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CONTROLLED DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Controlled drug delivery is one which delivers the drug at predetermined rate, for locally or synthetically, for a specified period of time. In CDDS the oral drug delivery is most preferred & convenient option as the oral route is provide maximum active surface area among all drug delivery system. The Controlled release drug delivery employs drug encapsulation devices for which therapeutic agents may be released at controlled rate for long period of time.The attractiveness if this dosage form is due to awareness ti toxicity and ineffectiveness of drug when administered. In CDDS with the use of polymers the system will deliver drug at variable rates. The maintenance of concentration of drug in plasma within the therapeutic index is very critical for effective treatment. These factors as well as factors such as repetitive dosing&unpredictable is leads to concept of oral controlled dosage form. The CDDS is word on many different mechanism to control the release rate of drugs such as, osmotic pressure, reservoir system, matrix system, altered density system etc.The present article contains brief review on various formulation approaches for controlled drug delivery system.

INTRODUCTION:

It is also known as smart drug delivery. The CDDS maintain drug concentration in the blood at desired value as long as possible **(1).**In CDDS the drug substance release from to maintain therapeutic response for extended period. It maintains the drug concentration in blood at desired value as long as possible. There is control on release drug**[1,5].**In the conventional drug delivery , the drug concentration in the blood increase to the toxic level as drug is taken, then drug concentration is decreased to an ineffective level and patient have to take the drug frequently. In order to reduce this this disadvantage CDDS was designed to maintain drug release with predetermined dose and prolong the curing-time in the targeted body compartment **[2].** The smart DDS are self-avident because the drug amount can be auto controlled by external changes such as temperature, electric field and pH **[3].**The CDDS in the extended release drug provide a greater selectivity of pharmacological activity by controlling the pharmacokinetics, pharmacodynamics and input rate of drug [4]. With modifying molecular structure or physiological parameter related to route of administration. Results improved patient compliances by reduction in dosing **[3-4]**.

The CDDS in cancer therapy

The controlled and targeted delivery of chemotherapeutic drugs at site of action is necessary to maximize the killing effect during the tumour growth phase and to avoid drug exposure to healthy adjacent cell, thereby reducing drug toxicity **[4].**The drug therapy of any disease is the one which immediately attains the desired therapeutic concentration of drug in plasma and maintain it constant for the entire duration of treatment. This is possible administration particular dose and at particular frequency. CDDS can improve the therapeutic efficacy and safety of drug by precise emporal and spatial placement in body , thereby reducing both size and number of dose required**[7].**The conventional dose that provide drug rapidly to body & the disintegration time is less than 15 minutes , so on this CDDS that provide sustained release dosage form**[8]** .

It is defined as one that releases the drug at a time other than immediately after administration. It is defined as the one that allows at least a twofold reduction in the dosing frequency as compared to that of conventional dosage form.

1] Controlled action

In this type of dosage forms it provides a prolonged duration of drug release with predictability and reproducibility of drug release kinetic. In this case, the rate of drug absorption is equal to the rate of drug removal from body.

2] Sustained release action

In this type of dosage from, a sufficient amount of drug is initially made available to the body to cause a desired pharmacological response. The remaining fraction released periodically and is required to maintain the maximum initial pharmacological activity for some desirable period of time in excess of time expected usual single dose.

3] Prolonged Action

These type of dosage form are designed in such a way that it release the drug over an extended period during which pharmacological response is obtained but dose not necessarily maintain the constant blood level.

4] Site specific and receptor release

It refers to targeting of drug directly to a certain biological location.

Rationale of CDDS [7]

The basic rationale for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system. It is desirable that the duration of drug action become more to design properly. Rate controlled dosage form & less or not at all, a property of the drug molecules inherent kinetic properties. This achieved by better control of plasma drug levels and frequent dosing.

Polymers that are used in controlled drug delivery system

Polymers are the compound with high molecular mass form by monomers. Polymers are becoming increasing the field of drug delivery. The pharmaceutical application of polymers range from their use as binder in tablet to viscosity and flow controlling agent in liquid, suspension and emulsion. Polymers can be used as film coating to disguise the unpleasant taste of drug, to enhance the drug stability & to modify drug release characteristics. Advanced drug delivery system today, receiving safer & more effective dose of the medicines they need to fight a variety of human ailments, including **cancer.** CDD occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug in such a way that the active agents are released from the material in a

predesigned manner. The release of the drug may be longer for the long period. In any case the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under & overdosing.Recently, a variety if biodegradable polymers have been widely used as implantable biomaterials, such as prosthetics and tissue support matrices and as drug delivery device. The main advantage of using bio-degradable polymer is that no retrieval of their device is need after a particular usage. Poly (esters) is the best characterized most widely studied biodegradable system. The synthesis of Poly (ester) has received as much attention as the degradation of these materials. The mechanism in degradation of poly (ester) materials is classified as bulk degradation with random hydrolytic scission of the polymer backbone.

