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Review Article

Sustained Release Drug Delivery: A Review

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ABSTRACT

Sustained-release matrix tablets are widely developed oral drug delivery systems designed to provide controlled and prolonged drug release, thereby improving therapeutic efficacy and patient compliance. These formulations are commonly prepared using techniques such as direct compression, wet granulation, or dispersion of drug particles within a polymeric matrix system. A variety of polymers, including polymethyl methacrylate (PMMA), polyglycolic acid, and hydroxypropyl methylcellulose (HPMC), are employed to regulate drug release behavior. The polymeric matrix plays a vital role in controlling drug diffusion and dissolution over an extended period by forming a barrier that modulates drug release kinetics. Hydrophilic polymers, particularly HPMC, function as release-retarding agents by forming a gel layer upon hydration, which governs drug diffusion and erosion mechanisms. Matrix tablets can be formulated either by direct compression of a homogeneous blend containing drug, polymer, and excipients or through granulation followed by compression. Depending on the nature of the polymer used, matrix systems may be classified as hydrophilic, hydrophobic, biodegradable, or mineral-based matrices. The drug release profile of sustained-release formulations is typically evaluated using in-vitro dissolution studies to ensure controlled and predictable drug delivery. Several therapeutic agents, including Ambroxol hydrochloride and Nateglinide, have been successfully developed as sustained-release matrix tablets. Overall, sustained-release matrix systems reduce dosing frequency, minimize fluctuations in plasma drug concentration, and enhance patient adherence, making them particularly advantageous in the long-term management of chronic diseases.

INTRODUCTION

Novel drug delivery systems (NDDS) play a significant role in improving the therapeutic effectiveness of pharmaceutical agents by enabling controlled, sustained, or targeted drug release. The fundamental objective of any drug delivery system is to deliver a therapeutically effective concentration of a drug to the desired site of action rapidly and to maintain this concentration

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within the therapeutic window for an extended duration.[1] Such systems help in optimizing drug therapy by reducing dosing frequency, minimizing side effects, and enhancing patient compliance.

The design and development of oral sustained-release drug delivery systems depend on several interrelated factors, including the physicochemical properties of the drug, characteristics of the delivery system, disease condition, patient compliance, and duration of treatment. Sustained-release dosage forms are defined as formulations that release the active pharmaceutical ingredient at a predetermined and controlled rate over a prolonged period, thereby maintaining consistent plasma drug levels.[2]

Among various sustained-release approaches, matrix tablets represent one of the most widely used and commercially successful dosage forms due to their ease of manufacturing, cost-effectiveness, fewer processing variables, and capability to incorporate high drug loads. In matrix systems, the drug is uniformly dispersed within a polymeric network that regulates drug release through mechanisms such as diffusion, erosion, or swelling of the polymer matrix.

There has been continuous interest in developing sustained-release formulations using economical, safe, and readily available excipients through matrix-based technologies. Over the past two decades, sustained-release drug delivery systems have experienced significant advancement owing to several factors, including the increasing cost of developing new chemical entities, expiration of patents for existing drugs, discovery of novel polymeric materials capable of controlled drug release, and improved therapeutic efficacy and safety achieved through modified drug delivery approaches.

In recent years, sustained-release technologies have also gained importance in veterinary pharmaceutical applications, where prolonged drug action reduces dosing frequency and improves treatment outcomes.[3] Overall, sustained-release matrix systems offer a promising strategy for enhancing drug performance and patient adherence in long-term therapeutic management.

Drawbacks of Conventional Dosage Forms

Conventional dosage forms possess several limitations that may negatively influence therapeutic effectiveness and patient outcomes:

1. **Poor patient compliance:** Conventional formulations often require frequent dosing, which increases the chances of missed doses, especially in patients undergoing long-term treatment for chronic diseases.

2. **Fluctuating plasma drug levels:** These dosage forms produce significant variations in drug concentration in the bloodstream, resulting in periods where drug levels may become either sub-therapeutic or toxic.

