Overview of the Controlled Drug Delivery System

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A B S T R A C T

Controlled drug delivery systems have been developed to improve the next staging of the drug in the body. 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

Keywords:Controlled drug delivery system, classification of CDDS, factor affecting, factor influencing

Introduction

Controlled drug delivery systems may be used to maintain drug levels within a desired range, reduce the number of doses required, make the medicine in question best use, and improve patient compliance. While these benefits may be substantial, there are also potential drawbacks that should not be overlooked, such as the higher cost of controlled-release systems compared to conventional pharmaceutical formulations, the potential for patient discomfort from the delivery device, the potential for toxicity or non-biocompatibility of the materials used, unwanted by-products of degradation, any surgery needed to implant or remove the system, and potential undesirable by-products of degradation. The optimal drug delivery system ought to be inert, biocompatible, mechanically robust, comfy for the patient, able to achieve high drug loading, safe from accidental release, straightforward to use and remove, and simple to construct and sterilize. Achieving the objective[1]

- The development of a Time release product may be difficult if the active compound's absorption requires an active transport.
- If the blood level of an active substance does not affect its pharmacological activity, time Releasing has done this on deliberately.
- Finally, a considerable quantity would be needed to maintain a prolonged effective dose if the active chemical has a short half-life. In this instance, a wide treatment window is required to prevent Selection of drug candidates or Characteristics that may make a drug unsuitable for Control release dosage form

- Short elimination half-life
- elimination half-life
- Narrow therapeutic index
- Poor absorption
- Active absorption
- Low or slow absorption
- Extensive first pass effect

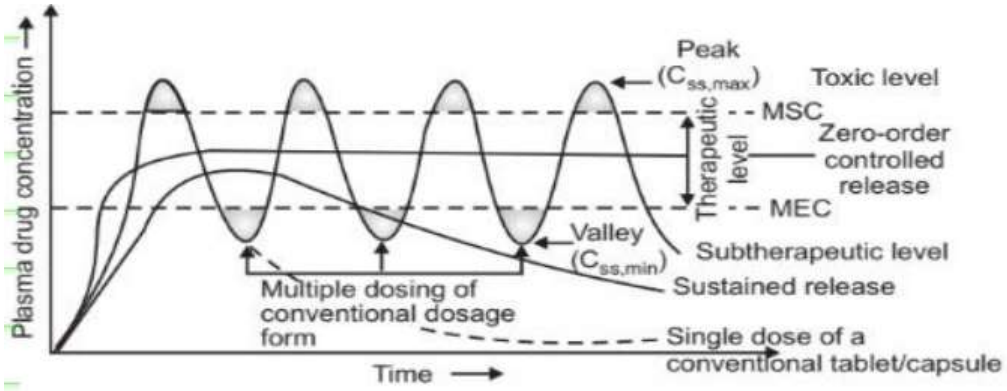

Fig.1: Plasma Drug Concentration-Profiles for Conventional Tablet or Capsule Formulation, a Sustained-Release Formulation and a Zero-Order Controlled Release Formulation

Parameters for drug selection
Parameter : Preferred value
Molecular weight/ size: < 1000
Solubility: > 0.1 µg/ml for pH 1 to pH 7.8
Pka Non ionized moiety: > 0.1% at pH 1 to pH 7.8
Apparent partition coefficient: High
Absorption mechanism: Diffusion
General absorbability: From all GI segments
Release: Should not be influenced by pH and enzymes
Controlled Release Drug Delivery System
Parameters for drug selection

Any medication delivery system that maintains adequate and intended drug release over an extended period of time is referred to as a controlled release system. A controlled dose form 2-4 is frequently manufactured using a hydrophilic polymer matrix. The ideal drug delivery system's job is to deliver the right dosage of the medication at the right time and place in order to keep the blood plasma concentration within the drug's therapeutic range. Some features, such as site targeting, controlled release rate, and dose maintenance, are absent from the IR drug delivery system. The regulated release rate and dose maintenance in plasma are two potential benefits of oral controlled medication administration. The release rate is controlled by waxes, polymers, or both in the CR formulations.

Advantages of controlled release drug delivery system [2]
· Reduced dosing frequency.
Dose reduction.
· Improved patient compliance.
· Constant level of drug concentration in blood plasma
· Reduced toxicity due to overdose.
· Reduces the fluctuation of peak valley concentration.
· Night time dosing can be avoided.

Limitation of Oral Conventional Dosage Form [3, 4]
1.Poor patient compliance, increased chances of missing the Dose of a drug with short half life for which frequent Administration is necessary.
2.The unavoidable fluctuations of drug concentration may Lead to under medication or over medication in narrow Therapeutic index drug.
3. typical peak-valley plasma concentration time profile is Obtained which makes attainment of steady-state condition Impossible.

Classification of Sustained Release System
Oral controlled delivery system can be classified in to the
Following category based on their mechanism of drug release.