Table 1: Advantages and disadvantages of CDDS

Advantages	Disadvantages
1.Sustained therapeutic blood levels of the drug	1. Removal of the drug product from the system if difficult in case of adverse effect or toxicity.
2. Prolonged & consistent clinical response in the patient.	2. Variable absorption rate might make the plasma concentration unpredictable.
3. Patient convenience leading to better patient compliance.	3. Unpredictable & often poor in-vitro in-vivo correlations dose dumping.
4. Improve bioavailability of the drug.	4. Poor synthetic availability in general.
5. Employ minimum drug .	5. Reduced potential for drug adjustment.

Advantages & Disadvantages of CDDS [7]

Selection of Drug for CR/SR Dosage Form Development [14]

The important parameters of drug based on their physicochemical, biological, pharmacokinetic & pharmacodynamics properties, which are to be take into consideration while developing a sustained release/controlled release dosage form.

Table 2: Properties of candidate Drug and Desired Factors

Properties of candidate Drug	Desired Factors
1. Biopharmaceutics properties.	
a. Molecular size	Less than 600Daltons
b. Aqueous solubility	More than 0.1 mg/ml
c. Partition coefficient Ko/w	1-2
d .Dissolution constant pKa	Acidic drug , pKa >2.5 Basic drug , pKa <11.0
e. Ionization at physiological pH	Not more than 95%
f . stability in GI milieu	stable at both gastric and intestinal pH
g. Absorption mechanism	Passive, but not through a window
2.Pharmacokinetic Properties	
a. Absorption rate constant Ka	-high
b. Elimination half-time t ½	-2-6 hour
c. Metabolism rate	-not too high
d. Dosage form index	-One
3. Pharmacodynamics properties	
a. Dose	-Maximum 1.0g (in controlled release form)
b. Therapeutic index	-Wide
c. Therapeutic range	-Wide

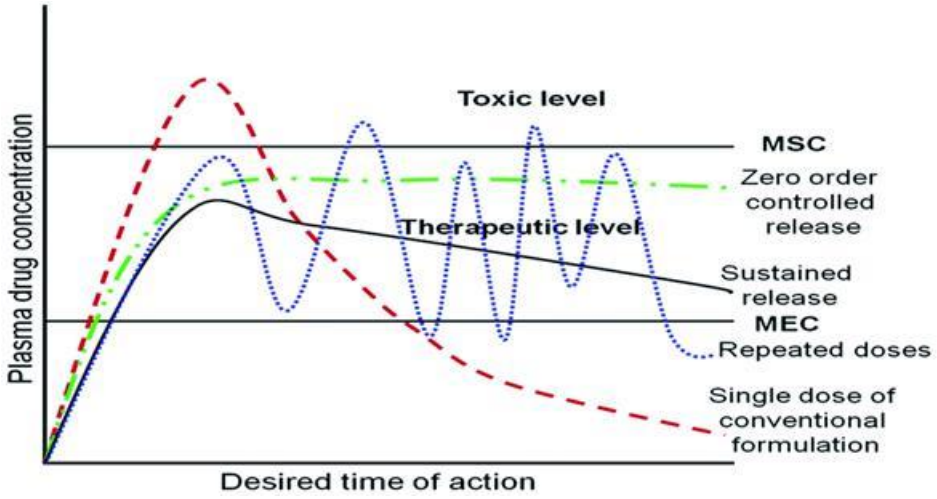

Fig. 1: Approaches to design controlled release formulation

Approaches to design controlled release formulation based on diffusion , dissolution & ion exchange principle [7,8,14]

Classification of controlled release system

A) Diffusion controlled system.

1) Reservoir Devices

2) Matrix devices

B) Dissolution controlled system.

1) Matrix Dissolution Controlled system

2) Encapsulation dissolution Controlled system

C) Diffusion & Dissolution controlled system.

D) Ion-Exchange system.

Diffusion controlled system

1) Reservoir devices

A core of drug surrounded by a polymeric membrane characterizes them. The nature of the membrane determines the rate of drug release.