3. **Peak–valley effect:** Conventional drug administration produces alternating peaks and troughs in plasma drug concentration over time, making it difficult to maintain a constant therapeutic level.

4. **Increased adverse effects:** Drugs with a narrow therapeutic index are particularly prone to side effects due to fluctuations in plasma concentration, especially when drug levels rise above the safe therapeutic range.[4–6]

Advantages of Sustained-Release Dosage Forms

i) Improved Patient Compliance

Poor patient compliance is commonly observed in chronic diseases requiring long-term medication. The success of pharmacotherapy depends greatly on the patient's adherence to the prescribed treatment regimen. Compliance is influenced by factors such as patient awareness, confidence in therapy, understanding of dosing schedules, treatment complexity, therapy cost, and occurrence of adverse effects.

Sustained-release drug delivery systems reduce dosing frequency and simplify medication schedules, thereby improving patient adherence and treatment outcomes.

ii) Reduced "See-Saw" Fluctuation

Conventional dosage forms often produce a "see-saw" pattern of plasma drug concentration due to repeated dosing. These fluctuations depend on pharmacokinetic parameters such as drug absorption, distribution, elimination rate, and dosing interval.

This variation is especially significant for drugs with a biological half-life of less than four hours because dosing intervals are usually longer than the drug elimination time. Sustained-release formulations minimize these fluctuations by maintaining relatively constant drug levels in systemic circulation and target tissues.

iii) Reduction in Total Drug Dose

Sustained-release systems may require a lower total quantity of drug to achieve the desired therapeutic effect. Controlled drug release improves drug utilization efficiency, which helps reduce dose-related adverse effects at both systemic and local levels. This enhances the overall safety profile of the medication.

iv) Improved Therapeutic Efficacy

Effective therapy requires adequate drug concentration at the target site. In conventional therapy, higher doses are often administered to achieve sufficient drug levels, which may cause toxicity in non-target tissues.

Sustained-release dosage forms provide controlled and prolonged drug delivery, maintaining optimal drug concentration at the site of action and improving the management of both acute and chronic diseases.

v) Economic Benefits

Although sustained-release formulations may have a higher initial manufacturing cost compared to conventional dosage forms, the overall treatment cost is often reduced during long-term therapy. This reduction results from decreased dosing frequency, improved patient compliance, and fewer adverse effects.[5–8]

Physicochemical Parameters for Drug Selection

The selection of a suitable drug candidate is essential for the successful development of sustained-release dosage forms. Certain physicochemical properties of the drug significantly influence formulation performance and drug release behaviour. The ideal criteria are summarized below:

Parameter	Criteria
Molecular size	Less than 1000 Daltons
Aqueous solubility	Greater than 0.1 mg/mL over pH range 1–7.8
Apparent partition coefficient	Preferably high
Absorption mechanism	Diffusion-controlled absorption
General absorbability	Drug should be absorbed throughout all regions of the gastrointestinal tract
Drug release characteristics	Drug release should not be significantly affected by pH

	changes or enzymatic activity

Disadvantages of Sustained-Release Dosage Forms

Although sustained-release dosage forms provide several therapeutic benefits, they also have certain limitations:

1. **Dose dumping:** Improper formulation design or manufacturing defects may cause rapid and uncontrolled drug release, leading to dose dumping and possible drug toxicity.
2. **Limited dose adjustment:** Once administered, sustained-release formulations offer limited flexibility for dose modification compared to conventional dosage forms.
3. **Higher cost:** Sustained-release products are generally more expensive due to complex formulation processes and specialized manufacturing requirements.
4. **Enhanced first-pass metabolism:** Increased gastrointestinal residence time may expose some drugs to greater first-pass metabolism, reducing their effectiveness.
5. **Need for patient education:** Patients must clearly understand how to use sustained-release formulations properly to prevent misuse, such as crushing or chewing tablets.
6. **Reduced systemic availability:** In some cases, incomplete drug release or absorption may lead to decreased bioavailability.
7. **Poor in-vitro–in-vivo correlation (IVIVC):** Predicting in-vivo drug release behaviour based solely on in-vitro dissolution studies can be difficult for certain sustained-release systems.[2,4,9]

Criteria to be Met for Incorporating a Drug into Sustained-Release Dosage Forms

The selection of an appropriate drug candidate is an important step in designing sustained-release dosage forms. The drug should possess suitable physicochemical and pharmacokinetic properties to achieve controlled and predictable drug release as well as effective absorption.

