# CONTROLLED RELEASE DRUG DELIVERY SYSTEM

# Rate Controlled Drug Delivery System

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**Controlled Release Drug Delivery Systems (CRDDS)**

Controlled release drug delivery systems provide uniform concentration of drug to the absorption

site and thus allows the maintenance of plasma concentration within the therapeutic range which

minimizes not only the side effects but also the frequency of administration.

**Advantages of Controlled Release Dosage Forms**

• Controlled administration of a therapeutic dose at a desirable rate of delivery.

• Maintenance of drug concentration within an optimal therapeutic range for prolonged

duration of treatment.

• Maximization of efficacy-dose relationship.

• Reduction of adverse side effects.

• Minimization of the needs for frequent dose intake.

• Enhancement of patient compliance.

• Employ less total drug

• Minimization or elimination of local or systemic side effects.

• Minimal drug accumulation on chronic usage.

• Improve efficiency of treatment.

**Disadvantages of Controlled Release Dosage Forms**

• 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.

• Administration of this type of dosage form does not permit the prompt termination of

therapy.

• 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.

• Economic factors include more costly processes and equipment that are involved in

manufacturing many controlled release dosage forms.

• All drugs are not suitable candidates for controlled release medication. Drugs with long biological half-life (e.g. Digoxin-34 hours) are inherently long acting and thus, are viewed as questionable candidates for sustained release formulations.

• Drugs with narrow requirements for absorption (e.g.: drugs which depend on position of

G1T for optimum absorption are also poor candidates).

• Drugs like Riboflavin and ferrous salt, which are not effectively absorbed in lower intestine

are poor candidates.

• Drugs which are having very short half-life (<1 hour) e.g.: Penicillin, Furosemide are poor

candidates for SR formulations.

**Sustained Release Drug Delivery System:**

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.

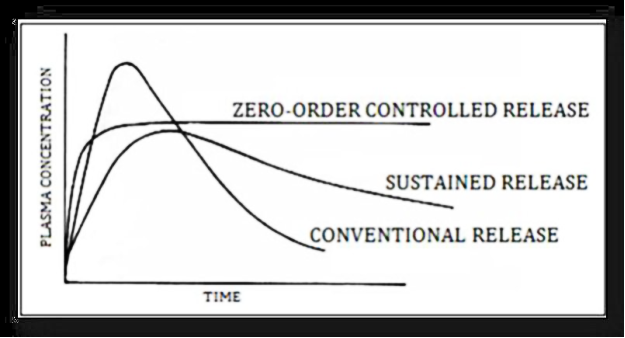


Fig.1 Plasma drug concentration-time profile of controlled release, sustained release and

conventional dosage forms.

**Factors Influencing the Design and act of Controlled Release Products**

1. **Physiological properties:**
2. **Aqueous Solubility:**

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.

1. **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.

1. **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.

1. **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.

1. **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.6: Protein binding

The drug-protein complex act as a reservoir in plasma for the drug. Drug showing high plasma

protein binding is 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.

**B. 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 drugged release from the dosage form. 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.

**2. Biological half-life (t1/2):**

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 t1/2 2-3 hrs. are a suitable candidate for CRDDS. Drugs have t1/2 more

than 7-8 hrs. not used for controlled release system.

**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.

**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.

**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 release6: **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.

**Table: Pharmacokinetic parameters for drug selection**



**Classification of Controlled Release System:**

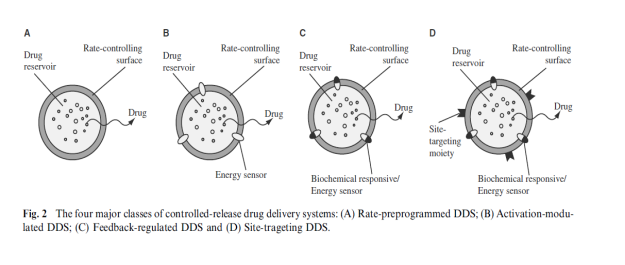
The controlled release system divided into following major classes based on release pattern.

(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 molecule from the delivery system is pre-planned with 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.

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.

1. **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.

1. **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

**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.

**(1) Activation by physical process:**

**a) Osmotic pressure activated system:**

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

**c) Vapor 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 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

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, 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.

**f) 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. 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 swellable polymer matrix fabricated

from a hydrophilic polymer. The induced hydration systems stimulate the release the drug. The

release of the drug is controlled by the rate of swelling of polymer matrix.

**(2) Activation by biochemical means:**

In this drug release is activated by the biochemical reaction.

**(3) Enzymatic activated system:**

In this system is 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

**4) Site targeting drug delivery system:**

Delivery of drugs to the targeted site (tissue) is complex, and it is consisting 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, drug delivery

system should be site targeting specific. It is divided into three parts.

**(1) First order targeting: -**In this, drugs carrier releases the drugs at the targeted site such as

organ, tissue, cavity, etc.

**(2) Second order targeting: -** In this, drugs carrier releases 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 releases the drugs to the intracellular site of

targeted cells. Site targeting drug delivery system also classified as

**a) Passive targeting:**

In this, drugs carrier releases the drug at the site due to the cause of physicochemical or

pharmacological signal.

**b) 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.