# World Journal of Pharmaceutical and Life Sciences
## WJPLS

www.wjpls.org

SJIF Impact Factor: 6.129

## CONTROLLED DRUG DELIVERY : AN UPDATED REVIEW

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**ABSTRACT**

Controlled release drug delivery systems provide uniform concentration of drug to the absorption site and thus allow the maintenance of plasma concentration within the therapeutic range which minimizes not only the side effects but also the frequency of administration. Generally controlled release products administered by any route are design such that rate of drug absorption should be equal to rate of drug elimination. There are different types of controlled drug delivery system. The development or selections of system further depend up on the physicochemical and pharmacological properties of active pharmaceutical ingredient. Controlled release products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutics, pharmacokinetic and Pharmacodynamics properties of drugs 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 providing maximum utility of drug with reduction in local and systemic side effects and cure or control condition in shortest possible time by smallest quantity of drug to assure greater patient compliance.

**KEYWORDS:** Controlled Release, Plasma Concentration, Frequency of Dosing.

## INTRODUCTION[1,2]

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively complete systemic drug absorption and onset of accompanying pharmacodyanmic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentration decline according to the drugs pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage from that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms. In recent years, various modified-release drug products have been developed to control the release rate of the drug and / (or) the time for drug release.

## Modified Drug Delivery System
The term Modified-release drug product is used to describe products that alter the timing and/ (or) the rate of release of the drug substance.

## Types of Modified Release Drug Products[3]
**1) Extended-Release Drug Products:** A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long acting drug products.

**2) Delayed-Release Drug Products:** A dosage form that releases a discrete portion or portions of drug at a time (or) at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

**3) Targeted-Release Drug Products:** A dosage forms that release drug at or near the intended physiologic site of action. Targeted-release dosage forms may either immediate (or) extended- release characteristics.

## Controlled Drug Delivery System
The term controlled-release drug product was previously used to describe various types of oral extended-release-rate dosage forms, including sustained-release, sustained action, long-action, slow-release, and programmed drug delivery.

## Advantages[4]
➢ Reduction in frequency of drug administration

➤ Improved patient compliance
➤ Reduction in drug level fluctuation in blood
➤ Reduction in total drug usage when compared with conventional therapy
➤ Reduction in drug accumulation with chronic therapy
➤ Reduction in drug toxicity (local/systemic)
➤ Stabilization of medical condition (because of more uniform drug levels)

**Limitations[4]**
➤ Delay in onset of drug action
➤ Possibility of dose dumping in the case of a poor formulation strategy
➤ Increased potential for first pass metabolism
➤ Greater dependence on GI residence time of dosage form
➤ Possibility of less accurate dose adjustment in some cases
➤ Cost per unit dose is higher when compared with conventional doses
➤ Not all drugs are suitable for formulating into ER dosage form

**Factor Influencing The Design And Performance Of Controlled Drug Delivery System[5,6]**
**1. Biopharmaceutic characteristic of the drug**
a) Molecular weight of the drug
b) Aqueous solubility of the drug
c) Partition coefficient
d) Drug pKa and ionization physiological PH
e) Drug stability
f) Mechanism and site of absorption
g) Route of administration.

**2. Pharmacokinetic characteristic of the drug**
a) Absorption rate
b) Elimination half life
c) Rate of metabolism
d) Dosage form index

**3. Pharmacodynamics characteristic of the drug**
a) Therapeutic range
b) Therapeutic index
c) Plasma–concentration–response relationship

**1. Biopharmaceutic characteristic of the drug**
**a) Molecular weight of the drug:-** Lower the molecular weight, faster and more complete the absorption. About 95% of the drugs are absorbed by passive diffusion. a drug to diffuse through the membrane is inversely related to the molecular size.

**b) Aqueous solubility of the drug:-** 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.

**c) Partition coefficient:-** Greater the apparent partition coefficient of a drug, greater its lipophilicity and thus greater is its rate and extend of absorption. These types of drugs even cross the highly selective blood brain barrier.

**d) Drug pKa and ionization physiological PH:-** 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.

**e) Drug stability:-** Drugs that are unstable in the GI environment are not suitable candidates for controlled release systems. Drugs that are unstable in gastric pH can be designed to release in intestine with limited or no release in stomach and vice versa.

**f) Mechanism and site of absorption:-** For a drug to be a variable candidate for per oral

CRDDS, its absorption mechanism must be by diffusion throughout the entire GI tract. The term diffusion here refers to the dual pathway of absorption either by partitioning into the lipid membrane (across the cells) or by passing through water filled channels (between the cells).

It is also important that absorption occurs from all segments of the GI tract which may depend on the drug's pKa, the pH in the segment, binding of drug to mucus, blood flow rate, etc.

