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REVIEW ARTICLE

Review on controlled release drug delivery system

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ABSTRACT

The controlled drug delivery systems consist in technologies that aim to release therapeutic agents in a specific target as needed to achieve the desired therapeutic outcome. Controlled release systems are well used to control the drug plasma concentration after administration by various possible routes. They can play the important part in targeted drugs delivery system in organs or tissues. It is to ensure safety and to improve strength of the drug as well as patient compliances. Pharmaceutical discovery and research are increasingly focused on delivery systems that enlarge desirable therapeutic objectives while decreasing the side effects. The maintenance of the concentration of drug in the plasma in therapeutic index is most important for effectual treatment. The controlled release drug delivery system works on many different mechanisms to regulate the release rate of drugs. Various mechanisms like osmotic pressure, matrix system, reservoir system etc. It also discusses the usual drug delivery systems and in addition controlled drug delivery systems are mentioned in detail with the design, classifications and drawings features. This article provides on an ideal requirement and different approaches, advantages, properties, types involved in the evolution of controlled release drug delivery system for the better delivery of the drugs.

INTRODUCTION

The controlled drug delivery system may include continuity of drug levels within desired ranges; less administration is required, optimal use of medication and increased patient compliance [1]. Drugs can be administered in different routes however out of all the routes the oral route of administration is the most favorable for administration and for dosage adjustment [2]. Controlled drug delivery system refers to system that provides some control to either temporal or spatial or both nature of the drug release. Controlling the rate of specific time of drug delivery to the targeted tissue is referred to as temporal. The term spatial refers to a drugs ability to target a specific organ or tissue [3]. Unlike conventional dosage forms, the controlled release dosage forms releases the total dose of drug available. The step of rate limiting for drug absorption such as biological fluids (i.e. controlled release) at a slower, the rate of medication release from dosage forms is more consistent after administration [4].

It is an ideal dosage drug therapy dose regimen that quickly recovers the required plasma concentration and maintained for the complete duration of treatment. The frequency of medication administration mainly depends on the mean residential time and biological half-life of the drug. Conventional drug delivery systems often produce more or less drug resulting in a variety of adverse drug reactions due to the unpredictable drug release patterns.

CRDDS alter drug delivery as well as decreases drug toxicity. Controlled release refers to predictability and reproducibility in drug release kinetic which means that drug release rate from the delivery system proceeds on rate profile not expected only kinetically, but also consistent from the division to another. CRDDS intended to control drug release into the body; it may be

temporary or spatial in nature or both [3].

Sustained release is used to describe a dosage form formulated for put off the release of the active pharmaceutical ingredients in this way as to delay its presence in the systemic circulation or prolonged and the plasma concentration is maintained over the period. The onset of drug action delayed and duration of therapeutic response is maintained [5, 6].

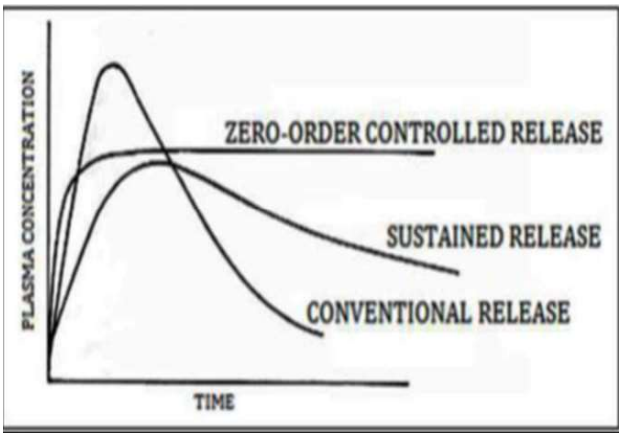

Figure 1: Drug plasma concentration- time profile

The following are the classifications for Modified release oral drug delivery systems [7]:

1) Controlled release
   a. Sustained release
   b. Extended release
   c. Prolonged release
2) Delayed release

Advantages of CRDDS [8, 9]

1) Improved patient compliances due to less several dose administrations.
2) Reduce the fluctuation in drug level.
3) Maximum utilization of drug enabling reduction in total amount of dose administered.
4) Reduction in healthcare costs.
5) Improved bioavailability of some drugs due to spatial control.
6) Reducing or eliminating of systemic or local side effects.
7) Improved efficiency in treatment.
8) Due to improved plasma level management, the safety margin of high potency medicines has increased
9) A suitable delivery system for drugs which having a low biological half-life (3-4 hr) and drug rapidly eliminate from the body.

