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ADVANCED DEVELOPMENT IN SUSTAIN RELEASE DRUG DELIVERY SYSTEM

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ABSTRACT

Sustained Release Drug Delivery Systems are advancing rapidly with the integration of innovative technologies such as nanotechnology, advanced biomaterials, and computational modelling. These systems are designed to overcome the limitations of conventional dosage forms by providing controlled and prolonged drug release, thereby improving therapeutic efficacy and patient compliance. The incorporation of nanocarriers will improve drug solubility, stability, and targeting efficiency, enabling the development of hybrid delivery platforms. Additionally, the shift toward personalized medicine will allow SRDDS to be tailored based on individual patient characteristics, including genetic profile, metabolic rate, and disease condition, ensuring optimized dosing and reduced adverse effects. Furthermore, advancements in in vitro–in vivo correlation models will facilitate more accurate prediction of drug behaviour, support regulatory approval and improve formulation reliability. Overall, future SRDDS hold significant potential to transform drug delivery into a more efficient, safe, and patient-centric approach.

KEYWORDS: Sustained Release, prolonged drug release, personalized medicine, in vitro–in vivo correlation.

INTRODUCTION

Sustained release dosage form

Sustained release dosage forms are designed to release a drug at a controlled rate over an extended period. These systems maintain therapeutic drug levels for prolonged durations. They reduce fluctuations in plasma drug concentration compared to conventional dosage forms.[1] Sustained release dosage forms are formulations designed to release drugs at a predetermined rate over an extended time. These systems maintain therapeutic drug concentration for prolonged periods. They reduce the variations in the drugs plasma level compared to immediate-release formulations.[2]

Need

Sustained release systems are developed to reduce dosing frequency. They improve patient compliance by minimizing repeated drug administration. These systems help maintain steady drug levels in the body. They reduce side effects associated with peak drug concentrations. Sustained release formulations are beneficial for drugs with short half-life.[3]

Sustained release systems decrease the frequency of medications administration. They improve patient compliance especially in chronic therapies. These formulations maintain consistent drug concentration in the blood. They reduce the dose-related side effects caused by peak concentrations. Drugs with a short biological half-life benefit from sustained release.[4]

Goal

- The primary goal is to achieve a constant drug release rate.
- To keep the drugs concentrations within the therapeutic range.
- To reduce dosing frequency and improve convenience.
- To minimize adverse effects due to fluctuating drug levels.
- To improve therapeutic efficacy of the drug.
- To provide predictable and reproducible drug release.
- Overall, the goal is to optimize drug therapy with minimal side effects.[5]

- **Factors affecting sustain release dosage form**

1. Drug-related Factors

1) Half-life

The biological half-life of a drug is a key factor in designing sustained release formulations. Drugs with shorter half-lives are more suitable for sustained release systems.

2) Drug solubility

Drug solubility directly influences the rate and extent of a drug release.

3) Partition coefficient

The partition coefficient influences drug penetration via biological membranes. Stability of the drug in physiological conditions is essential for effective delivery.[6]

2. Formulation-related Factors

1) Type of polymer

The type of polymer used significantly controls the drug release profile.

2) Polymer concentration

Polymer concentration affects the viscosity and diffusion rate of the drug.

3) Presence of excipients

The presence of excipients can modify drug release behaviour.

4) Manufacturing processes

Manufacturing processes influence the uniformity and performance of dosage forms.[7]

3. Physiological factors

1) pH

   Gastrointestinal pH affects drug solubility and release rate.

2) Gastric emptying time

   Gastric emptying time influences drug absorption and bioavailability.

3) Enzymatic activity

   Enzymatic activity can lead to drug degradation.

4) Food intake

   Food intake may alter drug release and absorption patterns.

5) Patient Factor

6) Patient-specific conditions can impact the effectiveness of sustained release systems.[8]

❖ **Advantages**

1) Sustained release dosage forms reduce the frequency of drug administration.
2) They improve patient compliance, especially in long-term therapies.
3) These systems maintain steady drug concentration in the bloodstream.
4) They minimize fluctuations in plasma drug levels.
5) Sustained release formulations lower the risk of dose-related adverse effects.
6) They enhance therapeutic efficacy of drugs.
7) These systems provide prolonged drug action.
8) They are beneficial for drugs with short biological half-life.[9]
9) Sustained release dosage forms improve bioavailability of certain drugs.
10) They reduce the total dose required for treatment.
11) These formulations decrease the incidence of local irritation in the gastrointestinal tract.
12) They provide uniform drug absorption over an extended period.[10]

