

A CONCISE REVIEW ON CONTROLLED DRUG DELIVERY SYSTEM

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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. Controlled drug delivery is one which delivers the drug at a predetermined rate, for locally or systemically, for a specified period of time. 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. Controlled release drug delivery employs drug-encapsulating devices from which therapeutic agents may be released at controlled rates for long periods of time, ranging from days to months. 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.

KEYWORDS: Conventional drug delivery systems, Controlled drug delivery systems, Tablets, Bioavailability.

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 favor 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]

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 are duction 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]

Terminology/Definitions

A. Immediate release dosage forms: The conventional dosage forms belong to this class. The dosage form releases the drug present in it after administration to achieve rapid and complete systemic absorption. After absorption of the drug from the dosage form, plasma concentration of the drug starts decreasing according to its pharmacokinetic profile. Finally, the concentration falls below the minimum therapeutic concentration (MEC) and therapeutic activity ceases. The period at which the drug concentration remains within the therapeutic window is called the *duration of action* and the time at which the maximum concentration is attained is called the *onset of action*. To maintain a steady state concentration, the next dose is administered. Thus, a conventional dosage form shows 'see-saw' or 'peak and valley' pattern of drug concentration in plasma and tissue compartments. Depending on the drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals, the magnitudes of these fluctuations varies.

B. Modified release dosage form: The dosage forms, in which the rate of release of the drug and the time at which the release of the drug would take place are different from conventional type, are called modified release dosage form. An enteric coated tablet can be considered as a common example of a modified release dosage form. For example, erythromycin gets decomposed in the stomach; hence it is formulated as an enteric coated tablet. The multi-layered tablet is a further advancement of the modified release delivery systems.

C. Site-specific targeting: These systems refer to targeting the release of a drug straight to a particular biological location. In this case, the target is adjacent to or in the diseased organ or tissue.

D. Receptor targeting: These systems refer to targeting a specific biological receptor. In this case, the target is the specific receptor for a drug within an organ or tissue. Site-specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be sustained drug delivery systems.

E. Delayed release dosage form: When a dosage form does not release the drug immediately after administration like immediate release or conventional dosage form but releases the drug in portions at a predetermined time or at times, it is called delayed release dosage form. However, in some cases, a portion of the drug may be released immediately after administration.

F. Extended-release dosage form: If a dosage form reduces the frequency of dose at least by two-fold as compared to the frequency of administration of immediate release or conventional dosage form, the dosage form is said to be the extended release dosage form. Sustained-release, controlled-release, or long-acting dosage forms belong to this class.

G. Sustained release dosage form: The drug release from sustained release dosage form exhibit a predetermined rate in order to maintain an approximately constant drug concentration in the body over a prolonged period. The rate of release of drug follows first-order kinetics. Usually, the drug content of one dose of SR dosage form is more than that of its conventional or immediate release dosage form.

H. Prolonged action dosage form: In this type of dosage form the drug is released at a rate relatively slower rate, but for a long period; so that, the therapeutic action of the drug remains for an extended period. In this type of dosage form, one dose of the drug is released immediately after administration and later on, the second dose is released.

Rationale of Controlled Drug Delivery

Therefore, extensive researches have been conducted to reduce the frequency of administration. The outcome is the development of controlled or sustained release drug delivery system. Controlled delivery of the drug is possible by combining a polymer with the drug or active agent; so that, the release of the drug can take place at the right time, at a predetermined rate and the right place. In this system, the release of drug cans be predesigned. Thus, controlled release dosage forms have gradually gained acceptance of the medical practitioner and popularity among the patients. Compared to conventional dosage forms such delivery systems offer numerous advantages including improved efficacy, reduced