A clear understanding of the drug's absorption mechanism in the gastrointestinal (GI) tract is essential because sustained-release systems rely on prolonged residence time and continuous drug absorption. For successful formulation, the drug should ideally be absorbed uniformly throughout a large portion of the GI tract.

If drug absorption occurs only in a specific region of the GI tract or depends on specialised transport mechanisms, sustained-release formulations may result in incomplete absorption and reduced bioavailability. Therefore, detailed evaluation of the drug's biological and absorption characteristics must be performed before developing a sustained-release dosage form.

Biological Factors Influencing Drug Release from Tablets

Several biological factors influence the performance of sustained-release dosage forms. These factors must be carefully evaluated during formulation development to ensure consistent drug release and therapeutic effectiveness.

1) Biological Half-Life

The main objective of oral sustained-release formulations is to maintain therapeutic drug concentration in the plasma for an extended period. To achieve this, the drug release rate should be comparable to the rate at which the drug is eliminated from the body.

Drug elimination occurs through metabolism, renal excretion, and other irreversible processes that remove the drug from systemic circulation. Drugs with a short biological half-life are generally suitable candidates for sustained-release formulations because they require frequent dosing in conventional dosage forms.

However, drugs with an extremely short half-life (less than 2 hours), such as levodopa, are not ideal because they are eliminated too rapidly. On the other hand, drugs with long half-lives (greater than 8 hours), such as digoxin and phenytoin, usually do not require sustained-release formulations since their therapeutic effects already last for a long duration.

2) Absorption

In sustained-release systems, the rate of drug release should be slower than the rate of drug absorption. The average gastrointestinal transit time of oral dosage forms through the absorption region is approximately 8–12 hours.

Therefore, the absorption half-life of a drug should ideally be 3–4 hours to allow sufficient absorption before the dosage form leaves the absorption site. Drugs that are absorbed uniformly throughout the small intestine are good candidates for sustained-release formulations.

In contrast, drugs absorbed only in specific intestinal regions or through active transport mechanisms may show reduced absorption when formulated as sustained-release products.

3) Metabolism

Drugs that undergo extensive metabolism before reaching systemic circulation may show reduced bioavailability in sustained-release formulations. This metabolism may occur in the gastrointestinal lumen or intestinal tissues.

Poorly water-soluble drugs can still be formulated as sustained-release systems after applying solubility enhancement techniques. However, care must be taken to prevent drug recrystallisation during absorption, as this may reduce therapeutic effectiveness.

4) Distribution

Drug distribution within the body also affects elimination rate. Drugs with a large apparent volume of distribution tend to be eliminated more rapidly and are therefore considered unsuitable for oral sustained-release dosage forms. Chloroquine is an example of such a drug.

5) Protein Binding

The pharmacological effect of a drug mainly depends on the concentration of free (unbound) drug rather than protein-bound drug. Many drugs bind to plasma or tissue proteins to varying degrees.

Extensive protein binding can prolong the biological half-life of a drug, which may reduce the necessity for sustained-release formulation. Therefore, protein-binding characteristics must be carefully evaluated during formulation design.

6) Molecular Size and Diffusivity

In matrix-based sustained-release systems, drug molecules must diffuse through a polymer matrix or membrane. Drug diffusivity is inversely related to molecular size; larger molecules diffuse more slowly through polymer networks.

Hence, molecular weight plays an important role in determining the diffusion rate and overall drug release behaviour from the matrix system.

7) Margin of Safety

The safety of a drug is determined by its therapeutic index. Drugs with a wide therapeutic index are safer and more suitable for sustained-release formulations because minor variations in drug release do not cause toxicity.

