A Review on Formulation And Evaluation of Sustained Released Tablets

Narayan D. Sule[1]; Swaraj S. Deshmukh [2]; Saurabh S. Bhusal[3]; Komal V. More[4]; Rajani Shettigar[5];

[1,2,3,4,5,]Department of Pharmacy, Kokan Gyanpeeth Rahul Dharkar College of pharmacy and research institute, Karjat, Mumbai university.

Abstract:

Sustained-release matrix tablets are commonly developed using techniques such as wet granulation, direct compression, or dispersion of solid drug particles within a polymeric matrix. Various polymers including polymethyl methacrylate (PMMA), polyglycolic acid, and hydroxypropyl methylcellulose (HPMC) are utilised to regulate the drug release pattern. The polymeric matrix plays a crucial role in controlling the diffusion and dissolution of the drug over an extended period. Hydrophilic polymers such as HPMC act as release retardants and form the core excipient of the formulation. Matrix tablets may be prepared either by direct compression of a blend containing the drug, polymer, and excipients or by granulating the mixture prior to compression. The matrices employed may be hydrophilic, hydrophobic, biodegradable, or mineral-based in nature. Drug release characteristics are generally evaluated using in-vitro dissolution studies. Several drugs, including Ambroxol hydrochloride and Nateglinide, have been successfully formulated as sustained-release matrix tablets. Overall, sustained-release matrix tablets enhance patient compliance by reducing dosing frequency and total drug dose, making them particularly beneficial in the management of chronic diseases.

Keywords: Sustained release, Polymer, Matrix tablet.

Introduction:

Novel drug delivery systems play a vital role in enhancing the therapeutic efficacy of drugs by providing controlled, sustained, or targeted drug delivery. The primary objective of any drug delivery system is to deliver a therapeutically effective concentration of drug to the desired site of action promptly and to maintain this concentration for a prolonged period.[1] The design of oral sustained-release drug delivery systems depends on several interrelated factors, including the nature of the delivery system, disease condition, patient compliance, duration of therapy, and physicochemical properties of the drug. Sustained-release systems are defined as dosage forms that release the drug slowly over an extended period of time.[2]

Matrix tablets represent one of the most commercially viable sustained-release dosage forms due to their simple manufacturing process, minimal processing variables, and ability to accommodate high drug loads. There is continued interest in the development of sustained-release formulations using economical and readily available excipients through matrix-based approaches. Over the past two decades, significant growth has been observed in the field of sustained-release drug delivery systems. This advancement is attributed to factors such as the high cost associated with the development of new chemical entities, expiration of patents of existing drugs, discovery of novel polymeric materials suitable for prolonged drug release, and improved therapeutic efficacy and safety profiles achieved through controlled drug delivery systems. In recent years, sustained-release technology has also been extended to veterinary pharmaceutical products.[3]

DRAWBACK OF CONVENTIONAL DOSAGE FORM :

Conventional dosage forms suffer from several limitations that can adversely affect therapeutic outcomes:

1. **Poor patient compliance:** Frequent dosing schedules increase the likelihood of missed doses, particularly in chronic disease management.
2. **Fluctuating drug plasma levels:** Conventional dosage forms often produce significant variations in plasma drug concentration, leading to periods of sub-therapeutic or toxic drug levels.
3. **Peak-valley effect:** The characteristic peak-valley plasma concentration-time profile associated with conventional dosage forms makes it difficult to maintain consistent therapeutic drug levels.
4. **Increased adverse effects:** Drugs with a narrow therapeutic index are particularly susceptible to adverse effects due to fluctuations in plasma concentration, especially during over-medication.[4–6]