toxicity, and improved patient compliance and convenience. All controlled release systems are developed to improve the therapeutic effectiveness of the drug. According to the patent history, the earliest patent on SR dosage form was filed by Israel Lipowski in 1938, who coated the pellets/particles. The basic objective of this therapy is to maintain a steady state therapeutic concentration of drug in blood or tissue for an extended period, as shown in Figure 1. The controlled or sustained release dosage form can be defined as; *The dosage forms that release a drug at a predetermined rate so that a constant drug concentration is maintained for a specific period with a minimum side effect.* A single dose of such dosage form is used for extending the therapeutic action. The dose size is more than a single conventional dose, but the total daily dose is reduced. The primary reason for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamic properties of the drug substance. This is possible by using a novel drug delivery system or by modifying the molecular structure and physiological parameters. A properly designed dosage form should provide the drug action for a prolonged period. The key objective of controlled drug delivery is to confirm safety and to improve the efficiency of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and frequency of dosing. For conventional dosage forms, only the dose (D) and dosing interval (C) can vary for each drug. For every drug, there is a definite therapeutic window. Below the MEC, the therapeutic effect of the drug is ineffective, and above MSC toxic side effects are elicited. The therapeutic index is defined as the ratio of the median lethal dose (LD50) to the median effective dose (ED50). The rationale of controlled release dosage form can be summarized as below.

- To provide a location-specific action within the GIT.
- To avoid an undesirable local action within the GIT.
- To provide a programmed delivery pattern.
- To increase the rate and extent of absorption/bioavailability.
- To extend the duration of action of the drug.^[13-19]

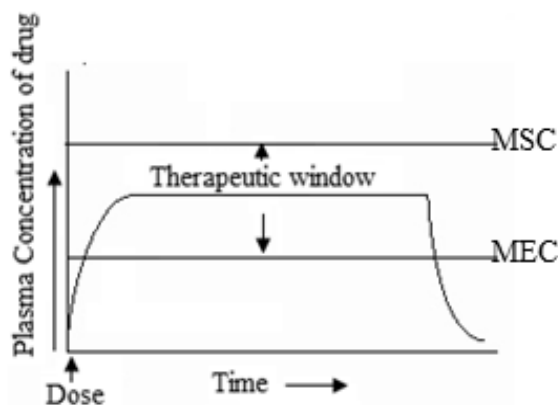


Figure 1: No fluctuation in plasma concentration of drug following controlled release dosage form.

General Advantages

The release of the active ingredient (drug) may be constant over a long period; it may be cyclic. The environment or other external events may trigger it. Controlled release drug delivery systems provide one or more of the following advantages.

- ❖ Maintenance of drug level within the desired range
- ❖ Delivery of 'difficult' drugs: the slow release of water-soluble drugs, and/or fast release of poorly soluble drugs
- ❖ Reduces dosing frequency
- ❖ Eliminates over or under dosing
- ❖ Prevention or reduction of side effects
- ❖ Reduction in total health care cost
- ❖ Improved efficacy in the treatment
- ❖ Reduction in adverse side effects and improvement in tolerability
- ❖ Improved patient compliance
- ❖ Employ less amount of total drug
- ❖ Minimizes or eliminates local or systemic side effects
- ❖ Minimal drug accumulation on chronic usage
- ❖ Cures or controls the condition more promptly
- ❖ Reduces the fluctuation in drug level
- ❖ Improves the bioavailability of some drugs
- ❖ Makes use of special effects

Disadvantages

Various disadvantages of the controlled drug delivery systems are mentioned below:

- ❖ Likely to be costly
- ❖ Unpredictable and often provide poor *in-vitro* – *in-vivo* correlations
- ❖ May cause dose dumping, if the release design is failed
- ❖ Provides less scope for dosage adjustment
- ❖ May increase the first pass clearance
- ❖ Poor systemic availability in some cases
- ❖ Effective drug release period is influenced and limited by the gastric residence time

Clinical Advantages of Control Release Dosage Forms

- ❖ 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)
- ❖ Improvement in bioavailability of some drugs because of spatial control
- ❖ Economical to the health care providers and the patient

Commercial / Industrial Advantages

- ❖ Illustration of innovative/technological leadership

- ❖ Product life-cycle extension
- ❖ Product differentiation
- ❖ Market expansion
- ❖ Patent extension

Major Limitations

- ❖ Delay in the onset of action
- ❖ The possibility of dose dumping in the case of a poor formulation strategy
- ❖ Increased potential for first-pass metabolism
- ❖ Greater dependence on the gastric residence time of the dosage form
- ❖ The possibility of less accurate dose adjustment in some cases
- ❖ Cost per unit dose is higher when compared with conventional doses
- ❖ All drugs are not suitable for formulating into ER dosage form.^[20-24]

Selection of Drug Candidates

All the drugs cannot be formulated as their controlled release dosage forms. A drug must have the following characteristics for the formulation of controlled release dosage forms.

