Review On Sustained Release Dosage Form: A Novel Approach And Its Evaluation

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Abstract
Sustained release dosage forms are made to release a medication at a predefined rate while minimizing side effects and keeping a steady drug level for a certain amount of time. The fundamental idea behind a sustained release drug delivery system is to increase a medicine's usefulness while minimizing its negative effects and achieving illness cure by optimizing its biopharmaceutical, pharmacokinetic, and pharmacodynamic qualities. Sustained release drug delivery has a number of benefits over traditional dosage forms, including increased patient compliance because it requires fewer doses to be administered, decreased fluctuations in steady-state drug levels, maximum drug utilization, increased safety margin of potent drugs, shorter treatment periods and improved therapy that lower healthcare costs. Water penetration, polymer swelling, drug dissolution, drug diffusion, and matrix erosion have all been used as formulation techniques to measure drug release through matrix systems. This article provides a concise overview of different formulation strategies for drug delivery systems with sustained release.

Keywords: sustained release system, Matrix tablet, Matrix type system, reservoir system, controlled release drug delivery system, SRDDS.

Introduction

Although it was developed later than expected, Dr. Paul Ehrlich's "magic bullet" idea provides a reasonable answer to the long-standing issue of the unintended and unrelated side effects of therapeutic agents and optimizes drug therapy in the genuine sense.
Despite the fact that "sustained/controlled" medication delivery is thought to have originated with the idea of a magic bullet in practice.[1]
The main objective of treatment is to bring the blood level down to a stable state that is both nontoxic and therapeutically effective over a prolonged length of time. A key component in achieving this objective is the formulation of appropriate dose schedules. The phrases "sustained release," "controlled release," "extended action," "timed release," "depot," and "repository" are used to describe drug therapy systems that aim to produce a prolonged therapeutic effect by releasing medication continuously over an extended period of time following the administration of a single dose. This duration, which is expressed in hours for injectable dose forms, is highly dependent on how long the dosage form stays in the gastrointestinal system. The phrase "controlled release" now refers to systems that may automatically give therapeutic chemicals over an extended period of time at predefined rates. These kinds of products are designed to be applied topically, injected, orally, and as inserts to be inserted into bodily cavities. Only the therapeutic blood or tissue levels of the drug are prolonged for a longer amount of time by prolonged or sustained release systems.[2]
Because oral drug delivery has several advantages over other drug delivery methods, including unit dosage form, low cost, and least expensive packaging, it is the most popular and practical choice. It also offers the highest active surface area for the administration of different medications. Tablets are among the most widely used and stable oral dose forms. Because of the benefits they provide to patients as well as pharmaceutical makers, tablets are still a popular choice for dosage forms. By localizing the medicine to the site of action, lowering the amount needed, and ensuring consistent drug distribution, sustained or controlled delivery

systems aim to either decrease the frequency of dosing or increase the effectiveness of the medication by using different types of polymers as shown in Table 3. One kind of customized drug delivery system that can be employed in place of a traditional drug delivery system is the sustained release system. These systems prolong the drug's release, keep its plasma concentration within the therapeutic window barring fluctuations, and boost the medication's therapeutic efficacy. They demonstrate their efficacy by eschewing dosage peaks and troughs and exhibiting a steady plasma drug concentration during the therapeutic window. Sustained release system have benefits like patient compliance, avoid multiple dosing, increase the plasma drug concentration, avoid side effects and overcome the problems associated with conventional system Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed, for sustained release systems, oral route of administration has received most of the attention with respect to research on physiological and drug constraints as well as design and testing of products.[3,4]

Both sustained release and controlled release have been applied inconsistently and erratically. They both signify different delivery processes. SR refers to any dose form that delivers drug over a prolonged period of time or indicates that the system can actually provide therapeutic control, whether that control is temporal, spatial, or both. It includes any medication delivery technology that produces a long-lasting, time-independent drug release. When creating a sustained dose form, hydrophilic polymer matrices are frequently employed. The purpose of the optimal drug delivery system is to sustain the therapeutic range of the drug in blood plasma by delivering the appropriate dosage at the appropriate site of action and at regular intervals.[4,5]

