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Oral Sustained Release Matrix Tablets – A Review

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ABSTRACT

Sustained drug release formulations are quite helpful in treating chronic diseases. Matrix tablets have been the most likely forms of sustained drug release forms designated by the oral route. Matrix tablets work by maintaining a constant plasma drug concentration and sustains the rate of release of the drug over time and produces therapeutic action for a prolonged period. Extended-release plays an important role in formulations having a shorter half-life and high dosing frequency. The matrix controls the rate of release of the drug. Retardants like hydroxypropyl methylcellulose (HPMC), polyglycolic acid, polymethyl methacrylate are used. The drug is inserted into a matrix core of the retardant. And matrices are used may be hydrophobic, biodegradable, or mineral types. Various classes of polymers are used in controlling the release of drugs in matrix tablets which may be formulated by wet granulation or direct compression methods. The process involved in drug release in matrix tablets includes both dissolution-controlled and diffusion-controlled. Therefore, matrix tablets improve patient compliance by reducing the frequent administration of the drug and produce better therapeutic efficacy.

INTRODUCTION:

Several terms have been used to describe the oral dosage forms that represent modified release properties; such as including modified release dosage forms, controlled release, delayed-release, extended-release, prolonged-release, repeated action, sustained release, and. Each drug delivery system is focused on eliminating the cyclical changes in plasma drug concentration seen after the administration of conventional delivery systems.[1]

Modified release dosage forms: Use to describe dosage forms of drug release characteristics of course or location are chosen to accomplish therapeutic and convenience objectives not offered by conventional dosage forms.

Controlled release: The drug is released at a constant (zero-order) rate and the drug concentration obtained after administration is in-variant with time.

Delayed-release: A delayed dosage form is designed to release the drug at a time other than immediately after administration.

Extended-release: An extended-release dosage form is defined as one that allows a reduced dosing frequency to that presented by a conventional dosage form.

Prolonged-release: These drugs are provided for absorption over a longer period other than from a conventional dosage form.

Repeat action: These are individual dose is released soon after that administration, and second or third doses are subsequently released at intermittent intervals.

Sustained-release: This drug is released slowly at a rate governed by the delivery system.[2]

Sustained release matrix tablets are the best commercial affordable sustained action drugs as they can accommodate large doses of drugs, and no special requirements while manufacturing. Sustained-release matrix-type drug delivery system is the novel drug delivery system (NDDS) which plays an important role in improving the therapeutic effectiveness of the drugs. There remains an interest in developing novel formulations that allow for sustained drug release using readily available, inexpensive excipients by matrix-based formulations.[3] Sustained release tablets and capsules are taken only once or twice in a day as compared with counterpart conventional forms that may have to be taken three or four times daily to attained the same therapeutic effect. The sustained-release formulation provides an immediate release

of a drug that produces the desired therapeutic effect, the sustained release dosage form provided sustained drug levels in plasma that often eliminates the need for night dosing, which benefits not only the patients but the caregiver as well. There is a growing interest in the pharmaceutical industry for sustained-release oral drug delivery systems. Also, there is a high interest for design a dosage product that allows high drug loading, particularly for drugs with high water solubility.[4] Matrix tablets are considered to be commercially feasible sustained action dosage forms involving the least processing variables.[5]

Classification of Matrix Tablets:

Matrix tablets can be classified as; [6, 7, 8]

- **Based on retardant materials used :**

Under this category the matrix tablets are divided into 5 types:

a. Hydrophobic matrices (plastic matrices)

b. Lipid matrices

c. Hydrophilic matrices

d. Bio-degradable matrices

e. Mineral matrices.

Hydrophobic Matrices (Plastic matrices):

In this method have been obtaining sustained-release an oral dosage form, the drug is mixed with an inert and/or hydrophobic polymer and then compressed into a tablet. Sustained release is produced due to the fact of the dissolving drug has diffused through a network of channels that survive between compacted polymer particles. Hydrophobic matrices comprise polyethylene, polyvinyl chloride, ethylcellulose, and acrylate polymers and their copolymers. The rate of controlling step in these formulations is liquid penetration into the matrix. The process of the mechanism of release drug incomparable type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

Lipid matrices:

These matrices are prepared by lipid waxes and related materials. Drug release from such material occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix.

Hydrophilic matrices:

A matrix is defined as a properly mixed with combined of one or more drugs using a hydrophilic polymer (gelling agent). The hydrophilic polymer matrix is often used in oral controlled drug delivery because of the efficiency in obtaining a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance. These matrices are further divided into three groups based on the polymers used;

- **Cellulose derivatives:**

The polymers used in the formulation are methylcellulose 400 and 4000cps, hydroxypropyl methylcellulose (HPMC) 25, 100, 4000, and 15000cps, hydroxyl ethyl cellulose, and sodium carboxymethyl cellulose.

