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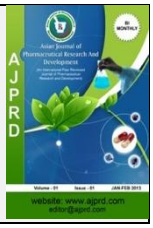

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Review Article

Sustained Release Matrix Tablet: An Overview

Mandev Mehta*, H.S Keerthy, Rajkumar Prasad Yadav

Department of Pharmaceutics, Mallige College of Pharmacy, Bangalore-560090, Karnataka, India

A B S T R A C T

Sustained Release is also a promising method for reducing medication side effects by preventing the therapeutic concentration of the drug from fluctuating in the body. The basic rationale of a sustained drug delivery system is to optimise a drug's biopharmaceutical, pharmacokinetic, and pharmacodynamic properties in order to maximise utility, minimise side effects, and cure the disease. The drug release rate is regulated by the matrix. HPMC and other release retardants can help with sustained release, so they are used as a key excipient in the formulation. The method entails compressing a mixture of medication, retardant material, and additives directly to shape a tablet with the drug embedded in a retardant matrix core; instead, granulation may be done prior to compression. Hydrophilic, hydrophobic, mineral, and biodegradable matrices may be used. To assess the drug release rate, in-vitro dissolution tests may be used. The primary goal of continuous release types is to improve drug therapy, which is determined by the relationship between the advantages and disadvantages of using one.

Keywords: Sustained release, Mechanism of drug release, Matrix tablet, Drug properties

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***Address for Correspondence:**

Mandev Mehta, Department of Pharmaceutics, Mallige College of Pharmacy, Bangalore-560090, Karnataka, India

INTRODUCTION

Sustained-release pharmaceuticals have become a very valuable tool in medical practice, providing patients with a wide variety of real and perceived benefits. Sustained release is also a promising way to reduce medication side effects by stopping the therapeutic concentration of the drug in the body from fluctuating. The traditional dosage types of drugs are increasingly being phased out in favor of modern and innovative drug delivery systems .In modern therapeutics, the controlled release/sustained release dosage forms have become extremely popular. The matrix system is a release system that prolongs and controls the release of a drug that has been dissolved or dispersed.[1]The oral route is the most common route for drug administration, owing to its ease of use and the fact that it is the least expensive. The term "Drug Delivery" encompasses a wide range of techniques used to deliver therapeutic agents into the human body. Drug administration's ultimate goal is to cure patient illnesses. Drugs are never given in their pure form; instead, they are transformed into a suitable formulation.[3]Sustained-release dosage forms are designed to release a drug at a fixed rate while retaining a constant drug level for a set period of time with the least amount of side effects. The basic premise of a controlled release drug delivery system is to maximize a drug's utility by optimizing its biopharmaceutical, pharmacokinetic, and pharmacodynamic properties, side effects are eliminated, and the disease is cured or controlled in the shortest time possible by using the smallest amount of medication delivered by the most appropriate route.[4]

Sustain release:

Sustained-release pharmaceuticals have become a very valuable tool in medical practice, providing patients with a wide variety of real and perceived benefits.

Oral sustained-release matrix dosage type objectives:

- To maintain a constant drug concentration for a specified period of time.
- As opposed to traditional drug forms, to minimize the number of doses administered.
- It should carry the active ingredient directly to the site of action, with minimal or no side effects.

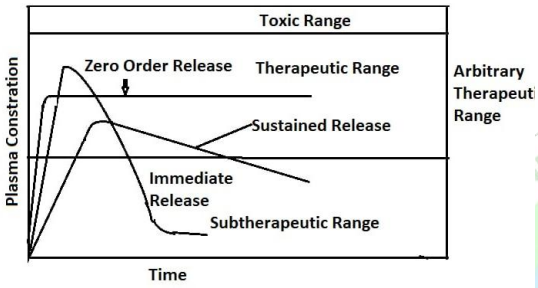
- This may necessitate targeting specific receptors or localization to specific cells or body regions.
- Potent drugs' safety margins can be improved.
- In sensitive patients, the incidence of both local and systemic adverse side effects can be reduced.

Advantages

- Intakes are being reduced in frequency
- Side effects should be minimised.
- Drug release that is consistent over time.
- Patient compliance is improved.

Disadvantages

- It does not allow for a quick end to therapy
- Dose change versatility is restricted.
- The average biological half-life is used to design these dosage types.
- They are pricey.