❖ **Classification**

1. Sustain release

1) Delayed absorption

Delayed absorption refers to the slow and prolonged uptake of a drug into systemic circulation. It occurs due to controlled and gradual release of the drug from the dosage form. The rate of drug absorption is dependent on the rate of drug release. Polymers used in sustained release systems retard drug dissolution. This leads to slow diffusion across biological membranes. Delayed absorption helps maintain prolonged therapeutic action. It prevents rapid increase in plasma drug concentration. The process ensures a more uniform drug absorption profile. It contributes to reduced dosing frequency. Overall, delayed absorption improves drug efficacy and safety.[11]

2) Prolong therapeutic levels

Prolonged therapeutic level refers to maintaining effective drug concentration in plasma for an extended duration. This is accomplished by regulating the rate of medication release from the dosage form. The drug is released slowly to sustain its concentration within the therapeutic window. This approach prevents rapid decline in drug levels after administration. It helps maintain steady-state plasma concentration over time. Fluctuations between peak and trough

levels are minimized. Sustained drug levels ensure continuous pharmacological action. It reduces the chances of sub-therapeutic and toxic levels. The system decreases the frequency of drug administration. Overall, it improves therapeutic efficiency and patient compliance.[12]

❖ **Mechanism**

1. Diffusion-Controlled Mechanism

In diffusion-controlled systems, the drug is uniformly dispersed within a polymer matrix. When the dosage form comes into touch with biological fluids, the drug starts to disperse out. The medication goes from a high concentration within the matrix to a low concentration outside. The polymer matrix acts as a barrier controlling the rate of drug release. The release rate depends on diffusion coefficient and matrix porosity. This mechanism provides a sustained and predictable drug release profile. It is commonly observed in matrix tablets and reservoir systems.[1]

2. Diffusion-Controlled Mechanism

In diffusion-controlled systems, drug release is determined by the rate at which the drug dissolves. Poorly soluble drugs dissolve slowly, resulting in prolonged drug release. Coating the medication with polymers can change the rate of disintegration. The thickness of the coating affects the release rate of the drug. The surrounding fluid environment also influences dissolution. This mechanism is useful for drugs with low aqueous solubility. It ensures gradual and controlled availability of the drug.[2]

3. Erosion-Controlled Mechanism

In erosion-controlled systems, the polymer matrix gradually degrades over time. When the polymers outer layer erodes, the medication is discharged. The rate of erosion determines the rate of drug release. Biodegradable polymers are commonly used in this mechanism. The system is suitable for controlled and site-specific drug delivery. It is widely used in implants and injectable formulations. The degradation products should be non-toxic and biocompatible.[13]

4. Swelling-Controlled Mechanism

The polymer absorbs water and swells in swelling-controlled devices. The swollen polymer forms a gel-like structure around the drug. Drug release occurs through diffusion from the swollen matrix. The rate of swelling controls the release rate of the drug. Hydrophilic polymers are commonly used in this system. The thickness of the gel layer affects diffusion distance. This mechanism provides controlled and extended drug release.[14]

5. Osmotic-Controlled Mechanism

Osmotic systems regulate medication release by means of osmotic pressure. A semipermeable membrane allows water to enter the dose form. The entry of water creates internal pressure inside the system. This pressure pushes the drug solution out through a small orifice. The release rate is independent of pH and gastrointestinal conditions. It provides a constant and controlled drug release rate. Osmotic systems are highly reliable and reproducible.[15]

❖ **Approaches to sustained release drug delivery system**

In order to maintain constant therapeutic levels in the bloodstream, sustained release drug delivery systems (SRDDS) are made to release medications at a regulated and planned pace over an extended period of time. These systems help to reduce dosing frequency, minimize, variations in the concentrations of drugs in plasma and improve patients complains.

The design of SRDDS is based on various approaches that utilize mechanism such as diffusion, dissolution, osmotic pressure, swelling, and biodegradation, depending on the physicochemical properties of the drug and the desired release profile.

1. Polymer matrix system

It is one of the most commonly used approaches in sustained release formulations. In this system, the drug is uniformly dispersed within a polymer matrix, which may be hydrophilic or hydrophobic in nature. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) swell in the presence of gastric fluid to form a gel layer through which the drug diffuses gradually. In contrast, hydrophobic matrices control drug release primarily through diffusion pathways. This approach is widely used due to its simplicity, cost-effectiveness, and ease of manufacturing.[16]

2. Reservoir system

Another important approach is the reservoir (coated) system, where the drug core is surrounded by a rate-controlling polymer membrane. The drug is released through diffusion across this membrane, and the release rate can be precisely controlled by adjusting the thickness and permeability of the coating. These systems are capable of achieving near zero-order release kinetics, although they require careful design to avoid dose dumping in case of membrane failure.[1]

