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Review Article

A Comprehensive Review on Sustained Release Matrix Drug Delivery System

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Abstract



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Formulations for sustained medication release are very useful in the treatment of chronic disorders. The oral route has selected matrix tablets as the most likely type of prolonged drug release. In order to generate therapeutic activity for a protracted duration, matrix tablets maintain a stable plasma drug concentration and sustain the rate of release of the drug throughout time. In preparations with a short half-life and high dosage frequency, extended-release is crucial. The matrix regulates how quickly the medication is released. Retardants such polyglycolic acid, polymethyl methacrylate, and hydroxypropyl methylcellulose (HPMC) are used. The retardant's matrix core contains the medication. The matrices employed can be mineral-based, hydrophobic, or biodegradable. Drug release is regulated in matrix tablets that can be made using wet granulation or direct compression techniques by the use of various kinds of polymers. Drug release from matrix tablets is controlled by both diffusion- and dissolution-controlled process. As a result, matrix tablets increase therapeutic efficacy while reducing the frequency of drug administration and increasing patient compliance.

Keywords: Sustained release, Matrix Tablets, HPMC, Retardants, Biodegradable

Introduction

Oral dosage forms with modified release properties have been referred to by a variety of names, include regulated or postponed release, protracted release, repetitive action, sustained release, and extended release, and others. Every drug delivery method aims to stop the periodic fluctuations in the concentration of drug in the plasma that follow administration of traditional delivery methods¹.

Dose formulations with a modified release^{1,2}: This term is used to describe drug dosage forms that have different course or location characteristics for drug release in order to achieve therapeutic and practical goals that traditional dosage forms do not.

Controlled release- When administered, the medication is delivered with zero-order rate, and the concentration measured is not affected by the passage of time.

Delayed-release: To deliver the medicine gradually, a delayed dose form is created after administration rather than right away.

Extended-release: A dosage form that permits a lower dosing frequency than that offered by a normal dosage form is referred to as an extended-release dosage form.

Prolonged-release: These medications come in a dosage form that allows for longer-term absorption than a typical dosage form.

Repeat action: The first dose is given shortly after ingestion, and then a second or third dose is delivered intermittently after that.

Sustained-release: The delivery mechanism controls the rate at which this medication is released into the body.

The best commercially available sustained action medications are sustained release matrix tablets since they can accept huge drug doses and don't require specific production processes. The innovative drug delivery system (NDDS) that significantly increases the therapeutic efficacy of pharmaceuticals is medication delivery method using a sustained-release matrix. There is still interest in creating new matrix-based formulations that enable sustained drug release utilising easily available, affordable excipients³. Sustained medication levels in plasma were supplied by the sustained-release dose form, usually eliminating the need for nighttime administration, which is advantageous for both the patient and the caregiver. The sustained-release formulation provides an immediate release of a medication that has the intended therapeutic outcome. In the pharmaceutical sector, sustained-release oral medication delivery technologies are gaining popularity. Additionally, there is a lot of interest in creating a dosage form that permits substantial drug loading, especially for

medications which is very water soluble. The least processing variable-containing prolonged action dosage form is thought to be matrix tablets from a commercial standpoint ^{4,5}.

Category of Matrix Tablets:

Tablets made by Matrix are categorised as; ^{6,7}

Based on the application of retardant materials:

The five following types of matrix tablets fall within this category:

- Water-repellent matrix
- Lipid matrix
- Water-loving matrix
- Material biodegradable

Hydrophobic Matrices (Plastic matrices)^{8,9}

The medication is combined using an inactive and/or water repellent polymer in this approach to generate a sustained-release oral dosage form, which is subsequently crushed into a tablet. The medication that is dissolving has dispersed using a system of channels that remain among tightly packed polymer particles, resulting in sustained release. Polyethylene, PVC, and acrylate polymers, as well as their copolymers, are examples of hydrophobic matrices. The rate-regulating stage in the procedure involves the matrix's fluid being absorbed. Diffusion is the method of the medicine's unique form of tablet release mechanism. Some varieties of matrix tablets become inert when exposed to water and gastric fluid.

Lipid matrices:

Lipid waxes and other similar substances are used to create these matrices. Such materials allow for the release of drugs via erosion and pore diffusion. As a result, release properties are much careful to the makeup of digestive juice than polymer matrices which is fully insoluble.

Hydrophilic matrices:

A hydrophilic polymer is used to correctly integrate one or more medicines into a matrix (gelling agent). Due to its effectiveness in achieving a desired drug release profile, affordability, and broad regulatory acceptance, water-loving polymer matrices are frequently employed in oral controlled drug delivery. Based on the types of polymers utilised, these matrices are further categorised into three classes.