ADVANTAGES OF SUSTAINED RELEASE DOSAGE FORM:

i) Patient compliance

Poor patient compliance is frequently observed in chronic diseases that require long-term therapy. The success of pharmacotherapy largely depends on the patient's ability and willingness to adhere to the prescribed treatment regimen. Compliance is influenced by several factors such as awareness of the disease condition, confidence in the treatment, understanding of dosing schedules, complexity of the regimen, cost of therapy, and the presence of local or systemic adverse effects. Sustained-release drug delivery systems help to overcome these issues by reducing dosing frequency and simplifying the treatment schedule, thereby improving patient adherence.

ii) Reduced 'see-saw' fluctuation

Conventional dosage forms often produce a pronounced 'see-saw' pattern in plasma drug concentration due to repeated dosing. The extent of these fluctuations depends on pharmacokinetic parameters such as absorption rate, distribution, elimination, and dosing interval. This effect is more prominent for drugs with a biological half-life of less than four hours, as dosing intervals are rarely shorter than this duration. A properly designed sustained-release system minimises these fluctuations by maintaining a relatively constant drug concentration in systemic circulation and target tissues.

iii) Reduction in total dose

Sustained-release drug delivery systems often require a lower total amount of drug to achieve the desired therapeutic effect. By reducing the overall drug dose, the incidence of dose-related adverse effects—both systemic and local—can be minimised. This also contributes to improved safety and therapeutic efficiency.

iv) Improvement in therapeutic efficacy

Effective treatment requires adequate delivery of the drug to the target tissues or organs. In many cases, doses much higher than those required at the site of action are administered to achieve therapeutic concentrations, which may lead to toxicity in non-target tissues. Sustained-release dosage forms allow controlled drug delivery, ensuring optimal drug levels at the site of action and better management of acute and chronic disease conditions.

v) Economy

Although sustained-release formulations generally have a higher initial unit cost compared to conventional dosage forms due to specialised formulation requirements, the overall cost of therapy over a prolonged treatment period is often reduced. This is achieved through decreased dosing frequency, improved compliance, and reduced incidence of adverse effects.[5–8]

Physicochemical parameters for drug selection:

Parameters	Criteria
Molecular size	Less than 1000 Daltons
Aqueous solubility	Greater than 0.1 mg/ml over pH 1–7.8
Apparent partition coefficient	Preferably high
Absorption mechanism	Diffusion
General absorbability	Absorption from all regions of the GI tract
Drug release	Should not be significantly affected by pH or enzymes

DISADVANTAGES OF SUSTAINED RELEASE DOSAGE FORM:

Despite several advantages, sustained-release dosage forms also exhibit certain limitations:

1. **Dose dumping:** Improper formulation or manufacturing defects may lead to rapid and uncontrolled drug release, resulting in dose dumping and potential toxicity.
2. **Limited dose adjustment:** Sustained-release formulations offer reduced flexibility for dose modification once administered.
3. **Higher cost:** The cost of sustained-release dosage forms is generally higher than that of conventional formulations.
4. **Enhanced first-pass metabolism:** Prolonged residence time in the gastrointestinal tract may increase first-pass metabolism for certain drugs.
5. **Requirement for patient education:** Proper understanding of the dosage form is essential to ensure correct use and avoid misuse.
6. **Reduced systemic availability:** In some cases, incomplete drug release or absorption may reduce bioavailability.
7. **Poor in-vitro–in-vivo correlation:** Predicting in-vivo drug release behaviour from in-vitro studies can be challenging for certain sustained-release systems.[2,4,9]

Characteristic	Examples of drugs
Poor absorption in lower intestine	Riboflavin, Ferrous salts
Rapid absorption and elimination (half-life < 1 h)	Penicillin G, Furosemide
Long biological half-life (>12 h)	Diazepam, Phenytoin
Large dose requirement (>1 g)	Sulphonamides
Drugs with cumulative action and narrow therapeutic index	Phenobarbital, Digitoxin
Drugs requiring precise individual dose titration	Anticoagulants, Cardiac glycosides[9]

CRITERIA TO BE MET TO INCORPORATE THE DRUG INTO SUSTAINED RELEASE DOSAGE FORM:

Selection of a suitable drug candidate is a critical step in the design of sustained-release dosage forms. The drug must possess appropriate physicochemical and pharmacokinetic characteristics to ensure predictable release and absorption. A thorough understanding of the drug's absorption mechanism from the gastrointestinal tract is essential, as sustained-release systems depend on prolonged residence time and consistent absorption throughout the GI tract.

