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Design And Formulation Of Sustained Release Drug Delivery System

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Abstract:
A medicine is released at a predetermined rate and with minimal adverse effects by means of a sustained release drug delivery system (SRDDS), which keeps the drug level constant for a predetermined amount of time. Oral drug administration is frequently considered the most common and patient-friendly mode of delivery. Developments in formulation technology, such as sustained release oral dosage forms or modified release dosage forms, have been widely accepted in comparison to conventional release formulations. A sustained release dosage form offers a longer duration of drug release, which improves patient adherence and increases the medicine's bioavailability. Increasing the duration of drug action, reducing side effects, reducing the frequency of dosing, lowering the required dose, and providing the shortest time by using the smallest quantity of drug administered by the most appropriate route were the main objectives of designing SR formulations in an effort to modify and improve the drug performance. SR dosage forms are made to quickly raise a drug's blood level to therapeutic concentrations through the use of an initial dose component, and then use a continuation portion to keep the level there for a predetermined amount of time. We will talk about in this essay. Overview of Drug Formulation for Sustained Release.

Keywords: Sustained Release Drug Formulation, Drug Delivery System, Bioavailability, Matrix Tablet, Water Soluble, Polymers, Oral Drug Delivery, Zero-Order, Plasma Drug, Diffusion Systems, Matrix System, Osmotic Pressure

Introduction:

Sustained release dosage forms are designed to minimize side effects by releasing medication at a specific rate and maintaining a consistent drug level for a predetermined amount of time. Enhancing the bioavailability and efficacy of the medications while simultaneously raising patient compliance is the basic idea underlying sustained-release drug delivery systems. Since the development of extended-release matrix tablets, sustained release has shown to be a useful technique for managing drug release without requiring intricate manufacturing processes. Sustained or controlled delivery systems work to increase drug efficacy or reduce dose frequency by distributing the drug uniformly, limiting dosage requirements, and localizing the drug to the site of action. Many sustain release oral dose forms have been devised, including osmotic methods, matrices containing water soluble or insoluble polymers or waxes, and membrane-controlled systems. Designating SR systems for medicines that are poorly soluble in water has been the subject of intense investigation in recent times. [1]

For many years, oral drug delivery has been recognized as the most popular mode of

administration out of all the routes investigated for the systemic distribution of pharmaceuticals through diverse pharmaceutical products with varying dosage forms. An instantaneous release and repeated dosing of the drug are characteristics of traditional drug delivery systems (DDS) that may increase the danger of dose variation. As a result, a formulation with controlled release is required to maintain a blood level that is almost constant or uniform. Therefore, creating the perfect DDS is a task that involves the majority of pharmaceutical experts nowadays. A single dose should be an advantage of this ideal system throughout the entirety of the treatment, and the drug should be delivered directly and in a regulated manner to a specified place. Optimizing the therapeutic effect of a drug by regulating its release in the body with a lower and less frequent dose should be the main goals of the design of oral sustain DDS. This will lead to more predictability and reproducibility in controlling the drug release, drug concentration in the target tissue, and drug concentration.

Advantages of Sustained Release Drug Delivery System

1. Reduced frequency of medicine administration leads to improved patient convenience and compliance.
2. Decrease in steady state level variations, which leads to improved illness management and a less severe local and systemic adverse effect.
3. Improved plasma level management results in an increased safety margin for high potency drugs.
4. Maximum medication usage allowing for a decrease in the overall dose given.
5. Reduction of health care expenses by means of better therapy, a shorter course of treatment, fewer dosages, and a reduction in staff time needed for patient monitoring, administration, and shipping.

Disadvantages of Sustained Release Drug Delivery System

1. Decreased systemic availability compared to conventional, immediate-release dose forms; possible causes include incomplete release, higher first-pass metabolism, increased instability, and insufficient residence time for full release site-specific absorption.
2. Insufficient in vitro-in vivo correlation.
3. Potential for dosage dumping as a result of food or formulation variations or patient chewing of an oral formulation, which increases the risk of toxicity.
4. Drug retrieval is challenging when toxicity occurs.
5. Higher formulary costs. [2]

Rational for development of SRDDS

1. In order to improve a drug molecule's therapeutic efficiency, sustained release drug delivery systems (SRDDs) limit the frequency of doses and ensure that a medication is available at the site of action throughout the course of treatment.
2. To lower the number of dosages required in order to lower treatment costs.
3. To minimize overdose toxicity, which is frequently the case with conventional dosage forms
4. To extend the duration of action of a medication with a brief half-life

The definition of a controlled release system, also known as a modified release system according to the US Pharmacopoeia, is one in which the drug release characteristics of time, course, and/or location are selected to achieve therapeutic or convenient goals not provided by standard dose forms. There is currently no standard nomenclature for the long-acting products

on the market due to the haphazard application of several terms and their frequent reapplication. A number of phrases have been used interchangeably to refer to drugs with continuous release.