• Cellulose derivatives:

HPMC 100, HEC, and SCMC are the polymers employed in the formulation.

• Natural/semi-synthetic polymers that are not cellulose:

Acrylic acid polymers: Carbopol-934 is the most frequently used polymer in this group.

• Matrices that biodegrade:

These polymer contents are made up of single units and operational groupings that are interdependent upon each other, and their backbones have unstable linkages. These are biologically broken down into oligomers and monomers that can be digested or released by non-enzymatic processes or by enzymes that are released into the vicinity of living cells. Examples include natural polymers like proteins and polysaccharides that have been changed.

Mineral matrices:

Polymers derived from various seaweed species are present in mineral matrices. Mineral matrices include hydrophilic

carbohydrates like alginic acid, which can be produced from some types of brown seaweed using diluted alkali.

Depending on the matrix's porosity:

This results in persistent release of the medicine as the drug molecules disperse throughout the matrix.

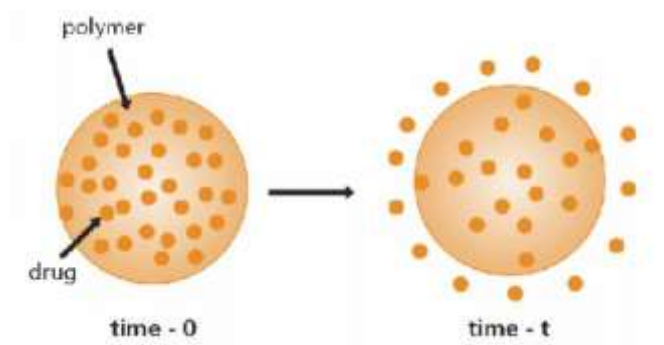


Figure 1: Drug Diffusion throughout the Matrix¹⁰

Three different categories are added to the matrix.

a) Systems with macropores

This type of matrix has pores that are between 0.1 and 1 m in size, which is larger than diffusion molecules. Through these pores, the medication permeates this type of system.

b) Systems with micropores

Medicinal molecules pass through holes about 50–200 nm in diameter.

c) Systems without pores

No pores exist in these systems. Molecular diffusion takes place through network meshes.

Where the polymeric phase is present, there is no pore phase.

The following serve as justifications for creating the SR matrix DDS ¹¹

- To lessen dose intervals,
- In order to lessen plasma level swings,
- Increased drug usage,
- Fewer negative impacts,

Sustained Release Matrix Tablet Benefits:

- Simple to produce.
- Flexible, efficient, and reasonably priced.
- The longer therapeutic concentrations may be maintained by the sustained-release formulations.
- Utilizing formulations with a sustained release prevents high blood concentration.
- Formulations with sustain release still have the potential to increase patient compliance. Drug absorption can be slowed to lessen toxicity.
- Boost the drug's stability by shielding it from the gastrointestinal tract's hydrolysis or other derivative modifications.
- Reduce the negative local and systemic consequences.
- A rise in therapeutic effectiveness.
- Reduce medication build up with long-term dosage.

- The use the few potent medication

Sustained Release Matrix Tablet drawbacks include:

- Once the medication has been released, the residual matrix should be eliminated.
- The hefty price of planning.
- The rate of transit through the stomach and other components, including food, have an impact on the release rates.
- The square root of time causes a difference in the medication release rates.

Polymers Used in Matrix Tablet:

Hydrogel:

Polyethylene Oxide (PEO), Cross-linked Polyvinyl pyrrolidone (PVP), Polyvinyl Alcohol (PVA), Polyhydroxyethyl methyl acrylate.

Soluble polymers

PEG, PVA, PVP, and HPMC (HPMC)

Biologically based polymers

PGA, PCL, polyanhydrides are examples of polymers.

Non-biodegradable polymers

Cellulose acetate (CA), Polyvinyl chloride (PVC), Polyether urethane (PEU), Polydimethylsiloxane (PDS), Polyethylene vinyl acetate (PVA), and Ethylcellulose (EC)

Mucoadhesive polymers

SCMC, Tragacanth.

Natural gums

Xanthan gum

Qualities of a Perfect Polymer:

- It needs to be adaptable and have a variety of properties that are structural, physiological, and molecular.
- Non-poisonous, possess strong mechanical power, and be simple to use.
- It should be affordable and simple to make.
- It must be environmentally friendly and inert to host tissue.

Guidelines for Polymer Selection:

- The polymer needs to simple to synthesise and soluble.
- It ought to have a set number of molecules.
- It ought to be suitable for the biological setting.
- It ought to decompose naturally.
- It ought to offer strong interaction in drug and polymer.

