

# An Overview On Controlled Drug Delivery Systems: Current Status And Future Directions

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**Abstract-** The drug delivery system enables the release of the active pharmaceutical ingredient to achieve a desired therapeutic response. Conventional drug delivery systems (tablets, capsules, syrups, ointments, etc.) suffer from poor bioavailability and fluctuations in plasma drug level and are unable to achieve sustained release. Without an efficient delivery mechanism, the whole therapeutic process can be rendered useless. Moreover, the drug has to be delivered at a specified controlled rate and at the target site as precisely as possible to achieve maximum efficacy and safety. Controlled drug delivery systems are developed to combat the problems associated with conventional drug delivery. There has been a tremendous evolution in controlled drug delivery systems from the past two decades ranging from macro scale and nano scale to intelligent targeted delivery. The initial part of this review provides a basic understanding of drug delivery systems with an emphasis on the pharmacokinetics of the drug. It also discusses the conventional drug delivery systems and their limitations. Further, controlled drug delivery systems are discussed in detail with the design considerations, classifications and drawings. This article's purpose is to discuss the most recent patents available while thoroughly reviewing drug delivery system design for controlled release.

**Keywords-** controlled release dosage forms, pharmacokinetics, nano-drug delivery, smart and stimuli-responsive delivery, intelligent biomaterials

## I. INTRODUCTION

The most frequent and favored method for delivering medicines has been oral administration. A perfect controlled drug delivery system is one that delivers the drug locally or systemically at a predetermined rate for a specific amount of time. Unlike the traditional immediate release system, this approach does not depend on the absorption process to control how quickly the medication manifests in the body. To maintain the safe effective medication concentration in the body over an extended period of time, the mechanism for controlled drug release is required. Drug concentrations should be kept in the body above the level at which they are effective and below the level at which they are poisonous in order to get the best results.

give the required therapeutic concentration of medication in the plasma and hold it constant during the treatment period. It should do this by delivering the medicine at a rate determined by the body's needs over the period of treatment. The appeal of various dose formulations stems from a number of factors. It is generally acknowledged that a sizable number of therapeutically useful compounds currently exist for many disease states. The effectiveness of these medications, however, is frequently constrained by side effects or the requirement that the molecule be administered in a clinical area. By localising the drug to the site of action, lowering the dosage needed, or ensuring uniform drug distribution, sustained- or controlled-delivery systems are designed with the intention of minimising the frequency of dosing or increasing the effectiveness of the medicine. Two fundamentals would be required to create the ultimate medicine delivery system. First, it would be a single dose for the entire course of treatment, whether it will be for few days or weeks, as in the case of an infection, or for the patient's entire life, as in the case of diabetes or hypertension. Second, it should bring the active entity directly to the site of action, thereby minimising or removing side effects. Delivery to particular receptors, localisation to cells, or localization to certain bodily parts may all be necessary for this. It goes without saying that this ideal delivery system will have varying requirements for various illness conditions and medications. As a result, we want to deliver the therapeutic substance at a particular location at a certain time. In other terms, the goal is to successfully place the medicine both spatially and temporally. Currently, the majority of medication delivery devices can only partially accomplish both of these specific goals(1,2,3,4)

## II. ADVANTAGE

- Reduced in frequency of drug administration.
- Uniform drug effect.
- Drug toxicity is reduced.
- Reduced GI side effects.
- Increases the safety margin drug which as high potency. [4, 5].

### III. DISADVANTAGE

- In vivo and in vitro correlation is poor.
- Dose dumping can occur. [4, 5].
- Initiation of pharmacological action is delayed.
- Enhanced first pass metabolism.
- GI residence time of dosage form has greater dependence.
- Compared to conventional doses, the price unit of medication is higher.
- Not all medications can be formulated into extended release(ER) dose forms [5].

