

CONTROLLED RELEASE DRUG FORMULATION IN PHARMACEUTICALS: A STUDY ON THEIR APPLICATION AND PROPERTIES

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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 targeted drug delivery system in organ or tissue. In 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 short time of drug release protection of breakable drugs and increased patient comfort and compliance. The review underlines the methodology of controlled drug delivery system preparation, their significance, disadvantages, detailed

classification and the relevant example wherever required are demonstrated. This review will give an insight to researcher and academician a current update on the topic. In this, a different method and different processes are involved. The paper deals with the stable drug delivery system.

KEYWORDS: Controlled release, dose size, drug delivery, physical process, enzyme activated system, self-regulated drug delivery system.

INTRODUCTION

The science of controlled release was first originated from the development of oral sustained release products in the 1940s and early 1950s^[1]. First of all, the controlled release of marine antifoulants (the 1950s) and controlled release of fertilizer (1970s) were formulated which had only a single application in the soil science^[2]. The development of the pharmacology and

pharmacokinetics demonstrated the importance of drug release rate in determining therapeutic effectiveness of therapy. This becomes the reason behind the development of controlled release^[1, 3].

The modified release dosage forms are entirely new. The first time Rhazes formulates mucilage coated pills about A.D 900^[4]. This technique widely adopted in the 10th century by European countries, in the form of gold, silver and pearl coated tablets; this coating modifies the drug release rates. Advancement in the coating technology including sugar & enteric coating on the pills & tablets in the late 1800s^[5]. The further coating developed to the enteric coating of tablets followed by incorporation of the second drug to sugar coating layer, this happened near about 1938. However, the first patent for oral sustained release preparation went in the favour of Lipowski; his preparation contained small coated beads that were releasing the drug slowly & constantly^[6]. This idea later developed by Blythe and launched the first marketed sustained release product in 1952. Over the past 30 years as the complication involves in the marketing of new drug increased and various advantages recognized of Controlled release drug delivery system (CRDDS), the greater attention is being paid in this field. Today the oral controlled drug delivery system becomes major drug delivery systems mainly drugs having high water solubility and short biological half-life^[7]. Other than oral, the various routes like transdermal, ocular, vaginal & parenteral route use for controlled release of various drugs^[8].

(1) CONTROLLED RELEASE

An ideal dosage regimen of drug therapy is one which rapidly attained the required plasma concentration and maintained for the entire period of treatment. The frequencies of drug administration primarily depend on the biological half-life of the drug and mean residential time (MRT). Conventional drug delivery system often produces over or under medication result in various adverse drug reactions (ADRs) due to unpredictable drug release pattern. The CRDDS alters the drug distribution along with reduction in drug toxicity^[9]. The term controlled release (CR) implies the predictability and reproducibility in the drug release kinetics which means the drug release from the delivery system proceed at the rate profile not only expected kinetically but also reproducible from one division to another. CRDDS intended to exercise control drug release in the body; this may be temporal or spatial nature or both^[10].

The term sustained release also mentioned during the description of controlled release^[11]. Sustained release (SR) used to describe a pharmaceutical dosage form formulated to retard the release of API such a way that its appearance in the systemic circulation is delayed or prolonged and plasma concentration sustained in duration. The onset of drug action delayed and duration of therapeutic effect is maintained^[12].