Features of a medication suitable for sustained-release tablets: ¹²

- The extended-release tablet should conform to the optimal pharmacokinetics and physiological standards, which is as follows:
- Atomic size must be less than a thousand Dalton.

- The method of absorption must be diffusion, and pH and catalysts must not have an effect on the general absorbability of all GI fragment discharge.
- The elimination half-life should be 2 to 8 hours.
- Drugs shouldn't metabolise in the presence of absorption because this lowers their bioavailability.
- Absolute bioavailability should be at least 75% and preferably higher.

Matrix Tablet Preparation Process^{13, 14}

1. Wet Granulation Technique

- Grinding and gravity blending of the excipients, polymer, and medication.
- Making the binder mixture.
- Wet massing with the inclusion of a granulating or binder solution.
- The filtration of moist matter.
- The wet grains are dried.
- Dry granule screening.
- Dissolving and stirring via emollient to create "running powder"
- The tablet has been compressed.

2. Dry Granulation Method

- Grinding and gravitational stirring of excipients, polymer, and drugs
- Slug compaction or roll compaction
- Grinding and screening of compacted powder and slugs
- Disintegrating after lubricant mixing
- The tablet has been compressed.

3. Sintering Method

- Sintering is the process through which nearby particle surfaces come together to form a powdery mass.
- Traditionally, sintering involves heating at a reduced temperature of the solid material.
- As a result of sintering, a change in the hardness and duration of tablet disintegration at high temperatures was described.
- In order to stabilize and delay the release of the medicine, sustained release matrix tablets are made using the sintering method.

Design Considerations for Dosage Forms¹⁵

The design of the dosage form is principally influenced by two different types of elements. They are broken down into:

1. Biological factors

- First-pass effect:** Drugs with a significant first-pass impact show a delayed release rate. The bioavailability is impacted by this delayed release rate.
- Half-life:** A drug's half-life is a measurement of how long it stays in the body. A excessively high concentration of medicine may be present in the dosing method if the substance has a short half-life of less than 2 hours. On the other hand, when given in conventional doses and using continuous drug delivery systems, a medication with a

half-life of removal of 8 hrs is properly maintained in the body.

- c. **Adverse effects:** Extending the medication release could result in undesired side effects.
- d. **Absorption and solubility:** absorbency and soluble both are related. Drugs that are less water soluble can reduce the effectiveness of absorption overall.
- e. **Metabolism:** Drugs that are extensively processed either in the intestine's lumen or tissue prior to absorption may have decreased bioavailability when taken in slower-releasing dose forms. It is possible to construct a medicine in a sustained release dosage form even if it has a poor ability to disintegrate; however, the drug's solubility first needs to be enhanced using the proper technique before formulation. However, since the medication is permitted to circulate throughout the body, crystallisation of the drug is occurring during this time and should be avoided at all costs.

2. Physiochemical Factors

- a. **Drug stability:** medicine leakage in the digestive system due to acidic digestion and/or acidic breakdown is a crucial factor in oral dose formulations. Drugs degrade in solid states much more slowly than they do in suspended or solution states. A control device that only activates its material in the intestines would be the most efficient. It is feasible to considerably increase the a measure of bio-availability of a medicine that is poisonous in the stomach.
- b. **Aqueous solubility & pKa:** A medicine that will be soak up, dissolved, and partitioned into the absorbing membrane within water-phase close to the administration site's route. The water solubility and, if the drug is a soft acid, the pKa of the drug are two of the most significant physicochemical characteristics that influence its absorption activities. Controlled release techniques are successful because of these characteristics. Drugs with high aqueous solubility degrade slowly and frequently experience problems with oral bioavailability.
- c. **Partition Coefficient:** It refers to how much medicine is present compared to the water phase, in the organic phase. Because They won't be leaving the phospholipid membranes through partitioning once they enter it, drugs with greater partition co-efficients are not suited for oral SRDDS. By using the formula, it may be determined.

$$K = C_o / C_w$$

C_o = Conc. at eq^m. in the oil phase.

C_w = Conc. in water phase at equilibrium.

- d. **Diffusivity and molecular size:** The form and size of the membrane cavities affect the diffusivity. The flexible polymer array contributes to the 100–400 Daltons, or 10–6–10–9 cm²/sec, drug diffusion coefficient for intermediate molecular weight drugs. For medications with molecular weights greater than 500 Daltons, many polymers have very low diffusion coefficients, or less than 10–12 cm²/sec. Medicines those are challenging to regulate degrees of medication distribution from the dose form include proteins and peptides.