- **Non-cellulose natural/semi-synthetic polymers:**

Polymers of acrylic acid: The most widely used polymer under this category is carbopol-934. Other polymers include agar-agar, alginates, carob gum, molasses, polysaccharides of galactose and mannose, chitosan, and modified starches.

Bio-degradable matrices:

These contents of the polymers are composed of monomers linked to one another through functional groups and have unstable linkage in the backbone. These are biologically degraded by enzymes lead to surrounding living cells or by the non-enzymatic process into oligomers and monomers that can be metabolized or discharge. Examples are natural polymers alike as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

Mineral matrices:

Mineral matrices contain polymers obtained from different species of seaweeds. Alginic acid, a hydrophilic carbohydrate obtained from species of brown seaweeds by using dilute alkali, is an example of mineral matrices.

➢ **Based on** the **porosity of the matrix:**

In this, the drug molecules diffuse across the matrix and produce sustained release.

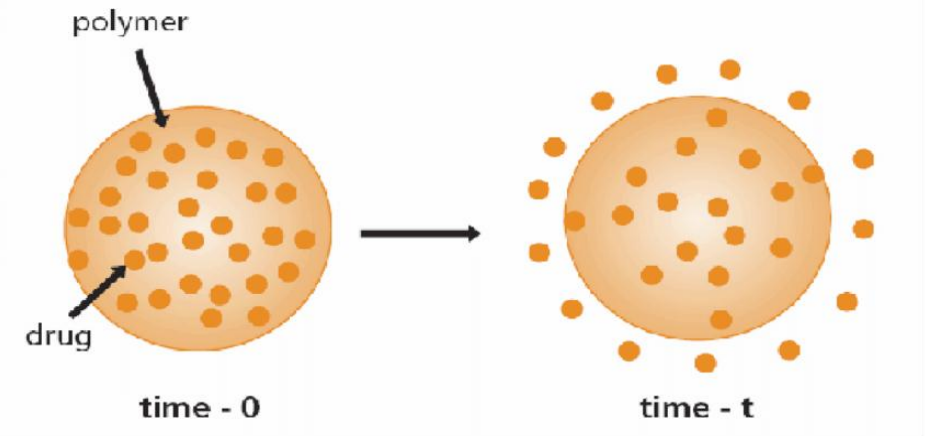

Figure No. 1: Diffusion of Drug across the Matrix

The matrix is further divided into 3 types.

a) Macroporous systems

The pores of this kind of matrix range from 0.1µm to 1µm which is larger than the diffusion molecule size. In this type of system permeation of drug occurs through these pores.

b) Microporous systems

Permeation of drug molecules occurs through pores of sizes ranging from 50-200Å.

c) Non-porous systems

These systems have no pores. The diffusion of molecules occurs through network meshes. There is no pore phase where the polymeric phase is present.

The following are the rationale for developing SR matrix DDS: [9, 10, 11]

- To sustain the duration of action of the drug,
- To reduce the frequency of dosing,
- To minimize the fluctuations in plasma level,
- Improved drug utilization,
- Less adverse effects,

- To reduce adverse effects.

Advantages of Sustained Release Matrix Tablet:

- Easy to manufacture.
- Versatile, effective, and low cost.
- This can be made to release high molecular weight compounds.
- The sustained-release formulations may maintain therapeutic concentrations across prolonged periods.
- The make use of sustain release formulations avoids the high blood concentration.
- Sustain release formulations retain the potential to improve patient compliance. Reduce the toxicity by slowing drug absorption.
- Increase the stability by protecting the drug from hydrolysis or other derivative changes in the gastrointestinal tract.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Usage of a less total drug.
- Improvement of the ability to provide certain effects. Ex: Morning relief of arthritis on bedtime dosing.