- Continuous Release (CR)
- Controlled Release (CR)
- Depot Release (DR)
- Long Term Release (LTR)
- Slow Release (SR)
- Long Acting (LA)
- Long Lasting (LL)
- Prolonged Action (PA)
- Extended Release (ER)
- Gradual Release (GR)

Nonetheless, controlled release and continuous release continue to be the most often used phrases today.

A controlled drug delivery system (also known as a CDDS) distributes the medication locally or systemically at a predefined pace for a predefined amount of time.

The term "targeted drug delivery system" (TDDS) refers to a drug delivery method that distributes the medication solely to the site of action, avoiding non-target organs or tissues.

The dosage form of medication known as the Sustained Drug Delivery System (SRDD) extends the drug's therapeutic activity.

Unlike sustained release systems, which only extend drug release and, consequently, plasma drug levels over an extended period of time, controlled release systems make no such claims. [3]

Review of Literature:

A particular kind of programmed release medication known as sustained release medication is one that includes the same amount of medication in one dosage form as multiple single doses. The medication is released into the body over an extended period of time, resulting in a sustained therapeutic effect. The pharmaceutical industry has long known the benefits of providing a single dose of a drug that releases over a prolonged period of time as opposed to many doses. In addition to improving patient compliance, the goal of maintaining a nearly constant or uniform blood level of a medication can also improve the drug's clinical efficacy when used as prescribed. Sustained release products often offer a slow release of extra medicine to maintain the intended therapeutic effect for a defined amount of time after the first release of the drug quickly produces the desired effect. Campbell, JA (1959). [4]

Objectives:

- Plasma drug concentration profile for conventional release, a sustained release and zero order controlled release formulation
- Design of Sustained Release Drug Delivery System
- Formulation of Sustained Release Drug Delivery System

Research Methodology:

Better patient compliance and increased bioavailability are achieved by using a sustained

release dosage form, which delivers a prolonged release of the medication over an extended period of time. When it comes to medications that need to be taken often and have short half-lives, sustain release systems are thought to be a better option. This review article's main focus has been on factors that affect the formulation of sustained-release matrix tablets, including factors that affect dosage form, criteria for choosing drugs for sustained release delivery with pros and cons, and different polymers employed in the system's design. The research paper is an endeavor that is founded on secondary data that was obtained from reliable online resources, newspapers, textbooks, journals, and publications. The research design of the study is mostly descriptive in nature.

Result and Discussion:

Many chronic disorders require frequent medication doses as part of their therapy. Medication with a brief half-life must be administered up to multiple times per day at brief intervals. In order to decrease the frequency of administration, long-term formulations have been created. Better patient compliance can be attained by using the SR technique to obtain a therapeutically effective concentration in the systemic circulation over an extended period of time. While administering medications conventionally is generally favored, there are certain drugs that become unstable and dangerous when dosed too frequently. These medications have a limited therapeutic window and struggle with solubility. Sustained DDS is utilized in these situations to keep the drug's plasma level within the therapeutic index. [5]

Maintaining therapeutic blood or tissue levels of the medication for a prolonged amount of time is the aim of an SR dose form. Usually, this is achieved by trying to extract the dose form with zero-order release. Zero-order release, also known as a constant release rate, is the release of the drug from the dosage form regardless of the quantity of the drug in the delivery system. Instead of achieving this kind of release, SR systems typically aim to replicate zero-order release by delivering the medication in a gradual first-order manner (i.e., concentration dependent). The relationship between plasma concentration and time is displayed in Fig. 1.

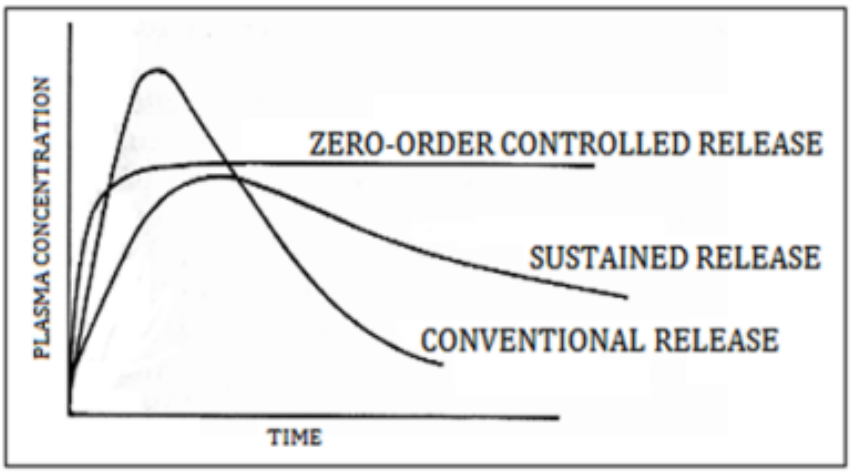

Figure 1: Plasma drug concentration profile for formulations with zero order-controlled release, sustained release, and conventional release [6]

