing hormone-releasing hormone (LHRH).

e) Magnetically activated system

In this, the Drug reservoir is made-up of peptide or protein powder in a polymer matrix. These reservoirs contain the macromolecule drug which is magnetically controlled and delivered the drug. In some cases, the electromagnetically vibration mechanism is also used.

f) Sonophoresis activated system

In this, the ultrasonic device is used for the activation of drug delivery. A very low frequency (55 kHz) for a very short time (15seconds) is used for the drug delivery through the skin. This

ultrasonic device is a battery-operated a handheld system that contains a control unit, ultrasonically generated horn, disposable coupling medium sealed unit, and a return electrode. These devices are fabricated by Bio-degradable and non-degradable polymer.

g) Iontophoresis activated system

Iontophoresis activated the system in which the penetration of ionized drug molecules through the biological membrane under the presence of external electric current. In this, a small amount of electric current is used to penetrate the drug (charge) into the skin by using an electrode of the same polarity as the charge on the drug. The drug enters the skin due to only electrostatic repulsion force. The penetration of the drug into the skin is directly proportional to the current density which can be adjusted.

h) Hydration activated system

In this drug, the reservoir is homogeneously dispersed in a sellable polymer matrix fabricated from a hydrophilic polymer. The induced hydration systems stimulate the release of the drug. The release of the drug is controlled by the rate of swelling of the polymer matrix.

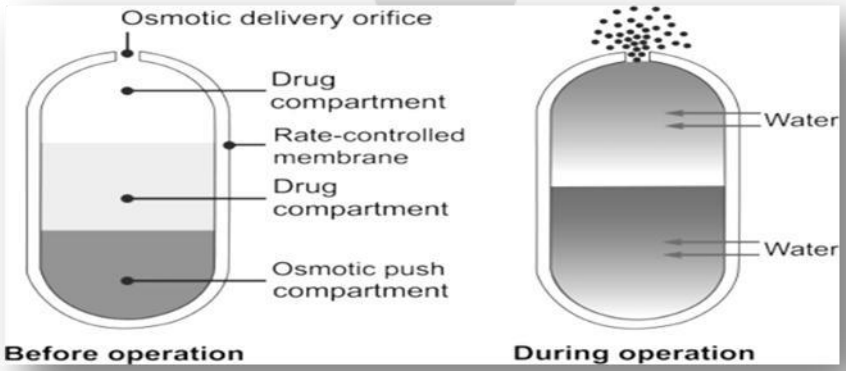


Figure No. 3: Osmotic drug delivery

- **Activation by chemical process :**

I. pH-activated system

Drugs are developed to target drug delivery only in the intestinal tract, not in the stomach. Drugs are coated with the gastric fluid-sensitive drug with a combination of intestinal fluid-insoluble polymers like ethyl cellulose and hydroxyl methyl cellulose phthalate. The coated

drugs have resistant against the gastric fluid (pH<3) thus drugs are protected from acidic degradation. In the small intestine, the intestinal fluid dissolves the coated membrane of drugs due to the high pH of intestinal fluid (pH>7.5). Thus, pH controls the delivery of drugs inside the human body.

II. Ion activated system

In this, only ionic and ionizable drugs are prepared because the gastrointestinal fluid has regularly maintained the level of ions and the delivery of drugs modulated by this method.

III. Hydrolysis activated system

In this, the drug reservoir is encapsulated in a microcapsule. It is also made up of the implantable device. All these systems are prepared from biodegradable polymers. The release of drug activated by the hydrolysis degradation of the polymer chain and the rate of drug delivery is controlled by the polymer degradation rate.

- **Activation by biochemical means:**

In this drug, the release is activated by the biochemical reaction.

- **Enzymatic activated system :**

This system depends upon the enzymatic activity for the release of drugs.