### IV. FACTORS AFFECTING ON CONTROLLED RELEASE PRODUCTS

#### 1. physiological properties:

##### Aqueous solubility:

A substance's solubilized in water is referred to as aqueous solubility. At a temperature of 30°C, the maximum amount of a chemical that will dissolve in clear water. The solid dosage form is a suitable option for controlled release system. Since it has good water solubility and is PH-independent .E.g. Pentoxifylline, has formulated in CRDDS as minimum solubility of 0.1 mg. drug with pH dependent aqueous solubility e.g. phenytoin and without PH dependent aqueous solvent e.g. steroid's for parenteral (IM) route [3, 6, 9]

##### partition coefficient:

Drug diffusion across the membrane or matrix that Control the rate of diffusion as well as drug penetration via biological Membranes is influenced by partition coefficient. A drug must diffuse through a variety of biological membranes, as lipid-like barriers. An important factor is determining a drug can pass through lipid membranes (i.e., it's permeable) its apparent oil/water partition coefficient [3, 6, 9]

##### drug stability:

Good candidates for CRDDS include medications that are resistant to enzymatic breakdown, acid/base, and other gastric fluids. Because the drug's bioavailability will diminish if it is metabolized in the stomach and small intestine, it is not suitable for controlled release formulations [3, 6, and 9].

##### drug pka:

The drug's ionization in the GIT at physiological PH is controlled by pka. The high ionized medicines are often not

good choices for CRDDS. Compared to ionized medications, the unionized drug is quickly absorbed from biological membranes. In order for an acidic medicine to ionize, the pH must be between 3.0 and 7.5, and for a basic drug, the pH must be between 7 and 11.

##### Molecular Weight And Size:

The molecular diffusibility across a biological membrane is significantly influenced by two key variables: molecular size and molecular weight. Drug diffusion is made more difficult by molecule sizes more than 400d as opposed to easier when they are less than 400d. The size and shape of the membrane's cavities affect diffusivity. Passive diffusion is responsible for absorbing more than 95% of medicines. For passive diffusion, a drug's Particle mass must be higher than 600 Dalton.

#### 2. Biological factor:

##### Absorption:

It must be consistently delivered from the controlled release mechanism and then uniformly absorbed in order to maintain constant blood or tissue levels of the medication. When determining the CRDDS, uniformity in the rate and degree of absorption is crucial. The rate-limiting stage, however, is the drug's release from the dose form. To avoid dosage dumping, the absorption rate should be higher than the release rate. The different elements that influence how well medications are absorbed, including water solubility, log P, and acid hydrolysis.

##### Biological half-life ( $t_{1/2}$ ):

The drug generally has a short half-life, requiring frequent doses. This makes it a good choice for controlled release systems. A medication with a lengthy half-life requires administration over an extended period of time. The best candidates for CRDDS are medicines with  $t_{1/2}$  of 2-3 hours. Drugs used for controlled release systems but with a  $t_{1/2}$  of more than 7-8 hours.

##### Therapeutic window:

Drugs having a limited therapeutic index are unsuitable for CRDDS. The delivery mechanism would dump doses and ultimately become hazardous if it were unable to manage release.

##### Dose size:

The CRDDS must have a higher dose than a traditional dosage form because it was designed to do away with recurrent dosing. However, the dose utilized in conventional dosage form provides a guide for the CRDDS dose. The volume of the sustained dosage ought to meet the acceptability requirements.

#### Distribution:

Since it reduces the concentration of circulating medications and can be rate-limiting in their equilibrium with blood and extracellular fluid, the distribution of pharmaceuticals into tissues can play a significant role in the overall kinetics of drug elimination. Binding of the medication to blood proteins and tissues is one of the components of this distribution. Example: furosemide, theophylline.

#### Metabolism:

As provided the rate of metabolism is not excessively high, a medicine that is extensively metabolized can be used in a controlled release system. When the medicine is supplied via several routes, the extent of metabolism ought to be consistent and predictable. An inadequate option for such a product is a medicine that can induce or inhibit metabolism since steady-state blood levels would be challenging to maintain.

#### Elimination:

A controlled release drug delivery system that has a drug absorption and elimination rate that is equal over an extended period of time is optimal. The amount of medicine to be included in the controlled release dosage form will be greater the  $t_{1/2}$ . To maintain the high release rate, drugs with  $t_{1/2}$  less than 2 hours need to be taken in much greater doses. Drugs with  $t_{1/2}$  between 2 and 4 hours make good CRDDS candidates for, Example: propranolol.

#### Different Routes of Drug Administration.

Dosage forms can be administered through different routes based on the target site, duration of treatment and the physicochemical attributes of the drug [9]. The most common dosage forms comprise tablets, capsules, pills, ointments, syrups and injections. Various routes of drug administration are tabulated in Table 1 and Figure 3.