Design and Formulation of Oral Sustained Release Drug Delivery System:

Because it offers more versatility in terms of dosage form, design, and patient compliance, the

oral route of administration is the most popular method. Nevertheless, in this case, care must be given to the different pHs that the dosage form may meet on its way, as well as the motility of the gastrointestinal tract and the impact of the enzyme system on the drug and the dosage form. Most oral sustained release systems produce a steady release of medication into the gastrointestinal environment through diffusion, dissolution, or a combination of the two methods.

A sustained release delivery system should, in theory and ideally, release the medication through a zero-order mechanism, producing a blood-level time profile resembling that of an intravenous constant rate infusion. Plasma drug concentration profiles for three different formulations: a sustained release formulation, a zero-order sustained release formulation, and a traditional tablet or capsule format. [7]

It has been attempted to achieve sustained (zero-order) medication release by using the following classes of sustained drug delivery systems.

A) Diffusion sustained system.
i) Reservoir type.
ii) Matrix type
B) Dissolution sustained system.
i) Reservoir type.
ii) Matrix type
C) Methods using Ion-exchange.
D) Methods using osmotic pressure.
E) pH independent formulations.
F) Altered density formulations.

A) Diffusion sustained system:

Diffusion, in its simplest form, depicts the flow of drug molecules from an area of higher concentration to one of lower concentration. Fick's law provides the drug J's flow (in amount / area - time) across a membrane in the direction of decreasing concentration.

J= - D dc/dx.

D = diffusion coefficient in area/ time

dc/dx = change of concentration 'c' with

distance 'x'

In common form, when a water insoluble membrane encloses a core of drug, it must diffuse through the membrane, the drug release rate dm/ dt is given by,

dm/ dt= ADKΔ C/L

Where A = area

K = Partition coefficient of drug between the membrane and drug core

L= diffusion path length [i.e. thickness of coat]

Δc= concentration difference across the membrane.

i) Reservoir type:

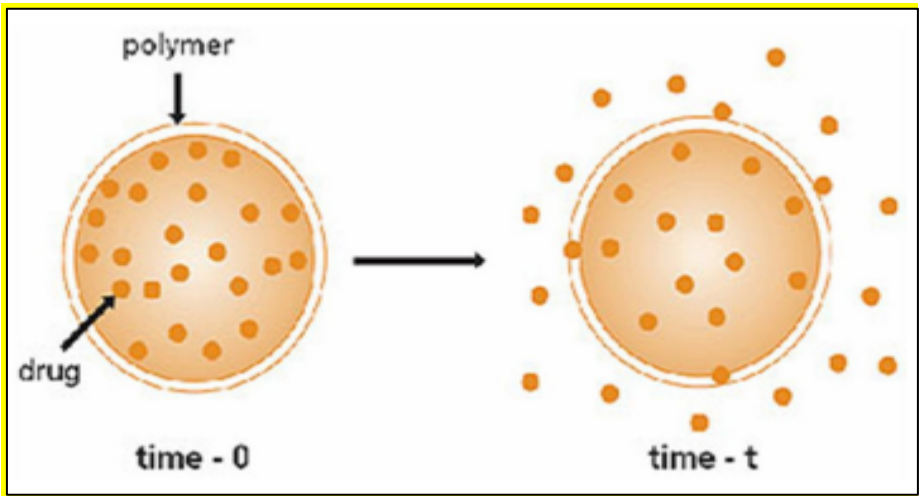

Figure 2: A schematic illustration of the reservoir system for diffusion sustained drug release.

A drug core is encased in a water-insoluble polymeric substance within the system. The medication will enter the membrane and swap places with the fluid that surrounds the pill or particle. More medication will seep into the polymer, spread to the edges, and interact with the surrounding substances.

ii) Type of matrix:

The rate of drug diffusion, not the rate of solid breakdown, determines the rate of drug release from a solid drug dispersed in an insoluble matrix.

For this system, Higuchi has determined the proper drug release equation.