Classification of sustained release drug delivery system[1,3]

Classification of oral Sustained or Controlled Release Systems The controlled release systems for oral use are mostly solids and are controlled by dissolution, diffusion, or a combination of both mechanisms. Based on how drugs are published, these systems are listed as follows:

1. System of continuous release
2. Mechanisms of delayed transit and continuous release
3. Systems with a delayed release

1. Continuous release systems:

Through standard transportation of the dosage type, continuous release systems release the drug for a prolonged period of time over the entire length of the gastrointestinal tract. The following are the different systems that fall into this category**:**

a. Diffusion controlled release systems
b. Dissolution controlled release systems
c. Dissolution and diffusion controlled release systems
d. Ion exchange resin- drug complexes
e. pH-independent formulation
f. Osmotic pressure controlled systems.

a. Diffusion controlled release systems:

The rate-limiting step in these systems is the diffusion of dissolved drug through a polymeric barrier. Since the diffusional path length increases over time as the insoluble matrix is steadily depleted of drug, the drug release rate is never zero-order. The regulated drug delivery systems are based on the diffusion of a drug molecule through a polymeric membrane.

b. **Dissolution-controlled release systems:**

Dissolution-controlled release can be achieved by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer, and coating drug particles or granules with polymeric materials of varying thicknessThe rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the substance provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer. The following equation can be used to approximate the rate of dissolution (dm/dt):

dm/dt = ADS/h…….(1)

Where,

A = Surface area of the dissolving particle or tablet

D = Diffusivity of the drug S = Aqueous solubility of the drug

h = Thickness of the boundary layer

The two types of dissolution-controlled release are:

Matrix (or monolith) dissolution controlled systems

The medication is suspended in an insoluble matrix of swellable hydrophobic or hydrophilic materials.

Reservoir dissolution controlled systems

This mechanism is hollow, with an inner drug core encased in a water-insoluble polymer membrane.

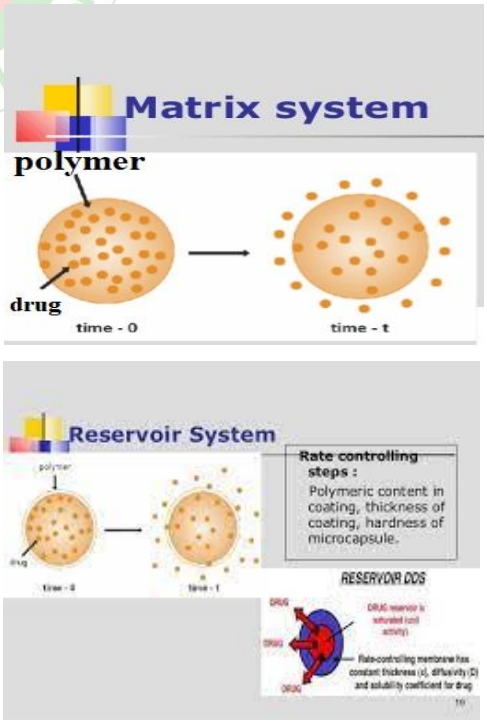


Figure 2: Matrix system and Reservoir system

c. Dissolution and diffusion controlled release systems

The drug centre is encased in a partially soluble membrane in such systems. Pores are formed when sections of the membrane dissolve, allowing aqueous medium into the centre and thus drug dissolution, as well as the diffusion of dissolved drug out of the system.

d. Ion exchange resin-drug complexes:

It is based on the formulation of a drug-resin complex that forms when an ionic solution comes into contact with ionic resins. The drug in this complex is exchanged in the gastrointestinal tract and released when there is an excess of Na+ and Cl present in most cases, an insoluble cross linked polymer resin is used in this system. They have a salt-forming function group in a polymer chain that repeats.

e. pH-independent formulation:

Because the majority of drugs are weak acids or bases, their release from sustained release formulations is pH-dependent. However, a buffer can be added to the formulation, such as citric acid salt, amino acid, or tartaric acid, to help maintain a constant pH by delaying pH-dependent drug release. Mixing a simple or acidic drug with one or more buffering agents, granulating with sufficient excipients, and coating with gastrointestinal fluid permeable film forming polymer results in a buffer retain release formulation. As gastrointestinal fluid passes through the membrane, the buffering agent changes the pH of the fluid within, resulting in a steady rate of drug absorption release.

f. Osmotic pressure controlled systems:

A semipermeable membrane is placed around the tablet, particle, or drug solution to allow water to enter the tablet, with drug solution eventually being pumped out through a small delivery aperture in the tablet centered. The following are two types of osmotic pressure-controlled systems: a. With drug b, Type 1 has an osmotic core. Type 2 contains the drug in a flexible bag with an osmotic core surrounding it. By optimising the formulation and processing factors, an osmotic system can be developed to deliver a variety of drugs at a predetermined rate.