In contrast, drugs with a narrow therapeutic index carry a higher risk of adverse effects and are generally unsuitable for oral sustained-release drug delivery systems.[7,12,13,14]

Physicochemical Factors Influencing Drug Release from Matrix Tablets

Drug release from matrix tablets is strongly affected by several physicochemical properties of the drug. These factors must be carefully evaluated during formulation development to achieve controlled and predictable drug release.

a) Dose Size

Generally, a single oral dose containing 500 mg to 1.0 g of drug is considered the upper acceptable limit for conventional dosage forms, and the same limitation applies to sustained-release formulations.

Drugs that require very large doses are usually not suitable for matrix-based sustained-release systems unless the total dose is divided or alternative drug delivery approaches are used. The margin of safety of the drug must also be considered when selecting an appropriate dose size, as excessive drug loading may increase the risk of toxicity.

b) Ionisation, pKa, and Aqueous Solubility

Most drugs behave as weak acids or weak bases. The unionised form of a drug can easily pass through lipid membranes, making the relationship between drug pKa and the pH of the absorption environment very important.

Although the unionised form improves membrane permeability, it often has lower aqueous solubility. Since sustained-release systems mainly depend on diffusion and dissolution processes, drug solubility in aqueous media significantly affects drug release.

Because oral dosage forms travel through different regions of the gastrointestinal tract with varying pH conditions, the influence of pH on drug release must be carefully studied.

- Poorly soluble drugs (<0.01 mg/ml) may naturally show sustained-release behaviour due to slow dissolution.
- Highly soluble drugs usually require release-retarding polymers or excipients to control drug diffusion and prevent rapid release.

c) Partition Coefficient

For an orally administered drug to produce systemic effects, it must cross multiple biological membranes, which are primarily lipid in nature. Therefore, the partition coefficient is an important factor determining membrane permeability.

- Drugs with high partition coefficients are lipophilic, poorly water-soluble, and may accumulate in fatty tissues, leading to prolonged drug retention.
- Drugs with very low partition coefficients may not adequately penetrate biological membranes, resulting in poor bioavailability.

Partition characteristics also influence drug diffusion through polymeric matrices and help determine the selection of suitable matrix-forming materials.

d) Stability

Drugs administered orally may degrade due to acid–base hydrolysis or enzymatic reactions within the gastrointestinal tract. Drugs in solid dosage forms generally degrade more slowly and are therefore preferred for sustained-release formulations.

For drugs unstable in gastric conditions, formulations designed to delay drug release until the intestine can enhance bioavailability. However, drugs unstable in intestinal environments may show reduced bioavailability in sustained-release systems because of prolonged exposure to degrading conditions.[7,8,10,12]

A) Diffusion Sustained Systems

Diffusion-controlled systems release the drug by movement of drug molecules from a region of higher concentration to lower concentration according to Fick's law of diffusion:

$$J = -D\,(dc/dx)$$

where D is the diffusion coefficient and (dc/dx) is the concentration gradient.

Drug release rate depends on membrane properties and can be expressed as:

$$dm/dt = ADK(C/L)$$

where A is surface area, D diffusion coefficient, K partition coefficient, C concentration difference, and L diffusion path length.

i) Diffusion Reservoir System

In this system, a drug core is surrounded by a water-insoluble polymer membrane. The drug diffuses through the membrane gradually, producing sustained drug release.

ii) Diffusion Matrix System

Here, drug particles are uniformly dispersed in an insoluble matrix. Drug release occurs through diffusion and dissolution mechanisms. Higuchi described release as:

$$Q \propto t^{1/2}$$

indicating drug release is proportional to the square root of time.

B) Dissolution Sustained Systems

In dissolution-controlled systems, drug release depends on the rate at which the drug or coating dissolves. Poorly soluble drugs naturally show sustained release, while highly soluble drugs may be modified using less soluble salts or coatings.

a) Soluble Reservoir System

Drug particles are coated with a slowly dissolving layer. Drug release occurs gradually as the coating erodes.