Disadvantages of CRDDS [8, 9]

1) Immediate release compared to conventional dosage forms reduced the systemic availability.
2) Poor *in vitro- in vivo* correlation
3) It is difficult to optimize the exact dose and dosing interval.
4) Doses may be dumped due to food, physiological variables or other formulation variables or by patient chewing and crunching of oral formulations and increased the risk of toxicity.
5) Cost per unit dose is higher when compared to other conventional doses.
6) More dependent on gastric intestinal residence time of dosage forms.

Classification of Oral CRDDS:

The mechanism of drug release from the dosage form is used to classify controlled release drug delivery systems [10].

1) Dissolution Controlled Drug Delivery System [10]:

Dissolution is defined as solid substances that are dissolved in a specific solvent it is rate determining step when liquid diffuses from solid. Sustained release oral products employing dissolution as the rate-limiting steps are in principle the simplest to prepare.

a) Matrix Dissolution Control

Another approach is to compress the drug for a carrier of some kind that slowly dissolves into a tablet form. The rate of medication availability is controlled here by the rate of dissolved fluid penetration into the matrix. The porosity of the tablet matrix, the presence of lipophilic additives, and the surface of tablets and particles may all influence this [10].

b) Encapsulation Dissolution Control

These methods generally apply to a single coating drug particles or granules with a slow dissolution subject. The coated particles could be directly compacted into tablets like space tabs or inserted in capsules as in spansule products. From time to time necessary to dissolve coat as a purpose of its thickness and solubility of waters, one can get repeat or continuous action by using narrow or broad spectrum of various coated particles with respective thickness [10].

2) Diffusion Controlled Drug Delivery Systems:

Diffusion controlled delivery systems are detecting increasing applications in the controlled release pharmaceutical areas. To achieve the best therapeutic effects especially for drugs has a short half-life, they are often it is desirable to have a drug releases of zero order. It is a large absorbing process that requires no energy. In these drug molecules diffuses from a region with a higher concentration until equilibrium is attained and it is directly proportional to its concentration activity beyond the membrane in this system release rate is determined by diffusion through a water insoluble polymer [11].

Two types of diffusion system [1]:

a) Reservoir Diffusion System

In this system, water insoluble polymer material includes a core drug, which controls the release rate. Drugs will divide into the membrane and exchange with the fluid surrounding the particles or tablet. Additional drugs will enter the polymer, diffuses and interchange with the surrounding media (Fig. 2) [1].

b) Matrix Diffusion System

The drug or active substances shall be distributed in polymer matrix in the homogenous system called a matrix system. Diffusion occurs as the drug travels into the environment outside the polymer matrix. If the release continues, this type of device usually its rate is reduced, because the active agent gradually has longer travel distance and takes longer to it was released (Fig. 3) [12].