(3) Feedback regulated drug delivery system:

In this, a physiological response activates the release of drugs from the carrier. A triggering agent activates the process of release of the drug, such as a biochemical substance, in the body via some feedback mechanisms. The rate of drug release is synchronized by the concentration of a triggering agent that is detected by a sensor used in the feedback-regulated drug delivery system. Feedback regulated drug delivery system is divided into three-part.

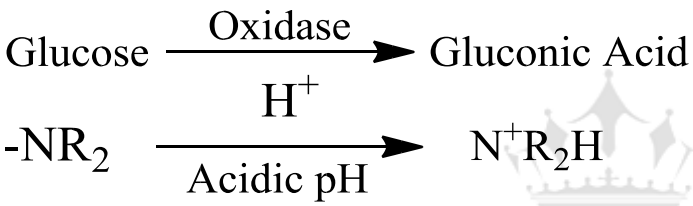
- **Bio-erosion regulated system**

In this, drug fabricated with polyvinyl methyl ether and coated with a layer of immobilized urease. In a solution with close to neutral pH, the polymer polyvinyl methyl ether erodes very slowly but in the presence of urea, urease forms ammonia at the surface of the drug and

metabolizes the urea. The cause of the change of pH increases the rapid degradation of polymer matrix and release of drug molecules.

- **Bio-responsive regulated system**

In this, the drug reservoir is enclosed in the bioresponsive polymeric membrane and permeability of the drug molecule is controlled the contraction of biochemical agents in the tissue. Ex. Glucose-triggered insulin delivery system. In this delivery system, the insulin reservoir is covered by the hydrogel membrane which contains the NR2 (amide group) group. In an alkaline solution, the NR2 group is fixed, and the membrane is unswollen and impermeable to insulin. As glucose entered into the membrane, oxidized inside the membrane and forms gluconic acid. This process triggered the protonation of NR_2 into N^+R_2H and the hydrogel layer becomes swollen and thus permeable to insulin molecule by the process of self-regulated processes.



- **Self-Regulating Drug Delivery Systems**

This mechanism is regulated by the reversible and competitive binding mechanism for the activation and release of drugs. In this, the drug reservoir encapsulated within a polymeric semipermeable membrane. The release of the drug is activated by the biochemical agent of the tissue. Ex. A biological derivative complex (insulin- sugar-lactin) is encapsulated within a semipermeable membrane to produce a controlled drug delivery system. As blood glucose diffuses into this system (CrDDS), it binds with lectin molecules and activates the release of insulin sugar from the binding site, and its concentration depends on the concentration of glucose. Thus, the whole process completed by a self-regulating drug delivery system.

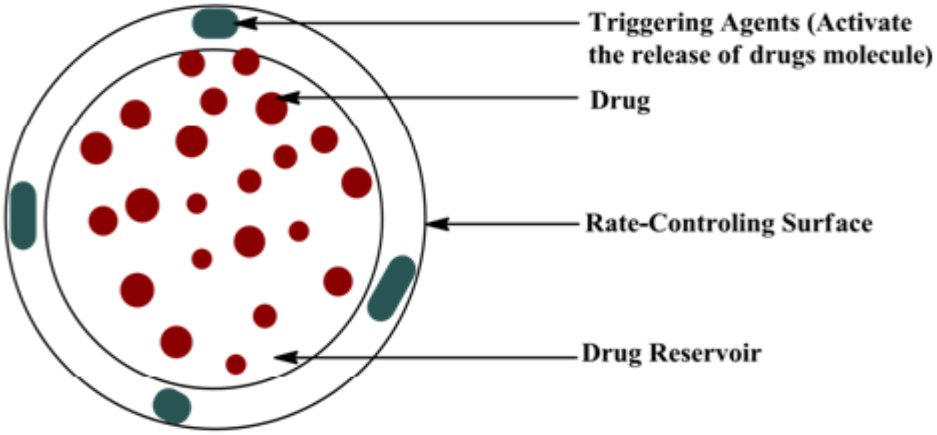


Figure No. 4: Feedback drug delivery system. Triggering agents activate the release of drugs.

