ADVANCES IN CONTROLLED RELEASE TECHNOLOGY IN PHARMACEUTICALS: A REVIEW

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ABSTRACT

Controlled drug delivery systems have been developed to improve the next staging of the drug in the body with two main purposes: to reduce the number of single doses per day improving patient compliance of treatments and to decrease the fluctuations of plasma levels, in order to obtain better therapeutic efficacy and lower toxicity. 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.

KEYWORDS: Controlled Drug Delivery, Dose, Efficacy, Toxicity, Pharmacokinetics, Pharmacodynamics, Compliance.

INTRODUCTION

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 are duction in drug toxicity.[1-3] 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.\textsuperscript{[4-5]} The term sustained release also mentioned during the description of controlled release.\textsuperscript{[6]} 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.\textsuperscript{[7]}

The performance of a drug can often be optimized by controlling the rate and extent of its release in the body. There are many controlled-release pharmaceutical systems currently known, ranging from monolithic matrices, membrane reservoirs, erodible polymers, to the more technologically complex and sophisticated pH independent formulations, ion exchange resins, osmotically, and geometrically modified systems. Many of these systems are not produced in a form that is amenable to large-scale manufacturing processes and usually do not exhibit the desirable zero-order release kinetics. In addition, the cost of formulation development, raw materials, and manufacture technology are among the principal factors in formulation for oral dosing.\textsuperscript{[8]}

The science of controlled release was first originated from the development of oral sustained release products in the 1940s and early 1950s.\textsuperscript{[9]} 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 soul science.\textsuperscript{[10-12]} 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.\textsuperscript{[13]} The modified release dosage forms are entirely new. The first time Rhozes formulates mucilage coated pills about A.D 900.\textsuperscript{[14]} 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.\textsuperscript{[15-17]} 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.[18-20] 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.[21] Other than oral, the various routes like transdermal, ocular, vaginal & parenteral route use for controlled release of various drugs.[22]

**Formulation challenges of CR delivery systems:** The three main challenges in the development of CR formulations include: the intersection of market expectations for once-daily dosing and the prevalence of lower-solubility, higher-dose compounds for the development of oral solid CR products; the development of CR dosage forms that impart abuse resistance; and the increasing need for pediatric CR dosage forms.[23-24]

Many compounds do not have sufficient colonic absorption for conventional CR formulations. Absorption technologies such as nanoparticles, amorphous-drug, and lipid-formulation technologies are needed to provide sufficient driving force for adequate absorption, especially in the lower part of the gastrointestinal (GI) tract. These absorption technologies have matured over the past two decades for immediate-release (IR) dosage forms, but substantial research is required to couple them with the processing technologies needed for CR capsules and tablets. This research requires a fundamental understanding of the *in-vivo* absorption and biotransformation using the ‘high-energy’ formulations as well as an understanding of the process-engineering fundamentals required for manufacturing with capsules (e.g., based on lipids and/or multiparticulates); tablets (e.g., based on gel matrix, osmotic, or compressed multiparticulates); and sachets or other bulk oral solid presentations. One additional challenge of coupling enabling technologies with CR technologies is achieving adequate drug loading and the desired dosage form size. The use of absorption-enabling technologies that also have intrinsic modified-release properties is, therefore, desirable. Two examples include the use of amorphous solid dispersions using enteric or controlled-release polymers and lipid-based systems—both of which can be used in monolithic and multiparticulate dose forms.[25-28]

The second challenge involves the development of CR dosage forms that impart abuse resistance, an increasingly important and legislated requirement for opioids and other
controlled substances. Designing an effective approach for deterring abuse requires understanding the typical approach an abuser may use to extract the drug inappropriately. The approaches have been novel and vary greatly using physical, chemical, and pharmacological approaches. Formulation scientists and dosage-form solution providers have devised an array of approaches that facilitate meeting target pharmacokinetic profiles while providing abuse resistance (e.g., waxy excipients, high melting point and viscosity modifiers, and others).

The third challenge surrounds the urgent and increasing need for pediatric CR dosage forms. This is a challenge because fewer excipients are deemed acceptable for pediatric use by regulatory agencies and/or have precedence of use for pediatric formulations than for adult formulations. Dosage forms for infants and very young children are especially challenging because these patients may not be able to swallow a solid-dosage capsule or tablet, and/or concern for dose dumping is of crucial importance. In these situations, sachets, sprinkles, and other suspendable dosage-form intermediates are preferred, although texture and taste constraints must be overcome. Generally, multiparticulates (e.g., 100- to 300-μm micropellets or lipid multiparticulates, coated or uncoated) offer the most viable path forward when designed properly for the target patient population. Nevertheless, the challenges remain high for designing pediatric formulations that meet target pharmacokinetic profiles, which has driven our development of a multiparticulate platform that includes multiple bead-layering approaches, mini-tablets, lipid multiparticulates, and specialized capsules for delivery.[28]

**ADVANTAGES OF CONTROLLED DRUG THERAPY**[29-30]

- 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\textsuperscript{[30]}

- 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.

Factors Influencing the Design and Act of Controlled Release Products

(1) Physiological properties

- **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.\textsuperscript{[31]}

- **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.\textsuperscript{[31]}

- **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.\textsuperscript{[32]}

- **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.\textsuperscript{[33]}
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.[34]

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.[35]

(2) Biological factors

Absorption: Uniformity in rate and extent of absorption is an important factor in formulating the CRDDS. However, the rate limiting step is druged 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.[36]

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.[37]

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.[38]

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.[39]

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.[40]
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.[41]

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: In this, the release of drug molecule from the delivery system is pre-planed 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.[42]

- 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.

- 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.
• **Micro reservoir partition controlled system:** The drug reservoirs are a suspension of solid particle in the aqueous solution of the watermiscible polymer. Micro-dispersion partition controlled system is prepared by the applying high dispersion techniques. In short reservoir and matrix dispersion forms micro-reservoir.

![Fig. 2: Matrix and membrane type delivery systems.](image1)

![Fig. 3: Reservoir type drug delivery system.](image2)

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.\[43\]

• **Osmotic pressure activated system:** In this osmotic pressure is used as the driving force for the release of drug in a controlled manner.

• **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.
• **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.

• **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).

• **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.

• **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 (15 seconds) 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.[35]

• **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.

• **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.

Fig. 4: Osmotic drug delivery.

- **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 (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 (pH>7.5). Thus, pH controls the delivery of drugs inside the human body.

- **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.

- **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.

3. **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, drug delivery system should be site targeting specific. It is divided into three parts.[44-47]
- **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.

![Fig. 5: Site targeted drug delivery system.](image)

4. **Feedback regulated drug delivery system:** In this, a physiological response activates the release of drugs from the carrier.\(^{[48]}\) 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.\(^{[49]}\)

![Fig. 6: Feedback regulated drug delivery system.](image)
CONCLUSION
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. 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. 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.

REFERENCES