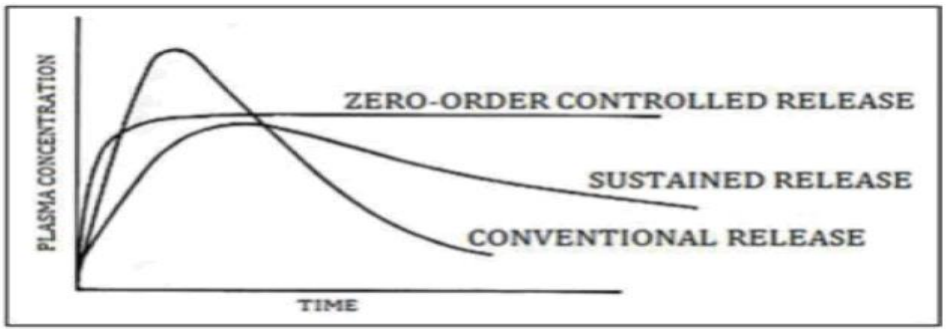

Figure 1: Plasma Drug Concentration Profiles for Conventional Tablet Formulation, a Sustained Release Formulation and a Zero Order Controlled Release Formulation

Medication products designed to speed up drug absorption and reduce dosage frequency have been available on the market for a considerable amount of time. Drug release from controlled-release drug delivery systems (CRDDS) happens at a set rate and is regulated and predictable. Good absorption of the drug throughout the gastrointestinal tract—preferably by passive diffusion—is essential to ensure continuous absorption of the released drug, as shown in figure below.[6,7]

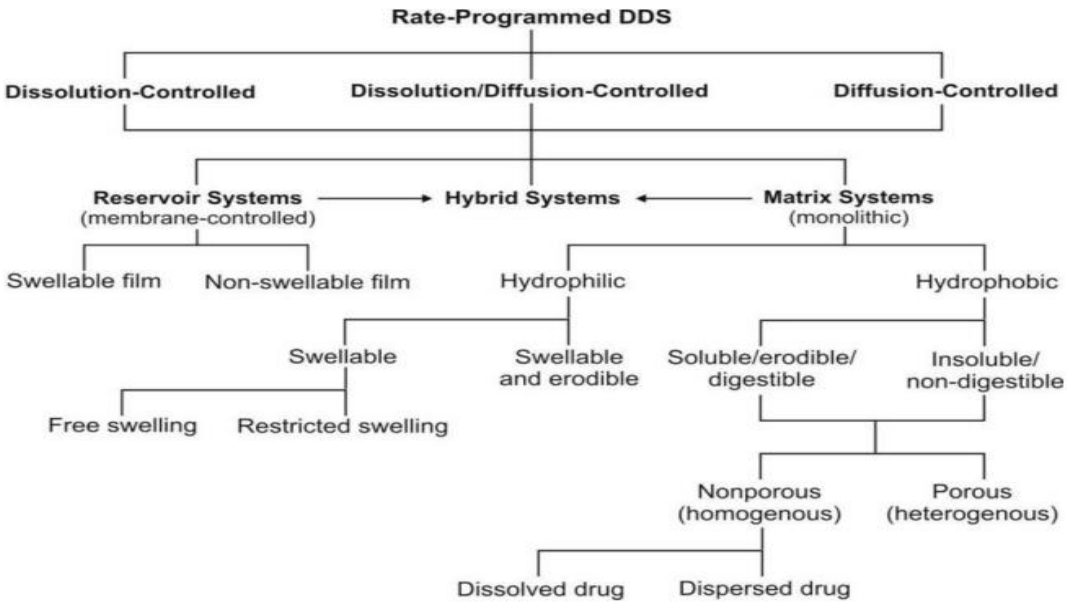

Figure 2: Classification of Modified Release Drug Delivery System

The process of choosing a drug for oral sustained release drug delivery systems involves considering various factors such as the drug's molecular weight, pKa, apparent partition coefficient, general absorbability, and solubility at different pH levels.[8,9]Drug is based on Physicochemical parameters that are given below table 1. As well as its pharmacokinetic parameters those are given in table 2.

Table 1:Drug selection based on physicochemical parameters

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

Table2: Pharmacokinetic factors in the choice of medications

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 (V_d)	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 V_d, 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.

Advantages of SRDDS

1. Decrease in the frequency of consumption
2. Consistent release of the medication throughout time
3. Lowering the dose
4. Boost adherence from patients.