The characteristics of reservoir diffusion system are.

1. Zero order drug release is possible.
2. The drug release rate is dependent on the type of polymer.
3. High molecular weight compounds are difficult to deliver through the device. Coating & microencapsulation technique can be used to prepare sub devices.

Types of diffusion controlled DDS

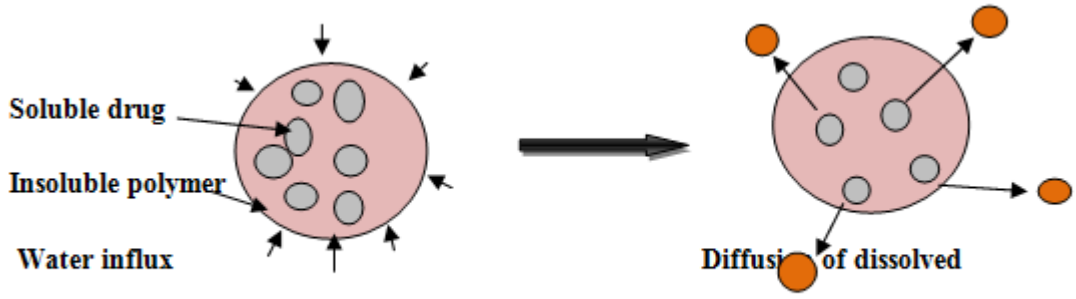

Fig.2. Non-Swellable matrix diffusion rate-controlled DDS

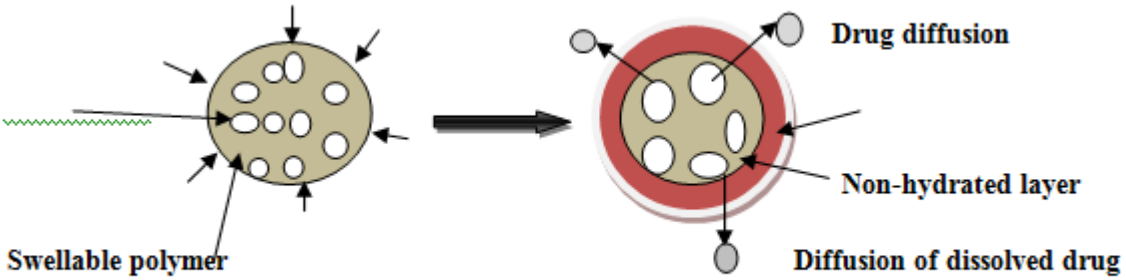

Fig.3: Swellable matrix Diffusion rate-controlled DDS

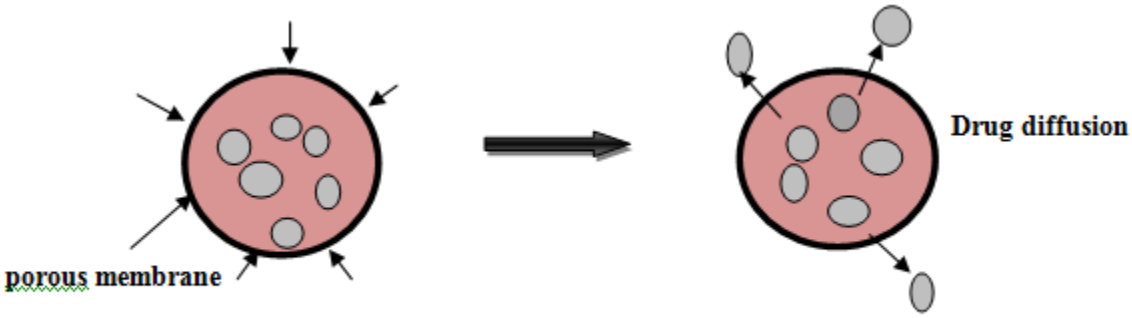

Fig.4: Membrane Diffusion rate-controlled DDS

2)Matrix devices

It consists of drug dispersed homogenously in a matrix. The characteristic of the matrix diffusion system are.

1. Zero order release cannot be obtained.
2. Easy to produce than reservoir devices.
3. High molecule weight compounds are delivered through the devices.

A) Dissolution controlled systems

1) Matrix dissolution controlled System

Aqueous dispersion, congealing, spherical agglomeration etc. can be used.

2) Encapsulation dissolution control

Particles, seed or granules can be coated by technique such as microencapsulation.

B) Diffusion and dissolution controlled system.

In a matrix, the drug is homogenously dispersed in a matrix and it is released either by swelling controlled mechanism or by hydrolysis or by enzymatic attack.