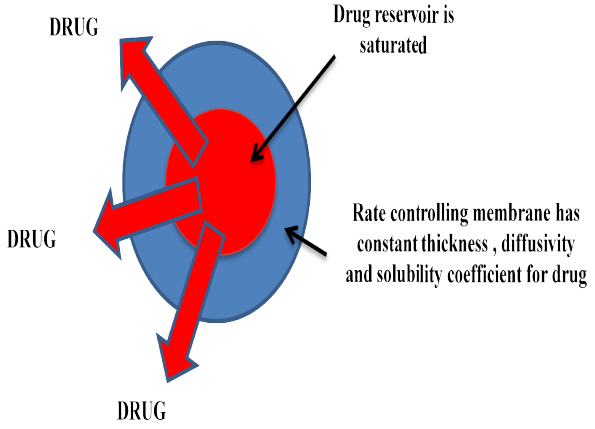

Figure 2: Reservoir type drug delivery system

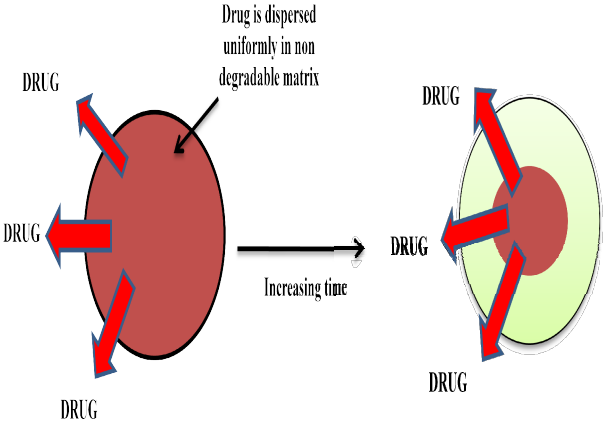

Figure 3: Matrix type of drug delivery system [12]

3) Water Penetration Controlled Drug Delivery System:

In this system drug releases achieved by the penetration of body fluids and water into the systems. Osmotically controlled systems and swelling controlled systems are two different sorts of this system.

a) Osmotic Controlled Drug Delivery System

In this type of drug delivery system osmotic pressure is the driving force that generates a constant drug release. This system is done by implementing a semi permeable film around the core of the osmotically active drug or core of osmotically idle drug in combination with osmotically active salt. Delivery orifice drilling is performed in all systems with the laser or high speed mechanical drill [13].

b) Swelling Controlled Drug Delivery System

In swelling controlled system, drug aggregates are homogeneously dispersed in a dry infusion 3D polymer network. When these systems are absorbed in water or body fluids, water flows into the 3D polymer network the systems will hydrate. Therefore, increasing the content of aqueous solvent and network mesh size within the system, resulting in dissolution and diffusion drugs throughout the polymer network, swelling properties of the systems and dissolving and diffuse properties of drugs are key factors in controlling drug release [14].

4) Chemically Controlled Drug Delivery System [15]:

Chemically controlled drug delivery systems divided into two types: Erodible controlled system and Drug polymer conjugate controlled system (Fig. 4).

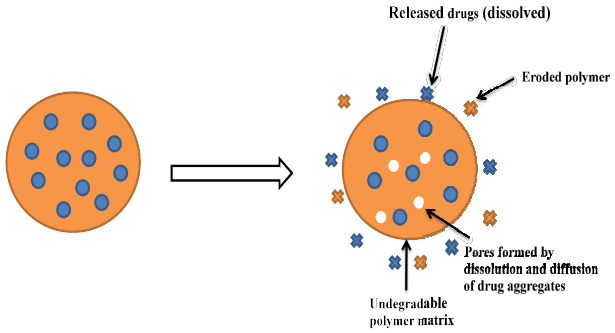

Figure 4: Chemically controlled drug delivery system [15]

a) Erodible Controlled System

In the erosion controlled systems, the drugs are loaded into inflatable polymer matrix by dispersion and molecular interactions (ionic, hydrophobic etc.) and can be released after degradation of the matrices and the diffusion and dissolution of drug molecules. The diffusion and dissolution of drugs in these systems and corrosion of polymeric matrices which may control the release profiles. It can be difficult to estimate the kinetics of release and corrosion of polymers toxic. However these systems can releases high molecular weight drugs, not requiring surgery, remove and in some cases can allow for zero order release kinetics [15, 16].

b) Drug Polymer Conjugate Controlled System

In polymer drug conjugated system drugs are covalently linked to polymer molecules by hydraulically or enzymatically degradable. These systems can use for controlled released in which drugs are formulated in colloidal forms and which is inert and stable in circulation. The environment of the desired specific target site governs the drug release mechanisms. The covalent bonds between the drug and the polymer are split by hydrolysis or enzymatic break down to release and activate the drug. For example, such systems are used to deliver drugs to the colon, bacteria in the gastrointestinal tract producing enzymes that degrade the covalent bonds. Provides polymer drug conjugated systems a way to enhance drug efficacy and can be used to control the release of drugs, proteins, targeting moieties and some imaging agents. They also present greater stability, water solubility, and long half-life of the drug as well as lower immunity, lower antigenicity, and more focus especially on tissues or cells [15, 17].