(4) Site targeting drug delivery system:

Delivery of drugs to the targeted site (tissue) is complex, and it is consists of multiple steps of diffusion and partitioning. It is an uncontrolled release of drugs from the drug delivery system, but the path of drug release should be in control. To get read of uncontrolled drug release, the drug delivery system should be site targeting specific. It is divided into three parts.

- **First-order targeting: -**In this, drugs carrier release the drugs at the targeted site such as organ, tissue, cavity, etc.

- **Second-order targeting**: - In this, drugs carrier release the drugs in the specific cell such as tumors cells not to the normal cells. This is also called as the selective drug delivery system.

- **Third-order targeting**: - In this, drugs carrier release the drugs to the intracellular site of targeted cells.

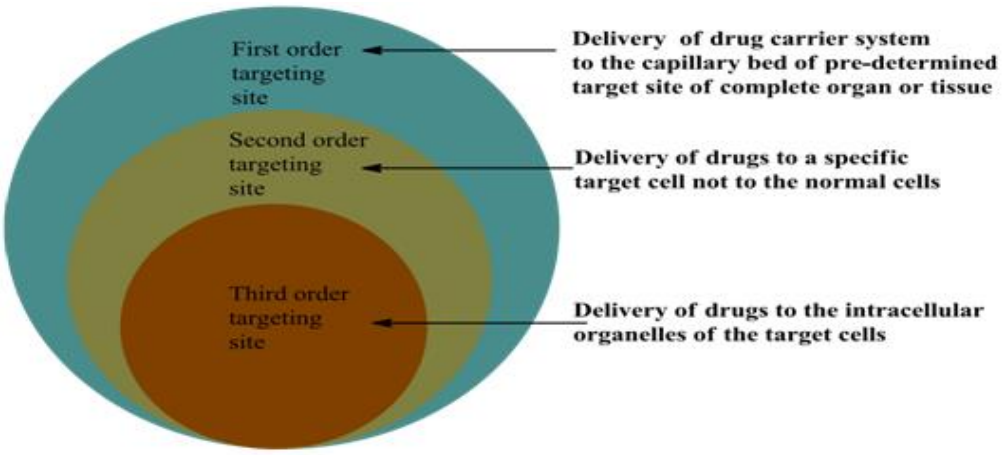


Figure No. 5:- Site targeted drug delivery system

❖ Site targeting drug delivery system also classified as:

➢ **Passive targeting**: -In this, drugs carrier releases the drug at a particular site due to the cause of physicochemical or pharmacological signal.

➢ **Active targeting:** Active targeting is also called as the ligand-mediated targeting. In this ligand (drugs) are present on the nanoparticle surface and interact with the cells or diseased cells. Ligand molecules are selected with the interaction of the infected cells, and it should not disturb the healthy cells. Therefore, it is aimed to design the specific ligand for specific diseased cells. Some physicochemical properties may affect the interaction of ligands cell binding, as the ligand density, the size of nanoparticles and choice of targeting ligand for cells. An example of active targeting is the use of the monoclonal antibody for the treatment of cancer.[3]

MECHANISM OF CONTROLLED DRUG RELEASE SYSTEM:

1. Diffusion Controlled System:

The diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. The flux of the drug J (in amount/area -time), across a membrane in the direction of decreasing concentration is given by Fick's law.

$$J = - D \, dc/dx$$

Where, D = diffusion coefficient in area/ time dc/dx = change of concentration 'c' with distance 'x' Diffusion systems are characterized by the release rate of the drug is dependent on

its diffusion through inert water-insoluble membrane barrier. There are two types of diffusion devices.

(a) Reservoir Type:

In the system, a water-insoluble polymeric material encloses a core of the drug, which controls the release rate. The drug will partition into the membrane and exchange it with the fluid surrounding the particle or tablet. The additional drugs will enter the polymer, diffuse to the periphery and exchange with the surrounding media. The polymers commonly used in such devices are Ethylcellulose and Poly-vinyl acetate.