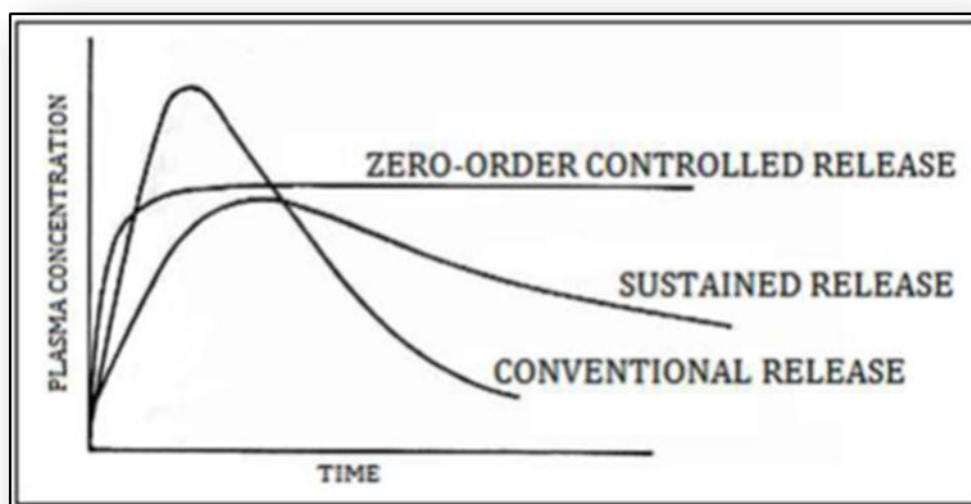


Fig. 1- Plasma drug concentration-time profile

ADVANTAGES OF CONTROLLED DRUG THERAPY^[13]

- This delivery system improved the 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 having a short biological half-life (3-4 hrs) and drug rapidly eliminate from the body.

DISADVANTAGES^[13c, 14]

- Dumping is a major disadvantage of CRDDS, which refers to the rapid release of a relatively large quantity of drug 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.

(2) FACTORS INFLUENCING THE DESIGN AND ACT OF CONTROLLED RELEASE PRODUCTS

(1) Physiological properties

(1) Aqueous Solubility's: Most of the active pharmaceutical moiety (API) are weakly acidic or basic in nature that affect the water solubility of API. 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. These types of drugs are a good candidate for CRDDS. The pH dependent solubility also creates a problem in formulating CRDDS. BCS class-III & IV drugs are not a suitable candidate for this type of formulations^[15].

(2) 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^[16].

(3) 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. The absorption of the unionized drug occurs rapidly as compared to ionized drugs from the biological membranes. The pKa range for an acidic drug that ionization depends on the pH is 3.0 to 7.5 and for a basic drug it lay between 7 and 11^[17].

(4) Drug stability: Drugs that are stable in acid/base, enzymatic degradation, and other gastric fluids are good candidates for CRDDS. If drug degraded in the stomach and small intestine, it not suitable for controlled release formulations because it will decrease in bioavailability of concern drug^[17].

(5) 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^[18].

(6) 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

the protein binding increases the biological half-life. So there is no need to sustain the drug release^[19].

(2) Biological factors

- (1) **Absorption:** Uniformity in rate and extent of absorption is an important factor in formulating the CRDDS. However, the rate limiting step is drug release from the dosage form. The absorption rate should be 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^[20].
- (2) **Biological half-life ($t_{1/2}$):** In general the drug is having short half-life required frequent dosing and suitable candidate for controlled release system. A drug with long half-life required dosing after a long time interval. 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^[20-21].
- (3) **Dose size:** The CRDDS formulated to eliminate the repetitive dosing, so it must contain the large dose than conventional dosage form. But the dose used in conventional dosage form give an indication of the dose to be used in CRDDS. The volume of sustained dose should be as large as it comes under acceptance criteria^[22].
- (4) **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^[23].
- (5) **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^[24].

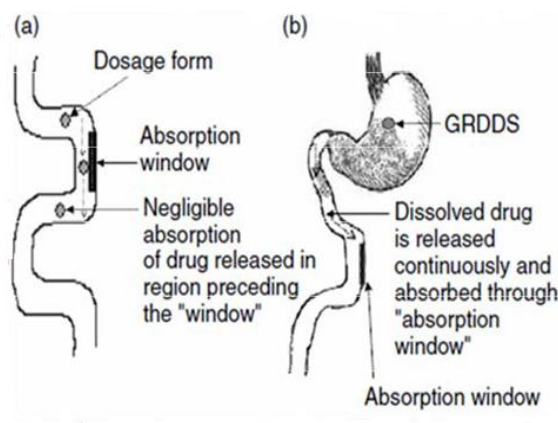


Fig.2- Absorption window

(6) **Patient physiology:** The Physiological condition of the patient like gastric emptying rate, residential time, and GI diseases influence the release of the drug from the dosage form directly or indirectly^[25].