Delayed transit and continuous release systems:

These systems are designed to keep them in the GI tract for a longer period of time after they have been written. This category includes mucoadhesive and size-based systems, which are designed to detain in the stomach and therefore contain a medication that is stable at gastric pH.

Delayed release systems:

Drug release is limited to a specific position in the GIT due to the nature of such systems. The following drugs can be contained in such a device:

- Known to cause gastric distress
- Destroyed
- Meant to extent local effect at a specific GI sit
- Absorbed from a specific intestinal site The two types of delayed release systems are:
- Intestinal release systems
- Colonic release systems.

Various Mechanisms of Medicament Release[1]

1.Diffusion is rate limiting:

Diffusion is the process by which drug molecules travel from a high concentration in the tablet to a lower concentration in the gastro intestinal fluids. This movement is determined by the amount of surface area exposed to gastric fluid, the diffusion pathway, the drug concentration gradient, and the system's diffusion coefficient. We may use any of the two approaches in operation.

The drug is formulated in an insoluble matrix:

The drug is released through diffusion after the gastric fluid penetrates the dosage form and dissolves the medication**.**

The drug particles are coated with a given thickness polymer, allowing a portion of the drug to slowly diffuse through the polymer and retain a constant drug level in the bloodstream.

Dissolution is rate limiting:

Drugs with low water solubility (BCS class II and IV) have a built-in sustained release mechanism. Water-soluble medications, on the other hand. It is possible to use a water insoluble carrier to avoid drug dissolution when the drug particles are covered with this form of material, such as polyethylene glycol. Polyethylene Glycol is a type of plastic. To support delayed release, it is possible to forego the use of a disintegrating agent.

Osmotic pressure is rate limiting:

Osmosis is a process in which liquid flows from a lower concentration to a higher concentration through a semipermeable membrane that allows only liquid to pass through. The entire drug is covered with a semipermeable membrane, with a laser-cut hole on one end of the pill.

Matrix Tablets

The active and inactive ingredients in a matrix system are homogeneously dispersed and mixed in the dosage form. The matrix systems are by far the most popular oral extended release technology, and their popularity can be attributed to a number of factors. Fick's first law of diffusion governs the release of matrix type formulationsMatrix systems are commonly used to achieve long-term release. It is the release system that controls and prolongs the release of the dissolved or dispersed drug. A matrix is a well-mixed composite of one or more drugs and a gelling agent, such as hydrophilic polymersThe sustained release approach allows for therapeutically efficient accumulation in the systemic circulation over a longer period of time, resulting in greater patient compliance.

Classification of Matrix Tablets:[12]

On the Basis of Retardant Material Used: Matrix tablets can be divided in to 5 types

Hydrophobic Matrices (Plastic matrices):

In 1959, the idea of using hydrophobic or inert materials as matrix materials was introduced for the first time. The drug is mixed with an inert or hydrophobic polymer and then compressed into a tablet in this method of obtaining sustained release from an oral dosage form. The dissolving drug diffuses through a network of channels that exist between compacted polymer particles, resulting in sustained release .Polyethylene, polyvinyl chloride, ethyl cellulose, and acrylate polymers and copolymers are examples of materials that have been used as inert or hydrophobic matrices.

Lipid Matrices:

Lipid waxes and other materials were used to create these matrices. Both pore diffusion and erosion are used to release drugs from these matrices. As a consequence, the structure of digestive fluid is more susceptible to release characteristics than a completely insoluble polymer matrix. Carnauba wax has been used in several continuous release formulations in conjunction with stearyl alcohol or stearic acid retardant base.

Hydrophilic Matrices:

Because of their versatility in achieving a desired drug release profile, cost effectiveness, and strong regulatory acceptance, hydrophilic polymer matrix systems are commonly used in oral regulated delivery. The preparation of medicines in gelatinous capsules or, more often, tablets.In the field of controlled release, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest.Infecting a matrix is a well-mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are known as swellable controlled release systems. Hydrophilic matrices are made from three different types of polymers.