Drugs intended for sustained-release formulations should ideally exhibit uniform absorption over a wide region of the gastrointestinal tract. If absorption is limited to a specific segment or occurs via specialised transport mechanisms, sustained-release formulations may lead to reduced bioavailability. Therefore, careful evaluation of the drug's biological behaviour is required prior to formulation.

Parameters	Comment
Elimination half-life	Preferably between 2–8 hours
Absolute bioavailability	Should be 75% or higher
Absorption rate constant (Ka)	Must exceed the drug release rate
Apparent volume of distribution (Vd)	Larger Vd and MEC require a higher dose
Total clearance	Should be dose-independent
Elimination rate constant	Essential for dosage form design
Therapeutic concentration (Css)	Lower Css and smaller Vd reduce dose requirement
Toxic concentration	Greater separation between MTC and MEC improves safety[4,10,11]

BIOLOGICAL FACTORS INFLUENCING RELEASE FROM TABLET

1) Biological half-life

The fundamental principle of oral sustained-release formulations is to maintain therapeutic plasma drug concentrations over an extended duration. To achieve this, the drug must be released at a rate comparable to its elimination from the body. 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 better candidates for sustained-release formulations. However, drugs with extremely short half-lives (less than 2 hours), such as levodopa, are poor candidates due to rapid elimination. Conversely, drugs with long half-lives exceeding 8 hours, such as digoxin and phenytoin, do not require sustained-release formulations as their effects are inherently prolonged.

2) Absorption

In sustained-release systems, the rate of drug release should be slower than the rate of absorption. The average transit time of dosage forms through the absorptive regions of the gastrointestinal tract is approximately 8–12 hours. Therefore, the absorption half-life should ideally fall within 3–4 hours to ensure adequate drug uptake before the dosage form leaves the absorption window. Drugs absorbed uniformly throughout the small intestine are suitable candidates for sustained-release formulations. In contrast, drugs absorbed via active transport or restricted to specific intestinal regions may exhibit reduced absorption when formulated as sustained-release products.

3) Metabolism

Drugs that undergo extensive metabolism before absorption—either within the gastrointestinal lumen or intestinal tissues—may show reduced bioavailability when administered as sustained-release formulations. Drugs with poor aqueous solubility can be formulated as sustained-release systems after employing solubility enhancement techniques. However, caution must be exercised to prevent recrystallisation of the drug during systemic absorption, which may compromise therapeutic efficacy.

4) Distribution

Drug elimination is influenced by the apparent volume of distribution. Drugs with a large volume of distribution are eliminated more rapidly and are therefore considered poor candidates for oral sustained-release drug delivery systems. An example of such a drug is chloroquine.

5) Protein binding

Pharmacological activity depends primarily on the concentration of unbound drug rather than protein-bound drug. Most drugs exhibit some degree of plasma or tissue protein binding. Extensive protein binding can prolong the biological half-life of a drug, potentially reducing the need for a sustained-release formulation. Thus, protein binding characteristics must be carefully evaluated during formulation development.

6) Molecular size and diffusivity

In matrix-based sustained-release systems, drug molecules must diffuse through a polymeric matrix or membrane. Diffusivity is inversely related to molecular size, meaning that larger molecules diffuse more slowly through polymer networks. Molecular weight therefore plays a significant role in determining the diffusion coefficient of the drug within the matrix.