Pharmacokinetic parameters consider during the drug selection listed as follow.

Table. 1-Pharmacokinetic parameters for drug selection

Parameter	Comment
Biological or elimination half-life	Should be between 2 to 6 hrs
Elimination rate constant(K_E)	Required for design
Total clearance(CL_T)	dose independent
Intrinsic absorption rate	should be greater than the release rate
Apparent volume of distribution (V_d)	V_d effect the required amount of the drug
Absolute bioavailability	Should be 75% or more
Steady state concentration (C_{ss})	lower C_{ss} and smaller V_d
Toxic concentration	The therapeutic window should be broader

(3) CLASSIFICATION OF CONTROLLED RELEASE SYSTEM

The controlled release system divided into following major classes based on release pattern^[26].

(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 molecule from the delivery system is pre-planned with particular flow rate profile of medicine. The system controls the molecular diffusion of drug molecules in or across the barrier medium within or surrounding the delivery system^[27].

(1) 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 drug reservoir, the drug can be solid or dispersion of solid drug particle or concentrated drug solution in a liquid or in a solid type dispersion medium. The polymeric membrane may be made-up of the fabricated form of homogeneous or heterogeneous non-porous or partial microporous or semipermeable membrane^[28].

(2) 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 defined surface area and controlled thickness^[29].

(3) Micro reservoir partition controlled system

The drug reservoirs are a suspension of solid particle in the aqueous solution of the water-miscible polymer. Micro-dispersion partition controlled system is prepared by the applying high dispersion techniques. In short reservoir and matrix dispersion forms micro-reservoir^[27]

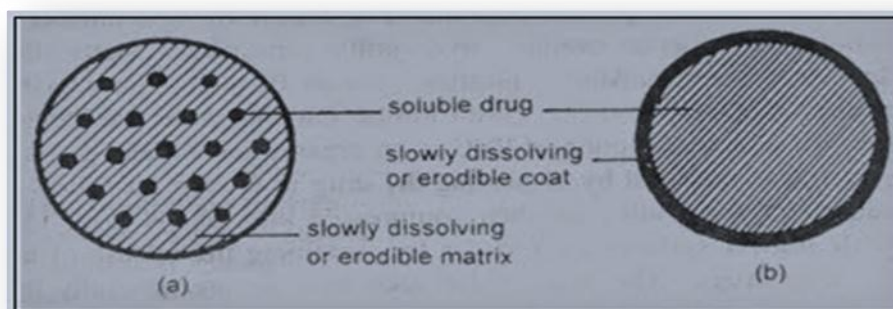


Fig. 3-Matrix and membrane type delivery systems

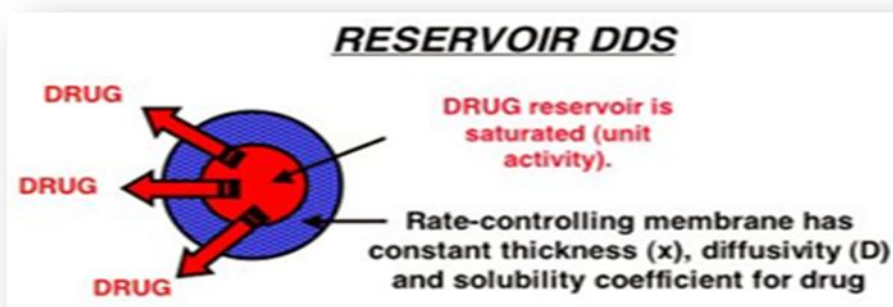


Fig. 4-Reservoir type drug delivery system

(2) Activated modulated drug delivery system

In this, the release of drugs from the delivery system is controlled or activated by the some physical, chemical and biological process 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^[27, 30].