Disadvantages of Sustained Release Matrix Tablet:

- The remaining matrix should be removed after the drug has been released.
- The high cost of preparation.
- The release rates are affected by various constituents such as food and the rate transit through the gut.
- The drug release rates differ with the square root of time. The release rate continuously reduces due to an increase in diffusional resistance and/or a decrease in the effective area at

the diffusion leading. However, a substantial sustained effect can be lead through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

Polymers Used in Matrix Tablet:

Hydrogels

Poly hydroxyethyl methyl acrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene Oxide (PEO), Polyacrylamide (PA)

Soluble polymers

Poly ethyl eneglycol (PEG), polyvinyl alcohol (PVA), Polyvinyl pyrrolidone (PVP), Hydroxypropyl methylcellulose (HPMC)

Biodegradable polymers

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

Non-biodegradable polymers

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

Mucoadhesive polymers

Polycarbophil, Sodium carboxymethyl cellulose, Polyacrylic acid, Tragacanth, Methylcellulose, Pectin

Natural gums

Xanthan gum, Guar gum, Karaya gum, Locust bean gum

Characteristics of an Ideal Polymer:

- It must be versatile and possess a wide range of mechanical, physical, chemical properties.
- It must be non-toxic and have good mechanical strength and should be easily administered.
- It must be inexpensive and easy to fabricate.

- It must be inert to host tissue and compatible with the environment.

Criteria Followed in Polymer Selection:

- The polymer should be soluble and easy to synthesis.
- It should have finite molecular weight.
- It should be compatible with the biological environment.
- It should be biodegradable.
- It should provide good drug-polymer linkage.

Characteristics of Drug Suitable for sustained Release Tablet: [12]

- The ideal physicochemical and pharmacokinetic standard of medications which can be defined as the extended-release tablet is as per the following:

- Atomic size must be beneath 1000 Dalton.
- Aqueous solvency must be in excess of 0.1 mg/ml for pH 1 to pH 7.8.
- The partition coefficient ought to be high 5.
- Absorption process requires to be diffusion and the general absorbability from all GI fragments discharge ought not to be impacted by pH and catalysts.
- Elimination half-life is to be between 2 to 8 hrs7
- Drugs ought not to metabolize in the sight of absorption it cause less bioavailability.
- Absolute bioavailability ought to be at least 75% or more.

Method of Preparation of Matrix Tablet: [13, 14]

1. Wet Granulation Technique

- Milling and gravitational mixing of drug, polymer, and excipients.
- Preparation of binder solution.
- Wet massing by addition of binder solution or granulating solvent.
- Screening of wet mass.
- Drying of the wet granules.

- Screening of dry granules.
- Blending with lubricant and disintegrates to produce “running powder”
- Compression of the tablet.

2. Dry Granulation Technique

- Milling and gravitational mixing of drug, polymer, and excipients
- Compression into slugs or roll compaction
- Milling and screening of slugs and compacted powder
- Mixing with lubricant and disintegrates
- Compression of the tablet.

3. Sintering Technique

- Sintering is the bonding of adjacent particle surfaces in a mass of powder.
- Conventional sintering involves heating at a temperature below the melting point of the solid constituents in administer.
- Transpose in the hardness of disintegration time of tablets stored at elevated temperatures was described as a result of sintering.
- The sintering mechanism is applied for the fabrication of sustained release matrix tablets for the stabilization and retardation of the drug release.

Factors Considered In Dosage Form Design: [15, 16]

There are mainly 2 kinds of factors that affect the dosage form design. They are divided into:

1. Biological factors

a. First-pass effect: Drugs that are suffering an extensive first-pass effect appear retarded release rate. This retarded release rate affects bioavailability.

b. Half-life: The half-life of a drug is the measure of its period residence in the body. If the medication has a short half-life of fewer than 2 hours, a prohibitively large amount of the drug may be found in the dosage form. On the other hand, a drug with a half-life of removal

of eight hours or more is adequately maintained in the body when administered in traditional doses and continuous delivery of drug systems.

c. Adverse effects: Extend the drug release may develop undesirable adverse reactions.

d. Absorption and solubility: absorption and solubility both are interconnected. Incorporation of poorly water-soluble drugs can cause a reduction in overall absorption efficiency.

e. Metabolism: Drugs that are significantly metabolized in advance of absorption, either in the lumen of the tissue of the intestine, can show decreased bioavailability from the slower-releasing dosage form. Even a drug that is poorly capable of disintegration can be formulated in the sustained release dosage form to same, the solubility of the drug should be increased by the suitable system and after that is formulated in the sustained release dosage form. But during this, the crystallization of the drug, that is taking place as the drug is allowed in the systemic circulation, should be prevented and one should be cautious for the prevention of the same.