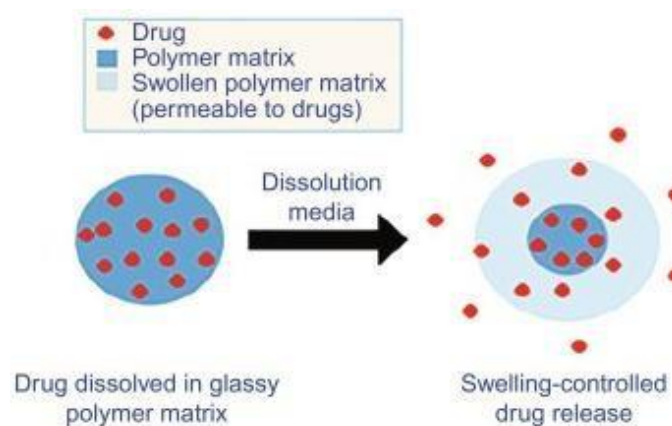
The preferred route of drug administration depends on three main factors: The part of the body being treated, the way the drug works within the body and the solubility.

## V. CLASSIFICATION OF CONTROLLED RELEASE SYSTEM

1. Rate pre-programmed drug delivery system
2. Activated modulated drug delivery
3. Feedback regulated drug delivery system
4. Site targeting drug delivery system

### 1. Rate Pre Programmed Drug Delivery System:

This has a pre-planned drug release from the delivery system with a specific medication Flow rate profile. The system regulates the drug molecules molecular diffusion into, through, or around the delivery system's barrier medium.



#### (1.1) Dissolution controlled drug delivery system:

Solid matter that has been dissolved in a suitable solvent is referred to as dissolution Process. After liquid diffuses from solid, it's a rate-determining step. The two primary categories of dissolution-mediated controlled release formulation are reservoir and matrix system. The most popular method for regulating release is called as matrix dissolving System, which involves uniformly dispersing the active pharmaceutical ingredient (API) throughout a polymer matrix when the polymer matrix breaks down (7, 18).

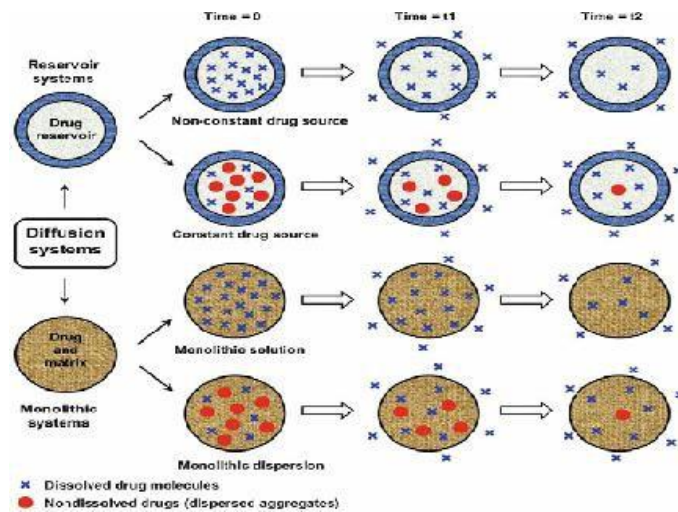
#### (1.2) Matrix Dissolution System:

The "monolithic dissolution controlled device" is generally used to study of matrix dissolution system. Changes to the Tablet's porosity, and reduction in its wetting capacity, and a slower rate of dissolution are used to control its disintegration.

#### (1.3) Encapsulation Dissolution Control:

These techniques often include coating individual medication particles or granules with a slowly dissolving

substance. In the case of products like space tablets or capsule, the coated particles can either be directly compacted into tablets or put inside of capsules. One can achieve repetitive or crosses the membrane. Drug diffusion from a site of greater concentration to a region with a lower concentration. Its diffusion through a polymer that is insoluble in water determines the dissolution rate in this system. Diffusion controlled system are classified into reservoir and matrix type delivery system. The drug release is covered by Fick's law of diffusion.