D)Ion-exchange system

Ion-exchange system generally used resins composed of water-insoluble cross-linked polymers. These polymers contain salt forming functional group in repeating position on the polymer chain. The drug is bound to the resin and released by exchanging with appropriately charged ions in contact with the ion-exchange groups.

$$\text{Resin}^{+}\text{-drug}^{-} + X^{-} \longrightarrow \text{Resin}^{+} - X^{+} + \text{drug}^{-}$$

$$\text{Resin}^{-}\text{-drug}^{+} + Y^{+} \longrightarrow \text{Resin}^{-} - X^{+} + \text{drug}^{+}$$

Where, X- and Y+ are ions the GIT tract.The rate of drug diffusing out of the resin is controlled by the area of diffusion, diffusion path length and rigidity of the resin, which is the function of amount of cross-linking agent used to prepare the resin. For the better release in the system is to coat the ion-exchange resin with hydrophobic rate-limiting polymer.

Physiochemical & biological properties of drugs relevant to controlled release formulation[14]

1] Physicochemical properties

Properties like solubility, protein binding propensity, stability & compatability play a major role in designing a controlled or sustained release dosage form.

a) Solubility

Amoxycillin is a poorly water-soluble drug while its sodium salt is highly water-soluble. A proper blending of these two forms of the drug is necessary while designing its controlled release dosage form.

b) Protein binding

Drugs which have high protein binding capacity, need special attention while formulation into modified release dosage form. Due to their protein binding ability, they have prolonged duration of action

c) Compatibility

Ramipril, an antihypertensive drug is incompatible with almost all the excipients used in formulation of controlled release dosage form. This aspect is highly crucial and was taken into consideration while developing in modified release tablets.

d)Stability

The drug should be stable for a sufficient duration of time for which the delivery system has to remain within the body. Drugs like Rabeorazole get degraded within 72 seconds in acidic pH of the stomach.

e) Partition coefficient

The compounds with a relatively high partition coefficient are predominantly lipid soluble and easily penetrate membranes resulting high bioavailability. Compounds with very low partition coefficient will have difficulty in penetrating membranes resulting poor bioavailability. Furthermore partitioning effects apply equally to diffusion through polymer membranes**.**

f) Ionization & aqueous solubility

The pH partition hypothesis simply states that the unchanged form of a drug species will be preferentially absorbed through many body tissues.

The compounds with low solubility are inherently controlled,since their release over the time course of a dosage form in the GIT will be limited by dissolution of a drug.

2] Biological properties

Every pharmacokinetic property and biological response parameter has a useful range for the design of controlled release products**.**

a) Absorption

Drugs which are absorbed by specialized transport process & drug absorption at special sites of the GIT tract are poor candidates for sustained release product.

To maintain a constant plasma/tissue concentration of drug, it must be uniformly released form & absorbed. The rate limiting step in case of controlled release drug delivery system is the release rate. It is expected that the drug will be absorbed at a faster rate as compared to its release rate from the dose form, which is always not the case.[2]

b) Distribution

The distribution of drugs into tissues is an important factor in drug elimination kinetics as it not only lower the concentration if circulating drug but also it can be rate limiting in its equilibration with blood & extracellular fluid.[2]

Binding of the drug with plasma proteins & tissues leads to prolonged drug action.

c) Metabolism

Metabolism of the drug can either inactive a pharmacologically active moiety or convert an inert molecule into its active metabolites. Metabolic alteration of the drug can occur in variety of tissue, some of which are richer in enzymes than the other e.g. Liver.

Drugs that are significantly metabolized especially in region of the small intestine can show decreased bioavailability from slower releasing dosage forms. This is due to saturation of intestinal wall enzyme system.The drugs should not have intestinal first pass effect and should not induce inhibit metabolism are good candidates for sustained release dosage forms.

d) Duration of action

The therapeutic action of drug depends on the biological half-life and hence the duration of a drug plays a major role in the process of considering a drug for controlled release. The biological half-life of a drug, in turn is influenced by its elimination, metabolism and distribution patterns.

Drug with short half-life require frequent dosing in order to minimize fluctuation in blood levels accompanying conventional oral dosage.

The duration of action of the drug it is also depends on the which type of polymer we use to design the proper drug.