Disadvantages of SRDDS

1. Insufficient in vitro-in vivo correlation
2. Less opportunity to change the dosage of medications that are often given in different strength
3. In cases of toxicity, poisoning, or hypersensitivity responses, recovering the medicine can be challenging.[10,11]

Table 3:Types of Polymers Used In Sustained Release DDS[12]

DIFFERENT POLYMERS USED IN SUSTAINED RELEASE DDS	
Hydrogels:-	
• Polyhydroxy ethyl methyl acrylate (PHEMA)	• Cross-linked polyvinyl alcohol (PVA)
• Cross-linked polyvinyl pyrrolidone (PVP)	• Polyethyleneoxide (PEO)
Soluble Polymers:-	
• Polyethylene glycol (PEG)	• Polyvinyl alcohol (PVA)
• Polyvinyl pyrrolidone (PVP)	• Hydroxy propyl methyl cellulose (HPMC)
BiodegradeblePolymers:-	
• Polylactic acid (PLA)	• Polyglycolic acid (PGA)

• Polycaprolactone (PLA)	• Polyanhydrides
Non BiodegradeblePolymers:-	
• Polyethylene vinyl acetate (PVA)	• Polydimethyl siloxane (PDS)
• Polyetherurethane (PEU)	• Polyvinyl chloride (PVC)
Mucoadhesive Polymers:-	
• Polycarbophil	• Sodium carboxymethyl cellulose
• Polyacrilic acid	• Methyl cellulose

CLASSIFICATION OF ORAL SUSTAINED/CONTROLLED RELEASE SYSTEMS

Types of diffusion matrix system

Hydrophobic matrix system

Despite the fact that insoluble polymers can be employed, this is the sole system where using polymers is not required to enable sustained drug release. Hydrophobic matrix's main rate-controlling elements are insoluble in water, as the name implies. Polymeric materials including methyl, ethyl, and acrylate copolymer, as well as waxes, glycerides, and fatty acids, are among these constituents.[13]

Diffusion sustained system

The process of diffusion demonstrates how drug molecules migrate from an area with a greater concentration to one with a lower concentration.[13]

Diffusion reservoir system

They are distinguished by a polymeric membrane encircling a drug core (reservoir). The rate at which drugs release is determined by the composition of the membrane. The following are the traits of reservoir diffusion systems: Drug release with zero order is feasible. The kind of polymer determines the release rate. Delivering high molecular weight molecules through the device is challenging.[13]

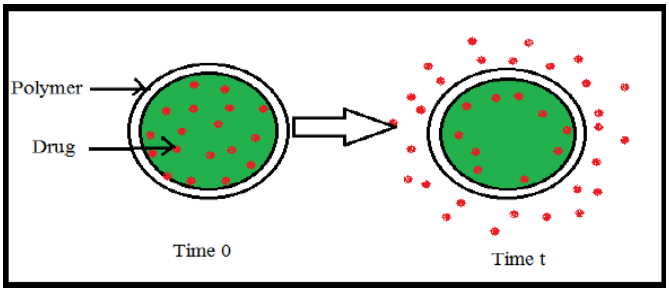

Figure3:SchematicRepresentationofDiffusionTypeReservoirSystem.

Matrix devices:

It is made up of medication evenly distributed within a matrix. The following are the traits of matrix diffusion systems: One cannot acquire a release of zero order. Producing reservoir devices is more difficult. Through the gadget, high molecular weight molecules are supplied.[13]

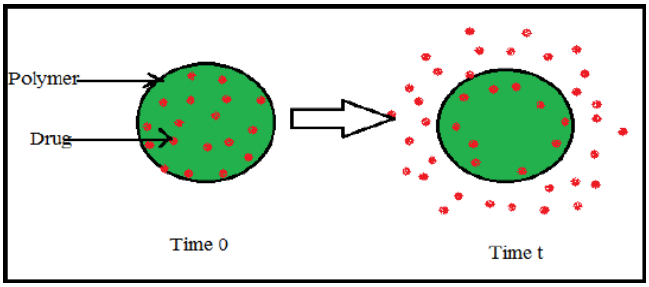

Figure4:SchematicRepresentationofDiffusionTypeMatrixSystem.