7) Margin of safety

The safety of a drug is largely determined by its therapeutic index. Drugs with a wide therapeutic index are safer and more suitable for sustained-release formulations. In contrast, drugs with a narrow therapeutic index pose a higher risk of toxicity and are generally unsuitable for oral sustained-release drug delivery systems.[7,12,13,14]

PHYSICOCHEMICAL FACTORS INFLUENCING RELEASE FROM MATRIX TABLET:

a) Dose size

In general, a single oral dose containing 500 mg to 1.0 g of drug is considered the upper limit for conventional dosage forms, and the same principle applies to sustained-release formulations. Drugs requiring very large doses may not be suitable for matrix-based sustained-release systems unless administered in divided doses or formulated using alternative delivery approaches. The margin of safety of the drug is also an important consideration when selecting dose size.

b) Ionisation, pKa and aqueous solubility

Most drugs are weak acids or weak bases. Only the unionised form of a drug can readily permeate lipid membranes, making the relationship between drug pKa and the pH of the absorption environment critically important. Although the unionised form enhances membrane permeation, it often exhibits reduced aqueous solubility. Sustained-release systems that depend on diffusion or dissolution are therefore strongly influenced by the drug's solubility in aqueous media. Since these dosage forms function across regions of varying pH within the gastrointestinal tract, the effect of pH on drug release must be well characterised. Poorly soluble drugs (<0.01 mg/ml) often exhibit inherently sustained release due to dissolution-limited absorption, whereas highly soluble drugs may require release-retarding excipients to control diffusion.

c) Partition coefficient

For a drug administered orally to exert systemic effects, it must cross several biological membranes. As these membranes are largely lipid in nature, the partition coefficient of the drug plays a key role in determining membrane permeability. Drugs with high partition coefficients are typically lipophilic, poorly water-soluble, and may accumulate in fatty tissues, resulting in prolonged retention. Conversely, drugs with very low partition coefficients may show inadequate membrane penetration and reduced bioavailability. Partitioning behaviour also affects diffusion through polymeric membranes, influencing the selection of appropriate matrix-forming materials.

d) Stability

Orally administered drugs may undergo degradation through acid–base hydrolysis or enzymatic processes. Drugs formulated in the solid state generally exhibit slower degradation rates and are therefore preferred for sustained-release delivery. For drugs unstable in gastric conditions, dosage forms designed to delay release until reaching the intestine can improve bioavailability. However, drugs unstable in intestinal environments may demonstrate reduced bioavailability when administered via sustained-release systems due to prolonged exposure to degrading conditions.[7,8,10,12]

PROCESS

A) Diffusion sustained systems

Diffusion-based sustained-release systems rely on the movement of drug molecules from regions of higher concentration to lower concentration. According to Fick's law, the flux (J) of drug across a membrane is expressed as:

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

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

When a water-insoluble membrane surrounds a drug core, drug molecules must diffuse through the membrane to reach the surrounding medium. The drug release rate (dm/dt) can be expressed as:

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

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

i) Diffusion reservoir system

In diffusion reservoir systems, a drug core is surrounded by a water-insoluble polymeric membrane. Drug molecules partition into the membrane and diffuse outward into the surrounding medium. As drug is released, additional molecules from the core diffuse into the membrane, maintaining sustained drug release through a diffusion-controlled mechanism.

ii) Diffusion matrix system

In matrix systems, solid drug particles are uniformly dispersed within an insoluble matrix. Drug release depends on both diffusion through the matrix and dissolution of drug particles. Higuchi derived an equation describing drug release from such systems:

$Q = (D/\tau) [2A - Cs] Cs\ t^{1/2}$

where Q is the amount of drug released per unit area at time t, D is the diffusion coefficient, τ is tortuosity, ε is porosity, Cs is drug solubility, and A is the initial drug concentration. Drug release rate may also be expressed as:

Release rate $= AD/L (C_1 - C_2)$

where C_1 and C_2 are drug concentrations in the core and surrounding medium, respectively.