$Q = D\varepsilon/ T [2 A – \varepsilon Cs] Cst ½$

Where;

Q = weight in gms of drug released per unit area of surface at time t

D = Diffusion coefficient of drug in the release medium

ε = porosity of the matrix

Cs = solubility of drug in release medium

T= Tortuosity of the matrix

A = concentration of drug in the tablet, as gm/ ml [8]

B) Dissolution sustained systems:

For medications that are highly soluble in water, dissolution can be slowed down by the appropriate synthesis of salt or derivative. medications with a slow dissolution rate are naturally sustained. Enteric coated dosage forms are produced using these technologies most frequently. The stomach is coated with a substance that dissolves in natural or alkaline media to shield it from the effects of medications like aspirin. As a result, the medication cannot be released from the device until it reaches the intestine's higher pH. Enteric coated dosage forms are often helpful in directing medication release to a specific region, although they are not genuinely sustaining in nature. For substances that are broken down by the severe climate present in the stomach, the same method might be used.

i) Reservoir type:

The medication is coated with a coating of a specific thickness, which dissolves gradually in the gastrointestinal tract's contents. A pulsed delivery can be accomplished by alternating drug layers with the rate-controlling coatings, as illustrated in the figure. Pulsed intervals can be

used to rapidly establish the drug's initial levels in the body if the drug's outer layer is rapidly releasing bolus doses. The biological effects can be comparable even though this is not a real sustained release method. Using a collection of beads with varying coating thicknesses is an other way to give the medication. The figure illustrates this. There is a progressive release of the beads because of the variations in coating thickness.

ii) Matrix type: As depicted in the figure, this is the more popular kind of dissolution sustained dosage form. It will be slowly eroded and can be either a drug-impregnated tablet or a drug-impregnated spherical. [9]

C) Ion exchange resin-drug combinations

It is based on the idea that when an ionic resin and an ionic solution come into contact, a drug-resin complex will develop. When the drug is exchanged in the gastrointestinal tract, it is released from this complex along with any excess Na^+ and Cl^-. Usually, an insoluble cross-linked polymer resin component is used in this process. They have a recurrent salt-forming function group on a polymer chain.

D) formulation that is pH-independent

Since most medications are weak bases or weak acids, their release from sustained release formulations is influenced by pH. However, buffers like citric acid salt, tartaric acid, and amino acids can be added to the formulation to help maintain a constant pH by postponing pH-independent drug release. To make a buffer sustain release formulation, an acidic or basic medicine is mixed with one or more buffering agents, granulated with appropriate excipients, and coated with a film-forming polymer that permeates gastrointestinal fluids. When gastrointestinal fluid permeates the membrane, the buffering agent keeps the fluid inside it at a suitable, constant pH, which produces a steady rate of medicine release.

E) Altered density formulations:

If a delivery system did not remain at the absorption site until most, if not all, of its medicine components were released, it is reasonable to suppose that it would be of little utility. To achieve this, several methods have been developed to prolong the duration of the drug delivery system's stay in the gastrointestinal tract.

F) Methods using osmotic pressure:

A tablet, particle, or drug solution is encircled by a semi-permeable membrane that permits the passage of water into the tablet and, in the end, the pumping of the drug solution out of the tablet through a tiny delivery aperture in the tablet coating.

There are two categories of osmotically maintained systems:

Type A has a medication-filled osmotic core.

Type B uses a flexible bag with an osmotic core to surround the medication. [10]

Parameters for the drug to be formulated as sustained release dosage form:

A few physicochemical factors must be taken into consideration when choosing a drug to be formulated in a sustained release dosage form. These factors primarily include understanding how the drug absorbs from the GI tract, its general absorbability, its molecular weight, its solubility at various pH levels, and its apparent partition coefficient, as indicated in Table 1.

Table 1: Physicochemical parameters for drug selection

Parameter	Preferred value
Molecular weight/ size	< 1000 Daltons
Solubility	> 0.1 mg/ml for 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

The medication's elimination half-life, total clearance, absolute bioavailability, potential first-pass effect, and the intended stable concentrations for peak and trough are among the pharmacokinetic parameters that are used in the drug selection process, as indicated in Table 2. [11]

Table 2: Pharmacokinetic parameters for drug selection

Parameter	Comment
Elimination half life	Preferably between 2 to 8 hrs
Total clearance	Should not be dose dependent
Elimination rate constant	Required for design
Apparent volume of distribution Vd	The larger V_d and MEC, the larger will be the required dose size.
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration C_{ss}	The lower C_{ss} and smaller Vd, the loss among of drug required
Toxic concentration	Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

Conclusion:

Though controls of drug action through formulation also involve regulating bioavailability to decrease drug absorption rates, SRDDS is often concerned with maximizing drug availability by attempting to attain a maximum rate and extent of drug absorption. One of the cutting-edge applications of sustained release drug delivery systems (SRDDS) is oral dose forms. The creation of oral dosage forms with sustained release is crucial for the best possible treatment in terms of safety, effectiveness, and patient compliance. The release of the active ingredient in sustained release dosage forms is influenced significantly by the external environment, even though it happens more slowly than in conventional formulations. It is clear from the discussion

above that prolonged release formulations aid to improve patient compatibility and dosage efficiency.

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