Table 3: Controlled and modified release formulation currently available in market

Product (trade name)	Drug	Type
Entocost	Budenoside Capsule [9 mg]	Controlled release capsule for colon specific drug delivery
Cifran OD	Ciprofloxacin Tablets [500mg/1g]	Effervescent Matrix type floating tablets
Contiflu OD	Tamsolusin Controlled release beads	Diffusion and dissolution controlled beads
Roliten OD	Tolterodine tartrate extended release capsule [2/4mg]	Reservior type controlled release beads encapsulated in empty gelatine shells.

Polymers[15,16]

Polymers means-"many parts"

Definition

"Polymers is a substance of high molar mass that is composed of repeating structural units".

Example- Ethyl cellulose & carboxy-methyl cellulose.

Classification of polymers

A) Based on origin of source

1) Natural polymers
2) Semisynthetic polymers
3) Synthetic polymers

B) Based on structure of polymer

1)Linear polymers

2) Branched polymers

3) Network or cross linked polymers

C) Based on molecular force

1) Elastomers

2) Fibres

3)Thermoplastic polymers

4) Thermosetting polymers

D) Based on polymerization process

1) Addition polymers

2) Condensation polymers

A) Based on source

1) Natural polymers

Polymers either obtained from plants or animals are called as natural polymers. They are called plant and animal polymers.

Ex. Cellulose, Jute, Silk, Wool, leather, natural rubber.

2) Semisynthetic polymers

The polymers obtained by simple chemical treatment of natural fibres to improve their physical properties like lustrous nature, tensile strength, are called Semisynthetic fibres. Ex. Acetate rayon, cup ammonium silk, Viscous rayon.

3) Synthetic fibres

The fibres obtained by polymerization of simple chemical molecules in laboratory are synthetic fibres. Ex. Nylon, terylene, polyethene, polystyrene, synthetic rubber, Bakelite.

B) Based on structure o polymers

1) Linear polymres

In these polymers monomers are linked with each other and form a long straight chain. These chains have no any side chain. There molecules are closely packed and have high density, tensile strength & melting point. Ex.PVC, Nylon, polyesters

2) Branched polymers

They have a straight long chain with different side chains. There molecules are irregularly packed hence they have low density, tensile strength & melting point. Ex. Polypropylene (side chain – CH3), amylopectin.

3) Network or Cross linked polymers

In these monomeric units are linked together to constitute a three dimensional network. The links involved are cross links. They are hard, rigid & brittle due to their network structure. Ex. Bakelite, melamine, formaldehyde resins.

A) **Based on molecular force**

Mechanical properties of polymer like tensile strength, toughness, elasticity depends upon intermolecular force like van-der walls force & hydrogen bonding.

1) Elastomers

These are the polymers in which polymer chains are held by weakest attractive force. They contains randomly coiled molecular chains having few cross link.as the stain is applied polymer get stretched and as the force is released polymer regain its original position.These polymers are elastic & called elastomers. Ex. Neoprene, vulcanised rubber, Buna-S.

3) Fibres

They have high intermolecular force like H-bonding. They have high tensile strength and used in textile strength.

Ex. Nylon-6, Nylon-66

3) Thermoplastic polymers

These are the polymers having intermolecular force between elastomers and fibres.They are easily moulded in desired shapes by heating and subsequent cooling at room temperature. They may be linear or branched chain polymers. They soft in hot & hard in cool. Ex. Polythene, PVC.

4) Thermosetting polymers

This polymers is hard & infusible on heating. These are not soft on heating under pressure and they are not remoulded. These are cross linked polymers and are not reused. Ex. Bakelite.

D) Based on polymerization process

1) Addition polymers

The polymers formed by the addition of monomers repetadely without removing by product are called addition polymers. These polymers contains all the atoms of monomers hence they are integral multiple of monomer unit.

Ex.Orion,Teflon.

The units are generally alkenes and its derivatives.

2) Condensation polymers

They are formed by the combination of two monomers by removal of small molecules like water, alcohol. They have ester and amide linkage in their molecules. Their molecular mass is not integral multiple of monomer units.

Ex. Polyamides (Nylons), polyester.

CONCLUSION:

The controlled release drug delivery system aims to release the drug at the desired rate over extended period of time to maintain the therapeutic level in blood. The best new therapeutic entity in the world is of little value without an appropriate delivery system. Tablet delivery system can range from simple immediate release dosage forms. The most important role of drug delivery to the

site of action in sufficient amount & at appropriate rate. However it should meet other important criteria such as physical & chemical stability, ability to be mass-produced in manners that assure content uniformity. The controlled drug delivery system is very helpful in increasing the efficacy of the dose as well as the patient compliance.

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