B) Dissolution sustained systems

Drugs with inherently slow dissolution rates may exhibit sustained-release properties without additional formulation modifications. For highly soluble drugs, dissolution can be slowed by forming less soluble salts or derivatives. Dissolution-controlled systems are commonly employed in enteric-coated dosage forms, where drug release is prevented in acidic gastric conditions and initiated in the more alkaline intestinal environment.

a) Soluble reservoir system

In this approach, drug particles are coated with an erodible layer that gradually dissolves in gastrointestinal fluids. Drug release occurs as the coating erodes, allowing sustained delivery over time.

C) Methods using ion exchange

Ion exchange resins offer an effective approach for sustained drug delivery, as drug release is largely governed by the ionic environment rather than enzymatic activity or pH variations. These systems are particularly useful for drugs susceptible to enzymatic degradation. Ion exchange resins may be classified as:

- **Cation exchange resins:** Contain acidic functional groups
- **Anion exchange resins:** Contain basic functional groups

Drug–resin complexes form insoluble polyelectrolytes that release the drug upon exposure to gastrointestinal fluids through ion exchange reactions.

D) pH-independent formulations

Drug release from sustained-release systems is often influenced by gastrointestinal pH variations. To minimise pH dependency, buffering agents such as citric acid, phosphoric acid, or amino acid salts may be incorporated into the formulation. These agents maintain a constant microenvironmental pH within the dosage form, enabling uniform drug release throughout the gastrointestinal tract.

E) Altered density formulations

Altered-density dosage forms are designed to prolong gastric residence time.

- **High-density systems:** Prepared using heavy materials such as barium sulphate or iron powder to ensure retention in the stomach.
- **Low-density systems:** Designed to float on gastric fluids using low-density carriers and polymer coatings, allowing prolonged drug release while remaining buoyant.[15–18]

POLYMERS USED IN TABLET:

A wide variety of polymers are employed in the formulation of tablets to achieve controlled and sustained drug release. The selection of polymer depends on factors such as drug properties, desired release profile, and route of administration. These polymers are broadly classified as follows:

Hydrogels

Hydrogels are three-dimensional polymeric networks capable of absorbing significant amounts of water while maintaining structural integrity. Upon hydration, they swell and form a gel barrier that controls drug diffusion. Commonly used hydrogel polymers include polyhydroxyethyl methacrylate (PHEMA), cross-linked polyvinyl alcohol (PVA), cross-linked polyvinyl pyrrolidone (PVP), polyethylene oxide (PEO), and polyacrylamide (PA).

Soluble polymers

Soluble polymers dissolve gradually in gastrointestinal fluids, contributing to drug release through polymer dissolution and diffusion mechanisms. Examples include polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), and hydroxypropyl methylcellulose (HPMC).

Biodegradable polymers

Biodegradable polymers undergo degradation within the body through enzymatic or hydrolytic processes, producing non-toxic by-products that are eliminated via normal metabolic pathways. Common biodegradable polymers include polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), polyanhydrides, and polyorthoesters.

Non-biodegradable polymers

These polymers remain structurally intact during drug release and control drug diffusion without undergoing degradation. Examples include polyethylene vinyl acetate (PVA), polydimethylsiloxane (PDS), polyetherurethane (PEU), polyvinyl chloride (PVC), cellulose acetate (CA), and ethyl cellulose (EC).

Mucoadhesive polymers

Mucoadhesive polymers enhance drug residence time at the site of absorption by adhering to mucosal surfaces. These polymers improve bioavailability and prolong drug action. Examples include

polycarbophil, sodium carboxymethyl cellulose, polyacrylic acid, tragacanth, methylcellulose, xanthan gum, guar gum, karaya gum, and locust bean gum.[2,3,9,20]

KINETICS OF DRUG RELEASE[2,21]

Understanding drug release kinetics is essential for characterising sustained-release dosage forms and predicting in-vivo performance.