3. Osmotic drug delivery system

It is a highly advanced approach that relies on osmotic pressure to control drug release. In this system, water enters through a semi-permeable membrane, generating internal pressure that pushes the drug solution out through a small delivery orifice. This method provides a consistent and predictable drug release profile that is largely independent of gastrointestinal pH and motility, making it a reliable and efficient sustained release strategy.[17]

4. Ion-exchange resin system

The approach involves binding the drug to an ion-exchange resin to form a stable complex. When the formulation comes into contact with gastrointestinal fluids, ions present in the fluid exchange with the drug molecules, leading to gradual release. This approach is particularly useful for taste masking and is commonly applied in liquid sustained release formulations.[18]

5. Floating drug delivery systems (FDDS)

The represent another important approach, especially for drugs that require prolonged gastric retention. These systems are designed to have a lower density than gastric fluids, allowing them to float on the stomach contents and remain in the stomach for an extended period. This enhances drug absorption and bioavailability. Raft-forming systems are a specialized type of floating system that forms a gel barrier in the stomach, combining sustained release with anti-reflux action.[19]

6. Mucoadhesive drug delivery system

The approach utilizes polymers that can adhere to the mucosal lining of the gastrointestinal tract. This adhesion prolongs the residence time of the drug at the absorption site, resulting in improved bioavailability and sustained drug release. Polymers such as chitosan, Carbopol, and polyacrylic acid are commonly used in these systems.[20]

7. Swelling and expandable systems

The are designed to increase in size after ingestion by absorbing gastric fluids. This expansion prevents the system from passing quickly through the pylorus, thereby prolonging gastric retention time and allowing sustained drug release. However, proper design is essential to ensure safety and avoid the risk of obstruction.[16]

8. Biodegradable polymer-based systems

The use polymers such as polylactic acid (PLA) and polylactic-co-glycolic acid (PLGA), which degrade gradually within the body to release the drug over time. These systems are particularly useful for long-term therapies, including implants and injectable sustained release formulations, as they eliminate the need for surgical removal.[21]

❖ **Evaluation Tests of Sustained Release Drug Delivery Systems (SRDDS)**

Evaluation of sustained release drug delivery systems is essential to ensure controlled drug release, stability, safety, and therapeutic effectiveness. These tests assess physical, chemical, and in vitro performance characteristics of the formulation.

1. Drug Content Uniformity

This test determines whether the drug is uniformly distributed throughout the dosage form. A specific number of units are analysed, and the drug content is measured using analytical techniques such as UV spectrophotometry or HPLC. Uniform drug distribution ensures consistent dosing and therapeutic efficacy.[16]

2. Weight Variation Test

In this test, individual dosage units are weighed and compared with the average weight. It ensures uniformity in manufacturing and dose accuracy, which is especially important for oral sustained release tablets and capsules.[20]

3. Thickness and Hardness (For Tablets)

Tablet thickness and hardness are evaluated to ensure mechanical strength and integrity. Adequate hardness prevents breakage during handling, while proper thickness ensures uniform drug release characteristics.[18]

4. Friability Test

Friability measures the ability of tablets to withstand mechanical stress during packaging and transportation. A friability value below 1% is generally acceptable. Excessive friability can affect drug release behavior.[20]

5. Swelling Index

This test evaluates the swelling behavior of hydrophilic polymers used in matrix systems. The increase in weight or volume of the dosage form is measured after immersion in dissolution medium. Swelling behavior directly influences drug release rate.[20]

6. In Vitro Dissolution Studies

This is the most critical evaluation test for SRDDS. It measures the rate and extent of drug release over time using dissolution apparatus (USP Type I or II). The release data is used to determine release kinetics (zero-order, first-order, Higuchi)[16]

7. Drug Release Kinetics Modelling

- Dissolution data is fitted into mathematical models such as:
- Zero-order kinetics
- First-order kinetics
- Higuchi model
- Korsmeyer–Peppas model[1]

This helps in understanding the mechanism of drug release (diffusion, erosion, swelling).