2. Physiochemical Factors

a. Drug stability: The important factor in oral dosage forms is the loss of medication in the GI tract utilizing acid hydrolysis and/or metabolism. While a drug undergoes degradation in solid states at a much slower rate than a suspended or solution substance. It is possible to significantly improve the relative bioavailability of a medication that is toxic in the stomach; the most effective control unit would be one that activates its substance only in the intestine.

b. Aqueous solubility & Pka: A medication to be absorbed and dissolved in the aqueous phase adjacent to the route of administration site and then partitioned into the absorbing membrane. Two of the most important physicochemical properties of a drug that affect its absorption activities are its aqueous solubility and if it is soft acid, its pKa. Such properties reward a dominant role in the success of controlled release schemes. Drugs with high aqueous solubility have poor degradation levels and are typically susceptible to oral bioavailability tribulations.

c. Partition Coefficient: It is the ratio of the drug in the oil phase to that of the aqueous phase. Drugs having higher partition co-efficient are not suitable for oral SRDDS as they

won't partition out of the lipid membrane once it gets in the membrane. It can be calculated by the formula.

$$K = Co / Cw$$

Co = Equilibrium concentration in organic phase

Cw= Equilibrium concentration in aqueous phase

d. Diffusivity and molecular size: The membrane cavities' size and shape influence the diffusivity. Intermediate molecular weight drug diffusion coefficient is 100-400 Daltons; 10-6-10-9 cm2/sec is due to flexible polymer array. For drugs having molecular weight > 500 Daltons, the diffusion coefficient in many polymers is very less i.e. less than 10-12 cm2/sec. Proteins and peptides are examples of drugs that are difficult to control drug release levels from the dosage form.

Mechanism of Drug Release from Matrix Devices: [17]

1) Dissolution controlled release

Sustained release of drug oral products employing dissolution as the time-limiting step are simplest to prepare. If a drug has a fast rate of dissolution it is possible to incorporate it into a tablet with a carrier that has a slow rate of dissolution. the dissolution process is diffusion layer control, the rate of diffusion of the drug from the solid surface to the bulk solution through an unstirred liquid film is the rate-limiting step. In this case, the dissolution process at steady state to be described by the Noyes-Whitney equation,

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

Where,

dc/dt - Dissolution rate.

KD - Dissolution rate constant.

Cs - Saturation solubility of drug.

C -The concentration of drug in the bulk of the solution.

Dissolution control formulations are categories as

- Encapsulation dissolution control
- Matrix dissolution control

Encapsulation dissolution control

This method cover coating individual particles or granules of the drug with slowly dissolving material. The coated particles can be compressed directly into the tablet as in Spacelab's or placed in capsules as in spansule products.

Matrix dissolution control

This method involves compression of the drug with a lightly dissolving carrier in a tablet form. then the rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix can be controlled by the porosity of the tablet matrix, the presence of hydrophilic, and the wettability of the tablet and particle surface.

(a) Matrix system, and

(b) Coated/encapsulated system

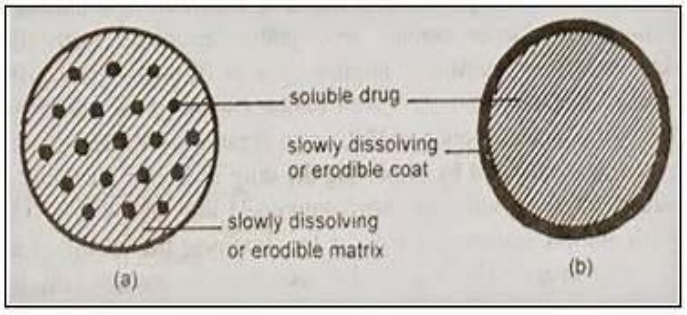

Figure No. 2: Schematic representation of dissolution controlled release systems

2) Diffusion controlled release

These systems are of two types:

a. Encapsulation diffusion control

In this system, water-insoluble polymeric material encases a core of the drug. Drugs will partition into the polymer membrane and exchange with the fluid surrounding the particle or tablet.

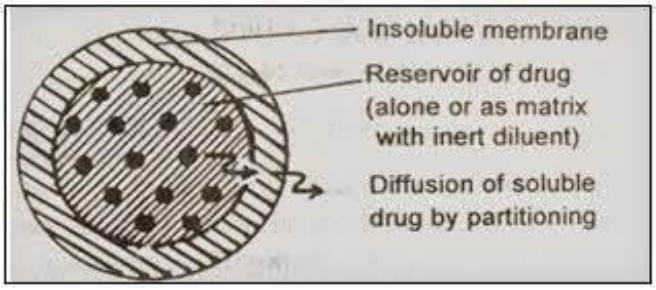

Figure No. 3: Drug release of diffusion across the insoluble membrane of the reservoir device.

The rate of drug release is given by the equation.

$$dm/dt = AdK\Delta c \text{---------- (2)}$$

Where,

A = Area

D = Diffusion coefficient

K = The partition coefficient of the drug between the membrane and the drug core

I = The diffusional path length

Δc = The concentration difference across the membrane.