C) Ion Exchange Systems

Ion-exchange resins form drug–resin complexes that release the drug through ion exchange reactions in gastrointestinal fluids. Drug release depends mainly on ionic conditions rather than enzymes or pH.

Types include:

- **Cation exchange resins** – contain acidic groups
- **Anion exchange resins** – contain basic groups

D) pH-Independent Formulations

Drug release may vary due to changes in gastrointestinal pH. Buffering agents such as citric acid or phosphate salts are added to maintain a

constant microenvironmental pH, ensuring uniform drug release throughout the GI tract.

E) Altered Density Formulations

These systems prolong gastric residence time:

- **High-density systems:** Use heavy materials (e.g., barium sulphate) to remain in the stomach.
- **Low-density systems:** Float on gastric fluids using low-density polymers, allowing prolonged drug release.[15–18]

Polymers Used in Tablets

A wide range of polymers are used in tablet formulations to achieve controlled and sustained drug release. The selection of a suitable polymer depends on factors such as the physicochemical properties of the drug, the required drug release pattern, and the route of administration. Based on their characteristics and functions, polymers used in tablets can be broadly classified into the following categories:

1. Hydrogels

Hydrogels are three-dimensional polymer networks that can absorb large amounts of water while maintaining their structural stability. When exposed to gastrointestinal fluids, these polymers swell and form a gel layer around the tablet. This gel barrier controls drug release by regulating the diffusion of the drug from the matrix.

Common examples of hydrogel polymers include:

- Polyhydroxyethyl methacrylate (PHEMA)
- Cross-linked polyvinyl alcohol (PVA)
- Cross-linked polyvinyl pyrrolidone (PVP)
- Polyethylene oxide (PEO)
- Polyacrylamide (PA)

2. Soluble Polymers

Soluble polymers gradually dissolve in gastrointestinal fluids. Drug release occurs through a combination of polymer dissolution and drug diffusion mechanisms. These polymers help in achieving uniform and controlled drug release.

Examples include:

- Polyethylene glycol (PEG)
- Polyvinyl alcohol (PVA)
- Polyvinyl pyrrolidone (PVP)
- Hydroxypropyl methylcellulose (HPMC)

3. Biodegradable Polymers

Biodegradable polymers break down inside the body through enzymatic or hydrolytic reactions. The degradation products formed are non-toxic and are eliminated through normal metabolic pathways. These polymers are especially useful for controlled drug delivery applications.

Common biodegradable polymers include:

- Polylactic acid (PLA)
- Polyglycolic acid (PGA)
- Polycaprolactone (PCL)
- Polyanhydrides
- Polyorthoesters

4. Non-Biodegradable Polymers

Non-biodegradable polymers do not degrade during drug release. Instead, they remain structurally intact and control drug release mainly through diffusion mechanisms.

Examples include:

- Polyethylene vinyl acetate (PVA)
- Polydimethylsiloxane (PDS)
- Polyetherurethane (PEU)
- Polyvinyl chloride (PVC)
- Cellulose acetate (CA)
- Ethyl cellulose (EC)

5. Mucoadhesive Polymers

Mucoadhesive polymers have the ability to adhere to mucosal surfaces of the gastrointestinal tract. This adhesion increases the residence time of the dosage form at the absorption site, thereby improving drug bioavailability and prolonging therapeutic action.

Examples include:

- Polycarbophil
- Sodium carboxymethyl cellulose
- Polyacrylic acid
- Tragacanth
- Methylcellulose
- Xanthan gum
- Guar gum
- Karaya gum
- Locust bean gum[2,3,9,20]

CONCLUSION

This review article discusses the basic principles and formulation approaches of sustained-release matrix tablets. Matrix systems provide an effective method for controlling drug release, improving patient compliance, and enhancing therapeutic effectiveness, especially in the treatment of chronic diseases. Due to their simple manufacturing process, cost-effectiveness, and ability to reduce dosing frequency, matrix tablets are widely preferred among sustained-release dosage forms. Overall, sustained-release matrix tablets represent an important and promising approach for improving oral drug delivery and achieving better clinical outcomes.

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