**g) Route of administration:-** For controlled release oral and parenteral routes are the most preferred which is the followed by transdermal.

**2. Pharmacokinetic Characteristic Of A Drug[7,8,9]**
**A) Absorption rate**
Uniformity in rate and extent of absorption is an important factor in formulating the CRDDS.
The absorption rate should rapid then release rate to prevent the dose dumping. The various factors like aqueous solubility, acid hydrolysis, which affect the absorption of drugs.

**B) Biological Half Life:** An ideal CRDDS is one in which the rate of drug absorption is equal the rate of drug elimination. If the t1/2 is smaller (less than 2 hours) for a given drug then more amount of drug is to be incorporated into the controlled release dosage form. Drugs having t1/2 in the range of 2-4 hours are ideal candidates for controlled release system. Drugs with long half life need not be formulated into such formulations.

**C) Metabolism:** Drug selected for controlled release system should be completely metabolized but the rate of metabolism should not be too rapid.

**D) Dosage Form Index: -** 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.

### 3. Pharmacodynamics characteristic of the drug
a) Therapeutic range
b) Therapeutic index
c) Plasma–concentration–response relationship

### a) Therapeutic range
A candidate drug for controlled release drug delivery system should have a therapeutic range wide enough such that variations in the release rate do not result in concentration beyond this level.

### b) Therapeutic index
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.

### c) Plasma–concentration–response relationship
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.

### Oral Drug Delivery System[10,11]
Oral controlled release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local (or) systemic action.

Oral route is one of the most extensively used routes of drug administration because of its obvious advantages of ease of administration, improved patient compliance and convenience.

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

### Based on the release mechanism these are classified as follows[12]
1. Diffusion-controlled products.
2. Dissolution-controlled products.
3. Erosion products.
4. Osmotic pump systems.
5. Ion exchange resins.

### 1. Diffusion – Controlled products[13]
In these systems, there is water – insoluble polymer which controls the flow of water and the subsequent release of dissolved drug from the dosage form. Diffusion occurs when a drug passes through the polymer that forms the controlled release device. The diffusion can occur through pores in the polymer matrix or by passing between polymer chains. These are broadly divided into two categories:-

### A. Reservoir Devices
### B. Matrix Devices
The basic mechanisms of drug release from these two systems are fundamentally different.

### A. 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.

### B. Matrix Devices
In the matrix devices the drug or active is dispersed in polymer matrix to form a homogeneous system known as a matrix system. Diffusion occurs when the drug passes from the polymer matrix into the external environment. As the release continues, its rate normally decreases with this type of system, since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release.

### 2. Dissolution-controlled products
In these products, the rate of dissolution of the drug is controlled by slowly soluble polymers or by micro encapsulation. Once the coating is dissolved, the drug becomes available for dissolution. By varying the thicknesses of the coat and its composition, the rate of drug release can be controlled.

### Dissolution-controlled products can be sub-divided into two types:-
A. Encapsulation Dissolution controls.
B. Matrix Dissolution control.

### A. Encapsulation Dissolution control
These systems method involves coating of individual particles (or) granules of drug with a slow dissolving material. The coated particles can be compressed directly into tablets (or) placed in capsules. The rate of dissolution of the drug (and thereby availability for absorption) is controlled by micro encapsulation. Once the coating is dissolved, the drug becomes available for

dissolution. By varying the thicknesses of the coat and its composition, the rate of drug release can be controlled.

### B. Matrix Dissolution control
In this system an alternative approach is to compress the drug with a slow dissolving carrier. Here the rate of drug release is controlled by the rate of penetration of the dissolution fluid into the matrix, porosity, presence of hydrophobic additives and the wet ability of system and surface of particle.

### 3. Erosion products
In this system drug or active agents are mixed with biodegradable polymers. These materials degrade within the body as a result of natural biological processes and drug release occurs at constant rate.

### 4. Osmotic pump systems
The osmotic pump is similar to a reservoir device but contains an osmotic agent (e.g., the active agent in salt form) which acts to imbibe water from the surrounding medium via a semi-permeable membrane. Pressure is generated within the device which forces the active agent out of the device via an orifice

### 5. Ion exchange resins
The drug is bound to the resin and released by exchanging with appropriately charged ions in contact with the ion exchange groups. This technique is applicable to certain drugs which have particular characteristics in terms of their relatively affinity for the polymers being used.

### CONCLUSION

Oral controlled release products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutic, pharmacokinetic and pharmacodynamic properties of drugs 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 providing maximum utility of drug with reduction in local and systemic side effects and cure or control condition in shortest possible time by smallest quantity of drug to assure greater patient compliance.

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