Zero-order kinetics

Zero-order release describes a system where drug release occurs at a constant rate, independent of drug concentration. This can be represented by the equation:

$$Wo - Wt = K_0 t$$

where Wo is the initial amount of drug, Wt is the amount of drug released at time t, and K_0 is the zero-order release rate constant. A linear plot of cumulative percentage drug released versus time indicates zero-order kinetics. This release profile is considered ideal for maintaining prolonged therapeutic activity.

First-order kinetics

In first-order kinetics, the rate of drug release depends on the concentration of drug remaining in the dosage form and is expressed as:

$$\text{Log } Qt = \text{Log } Q_0 - (K_1 t / 2.303)$$

where Qt is the amount of drug released at time t, Q_0 is the initial amount of drug, and K_1 is the first-order release rate constant. A straight-line relationship is obtained when log cumulative percentage drug remaining is plotted against time.

Korsmeyer–Peppas model

The Korsmeyer–Peppas model is a semi-empirical equation used to analyse drug release from polymeric systems when the release mechanism is not well defined or involves more than one process. The equation is given by:

$$At / A\infty = k\, t^n$$

where $At/A\infty$ is the fraction of drug released at time t, k is a kinetic constant, and n is the release exponent that indicates the mechanism of drug release.

Higuchi model

Higuchi described drug release from matrix systems based on diffusion principles. The Higuchi equation is expressed as:

$$Q = K_H\, t^{1/2}$$

where Q is the amount of drug released at time t and K_H is the Higuchi dissolution constant. A linear relationship between cumulative drug release and the square root of time indicates diffusion-controlled release.[2,21]

EVALUATION TEST FOR SUSTAINED RELEASE TABLETS

Weight variation

Twenty tablets from each formulation batch were weighed individually and collectively using a calibrated analytical balance. The average tablet weight was calculated, and individual tablet weights were compared with the average to ensure compliance with pharmacopeial limits.

Hardness

Tablet hardness was determined using a Monsanto hardness tester. Tablets from each batch were tested, and the mean hardness value was calculated to ensure adequate mechanical strength for handling and transportation.

Friability

Friability testing was carried out using a Roche friabilator operated at 25 rpm for 4 minutes. Tablets were weighed before and after the test, and the percentage weight loss was calculated to assess resistance to abrasion.

Thickness

Tablet thickness was measured using a micrometre screw gauge. Uniformity of thickness ensures consistent tablet dimensions and contributes to dose uniformity.

Content uniformity

The drug content of tablets was analysed using a UV–Visible spectrophotometer. The amount of drug present in each tablet was calculated from a previously prepared calibration curve to confirm uniform distribution of the active ingredient.

IN-VITRO DISSOLUTION STUDY

In-vitro drug release studies were performed using a rotating paddle dissolution apparatus. An appropriate buffer solution was used as the dissolution medium, and the temperature of the dissolution bath was maintained at 37 ± 0.5°C. Samples were withdrawn at predetermined time intervals, and an equal volume of fresh dissolution medium was added to maintain sink conditions. The withdrawn samples were analysed using a UV–Visible spectrophotometer. The cumulative percentage of drug released was plotted against time to evaluate the release profile of the sustained-release matrix tablets.

SHORT-TERM STABILITY STUDY

Short-term stability studies were conducted to evaluate the effect of storage conditions on the in-vitro drug release profile of the optimised formulation. Tablets were stored under specified conditions for a defined period, after which dissolution studies were repeated to determine any changes in drug release behaviour.[22,23,24]

CONCLUSION

This review article highlights the principles and approaches involved in the formulation of sustained-release matrix tablets. Matrix-based systems offer an effective means of controlling drug release, improving patient compliance, and enhancing therapeutic efficacy, particularly in the management of chronic diseases. The simplicity of formulation, cost-effectiveness, and ability to achieve once-daily dosing make matrix tablets a preferred choice among sustained-release dosage forms. Overall, sustained-release matrix tablets represent a promising strategy for optimising oral drug delivery and improving clinical outcomes.

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