Cellulose derivatives
Sodium carboxy methylcellulose; Methylcellulose 400 and 4000cPs; Hydroxy ethyl cellulose; Hydroxy propyl methylcellulose (HPMC) 25, 100, 4000, and 15000cPs; and Hydroxy propyl methyl cellulose (HPMC) 25, 100, 4000, and 15000cPs

Non cellulose natural or semi synthetic polymers: Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches**.**

Biodegradable Matrices:

These are polymers that are made up of monomers joined together by functional groups and have a backbone with an unstable linkage. They are biologically degraded or eroded into oligomers and monomers that can be metabolized or excreted by enzymes generated by surrounding living cells or by no enzymatic processes. Natural polymers like proteins and polysaccharides, as well as modified natural polymers and synthetic polymers like aliphatic poly (esters) and poly anhydrides, are examples.

Mineral Matrices:

These are made up of polymers derived from different seaweed plants. Alginic acid, for example, is a hydrophilic carbohydrate derived from algae.

On the Basis of Porosity of Matrix[14]

In this the drug molecules diffuse across the matrix and produce sustained release. The matrix is further divided into 3 types.

Macro porous systems:

This type of matrix has pores that are larger than the diffusant molecule dimension, ranging from 0.1m to 1m. Drug permeation occurs through these pores in this type of system.

Micro porous systems:

Drug molecules pass into pores with diameters ranging from 50 to 200 microns.

Non-porous systems:

There are no pores in these structures. Molecule diffusion is mediated by network meshes. The polymeric phase is present, but there is no pore phase**.**

Mechanism of Drug Release from Matrix Tablet:[12]

The drug in the bathing solution-exposed outer layer dissolves first, then diffuses out of the matrix. The interface between the bathing solution and the solid drug moves toward the interior as this step progresses. The following assumptions are made during the creation of the mathematical model that will be used to explain this system:

a) During drug release, a pseudo-steady state is maintained;

b) the diameter of the drug particles is smaller than the average distance of drug diffusion through the matrix.

c) The bathing solution maintains sink conditions at all times. The system's release behaviour can be mathematically explained using the equation below.

dM/dh = Co. dh - Cs/2 …… (2)

Where,

dM = Change in the amount of drug released per unit area

dh = Change in the thickness of the zone of matrix that has been depleted of drug

Co = Total amount of drug in a unit volume of matrix Cs = Saturated concentration of the drug within the matrix.

Additionally, according to diffusion theory:

dM = (Dm. Cs / h) dt..... (3)

Where,

Dm = Diffusion coefficient in the matrix.

h = Thickness of the drug-depleted matrix

dt = Change in time

By combining equation 1 and equation 2 and integrating:

M = [Cs. Dm (2Co −Cs) t] ½ …… (4)

When the amount of drug is in excess of the saturation concentration then:

M = [2Cs.Dm.Co.t] 1/2 …… (5)

The sum of drug released is related to the square-root of time in equations 3 and 4. As a consequence, if a system is primarily diffusion regulated, a plot of drug release vs. square root of time is expected to yield a straight line. A porous monolithic matrix allows drugs to be released.involves drug penetration, dissolution, and leaching out of the drug through tortuous interstitial channels and pores all at the same time. In the case of drug release from a porous or granular matrix, the volume and duration of the openings must be taken into account:

M = [Ds. Ca. p/T. (2Co – p.Ca) t] 1/2 ……. (6)

Where,

p = Porosity of the matrix

t = Tortuosity

Ca = solubility of the drug in the release medium

Ds = Diffusion coefficient in the release medium.

T = Diffusional path length

For pseudo steady state, the equation can be written as:

M = [2D.Ca .Co (p/T) t] ½ …….. (7)

The total porosity of the matrix can be calculated with the following equation:

p = pa + Ca/ ρ + Cex / ρex …… (8)

Where,

p = Porosity

ρ = Drug density

pa = Porosity due to air pockets in the matrix

ρ_{ex} = Density of the water soluble excipients

Cex = Concentration of water soluble excipients

For the purpose of data treatment, equation 7 can be reduced to:

M = k. t 1/2 …….. (9)

Where,

k = a constant, so that the amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion-controlled. The following parameters are

• Initial concentration of drug in the matrix

• Porosity

• Tortuosity

• Polymer system forming the matrix

• Solubility of the drug

Different Polymers Used in Sustained Release DDS[7]

Hydrogels: Polyhydroxy ethyl methyl acrylate (PHEMA)**,** Cross-linked polyvinyl alcohol (PVA) **,**Cross-linked polyvinyl pyrrolidone (PVP)**,** Polyethyleneoxide (PEO)

Soluble Polymers: Polyethylene glycol (PEG)**,**Polyvinyl alcohol (PVA)**,** Polyvinyl pyrrolidone (PVP), Hydroxy propyl methyl cellulose (HPMC)