**(1.5) Hydrophilic Swellable Matrix Diffusion:**

It also known as glassy hydrogels is widely known for maintaining the release of Medication that is extremely water soluble. Hydrophilic gums are the materials [19]. Natural examples include tragacanth and semi-synthetic: xanthium gum, hpmc, and Cmc. Artificial polyacrylamides examples are Procardia and Glucotrol xl.

**(1.6) Micro reservoir partition controlled system:**

The drug reservoirs are composed of solid particles suspended in an aqueous solution of a polymer that is water-miscible. High dispersion methods are used to create a Micro-dispersion partition controlled system. In a nutshell, micro-reservoir and matrix Dispersion

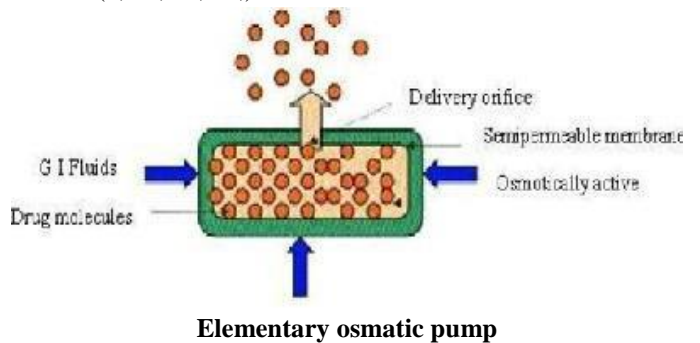
**2. Activated Modulated Drug Delivery System:**

In this, a physical, chemical, or biological mechanism, as well as any external energy Source supplied, control or initiate the release of medications from the delivery system. Energy input or any other applied method can regulate drug release. The following Categories apply to this activation procedure.

**A. Activation by physical process:**

**1. Osmatic pressure activated system:**

The most promising strategy based system for regulated medication delivery is osmotic Technology. The movement of water across membrane that is selectively permeable is Known as osmosis and caused by different osmotic pressure in this method of controlled Drug administration, a solution formulation serving as the drug reservoir is housed in a Semi-permeable structure. Under an osmotic pressure gradient, the medication is delivered in solution form at a controlled, stable rate. Drug release rate is constant. Examples: methylene chloride, ethanol, isopropyl alcohol (3, 11, 17, 18,).

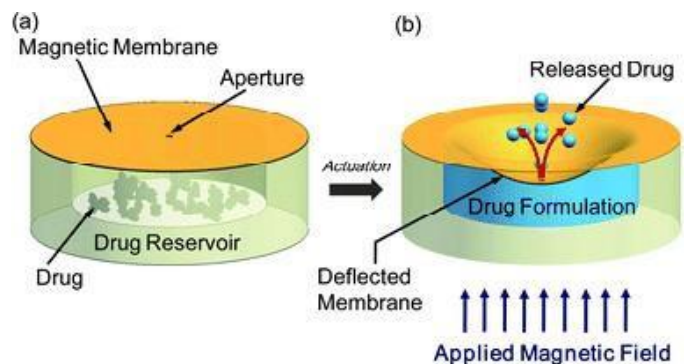


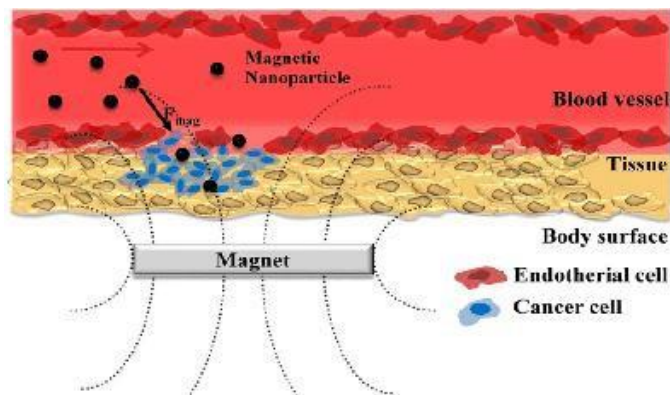
**2. Hydration activated system:**

Depends on the hydration included swelling process to activate the release of drug. Drug Dispersed is homogeneously in a hydrophobic polymer .release of the drug is controlled by swelling polymer matrix. Example: diazepam. (6)

**3. Magnetically Activated System:**

The principle behind the magnetic drug delivery method is that the medication can either be conjugated on the surface of a magnetic microsphere (or Nano sphere) .an external Pement magnetic field is applied on the desired area to guide and concentrate the Drug (3, 20).