(1) Activation by physical process**(1) Osmotic pressure activated system**

In this osmotic pressure is used as the driving force for the release of drug in a controlled manner^[31].

(2) Hydrodynamic pressure activated system

In this drug is placed into the collapsible impermeable container which contains liquid drugs and forms drugs reservoir compartment. It is present inside the rigid shape cover^[32]

(3) 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, device consist 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 vapour pressure that compresses the below chamber, which releases the drug in a controlled way^[33].

(4) 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 delivered drug is fixed in each pumped spray. Ex metered-dose nebulizer for the luteinizing hormone-releasing hormone (LHRH)^[27]

(5) Magnetically activated system

In this, 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, electromagnetically vibration mechanism is also used^[34].

(6) Sonophoresis activated system

In this, the ultrasonic device is used for the activation of drug delivery. A very low frequency (55 kHz) for very short time (15seconds) is used for the drug delivery through the skin. This ultrasonic device is a battery operated a handheld system which contains a control unit, ultrasonically generated horn, disposable coupling medium sealed unit, and a return electrode^[29]. These devices are fabricated by Bio-degradable and non-degradable polymer.^[35]

(7) 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^[29, 36]

(8) Hydration activated system

In this drug, the reservoir is homogeneously dispersed in a swellable 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 polymer matrix^[27].

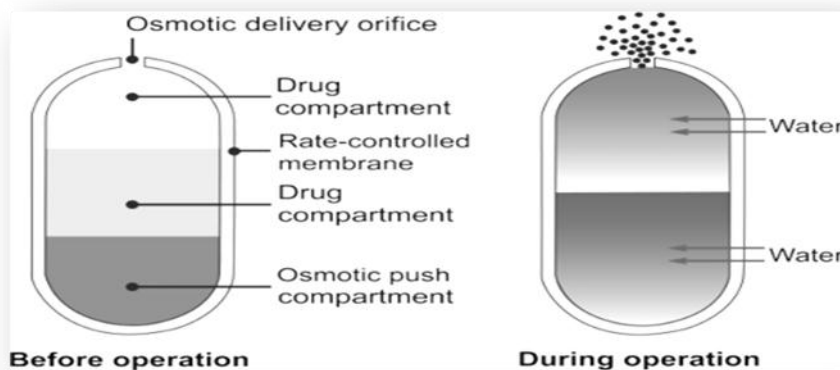


Fig. 5-Osmotic drug delivery

1. Activation by chemical process

(9) pH-activated system

In this drugs are developed to target the 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 ($\text{pH} < 3$) thus drugs are protected from the acidic degradation. In the small intestine, the intestinal fluid dissolves the coated membrane of drugs due to high pH of intestinal fluid ($\text{pH} > 7.5$). Thus, pH controls the delivery of drugs inside the human body.^[27]

(10) 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^[37].

(11) 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^[15].

(2) Activation by biochemical means

In this drug release is activated by the biochemical reaction^[38].

(3) Enzymatic activated system

In this system is depends upon the enzymatic activity for the release of drugs.

(4) Feedback regulated drug delivery system

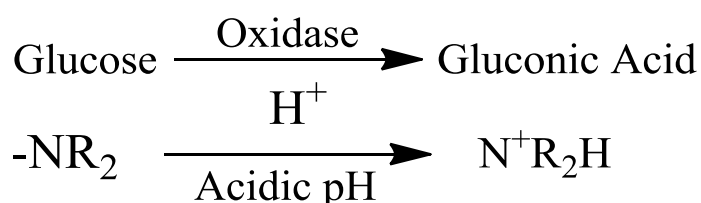
In this, a physiological response activates the release of drugs from the carrier.^[39] A triggering agent activates the process of release of the drug, such as a biochemical substance, in the body via some feedback mechanisms. The rate of drug release is synchronized by the concentration of a triggering agent that is detected by a sensor used in the feedback-regulated drug delivery system^[27]. Feedback regulated drug delivery system are divided into three part