Drug Release Mechanism from Matrix Devices: 16

1) Controlled release for dissolution:

Dissolution is used as the time-limiting phase in oral medication formulations for sustained release, making them the easiest to create. It is conceivable to combine a medicine

with a quick rate of disintegration into a tablet with a slow-dissolving carrier. The rate-limiting stage in The diffuse layer relates to how the medication diffuses across an unaltered fluid layer from the solid object to the bulk solution. The Noyes-Whitney equation will be used in this instance to describe the dissolution process at steady state.

$$dc/dt = KDA (C_s - C) \text{ ----- (1)}$$

Encapsulation dissolution control:

This technique entails covering individual medication granules or particles with a slowly disintegrating substance. The covered particles may either be immediately compacted within tablet, as with Spacelab's, or put into capsules, as with goods made with spansules.

Matrix dissolution control:

In this procedure, the medicine is compressed into a tablet shape with a carrier that readily dissolves. The tablet's matrix's porosity, the presence of hydrophilic molecules, and the tablet and particle surfaces' wettability can all affect how quickly a drug becomes available by regulating how quickly the dissolution fluid penetrates the matrix.

(a) Matrix system, and

(b) Coated/encapsulated system

2) Diffusion-controlled release systems come in two different varieties:

(a) Control of encapsulation diffusion

A core of the medicine is enclosed in a water-insoluble polymeric substance in this arrangement. Drugs will interchange along with liquid around the pill or powder after partitioning into the polymer membrane.

The equation provides the rate of medication release..

b. Matrix diffusion control

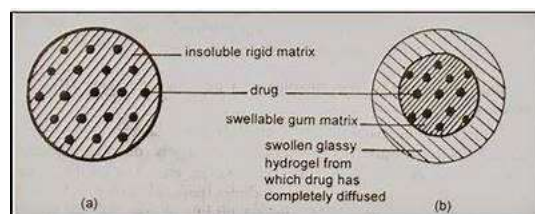


Figure 3: shows diffusion-controlled devices with rigid and swellable matrixes, respectively¹⁷

Strategies for Oral Sustained Release Formulation:

- Sustained Method Diffusion Release
- Dissolution and Continuous Release
- System Dependent on pH
- System of Alternate Density
- System for osmotic pumps
- Ion Exchange System

Diffusion sustaining system types:

- elastic matrix
- Laminate/Reservoir matrix.

Dissolution maintained system types:

- System for Matrix Monolith Dissolution.
- Capture, Coating, and Reserve System.

Affected density system types:

- Higher-DensitySystem.
- Lower-Density System.
- Muco Adhesive System

Assessment of Sustained-Release Tablets:

The development of IVIV studies, as well as the connection between the two, is required for the sustained-release product in order to guarantee the product's durability, safety, stability, and dependability.

Evaluation criteria have been discussed as follows:

1. *In-vitro* Methods

- Beakertechnique
- Rotatingdisc procedure
- RotatingBottle technique
- RotatingBasket technique
- StationaryBasket technique
- Oscillatingtube process
- Dialysisprocess
- USPdissolution technique.

2. *In-vivo* Methods

After obtaining the appropriate in-vitro profile, it is need to develop an in-vivo assessment and IVIVC.

The different in-vivo evaluation techniques include:

- Clinicalreaction
- Bloodlevel information
- Blood level information
- Nourishing research,
- Toxicology research
- Radioactive tracer technique

3. Stability Studies

In order to assure the potency, clarity, authenticity, quality, security, and IVIV releasing speeds which they state to the time of consumption, sufficient stabilization statistics of the medication and its dosage form are necessary. Also, the SR medication must deliver a constant amount of the medication at regular intervals, and this amount must not change while being stored. The in-vitro and in-vivo release rates of the SR medication can be influenced by acceleration or climatic factors like temperature and moisture. The stabilization programmer of a sustained-release product is kept at situations that are both standard and rapid of temperature and moisture to make that the material can withstand these circumstances.

Bioavailability Testing:

The phrase "bioavailability" refers to a particular medication moiety, typically an active pharmaceutical ingredient, which could be the medication as-is or a metabolite, as with prodrugs, for example. The word "absorption" is frequently used to describe the net movement of drug-related material from the place of administration into the body. Therapeutic dosage form optimization may be necessary to advanced the drug's absorption properties and, consequently, its bioavailability. Bioavailability studies typically compare the tested medication product at a single dose in healthy people who are fasting.

Conclusion:

The composition of long-lasting matrices pills, their benefits and drawbacks, and the different polymers employed to create a method were the main topics of this review paper. The conclusion of the discussion above is that the matrix tablets are useful in overcoming patient compliance issues and dosage form efficiency issues that are related to conventional dosage forms' inability to produce the required therapeutic response. Along with other advantages, cost-efficient and a single or every day intake are the pluses. As a result, the dosage form design is being optimised for sustained release matrix tablets.

Conflict of Interest

The authors have no conflict of interest.

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