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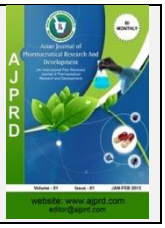

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Review Article

Sustained Release Drug Delivery Systems: A Comprehensive Review

Deepak Chouhan *, Meenakshi Bharkatiya

B.N. Institute of Pharmaceutical Sciences, Bhupal Noble's University, Udaipur, Rajasthan 313001, India

A B S T R A C T

Sustained release (SR) drug delivery systems have gained significant attention in modern pharmaceutics due to their ability to maintain therapeutic drug levels over extended periods, reduce dosing frequency, and enhance patient compliance. Unlike conventional dosage forms, which often result in fluctuating plasma concentrations and require frequent administration, SR systems are engineered to deliver drugs at a controlled rate, targeted time, and specific site within the body. These systems utilize various formulation strategies, including matrix tablets, reservoir systems, and osmotic devices, often employing hydrophilic or hydrophobic polymers to modulate drug release. Matrix tablets, in particular, represent a versatile and widely used SR approach, providing ease of manufacturing, reproducibility, and cost-effectiveness. Factors influencing the design of SR formulations include drug solubility, polymer type, tablet geometry, and physiological conditions, all of which impact release kinetics and bioavailability. Despite their numerous advantages, challenges such as dose dumping, complex formulation requirements, and stability considerations remain. This review comprehensively explores the principles, classifications, and design considerations of SR drug delivery systems, with a special focus on matrix tablets. Furthermore, examples of marketed SR formulations are discussed to illustrate current industrial applications and trends, highlighting the relevance of these systems in enhancing therapeutic outcomes and patient adherence.

Keywords: Sustained release, controlled release, drug delivery, matrix tablets, polymers, marketed formulations.

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*Address for Correspondence:

Deepak Chouhan, B.N. Institute of Pharmaceutical Sciences, Bhupal Noble's University, Udaipur, Rajasthan 313001, India

INTRODUCTION

Traditional drug delivery systems are often associated with several drawbacks, including rapid drug clearance, short half-life, and the need for frequent dosing. These issues can compromise patient compliance and therapeutic outcomes. To address these concerns, sustained release drug delivery systems (SRDDS) were developed to release therapeutic agents gradually over an extended period, maintaining consistent plasma drug levels and enhancing treatment efficiency.[1]

Over the past three decades, advances in polymeric materials, formulation technology, and biopharmaceutics have significantly boosted the development of SRDDS. This review discusses the concept, design principles, and classification of SRDDS, focusing on their pharmaceutical importance. The term "controlled release" refers to a dose form where the rate or speed of drug release is predetermined (e.g., Adalat CR tablets for nifedipine, Dynacirc CR tablets for isradipine). Due to increased design freedom for dosage forms, the oral mode of administration for sustained release systems has drawn considerable attention. The kind of delivery system, the ailment being treated, the patient, the length of therapy, and the qualities of the medication are only a few of the linked, significant factors that affect how oral sustained release delivery systems are designed.

A sustained release oral dosage form should ideally be created to quickly release a preset portion of the entire dose into the GI tract. The remaining portion of the entire dosage, known as the maintenance dose, is then released at a regulated pace. This portion of the dose, known as the loading dose, is an amount of medication that will generate the intended pharmacological reaction as quickly as feasible. When a desired level of pharmacological response is needed, the rate of drug elimination from the body by all processes must match the rate of drug absorption from the total maintenance dosage.

These systems should ideally have the following two goals: Spatial delivery, which has to do with having some control over where drugs are released. The medicine is administered temporarily and over a longer length of time while receiving therapy[2-5]

Sustained Release Drug Delivery Systems

SRDDS are designed to release the drug in a controlled manner over time, thereby maintaining therapeutic concentrations for prolonged periods. Unlike conventional formulations, which produce peaks and troughs in plasma drug levels (saw-tooth kinetics), SRDDS aim for steady and predictable delivery.[6-8]

Key design principles include:

- **Controlled drug release profile** to maintain consistent plasma concentration.
- **Use of polymers** (hydrophilic, hydrophobic, biodegradable, or synthetic) to modulate release rate.
- **Improved pharmacokinetics and pharmacodynamics**, ensuring better therapeutic outcomes.