Biodegradables Polymers: Polylactic acid (PLA), Polyglycolic acid (PGA)**,** Polycaprolactone (PLA)**,** Polyanhydrides

Non-Biodegradeble Polymers: Polyethylene vinyl acetate (PVA)**,**Polydimethyl siloxane (PDS)**,** Polyetherurethane (PEU)**,** Polyvinyl chloride (PVC)

Mucoadhesive Polymers: Polycarbophil**,** Sodium carboxymethyl cellulose**,** Polyacrilic acid**,** Methyl cellulose

Factor affecting of sustained release drug delivery system[1,2,6,7]

Biological Factors

Biological half-life:

Short-half-life therapeutics are ideal candidates for sustained-release formulations because they can minimise dosing frequency.

Absorption:

The absorption rate constant is a fictitious rate constant that should be the drug's release rate constant from the dosage form. Sustained-release preparations may be detrimental to absorptions if a drug is absorbed by active transport or if transport is restricted to a particular region of the intestine.

Metabolism:

Slower-releasing dosage types can have poorer bioavailability for drugs that are substantially metabolised before absorption, either in the lumen or tissue of the intestine. The majority of intestinal enzyme systems are saturable. Since the drug is released at a slower rate in these areas, there is a lower overall dose. During a particular time, the drug is exposed to the enzymatic process, allowing for a more complete conversion of the drug to its metabolite.

Distribution:

Drugs with a large apparent amount of distribution, which affects the rate of drug removal, are poor candidates for the oral SR drug delivery system, for example. Chloroquine is a medication that is used to prevent malaria.

Protein Binding:[2]

The Pharmacological response of drug depends on drug concentration drug rather than total concentration and all drug bound to some extent to plasma and or tissue proteins. Proteins binding of drug play a significant role in its therapeutic effect regardless the type of dosage form as extensive binding to plasma increase biological half-life

and thus sometimes SR drug delivery systemis not required for this type of drug.

Margin of safety:

As we all know, the higher the therapeutic index rating, the better the medication. Due to technical limitations in control over release speeds, drugs with a lower therapeutic index are typically poor candidates for formulation of an oral SR drug delivery system. 2

Physicochemical factors[2,3,6,7,8,12]

Dose Size:

A single dose of 0.5–1.0 g is generally considered the maximum for a traditional dosage type. This is also applicable in the case of long-acting medication formulations. Another factor to consider is the margin of protection that comes with administering massive doses of a medication with a limited therapeutic range.

Ionization, pKa and aqueous solubility:

The majority of medications are weak acids or bases. Since the unchanged form of a drug preferentially permeates through lipid membranes, the relationship between the compound's pKa and the absorptive environment is critical. The solubility of the drug in the aqueous media will be critical for delivery systems that depend on diffusion or dissolutionMost of the drug will arrive in the small intestine in solid form for dissolution or diffusion sustaining forms, meaning that the drug's solubility can change by several orders of magnitude during its release. The solubility of a drug formulated in a sustained release system must be less than 0.1 mg/ml, according to reports.

Partition coefficient:

Compounds with a high partition coefficient are often lipid-soluble and, as a result, have very low aqueous solubility. Furthermore, since these compounds can localise in the lipid membranes of cells, they can normally remain in the body for long periods of time.This means that the drug's solubility can change by several orders of magnitude as it is released. The solubility of a drug formulated in a sustained release system must be less than 0.1 mg/ml, according to reports.

K = C0/CW

Where,

Co = Equilibrium concentration of all forms of the drug e.g. ionized and unionized in an organic phase at equilibrium.

Cw = Equilibrium concentration of all forms in aqueous phase.

Molecular size and diffusivity:

In many sustained-release systems, drugs must diffuse through a rate-controlling membrane or matrix. The molecular size of a drug determines its ability to disperse across membranes (diffusion coefficient) (or molecular weight). The importance of diffusivity is influenced significantly. In polymers, the letter 'D' represents the diffusing species' molecular size.

Stability:

Both acid-base hydrolysis and enzymatic degradation can occur when drugs are taken orally. Systems that prolong distribution over the entire duration of transit in the GI tract are useful for drugs that are unstable in the stomach. Compounds that are unstable in the small intestine may have lower bioavailability when delivered from a sustaining dosage type.

CONCLUSION:

This review article focuses on the formulation of sustained-release matrix tablets, patient compliance, and the efficacy of the dosage form in eliciting the desired therapeutic response, as well as problems associated with traditional dosage forms. The term "sustained release" refers to a drug's gradual release over time. Sustain released formulations can be controlled or uncontrolled.

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