- ❖ Very short elimination half-life
- ❖ Very long elimination half-life
- ❖ Narrow therapeutic index
- ❖ Rate of absorption
- ❖ Mechanism of absorption
- ❖ First pass effect

Factor Influencing the Design and Performance of Controlled Drug Delivery System

1. Biopharmaceutic characteristics of the drug

- ❖ The molecular weight of the drug
- ❖ The aqueous solubility of the drug
- ❖ Apparent partition coefficient
- ❖ Drug pKa and ionization physiological pH
- ❖ Drug stability
- ❖ Mechanism and site of absorption
- ❖ Route of administration.

2. Pharmacokinetic characteristics of the drug

- ❖ Absorption rate
- ❖ Elimination half-life
- ❖ Rate of metabolism
- ❖ Dosage form index

3. Pharmacodynamic characteristic of the drug

- ❖ Therapeutic range
- ❖ Therapeutic index
- ❖ Plasma-concentration-response relationship

The fabrication of the formulation depends on the physicochemical properties of the drug and on the pharmacokinetic behavior of the drug. In conventional dosage form, the rate-limiting step in drug's bioavailability is usually absorption through the biomembrane; where as in controlled drug delivery

system the rate-limiting step is the release of drug from the dosage form.^[25-27]

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 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.^[28]

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.^[29]

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.^[30]

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.^[28]

(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.^[28,31]

Activation by physical process

Osmotic pressure activated system

In this osmotic pressure is used as the driving force for the release of drug in a controlled manner.^[32]

Hydrodynamic pressure activated system

In this drug is placed into the collapsible impermeable container which contains liquid drugs and forms drug reservoir compartment. It is present inside the rigid shape cover.^[33]

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.^[34]

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).^[28]

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.^[35]

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.^[30] These devices are fabricated by Bio-degradable and non-degradable polymer.^[36]

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.^[30, 37]

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.^[28]

Activation by chemical process**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.^[28]

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.^[38]

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.

Activation by biochemical means

In this drug release is activated by the biochemical reaction.^[39]

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.^[40] 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.^[28]

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.^[34, 41]

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 contains 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 becomes swollen and thus permeable to insulin molecule by the process of self-regulated processes.^[28]

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 is 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 is completed by self-regulating drug delivery system.^[28]

(4) 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 read of uncontrolled drug release, drug delivery system should be site targeting specific. It is divided into three parts.

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 tumor 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.

Site targeting drug delivery system also classified as.

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

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.^[42]

CONCLUSIONS

The dosage form is a combination of drugs and excipients. Excipients are used to get a structure, enhance stability and mask the taste. Solid, semisolid and liquid dosage forms are the conventional dosage forms that suffer from fluctuations in plasma drug levels which demands high dosing and dosing frequency with poor patient compliance. The bioavailability of a drug is crucial to achieving the desired action from any dosage form. Controlled drug delivery systems have emerged as an alternative to the conventional sort, to improve the bioavailability, extend the drug release and maintain drug plasma levels within the therapeutic window with minimal side effects. Controlled drug delivery increases the drug solubility and stability and offers the selective delivery of drugs with a predictable rate and mechanism to specific organ/tissue/cells. Dissolution, diffusion, water penetration and chemically controlled drug delivery systems are the types of controlled drug delivery systems. Stimuli-responsive delivery systems are useful in various disease conditions (cancer, infections, etc.) to target as well as control the release. Further, nanocarriers with intelligent biomaterials and additive manufacturing techniques can be developed to achieve controlled targeted delivery. The future of drug delivery is focused on patient-specific therapy using microfluidic-based, 3D-printed devices and CRISPR cas9 based delivery systems integrated with quantum sensing.

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