Advantages of Sustained Release Systems

Table 1: Advantages of Sustained Release Systems

Advantages	Description
Reduced dosing frequency	Minimizes patient inconvenience and improves compliance
Uniform drug release	Avoids peaks and troughs in plasma concentration
Minimized side effects	Reduced fluctuations lower adverse reactions
Better compliance	Especially beneficial for chronic therapies
Reduced healthcare costs	Less frequent dosing and improved therapy outcomes
Safety margin	Increases safety for potent drugs
Prolonged therapeutic effect	Maintains efficacy for longer durations

Disadvantages of Sustained Release Systems [8-11]

Table 2: Disadvantages of Sustained Release Systems

Disadvantages	Description
High cost	Due to advanced formulation technologies
Risk of dose dumping	Sudden release can cause toxicity
Variable in vivo-in vitro correlation	May lead to unpredictable therapeutic outcomes
First-pass metabolism	May affect drug bioavailability
Patient education needed	Additional instructions for proper use

Classification of SRDDS[12-16]

SRDDS are broadly classified based on their release mechanisms:

1. Continuous Release Systems

Designed for prolonged release throughout the GI tract. Examples include:

Diffusion-controlled systems

- *Matrix diffusion systems*
- *Reservoir devices*

Dissolution-controlled systems

- Slow dissolving drugs or coated particles regulate release.

Diffusion + dissolution systems

- Semi-permeable membranes form pores after partial dissolution.

Ion-exchange resin complexes

- Drugs bound to resins release via ion exchange.

pH-independent systems

- Buffers incorporated to minimize pH variability.

2. Delayed Release Systems

- Release drug at a later stage or site.
- Examples: Enteric-coated tablets, pulsatile release systems.

Factors Affecting Design of SRDDS

A. Pharmacokinetic & Pharmacodynamic Factors

Table 3: Pharmacokinetic & Pharmacodynamic Factors

Factor	Impact
Biological half-life	Ideal drugs: 2–8 hours; very short or very long half-lives are unsuitable
Absorption	Controlled release depends on drug absorption characteristics
Distribution	Volume of distribution influences elimination and plasma levels
Metabolism	Drugs with extensive first-pass metabolism require special consideration

B. Drug Properties

Table 4: Drug Properties

Property	Significance
Dose size	Limited to 500–1000 mg
Ionization & solubility	Affects absorption and release
Partition coefficient	Impacts membrane permeability
Stability	Instability in GI tract may hinder formulation success

Matrix Tablets[17-19]

Matrix tablets are the most common oral SRDDS. The drug is embedded within a polymeric matrix, from which it diffuses gradually.

Advantages

- Cost-effective and versatile.
- Suitable for both high and low molecular weight drugs.
- Improved patient compliance.
- Reduced drug toxicity.

Disadvantages

- Non-uniform release rates.
- Drug release influenced by food and GI transit.
- Difficulties in achieving true zero-order release.

Matrix Tablets:[20-21]

The controlled drug delivery technology known as matrix tablets releases the medication continuously using both diffusion- and dissolution-controlled processes. Medications are distributed in swellable hydrophilic substances, an insoluble matrix of stiff non-swellable hydrophobic materials, or plastic materials to regulate the release of the drugs, which have varying solubility qualities. In order to create a tablet with the drug embedded in a matrix of the release retardant, a direct compression of a mixture of drug release, retardant material, and additives is one of the simplest methods for creating sustained release dosage forms.

Advantages of Matrix Tablet:

- Versatile, effective and low cost
- Can be made to release high molecular weight compounds
- The sustained release formulations may maintain therapeutic concentrations over prolonged periods. The use of sustain release formulations avoids the high blood concentration.
- Sustain release formulations have the potential to improve the patient compliance.
- Reduce the toxicity by slowing drug absorption.