Hydrophilic matrix system:

The hydrophilic matrix's main rate-limiting components are polymers, which expand upon coming into touch with an aqueous solution and produce a gel layer on the system's surface. The solvent enters the gaps between macromolecular chains when the releasing medium and polymer are thermodynamically compatible. The tension of the absorbed solvent may cause the polymer to relax, increasing the flexibility of the polymer chains and causing the matrix to expand. As a result, the medication that is encapsulated can diffuse out of the matrix more quickly. Hydroxy propyl methyl cellulose (HPMC) and Hydroxy propyl cellulose (HPC), xanthan gum, carbopol, and alginates are the primary polymers utilized in hydrophilic matrices.[13]

Fat-wax matrix system:
The medication can be added to fat wax granulations through spray-drying, blend-congealing in an aqueous medium with or without the use of a surfactant, and spray-congealing in the air. Using the bulk congealing process, a medication suspension mixed with melted fatwax is let to harden before being ground into granulations for prolonged release.[13]

Dissolution controlled release systems:
These systems are easy to formulate. Drugs that are designed with this method have a sluggish rate of dissolution; they also produce forms of the medication that dissolve slowly when combined with stomach intestinal fluids and have a high rate of solubility and dissolution in water. There are two varieties of it:

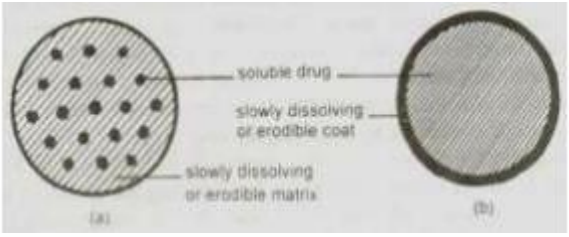

Figure 5: Dissolution controlled release systems

Reservoir dissolution controlled release system:
Using gradually dissolving substances like cellulose, polyethylene glycol, and waxes, one of the various microencapsulation processes is used in the reservoir system to coat or encapsulate the drug particles. This product can be compacted into tablets or enclosed in capsules. The coating's thickness and solubility are key factors in the drug's rate of dissolution.[14]

Dissolution and diffusion controlled release system:
The medication is contained in a membrane that is only partially soluble in water in this type of device. Because of the membrane's disintegration, pores are created, which let aqueous media pass through the membrane. This leads to the drug's dissolution in the membrane and its subsequent diffusion out of the system. Combining ethyl cellulose with PVP or methyl cellulose is one example of such a coating.[15]

Ion exchange resin- drug complexes:
Materials that are insoluble in water are known as resins. Anionic groups like amino or quaternary ammonium groups and cationic groups like carboxylic groups or sulfonic groups that repeat along the chain are both present in resin. When a drug is exposed to resin for an extended period of time, a drug–resin complex forms. The medication included in these complexes is exchanged throughout the gastrointestinal system before being released along with an excess of Na^+ and Cl^-.[16,17]

pH dependent formulation:
Because some medications alter the pH of the gastrointestinal tract during absorption and dissolution in the GIT, dosage forms are designed with an adequate amount of a buffering agent, such as tartaric, citric, or phosphoric acid salt. As the dose form passes through the digestive system, these salts bring the pH back to the appropriate level. In order to coat the medication and buffer in the dosage form, permeability coating agents are utilized. This permits aqueous medium to enter the dosage form while preventing tablet dispersion.[18]

Osmotic pressure controlled systems:

These kinds of systems, also referred to as oros, release the medicine at a steady zero order rate using the osmotic pressure mechanism. The medication plus an osmotic agent, such as mannitol or KCl, comprise the reservoir, which is encased in a semi-permeable membrane. The dosage form has a tiny opening that lets water into the reservoir and facilitates the dissolved medication's osmotic pressure-induced pumping out at the predetermined rate. The GIT's state has no bearing on the medication's release from the reservoir. The size of the orifice, the thickness of the semi-permeable membrane, the permeability of the membrane, the osmotic characteristics of the core, and the stability of the medication all affect how much of the drug is released.[15,19]

FACTORS AFFECTING SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Physicochemical factor:

Dose size:

For a standard dosage form, a single dose containing roughly 500 mg to 1.0 g of the medicine is generally regarded as the maximum. Substance with enormous dosage sizes that, on occasion, can be administered in numerous doses or combined into liquid formulations The sustained release dose form meets the same requirements.[18]

Ionization, pka and aqueous solubility:

Most medications are weak bases or acids. Since pharmaceuticals in their unaltered state can pass across lipid membranes, the link between the compound's pka and the absorptive environment is crucial. The drug's solubility in aqueous fluids will affect delivery systems that rely on diffusion or dissolution in the same way. Since the stomach is acidic and the small intestine is more neutral, these dosage forms must work in a pH-changing environment. Additionally, the impact of the phone release mechanism needs to be specified.