5) Ion Exchange Resin System:

Resins are water insoluble materials carry anionic or cationic groups in the repeat positions on the resin chain.[10]theresin charged drug is prepared with mixing the resin with the drug solution by repeated showing of the resin to the drug in a chromatographic column or by holding the resin in attach with the drug solution for prolonged period of time. The drug resin is then washed for removal contaminated and dried ions to form particles or beads. When high concentrations of appropriate a charged ion is in exposure with the ion exchange group, the drug substances are exchanged and diffused from the resin to the bulk solution [10].

Factors Influencing the Design and Act of Controlled Release Products [18]

1) Physiological Properties:

i. Partition Coefficient

Partition coefficient is defined as the fragment of the drug in oil phase to adjacent aqueous phase. Drugs go through biological membrane, if partition coefficient of the drug impacts indicates bioavailability largely due to hydrophobic nature of biological membrane. Drugs containing lower partition coefficient is not acceptable for oral controlled release drug delivery system and drug have greater partition coefficient are also not acceptable for oral CR drug delivery system. Because they will not be partitioned out of the lipid membrane once it gets in the membrane [18].

ii. Aqueous Solubility

Most forms of active pharmaceutical (API) are weakly acidic or basic in nature affecting API water solubility. Weak water soluble drugs are difficult to design the controlled release formulas. High aqueous solubility drugs subsequent burst release rapidly increased plasma drug concentrations. These types of drugs are good substances for CRDDS. The solubility of the pH dependent also makes a problem with CRDDS formulation. BCS Class III and IV drugs are not applicable drug substances for this type of formulations [19].

iii. Molecular Weight and Molecular Size [20]

Molecular weight and molecular size are two important factors affecting the molecular diffusion across biological membrane. The molecular size is less than 400D is easily diffuses but more than 400D prove a problem with drug diffusion [20].

iv. Drug pKa

The drug pKa is the factor determining the ionization of drugs at physiological pH in the GIT. Drugs that are highly ionized are generally unsuitable for use in a controlled release medication delivery system. Unionized drug absorption is closely associated with ionized drug absorption from biological membranes. The pKa ranges from 3.0 to 7.5 for acidic drugs whose ionization is dependent on pH, and from 7 to 11 for basic pharmaceuticals [21].

v. Stability of Drugs

Drugs that are stable in acids and bases, enzymatic degradation and gastric fluids are good substances for controlled release drug delivery system. If the drugs degrade in small intestine and stomach, which is not convenient for controlled release formulations because it will decreases in availability of concern drugs [22].

vi. Protein Binding

The drug protein complex acts as a reservoir in plasma for the drug. Drugs that shows high plasma protein binding are not good substance for the CRDDS. Because the protein binding increases the biological half life, hence no need to perpetuate the drug releases [23].

2) Biological Factors:

i. Dose Size

The CRDDS together to eliminate the repetitive dosing, so it must be there the large dose is the traditional dose form. But the doses used in conventional dosage form indicate the dose to be used in CRDDS. The amount of sustained doses it should be as large as it meets acceptance criteria [24].

ii. Biological / Half Life:

The shorter the t ½ of a drug the greater the fluctuations between the maximum steady state concentration and minimum steady state concentration focus on repetitive dosing. Thus drugs needs to be administered more and more often [1].

iii. Patient Physiology:

The patient's physiological conditions; such as residence time, gastric emptying rate, gastro intestinal diseases affects to the release of the drug from the dosage form directly or indirectly [25].

iv. Absorption Window:

Some drugs are absorbed when given orally only from a specific section of the gastrointestinal tract. This section is referred to as the absorption window. These are not applicable for CRDDS [26]. Drugs showing absorption from the specific segment in gastro intestinal tract they are poor substances for CRDDS and the drugs which are absorbed throughout GIT are good drugs for controlled release [27].

v. Therapeutic Window:

Controlled release medication delivery systems are not appropriate for medicines having a restricted therapeutic index. If the delivery method fails to manage the release, dosage dumping and eventual toxicity will occur [28].