(1) 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 drug and metabolize the urea. The cause of the change of pH increases the rapid degradation of polymer matrix and release of drug molecules^[33a, 40]

(2) Bio-responsive regulated system

In this, the drug reservoir is enclosed in the bioresponsive polymeric membrane and permeability of drug molecule is controlled contraction of biochemical agents in the tissue. Ex. Glucose-triggered insulin delivery system. In this delivery system, insulin reservoir is covered by the hydrogel membrane which contain NR₂ (amide group) group. In alkaline solution, 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 NR₂ into N⁺R₂H and hydrogel layer become swollen and thus permeable to insulin molecule by the process of self-regulated processes.^[27].



(3) 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, 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 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 self-regulating drug delivery system.^[27]

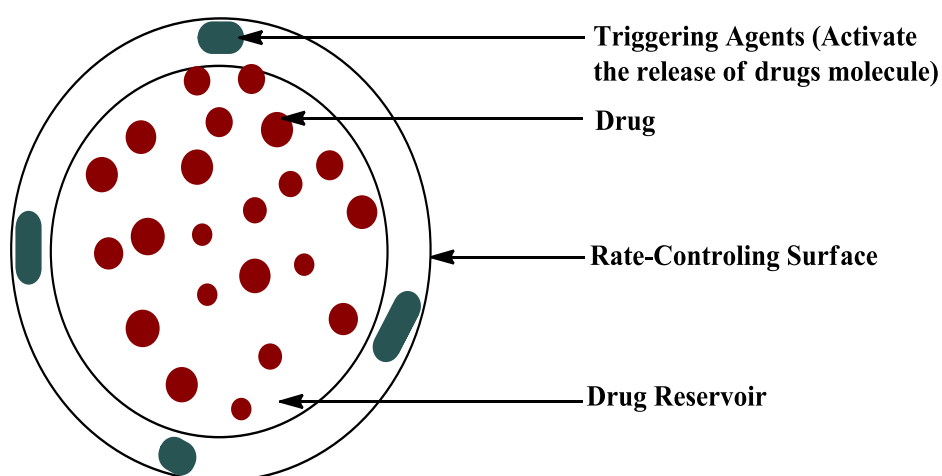


Fig.6- Feedback drug delivery system. Triggering agents activate the release of drugs

(5) Site targeting drug delivery system

Delivery of drugs to the targeted site (tissue) is complex, and it 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 rid of uncontrolled drug release, drug delivery system should be site targeting specific. It is divided into three parts.

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

(2) 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.