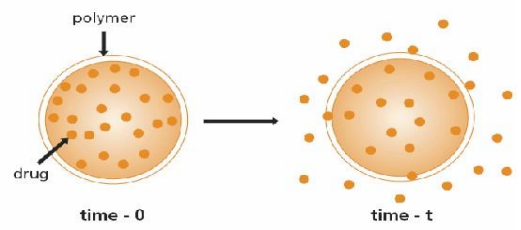


Figure No. 6: Schematic Representation of Reservoir Diffusion Controlled Drug Delivery Device

The rate of drug released (dm/dt) can be calculated using the following equation:

$$\frac{dm}{dt} = ADK \frac{\Delta C}{\ell}$$

Where, A = Area,

D = Diffusion coefficient,

K = Partition coefficient of the drug between the drug

Core and the membrane, ℓ = Diffusion path length and

ΔC= Concentration difference across the membrane.

Advantage: By this system Zero-order delivery is possible, release rates variable with polymer type.

Disadvantages: The system must be physically removed from implant sites. Difficult to deliver high molecular weight compound, generally increased the cost per dosage unit, potential toxicity if the system fails.

(b) Matrix Type:

A solid drug is homogeneously dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution.

2. Dissolution Controlled Systems:

Drugs having high aqueous solubility and dissolution rate, show challenges in controlling their dissolution rate. The dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. The rate-limiting step for the dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusion boundary layer. The rate of dissolution (dm/dt) can be approximated by:

$$\frac{dm}{dt} = \frac{ADS}{h}$$

Where, S = Aqueous solubility of the drug.

A = Surface area of the dissolving particle or tablet. D = Diffusivity of the drug and h = Thickness of the boundary layer.

(a) Encapsulation Dissolution Controlled Systems:

The drug particles are coated or encapsulated by microencapsulation techniques with slowly dissolving materials like cellulose, polyethylene glycols, polymethacrylates, waxes, etc. the dissolution rate of the coat depends upon the solubility and thickness of the coating.

(b) Matrix Dissolution Controlled Systems:

In matrix systems, the drug is homogeneously dispersed throughout a rate-controlling medium. They employ waxes such as beeswax, carnauba wax, hydrogenated castor oil, etc.

which control drug dissolution by controlling the rate of dissolution fluid penetration into the matrix by altering the porosity of the tablet, decreasing its wettability or by itself getting dissolved at a slower rate. The drug release is often first order from such matrices. The wax embedded drug is generally prepared by dispersing the drug in molten wax and solidifying and granulating the same.

3. Dissolution and Diffusion Controlled Release Systems:

The drug core is enclosed in a partially soluble membrane. Pores are thus created due to the dissolution of parts of the membrane which permit entry of aqueous medium into the core and hence drug dissolution and diffusion of the dissolved drug out of the system. An example of obtaining such a coating is using a mixture of ethylcellulose with polyvinyl pyrrolidine or methylcellulose

4. Water Penetration Controlled Systems:

In water penetration controlled delivery systems, rate control is obtained by the penetration of water into the system. They are:

(a) Swelling Controlled Systems:

Swelling controlled release systems are initially dry and when placed in the body absorbs water or other body fluids and swells. Swelling increases the aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into the external environment.

(b) Osmotically Controlled Release Systems:

These systems are fabricated by encapsulating an osmotic drug core containing an osmotically active drug (or a combination of an osmotically inactive drug with an osmotically active salt eg. NaCl) within a semi-permeable membrane made from a biocompatible polymer, e.g. cellulose acetate. A gradient of osmotic pressure is created, under which the drug solutes are continuously pumped out of tablet through a small delivery orifice in tablet coating over a prolonged period through the delivery orifice. This type of drug system dispenses drug solutes continuously at a zero-order rate. The release of a drug is independent of the environment of the system.