Disadvantages of Matrix Tablet:

- The remaining matrix must be removed after the drug has been released.
- High cost of preparation.
- The release rates are affected by various factors such as, food and the rate transit through the gut.
- The drug release rates vary with the square root of time.
- Release rate continuously diminishes due to an increase in diffusion resistance and/or a decrease in effective area at the diffusion front.
- However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

Matrix tablet generally classified into different types:

a) Hydrophilic Matrix Tablet:

Drug release rate is often controlled using a hydrophilic matrix. The medication and hydrophilic matrix materials can be combined in a wet granulation to create the matrix, or the mixture can be directly compressed into tablets. The hydrophilic matrix needs water to activate the release mechanism and explore its benefits, which include ease of production and great tablet consistency. It is advisable to choose a matrix construction material that has quick polymer hydration capabilities for creating a hydrophilic matrix tablet. Due to the quick water absorption, an insufficient polymer hydration rate may result in early drug diffusion and tablet disintegration. It is appropriate for water soluble medication preparation.

b) Fat-wax Matrix Tablet:

There are several methods for incorporating drugs into fat wax granulation, including spray drying, blend congealing in an aqueous medium with or without the application of a surfactant, and blend congealing in the air. Using the bulk congealing technique, a dissolved medication and melted fat wax are mixed, allowed to set, and then ground into sustained-release granules. When the active chemicals, waxy materials, and fillers have been combined, the combination is compacted using a compactor, heated in a suitable mixture, such as a fluidized-bed and steam jacketed blender, or ground with a waxy material solution.The medication, which is dissolved in a melt of lipids and wax, is released through leaching, hydrolysis, and fat dissolution due to enzyme action and pH changes in the GI tract. The addition of different surfactants to the formulation can also affect the amount of drug that can be integrated into a matrix overall and the rate at which the medication is released.

c) Plastic Matrix Tablet (Hydrophobic matrices):

Widespread use has been made of sustained release tablets built on an inert compressed plastic matrix. Because the dissolved medicine must diffuse through the capillary network between the compressed polymer particles, release is often delayed. Direct compression of the drug with plastic materials can easily produce plastic matrix tablets, in which the active ingredient is embedded in a tablet with a coherent and porous skeletal structure, provided the plastic material can be comminuted or granulated to the desired particle size to facilitate mixing with the drug particle.

d) Biodegradable Matrices:

These are made up of polymers with unstable backbone linkages made up of monomers connected to one another by functional groups. By enzymes produced by nearby live cells or by non-enzymatic processes, it is physiologically eroded or decomposed into oligomers and monomers that can be metabolised or expelled. Examples include synthetic polymers such aliphatic poly (esters) and poly anhydrides, as well as natural polymers including proteins, polysaccharides, and modified natural polymers.

e) Mineral Matrices:

Mineral matrices are made up of polymers that come from different kinds of seaweed. Using diluted alkali, several species of brown seaweeds (Phaephyceae) may produce alginic acid, a hydrophilic carbohydrate.

On the Basis of Porosity of Matrix:

Matrix system can also be classified according to their porosity and consequently, Macro porous; Micro porous and Non-porous systems can be identified:

Macro porous Systems:

In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 µm. This pore size is larger than diffusant molecule size.

Micro porous System:

Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.

Non-porous System:

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

Polymers Used[22-23]

Table 5: Polymers Used

Category	Examples
Hydrogels	PHEMA, cross-linked PVA, PEO
Soluble polymers	PEG, PVA, HPMC
Biodegradable	PLA, PGA, PCL, polyanhydrides
Non-biodegradable	PVC, ethyl cellulose, polyurethanes

Marketed Formulations

Table 6: Examples of Marketed Sustained Release Formulations

Name of Product	Active Ingredient(s)	Manufacturer
Histac	Ranitidine HCl	Ranbaxy
Effcal	$CaCO_3$, Vitamin D_3	Ranbaxy
Tagamet	Cimetidine	GSK
Zantac	Ranitidine	GSK
Calcium Sandoz	Calcium	ICN Hungary
Solpadeine	Paracetamol + Codeine phosphate	Sanofi
Prolyte Fizz	Glucose, electrolytes, citric acid	Cipla

CONCLUSION

Sustained release drug delivery systems represent a transformative approach in modern therapeutics, offering improved efficacy, safety, and patient compliance compared to conventional dosage forms. Among various approaches, **matrix tablets** remain the most widely adopted due to their simplicity, versatility, and cost-effectiveness. However, limitations such as high cost, dose dumping, and variability in release mechanisms must be addressed through advanced research. With ongoing innovations in **biodegradable polymers, nanotechnology, and targeted systems**, SRDDS are expected to further revolutionize the pharmaceutical industry and patient care.

Conflict of Interest:

The authors declare no conflict of interest.

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