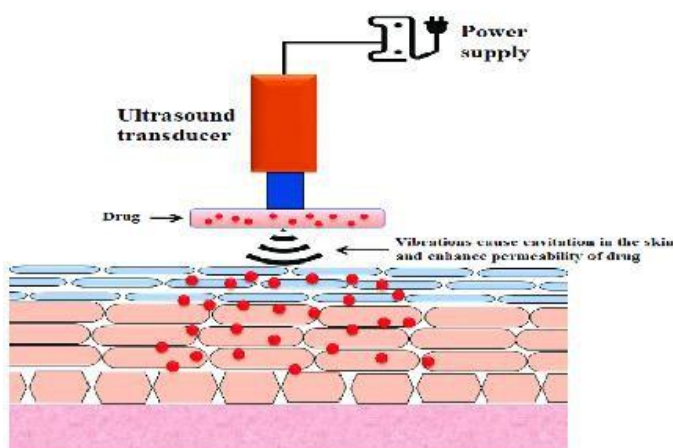


#### 4. Photochemical waves activated system:

This category of drug delivery device uses covalent bond cleavage that is controlled by Light irradiation to speed up the release of the payload that is enclosed .which upon uv Light irradiation irreversibly cleavage to liberate a free carboxylic acid and o nitrobenzaldehyde is Workhorse for photochemical trigged drug delivery system example: acetone and HCHO(13 ,21).

#### 5. Sonophoresis activated system:

The activation of medication delivery in this uses an ultrasonic instrument. For the Administration of drugs through the skin, a very low frequency (55 kHz) for a very less Period of time (15 seconds) is utilized. This ultrasonic gadget is a battery-operated handheld system that includes a control unit, an ultrasonically produced horn, a Disposable coupling medium sealed unit, and a return electrode .these gadgets are made of biodegradable and non-biodegradable polymer (13).



#### 6. Vapor pressured activated system:

In this system, a liquid exists in equilibrium with its vapor phase and pressure of the Independent volume of fluid. One device used to pressure control delivery, device Consist

of two chambers, one contains the drug solution and second with a vaporizable Fluid such as fluorocarbon. When a drug is injected, a volatile liquid vaporizes at body Temperature, creating a vapor pressure that compresses the chamber below and delivers the medication in a regulated manner. (13).

#### 7. Electrically activated system:

This system is used for electrical current to activate and modulate the diffusion of a Charge drug molecule across the skin a facilities rate. Example; dexamethasone sodium Phosphate (13 22).

#### 8. Mechanically activated system:

A medication reservoir or storage space that has a pumping device that is mechanically triggered. A spray system that utilizes a mechanical drug delivery pumping system delivers a controlled dose of medication into a bodily cavity, such as the mouth or nose. The each pumping spray has a predetermined spray volume of the medicine being administered. For former metered-dose nebulizer lhrh, or luteinizing hormone-releasing Hormone (23 13).

#### 9. Hydrodynamic pressured activation system:

The source of energy is used for activate the drug release process are also known for Hydrodynamic pressured action system (13).

#### 10. Photo activated system:

The photo activated approach has sparked a significant deal of scientific interest due to its ability to accurately control the release of pharmacological compounds and the Activation of bio imaging agents. The best photo responsive systems, which are frequentlyUV or visible light-sensitive (13)

#### B. Activation by chemical press:

##### 1. pH activated system:

The significance of pH Sensitive Drug Delivery Systems (PSDDS) is growing because these systems produce the medication at precise times in accordance with the pathophysiological requirements of the disease, improving patient therapeutic efficacy and compliance. At acidic pH, cationic polymers containing amino groups are more water soluble than they are at neutral ph. When the pH is basic compared to when it is acidic, anionic polymers having carboxyl groups are more water soluble. These are used for

preventing gastric degradation, peptic ulcer, cardiovascular disease Drawbacks of conventional drug formulations, pH-responsive drug-delivery systems have gained increasing attention. This is because these systems can deliver drugs in a Controlled manner at a specific site and time, leading to high therapeutic efficacy (6, 13, and 17).