8. Floating Lag Time and Total Floating Time (For Gastroretentive Systems)

For floating systems, the time required to start floating (lag time) and the total duration of floating are measured. These parameters indicate gastric retention capability.[19]

9. Mucoadhesion Strength (For Mucoadhesive Systems)

This test measures the adhesive strength between the dosage form and mucosal surface. It ensures prolonged residence time at the absorption site.[20]

10. Stability Studies

Stability studies are conducted as per ICH guidelines to evaluate the effect of temperature, humidity, and light on the formulation. These studies ensure:

- Drug stability
- Shelf-life determination
- Maintenance of release profile over time.[18]

11. In Vivo Studies

In vivo studies evaluate the actual performance of SRDDS in biological systems. These include:

- Pharmacokinetic studies (Cmax, Tmax, AUC)
- Bioavailability studies

They confirm correlation between in vitro and in vivo performance (IVIVC).[19]

12. Mechanical Strength and Integrity

This test ensures that the dosage form maintains its structure during the entire release period, especially for matrix and gastro retentive systems.[16]

❖ Current Challenges of Sustained Release Drug Delivery Systems (SRDDS)

Sustained release drug delivery systems (SRDDS) offer significant therapeutic advantages; however, their development and clinical application are associated with several formulation, physiological, technological, and regulatory challenges. Understanding these limitations is essential for improving system design and performance.

1. Poor Drug Solubility and Permeability

One of the major challenges in SRDDS is the poor aqueous solubility and low permeability of many drugs (especially BCS Class II and IV drugs). Such drugs may not release at the desired rate or may exhibit incomplete absorption, leading to reduced bioavailability. Achieving a balance between drug release rate and absorption window remains difficult.[16]

2. Dose Dumping Risk

SRDDS formulations, particularly reservoir systems, are susceptible to dose dumping, where a large amount of drug is released suddenly due to failure of the rate-controlling membrane or environmental changes (e.g., alcohol intake). This can lead to toxicity and serious adverse effects.[1]

3. Variable Gastrointestinal Conditions

The pH, gastric emptying rate, motility, and enzyme activity in the gastrointestinal tract vary significantly among patients and even within the same individual. These variations can affect drug release and absorption, making it difficult to achieve consistent therapeutic outcomes.[19]

4. Limited Drug Candidates

Not all drugs are suitable for sustained release formulation. Ideal candidates should have:

- Moderate half-life
- Good stability
- Suitable absorption window
- Drugs with very short or very long half-lives, narrow therapeutic index, or poor stability are difficult to formulate as SRDDS.[20]

5. Complexity in Formulation Design

Designing SRDDS requires careful selection of:

- Polymers
- Drug-polymer compatibility
- Release mechanisms
- Achieving the desired release kinetics (zero-order) is complex and often requires extensive optimization and testing.[16]

6. Scale-Up and Manufacturing Challenges

Translating laboratory formulations into large-scale production is challenging due to:

- Process variability
- Equipment limitations
- Reproducibility issues
- Maintaining consistent drug release profiles during scale-up is a critical issue[18].

7. Stability Issues

SRDDS formulations may face stability problems such as:

- Polymer degradation
- Drug–excipient interactions
- Moisture sensitivity
- These factors can alter drug release characteristics and shelf-life.

8. In Vitro–In Vivo Correlation (IVIVC) Limitations

Establishing a reliable correlation between in vitro dissolution and in vivo drug release is difficult. Variability in physiological conditions makes it challenging to predict actual drug performance based on laboratory studies.[1]

9. Patient Variability

Differences in patient-specific factors such as:

- Age
- Diet
- Disease condition
- Gastric pH can significantly influence the performance of SRDDS, leading to inconsistent therapeutic effects.[19]

10. Risk of Dose Accumulation

Sustained release systems may lead to drug accumulation in the body, especially if dosing intervals are not properly adjusted. This can increase the risk of toxicity, particularly for drugs with a narrow therapeutic index.[20]

11. Limited Control over Release in Complex Systems

In some systems (e.g., matrix systems), achieving precise control over drug release is difficult due to:

- Polymer swelling variability
- Environmental influences
- This may result in non-uniform release profiles.[16]

❖ **Future Perspective of Sustained Release Drug Delivery Systems (SRDDS)**

Sustained release drug delivery systems are rapidly evolving with advancements in materials science, nanotechnology, and computational design, aiming to overcome current limitations and enhance therapeutic outcomes. The future of SRDDS is focused on developing more precise, patient-specific, and intelligent delivery systems that can provide controlled drug release with high efficiency and safety. Future SRDDS will enable site-specific and on-demand drug release, reduce side effects and improve therapeutic precision.[19] Drug solubility, stability, and targeting efficiency, and can be combined with sustained release matrices to create hybrid delivery platforms.[20] Future SRDDS will be tailored according to individual patient characteristics, such as genetic profile, metabolic rate, and disease condition. Personalized drug delivery will ensure optimized dosing, improved efficacy, and reduced adverse effects, aligning with the concept of precision medicine.[17] Future research will focus on developing better models to establish strong IVIVC, enabling more accurate prediction of in vivo drug behaviour based on in vitro studies. This will enhance regulatory approval and formulation reliability.[1]

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