1. **Dissolution controlled release**
2. **Encapsulation dissolution control**
3. **Matrix dissolution control**
4. **Diffusion controlled release**

a. **Reservoir devices**
b. **Matrix devices**

5. **Ion exchange resins**
6. **Osmotic controlled release**
7. **Gastro retentive system**

1.Dissolution Controlled Release:
controlled release of dissolution can be attained by decreasing the rate at which a medication dissolves in the GIT medium, encapsulating the drug in an insoluble polymer, and covering the drug particle with polymeric material of Variable Thickness.

Dm/DC=ADS/h can be used to calculate the dissolving rate (dm/dt).
S represents a drug's water solubility.
The tablet's surface area is A.
D stands for drug diffusion.
The boundary layer's thickness is H.
Examples of medications with a slow rate of disintegration include
Salicylamide, nifedipine, digoxin, and griseofulvin.
Drug dissolution from the polymer matrix is the control.

Or encapsulated forms.
• The dissolution process at a steady state is described by
Noyes Whitney equation:
Dc / DC= k A/V (Cs – C)
Dc / DC= (D/h) A (Cs – C)
Where, dC/DC=dissolution rate
V = volume of the solution
K = dissolution rate constant
D = diffusion coefficient of drug through pores
H = thickness of the diffusion layer
A = surface area of the exposed solid
Cs = saturated solubility of the drug [6]
C = conc. Of drug in the bulk solution 42

2.Encapsulation dissolution control
The speed of disintegration A sustained release of the drug is made possible by encasing the drug polymer matrix in a relatively insoluble polymeric membrane. The coated beads can then be compressed into tablets or used in granules of varying thickness. Anticholinesterase, a combination of the antispasmodic medicine phenothiazine, is an example of a medication administered in this way.

3.Matrix dissolution control:
It entails the inclusion of the drug into a hydrophobic matrix, such as wax, polyethylene, polypropylene, or ethyl cellulose, or a hydrophilic matrix, such as hydroxyl propyl cellulose or hydroxyl propyl methyl cellulose. The speed at which the dissolution fluid penetrates the matrix determines how quickly drugs become available.

4.Diffusion Control Release System:
Diffusion of the dissolved medication across the polymeric barrier is involved. The drug release rate is never

zero because the diffusional path length lengthens with time as the drug levels in the insoluble matrix steadily decline.
The two type of diffusion controlled system

a. Matrix system
b. Reservoir system

a. **Matrix system**
The medicine in question is disseminated in a matrix made of stiff hydrophobic or hydrophilic material that can expand. Insoluble plastics like polyvinyl chloride and fatty materials like stearic acid, beeswax, etc. are utilised to make stiff matrix. Highly water soluble medicines are frequently released via swellable matrix systems. These matrix's components, hydrophilic gum, may come from natural sources (guar gum, tragacanth). In part synthetic (HPMC, CMC). A solvent, such as alcohol, is used to granulate the drug and the gum, which is then compacted into a tablet.

b.**Reservoir system:**
The systems are hollow containing an Inner core of drug surrounded in a water insoluble polymer
Membrane. The polymer is applied by coating and Microencapsulation techniques. The drug release across the Membrane involve its partitioning in to membrane with Release in to surrounding fluid by diffusion .the polymer Commonly used in such devices are Hydroxypropylcellulose, Ethyl cellulose and polyvinyl acetate.

Ion Exchange Resin System:
There has been considerable research done on ion exchange resin complex, which may be made from both acidic and basic drugs. Salts of cationic or anionic exchange resin are insoluble compounds in which drug release is caused by the exchange of "bound" drug ions with ions in the GIT. Through the Resin structure, there are several Ion active spots. The resin's permeability, swelling potential, and excess of exchange sites for the drug ion are all dependent on the degree of cross-linking.

Osmotic Controlled Release System
Olfactory system Osmosis is a scientific theory that describes how a medicinal substance is released at a fixed, usually zero Order, delivery rate. Osmosis is the process by which a solvent naturally passes through a semipermeable membrane into a solution of higher solute concentration to lower concentration, resulting in equal concentrations of solute on both sides of the membrane. Osmosis systems absorb water from the body through a semi-permeable membrane into osmotic material, which swells and slows down the absorption of drug formulation. The semipermeable membrane is driven by osmotic pressure, which also acts as a driving force for fluid flow. The rate of solvent transport through the membrane will increase in direct proportion to the gradient in osmotic pressure.

Gartroretentive Drug Delivery System:
Release the control mechanism for delivering drugs with the capacity for retention They are referred to as gastro retentive drug delivery systems and they work to continually improve oral controlled medication administration with an absorption window. Releasing the medication before the window for absorption for a lengthy duration

Factors influencing design and fabrication of controlled release products[6]
The design of a CDDS depends on several factors like physicochemical or biopharmaceutical properties
Of the drug, route of administration, type of drug delivery system, type of disease to be treated and the Length of drug therapy etc. Properties of the drug play the most important role in formulation of CDDS.