Partition Coefficient:

When a medication is given to the GI system, it must pass through several biological membranes in order to have a therapeutic impact in another part of the body. Since these membranes are frequently thought of as lipidic, an important factor in assessing the efficiency of drug penetration through membrane barriers is the partition coefficient of oil-soluble substances. Lipophilic compounds with a high partition coefficient are poorly soluble in water and remain in lipophilic tissues for extended periods of time. Poor bioavailability occurs when a drug has a very low partition coefficient because it is extremely difficult for the component to cross the membrane.[18]

Stability:

Orally given medicines are vulnerable to both enzymatic degradation and acid-base hydrolysis. Since a drug's breakdown in a solid state will proceed at a slower pace, this is the recommended delivery composition in problematic situations. Systems that extend distribution across the whole GI tract's transit are advantageous for dose forms that are unstable in the stomach. Systems that hold off on releasing the dose form until it reaches the small intestine likewise fall under this category. Substances that exhibit instability in the small intestine may exhibit reduced bioavailability when given in a sustained dosage form. This is due to the fact that more medications are absorbed in the small intestine, where they also undergo deterioration.

Biological factor:

Half-life:

A medication's half-life serves as a gauge for how long it stays in the body. Should the medication have a brief half-life (less than two hours), the dose form can include an excessively high amount of the substance. Conversely, drugs having an 8-hour or longer elimination half-life are well-regulated in the body when taken as prescribed; in these situations, a sustained release drug delivery device is usually not required. When formulating a medication delivery system, the drug's half-life should ideally be between three and four hours.

Therapeutic index:

A medication is a less good option for SRDDS if its dose in the normal dosing form is high. This is because a unit dose sustained release oral formulations size would grow to the point where it would be impossible to deliver.

Absorption window:

When taken orally, some medications exclusively absorb from a particular area of the digestive system. The "absorption window" is the name given to this section. Additionally, these applicants are unfit for SRDDS.

Plasma concentration response relationship:
Generally speaking, pharmacological activity is more dependent on plasma drug concentration than dose. However, medications with pharmacological activity that is not dependent on plasma concentrations are not good choices for oral SR drug delivery systems.

Concentration dependency on transfer of drug:
If the medication is transferred from one compartment to another using a zero order kinetic process, it is not a good fit for an oral SR delivery system. The kinetics should be first order.[19,20]

Assessment criteria for Sustained release matrix tablet

1. **Thickness and Diameter of Tablet**
2. **Hardness of the Tablet**
   The definition of tablet hardness is "the force necessary to break a tablet in a diametric compression test." The Monsanto hardness analyzer is used to measure the hardness of three tablets for each formulation; the tablet's end point is determined by shattering it.[21]
3. **Friability**
   Weighed twenty pills are put in the friabilator. The chamber rotates at a rate of 25 revolutions per minute for four minutes. After being taken out of the chamber, the tablets are weighed once again. Weight loss is a sign of friability. If there is less than 0.8% weight loss, the tablets should be regarded as high-quality.[22]
4. **Weight variation test**
   This is a crucial procedure that falls within the purview of quality control testing since every tablet in a batch should weigh the same. To get the average weight, twenty pills are weighed and then the weight of a single tablet is compared. The computation of the % weight variation is based on Indian Pharmacopoeial specific.[23]
5. **Determination of drug content**
   The drug concentration of is ascertained by dissolving in an appropriate solvent, such as pH 7.4 phosphate buffer solution, and analyzing the sample using a visual spectrophotometer and the pure drug standard calibration curve.[24]
6. **In-vitro dissolution testing**
   Testing for in vitro dissolution is an essential tool for determining the optimal formulation. The purpose of the test is to determine how long it takes for a certain percentage of the drug to dissolve in the solution under the particular test circumstances. Devices of the rotating paddle and basket types may be employed in accordance with pharmacopoeial standards or as specified in the monograph of a specific medication.[25]

CONCLUSION

The above discussion makes it clear that these dosage forms: increase the drug's bioavailability; decrease the frequency of administration to extend the duration of effective blood levels; lessen side effects and fluctuations in peak trough concentration; and potentially enhance the drug's specific distribution. All of these are also reasonably priced. The dosage form is simple to adjust and is especially useful for antibiotics, where overuse can lead to resistance.

Acknowledgement
Author expresses his sincere thanks to Sunrise University Rajasthan for providing support and facilities to carry out this review work.

Conflict of Interest
The authors declare that they have no conflict of interest.

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