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

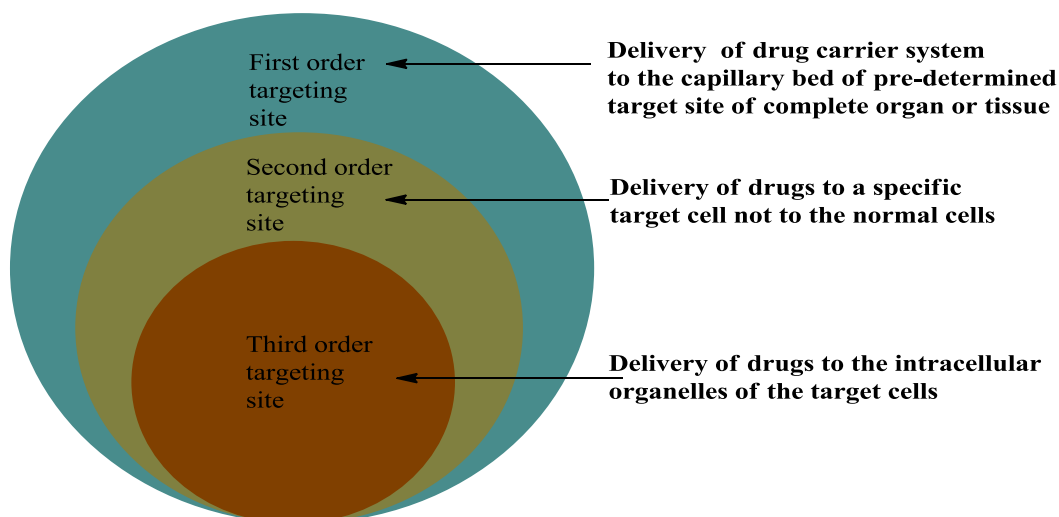


Fig: 7- Site targeted drug delivery system

Site targeting drug delivery system also classified as

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

(2) Active targeting: Active targeting is also called as the ligand-mediated targeting. In this ligand (drugs) are present on nanoparticle surface and interact with the cells or diseased cell. Ligand molecules are selected with the interaction of infected cell, and it should not disturb the healthy cells. Therefore, it is aimed that 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. Example of active targeting is the use of the monoclonal antibody for the treatment of cancer^[41]

(4) ORAL CONTROLLED RELEASE SYSTEM

Oral controlled release system (OCRS) is the widely used system for delivering the drugs to body in a controlled release pattern because^[42]:

- Easy and convenience administration
- Easy to formulate or design the dosage form
- Easy production and low-cost system
- Greater flexibility in dosage form due to versatility in GI anatomy and physiology

OCRS mainly given as solid form and the drug release depend on:

- Drug dissolution rates from polymeric matrix
- Drug diffusion from polymeric membrane
- Combination of both

Depending on drug release pattern OCRS classified into three major classes^[43].

- ❖ Continuous release system
- ❖ Delay transit & continuous release system
- ❖ Delay release system

- ❖ **Continuous release system:** These systems release the drug throughout the GIT especially terminal end of the small intestine^[44]. This included:
 - Dissolution controlled release system
 - ✓ Matrix dissolution controlled
 - ✓ Encapsulation dissolution controlled
 - Diffusion controlled release system
 - ✓ Matrix diffusion controlled
 - ✓ Reservoir/ laminated matrix device
 - Dissolution & diffusion-controlled release system
 - Osmotic pressure controlled release system
 - Hydrodynamic controlled release system
 - Ion-exchange resin drug complexes
 - pH-dependent system

- ❖ **Delayed transit & continuous release system:** This system formulated in such a way their residence time in GIT increased and released the drug throughout GIT^[45]
 - ✓ altered density system
 - ✓ mucoadhesive system
 - ✓ size-based system.

- ❖ **Delay release system:** These systems formulated to deliver the drugs in the controlled release manners^[24].
 - ✓ Intestinal release system
 - ✓ Colon targeted system

CONCLUSION

A suitably deliberate controlled release drug delivery system can be a significant progress towards solving problems regarding the targeting of a drug to a particular organ or tissue and controlling the rate of drug delivery to the target site. Controlled release (C.R) stuff provide an advantage over conventional quantity forms by optimizing bio-pharmaceutics,

pharmacokinetic and pharmacodynamics properties of medicinal products. In such a way that controlled the release of drugs reduces the drugs dosing rate to an extent. Once the daily dose is enough for remedial management through the uniform plasma, focus providing maximum efficacy of drug with a reduction in local and systemic side effects and treatment or control circumstance in shortest possible time by the smallest amount of drug to assure greater patient compliance. The most significant role of drug release system is to find the drug delivered to the site of action in ample quantity and at the proper rate, and it should meet other relevant criteria as physical and chemical stability, ability to be mass-produced at the particular site. With improved understanding of controlled-release mechanisms and improved development of technologies, it may be possible to design an appropriate method for efficient drug delivery system at the particular site.

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Conflict of interest

The author declares there is no any conflicts of notice in preparing the manuscript.

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