5. Methods using Ion Exchange:

This system is designed to provide the controlled release of an ionic or ionizable drug. It is prepared by first absorbing an ionized drug onto the ion-exchange resin granules such as codeine base with Amberlite, and then after filtration from the alcoholic medium, coating the drug resin complex granules with a water-permeable polymer, e.g. a modified copolymer of polyacrylic and methacrylic ester, and then spray-drying the coated granules to produce the polymer-coated drug resin preparation. The drug is released by exchanging with appropriately charged ions in the GIT. The drug is then diffuse out of the resin.

$$\mathbf{Resin^{+} - drug^{-} + X^{-}Resin^{+} - X^{-} + drug^{-}}$$

Where X- are ions in the GI tract

✓ The rate of diffusion control by the area of diffusion, diffusion path length, and rigidity of resin.

✓ Thus, drug release depends on the ionic environment (pH, electrolyte conc.) and the properties of the resin.

✓ **Advantage -** for those drugs which are highly susceptible to degradation by enzymatic processes since it offers a protective mechanism by temporarily altering the substrate.

✓ **Limitation -** The release rate is proportional to the conc. of the ions present in the vicinity of the administration site. So variable diet, water intake & intestinal contents affect the release rate of the drug.

✓ They are mainly of **2 types -** cation exchange and anion exchange resin.

Cationic Drugs

A cationic drug forms a complex with an anionic ion-exchange resin e.g. a resin with a SO_3^- group. In the GI tract Hydronium ion (H^+) in the gastrointestinal fluid penetrates the system and activity the release of cationic drugs from the drug resin complex.

$$\mathbf{H^{+} + Resin - SO_3 - Drug + \longrightarrow Resin - SO_3 - H^{+} + Drug^{+}}$$

Anionic Drugs

An anionic drug forms a complex with a cationic ion exchange resin, e.g. a resin with a [N $(CH_3)_3^+$] group. In the GI tract, the Chloride ion (Cl^-) in the gastrointestinal fluid penetrates the system and activates the release of anionic drugs from the drug resin complex.

$$Cl^- + Resin - [N(CH_3)_3^+] - Drug^- \longrightarrow Resin - [N(CH_3)_3^+] - Cl^- + Drug^-$$

6. Chemically Controlled Release Systems:

Chemically controlled release systems are the systems that change their chemical structure when exposed to the biological fluid. Mostly, biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains into biologically safe and progressively smaller moieties. It is of two types and they are:

Erodible systems and **Pendent chain system**

(i) Erodible Systems: In erodible systems, the mechanism of drug release occurs by erosion. Erosion may be two types and they are:

- **Bulk Erosion** process polymer degradation may occur through bulk hydrolysis.

✓ When the polymer is exposed to water hydrolysis occurs.

✓ Hydrolysis degrades the large polymers into smaller biocompatible compounds.

✓ These small compounds diffuse out of the matrix through the voids caused by swelling.

✓ Loss of the small compounds accelerates the formation of voids thus the exit of drug molecules.

✓ e.g. polylactide, polyglycolic acid

- **Surface Erosion** process Polymers like polyorthoesters and polyanhydrides etc. occur degradation only at the surface of the polymer, resulting in a release rate that is proportional to the surface area of the delivery system.

✓ When the polymer is exposed to water hydrolysis occurs

✓ Hydrolysis degrades the large polymers into smaller biocompatible compounds

- ✓ These small compound diffuse from the interface of the polymer
- ✓ Loss of the small compounds leads to drug loss
- ✓ Note these polymers do not swell.
- ✓ e.g. polyanhydrides