An important parameter in the above eq. (2) is the partition coefficient, which is defined as the concentration of the drug in the membrane over the concentration of the drug in the core.

b. Matrix diffusion control

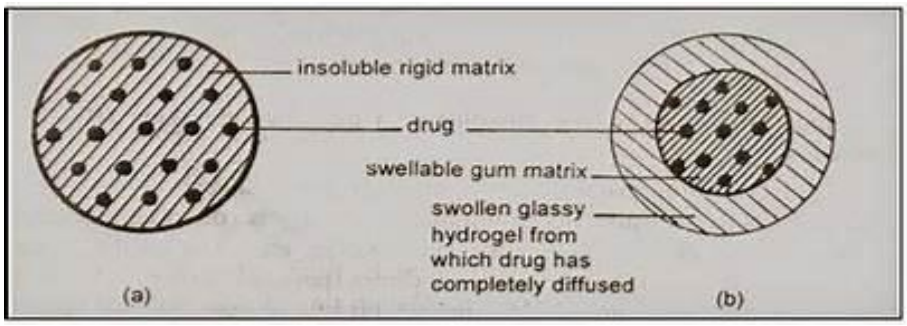

Figure No. 4: Diffusion controlled devices (a) rigid matrix, and (b) swellable matrix.

In this system, a solid drug is dispersed in a lipophilic or a hydrophilic polymer matrix and the rate of release of the drug depends on the rate of drug diffusion and not on the rate of solid dissolution.

Formulation Strategies for Oral Sustained Release: [18]

System Diffusion Sustained Release

Dissolution Sustained Release

pH-Dependent System

Altered Density System

Osmotic Pump System

Ion Exchange System

Types of diffusion sustained system:

• Swellable matrix.

• Reservoir/Laminate matrix.

Types of dissolution sustained system:

- Matrix Monolith Dissolution System.
- Encapsulation/Coating/Reservoir System.

Types of altered density system:

- High-Density System.
- Low-Density System.
- Muco Adhesive System

Evaluation of Sustained-Release Tablets: [19]

The sustained-release product must be to assure the strength, safety, stability, and reliability of a product by forming in-vitro and in vivo analysis and the correlation between the two.

Evaluation parameter have discussed as given below:

1. *In-vitro* Methods

a. Beaker method

b. Rotating disc method

c. Rotating Bottle method

d. Rotating Basket method

e. Stationary Basket Method

f. Oscillating tube method

g. Dialysis method h. USP dissolution method.

2. *In–vivo* Methods

Once the satisfactory in-vitro profile is achieved, it becomes necessary to conduct an *in-vivo* evaluation and establish an *in-vitro in-vivo* correlation.

The various in-vivo evaluation methods are:

a. Clinical response

b. Blood level data

c. Urinary excretion studies

d. Nutritional studies.

e. Toxicity studies

f. Radioactive tracer technique

3. Stability Studies

Suitable stability data of the drug and its dosage form is essential to ensure the strength, purity, identity, quality, safety, and *in-vitro in-vivo* release rates that they claim to have at the time of use. And SR product is to be release a predetermined amount of the drug at specified time intervals, which should not change on storage. Let the in-vitro and in-vivo release rates of the sustained-release product may be altered by atmospheric or accelerated conditions such as temperature & humidity. The stability programmer of a sustained-release product is stored

at both nominal and accelerated conditions alike as temperature & humidity to ensure that the product will withstand these conditions.

Bioavailability Testing:

Bioavailability is said to be in terms of a specific drug moiety, usually an active therapeutic entity, that may be the unchanged drug or as with prodrug, for instance, a metabolite. Inset off the term "absorption" often refers to net transport of drug-related mass from its site of application into the body. Pharmaceutical optimization of the dosage form may be warranted to better absorption characteristics of the drug and thereby also its bioavailability. Bioavailability studies are ordinarily single dose comparisons of the tested drug product in normal adults in a fasting state. And single-dose studies are usually sufficient to establish the validity of SR dosage form design; multiple-dose studies are required to establish an optimum dosing regimen. And there is excessive subject-to-subject transpose or the observed blood levels after a single dose is too low to be measured accurately.

CONCLUSION:

The focus of this review article has been on the formulation of sustained-release matrix tablets, advantages, and disadvantages and various polymers used to design such a system. Up above discussion concludes the matrix tablets are helpful to overcome the patient compliance and efficiency of dosage form bring out desired therapeutic response related problems associated with the conventional dosage forms. Cost-effectiveness and once or daily dose are the plus points along with other benefits. Accordingly, sustained release matrix tablets trends towards the optimization of the dosage form design.

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