Biopharmaceutics characteristics of[6]
A drug's potential biopharmaceutical characterization for Use in CDDS necessitates understanding of a drug's gastrointestinal tract absorption process, general absorbability, molecular weight, pKa, solubility at various pH levels, and partition coefficient.

Objective:
To ensure and maintain a steady drug blood level by delivering the drug at the appropriate rate. To do this, it is possible to try to achieve zero order release from dosage forms, which means that drug release from dosage forms is independent of the amount of medication in the delivery system.

Generally sustain release system do not attain this type of release And try to mimic zero order release by providing drug in slow first Order fashion as shown by following equation.

Rate in = Rate out = K. Cd.Vd
Where, Cd = Desired drug level,
Vd = Volume of distribution
K = elimination rate constant

Factors Influencing The Design and Act Of Controlled Release Product

(I) Physiological properties

(1) Aqueous Solubility:

]The majority of active pharmaceutical ingredients (API) have weakly acidic or basic properties, which have an impact on the API's solubility in water. It is challenging to create controlled release formulations for weak water soluble medications. Drugs with high water solubility release in bursts, followed by a sharp rise in plasma drug concentration. These medicines make ideal candidates for CRDDS. Additionally, the pH dependent solubility makes it difficult to formulate CRDDS. Drugs in BCS classes III and IV are not good candidates for these formulations. [7]

(2) **Partition coefficient (P-value):**

The drug's percentage In the oil and aqueous phases, which is a crucial factor influencing the drug's passive diffusion through the biological membrane, is known as the P-value. Drugs with high or low P values shouldn't be used in CR; instead, they should dissolve properly in both phases[8].

(3) Drug pKa:

The drug's ionisation at physiological pH in the GIT was determined by pKa. Drugs with high ionisation tend to be poor CRDDS candidates. In contrast to ionised medicines, unionised pharmaceuticals are rapidly absorbed from biological membranes. In order for an acidic medicine to ionise, the pH must be between 3.0 and 7.5, and for a basic drug, the pH must be between 7 and 11[9].

(4) Drug stability:

A good option for CRDDS is a drug that is stable in acid/base, enzymatic breakdown, and other gastric fluids. Because it will reduce the bioavailability of the problematic medicine, a substance that is destroyed in the stomach and small intestine is not suited for controlled release formulations[9].

(5) **Molecular size & molecular weight**

The molecular size and molecular weight are two critical factors that have a substantial impact on the molecular diffusibility across a biological membrane. Drug diffusion is more challenging for molecules larger than 400D than for those less than 400D[10].

(6) Protein binding:

The drug is stored in plasma by the drug and protein combination. Drugs having substantial plasma protein binding are not the best options for CRDDS because protein binding lengthens the biological half-life. Therefore, continuing the medication release is not required[11].

(II) Biological factors

(1) Absorption:

Uniformity in the rate and degree of absorption is essential while developing the CRDDS. Nevertheless, the drug's release from the dosage form is the rate-limiting step. The absorption rate should be higher than the release rate to prevent dose dumping. The plethora of factors, including acid hydrolysis, log P, and water solubility, that influence drug absorption[12].

(2) **Biological half-life (t1/2):**

The medication generally has a short half-life, necessitating frequent administration, and is an excellent choice for a controlled release device. A medication with a lengthy half-life required administration over an extended

period of time. The best candidates for CRDDS are medicines with t1/2 of 2-3 hours. The use of drugs with t1/2 values more than 7-8 hours is not recommended[12–13].

(2) Dose size

The CRDDS must have a higher dose than a traditional dosage form because it was designed to do away with recurrent dosing. However, the dose utilised in conventional dosage form provides a guide for the CRDDS dose. The volume of the sustained dose ought to meet the requirements for acceptance[14].

(4) Therapeutic window:

For CRDDS, medications having a restricted therapeutic index are not advised. If the discharge was not under control, the delivery system would discharge doses and eventually became poisonous[15].

(5) Absorption window:

Drugs with GIT segment-specific absorption should not be used in CRDDS. The majority of medications are absorbed in the GIT, making them prime candidates for controlled release[16].

(6) patient physiology:

Drug release from the dose form is influenced indirectly or directly by the physiological state of the patient, including gastric emptying rate, residence time, and GI disorders[17].

1-Pharmacokinetic parameters for drug selection

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

Conclusion:

The benefit of oral sustained release (SR) products over conventional dosage forms is that they optimise the bio-pharmaceutic, pharmacokinetic, and pharmacodynamic properties of drugs in such a way that a once-daily dose is sufficient for therapeutic management through uniform plasma concentration, providing the maximum utility of drug with a reduction in local and systemic side effects, and curing or controlling condition in the shortest amount of time.

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