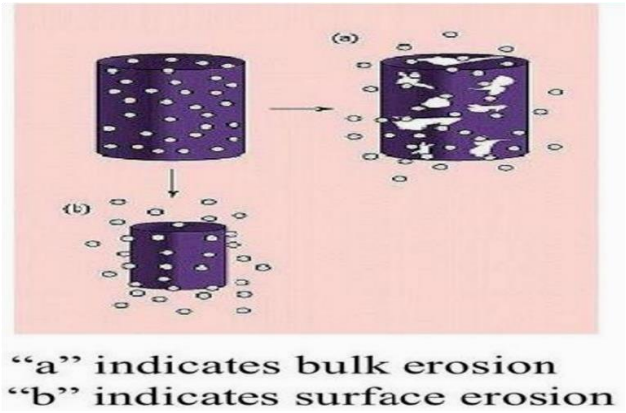


Figure No. 7: Bulk Erosion and Surface Erosion

(ii) Pendant Chain System:

Pendent chain systems consist of linear homo or copolymers with the drug attached to the backbone chains. The drug is released from the polymer by hydrolysis or enzymatic degradation of the linkages. Zero-order can be obtained and the cleavage of the drug is the rate-controlling mechanism. Example for polymers used in pendant chain systems like n-(2hydroxy propyl) methacrylamide etc.

7. pH– Independent Formulations:

The gastrointestinal tract presents some unusual features for the oral route of drug administration with relatively brief transit time through the gastrointestinal tract, which constraint the length of prolongation, further the chemical environment throughout the length of the gastrointestinal tract is a constraint on dosage form design. Since most drugs are either weak acids or weak bases, the release from sustained release formulations is pH-dependent. However, buffers such as salts of amino acids, citric acid, phthalic acid phosphoric acid or tartaric acid can be added to the formulation, to help to maintain a constant pH thereby rendering pH-independent drug release. A buffered controlled release formulation is prepared by mixing a basic or acidic drug with one or more buffering agents, granulating with

appropriate pharmaceutical excipients and coating with gastrointestinal fluid-permeable film-forming the polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH thereby rendering a constant rate of the drug.

8. Hydrogels:

Hydrogels are water-swollen three-dimensional structures composed of primarily hydrophilic polymers. They are insoluble because of chemical or physical cross-links. The physical cross-links include crystallites, entanglements or weak associations like hydrogen bonds or van der Waals forces. These cross-links provide physical integrity and network structure. Hydrogels provide desirable protection of labile drugs, peptides, and proteins.

9. Altered Density Formulations:

Several approaches have been developed to prolong the residence time of the drug delivery system in the gastrointestinal tract like a High-density approach and Low-density approach. [4]

- **ADVANTAGES OF CONTROLLED DRUG THERAPY:**

- This delivery system improved patient compliance especially with long-term treatments for chronic diseases.

- Conventional dosages form produce fluctuation in plasma drug concentration. These fluctuations depend on the drug kinetics within the body like absorption, distribution, metabolism, and excretion. Controlled release eliminates this type of fluctuation in plasma drug concentration.

- Reduction in dose and dosing frequencies

- Maintenance of required drug concentration in plasma thus eliminates the failure of drug therapy and improved the efficiency of treatments.

- A suitable delivery system for drugs which have a short biological half-life (3-4 hrs.) and drug rapidly eliminate from the body.[3]

- **DISADVANTAGES OF CONTROLLED DRUG THERAPY:**

- Dumping is a major disadvantage of CRDDS, which refers to the rapid release of a relatively large quantity of drugs from a controlled release formulation. This phenomenon becomes hazardous with potent drugs.

- Poor *in-vivo* & *in-vitro* correlations

- Difficult to optimize the accurate dose and dosing interval

- Patient variability affects the release rate like GI emptying rate, residential time, fasting or non-fasting condition, etc.[3]

CONCLUSION

Now a day's modern technologies including target concept have emerged for successful oral controlled delivery. Oral controlled release products provide advantages over conventional dosage form by optimizing bio-pharmaceutics, pharmacokinetics and pharmacodynamics properties of the drug in such a way that it reduces dosing frequency to an extent that once-daily dose is sufficient for therapeutic management through uniform plasma concentration provide the maximum utility of drug. From the above discussion, it is concluded that the oral controlled release drug delivery system has been commonly adopted and the most convenient route for drug delivery.

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