## 2. Ion activated system:

This system is used for resin and contain ion groups .An ion exchange resin is a polymer (often styrene) having electrically charged spots Where one ion can swap places with another. Resins are water insoluble particles containing cationic and anionic groups. These resin used to CR (controlled release) System Example: Levodopa and carbidopa. [13, 17, 25].

### Cation exchange resin:

Positively charged ions are exchanged by covalently attached negatively charged functional groups in cation exchange resins. They are created by copolymerizing styrene and divinyl benzene, and the majority of them include sulfonic acid groups ( $\text{SO}_3\text{H}$ ) Example: Morphine sulphate, (17 2).

### Anion exchange resin:

Positively charged functional groups are exchanged by negatively charged ions in anion exchange resins. These are made by first attaching  $\text{CH}_2\text{Cl}$  groups to the benzene rings of the styrene-divinylbenzene copolymer using chloromethylation, and then inducing these to react. Either triaryl amines, like diethyl amine. For example: chloromethylating. (17).

## 3. Hydrolysis Activated System:

Hydrolysis is also known as chemical reaction; the interaction of water with chemical .This uses a microcapsule to enclose the drug reservoir. The implanted device is also a Part of it. These systems are all constructed with biodegradable polymers. The rate of Drug delivery is controlled by the hydrolysis breakdown of the polymer chain, which Activates the release of the medication (6, 13).

### C. Activation by Biological Process:

#### 1. Enzyme activated system:

An enzyme-activated system, the enzymatic process activates the system to release Medications. Liposomes, nanoparticles, prod rugs, micro particles, and other methods of enzymatic drug delivery are available. Drug, nano carrier,

promoiety, coated polymer, Ligand, and other substances are the system's primary constituents (23).

#### 2. Anti body interaction activation system;

Antibody interaction blocks the enzymatic breakdown of the polymer matrix or the Permeability of the medication in the polymeric reservoir (13, 20).

#### 3. Feedback Regulatory Drug Delivery System: Bio Responsive DDS:

In this system, the drugs reservoir is contained in a device enclosed by a bio responsive Polymeric membrane whose rug permeability is controlled by concentration of Biochemical agent in tissue where the located in system (13, 18, 23).

#### Bio Erosion Regulated DDS:

This system is consists of drug dispersed bio erodible from poly (vinyl and ethyl ether) Half ester which is coated with a layer of immobilized urease, in solution with nature ph. Polymer (23).

#### Self-controlling drug delivery mechanisms:

The reversible and competitive binding mechanism for the activation and release of Medicines controls this mechanism. In this, a polymeric drug reservoir contained within Membrane that is semipermeable. The biological component of activates the drug's Release a tissue. Example: an insulin-sugar-lactin-derived biological complex is Enclosed (23, 24).

#### 4. Site Targeting Drug Delivery System:

##### Active targeting:

The foundation of an active targeted drug delivery system is a technique that administers a specific dosage of a therapeutic, diagnostic, or both to a specific location of a damaged Organ in the body (26).

##### Passive targeting

The drug's efficacy in passive targeting is directly correlated with its circulation time. The Nanoparticle is covered with a coating to accomplish passive targeting. This can be Accomplished by a number of chemicals, one of which being polyethylene glycol (PEG) (23, 25).

## CONCLUSION

systemic side effects, and curing or controlling condition in the shortest possible time. The most of the device use on the fundamental principles of dissolution, diffusion, osmosis, ion exchange and etc...For a drug delivery system to be designed in the best possible way, it is necessary to have a better understanding of the release mechanisms, carrier material elements, barrier characteristics, pharmacological effects, and pharmacokinetics of the medicine. This review includes appropriate examples and a detail of the various factors that influence the performance and design.

Modern technologies including the goal concept for successfully controlled delivery have now emerged.

By optimizing the biopharmaceuticals, pharmacokinetics, and pharmacodynamics of drugs, controlled-release products offer benefits over conventional dosing formulas so that dosing frequency is greatly reduced. DDS play the most important role in getting the drugs to the site for sufficient action at the appropriate rate & at the appropriate level. It should therefore conform with other essential requirements such as physical, chemical, and solid-production stability in a way that ensures uniformity of material.

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