Characteristics of Drugs Suitable for Controlled Release [10]:

1) Show moderate absorption rates and excretion.
2) Uniform absorption all over the gastro intestinal tract.
3) Administered in relatively small doses.
4) Have a good safety margin.

In general controlled drug delivery seeks to [10]:

1) Maintain a fixed rate of medication activity by maintaining a generally consistent, effective level of drugs in the body while minimizing undesired side effects [10].
2) Localization of drug action by spatial arrangement of control release system near or in the diseased tissues or organs.
3) Targeting drug action using carriers or chemical derivatives for the delivery of drugs to a specific target cell type [10].

Pharmacokinetic Parameters for Drug Selection

Table 1: Drug selection pharmacokinetic parameters [29]

Parameter	Comment
Intrinsic absorption rate	Should be greater than the release rate
Absolute bioavailability	Should be 75% or more
Biological or elimination half life	It Should be between 2 to 6 hrs
Steady state concentration	Lower Css and smaller Vd
Elimination rate constant	Required for design
Toxic concentration	The therapeutic window should be broader
Total clearance	Dose independent
Apparent volume of distribution	Vd effect the required amount of the drug

Polymers Used in Controlled Drug Delivery System

Polymers are becoming increasingly important in the field of drug delivery; this is the most significant factor. Polymers are used in pharmaceutics for a variety of purposes, from binders in tablets to viscosity and flow control agents in liquids, suspensions, and emulsions. Polymers can be used as film coatings disguising the bad taste of a drug, improving drug stability and modifying drug release traits. Controlled drug delivery occurs when a synthetic or natural polymer is sensibly coupled with a drug or other active agents in such a way that the active agent is released from the material in a pre-designed way [30-34]. The release of active agents may be stable over a long duration of time; it may be cyclical over a long duration of time, or it they may result in the environment or another external practice. In any cases, the purpose behind the controlling drug delivery is about achieving more effective the therapies and eliminating the possibility of overdose [30-34]. A range of materials were used to control the release of drugs and other active agents. They were the polymers of the originally intended for different non biological uses and were selected because of its physical properties, such as [1]:

- Poly vinyl pyrolidone
- Poly urethanes
- Poly ethylene
- Poly methyl methacrylate
- Poly siloxanes
- Poly vinyl alcohol

Features of Ideal Polymer System [10, 35]**:**

The polymer system should be ideal following attributes:

1) It should be stable and compatible with the environment.
2) It should be easy to administer.
3) It should be non-toxic.
4) It should have better mechanical strength.
5) It should be simple and cheap to make.

Criteria Followed in Polymer Selection[10, 36-38]**:**

A polymer selected as a potential drug carrier must be shown certain properties, as listed below:

1) The polymer must be soluble and easy to synthesis; it must have finite molecular weight and narrow distribution.
2) It should provide a drug attachment or release sites to incorporate the possibility drug polymer bonds.
3) It should be biodegradable or discontinued from the organism after compliance function.
4) The polymer should be compatible with the biological environment i.e. non-toxic, non-antigenic and non-stimulant in any other meas.

CONCLUSION

The controlled drug delivery system could be a significant step forward in addressing issues such as directing a drug to a particular organ or tissue and managing the pace of drug administration to that spot. Controlled release products provide the over traditional dosage form at biopharmaceuticals, pharmacokinetics and the Pharmacodynamic properties of the drug in this way that it reduce the frequency of dosing to an extent once the daily dose is sufficient for therapeutic management by providing a uniform plasma concentration and maximum utility for the drug. With improved understanding of controlled and enhanced release mechanisms developing technologies, it may be possible to design a suitable method for efficient site specific drug delivery system. Controlled drug delivery systems has appeared as a different to traditional systems to improve bioavailability, drug release extent and plasma drug maintenance levels within the therapeutic window with less side effects. From the above discussion it is concluded that the controlled release drug delivery system has been commonly accessible and most convenient a drug delivery system's path.

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