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Review on Sustained Release Matrix Tablets: An Approach to Prolong the Release of Drug

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ABSTRACT:

The advantage of administering a single dose of a drug that is released over an extended period of time instead of numerous doses is now a day's area of interest for formulation scientists in Pharmaceutical industry. With many drugs the basic Goal of therapy is to achieve a steady-state blood or tissue level that is therapeutically effective and nontoxic for an extended period of time. Sustain release system are considered a wiser approach for the drugs with short half-lives and which require repeated dosing, they are easy to formulate and are irrespective of absorption process from gastrointestinal tract after oral administration. The basic rationale of sustained release drug delivery system optimizes the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of a drug in such a way that its utility is maximized, side-effects are reduced and cure of the disease is achieved. There are several advantages of sustained release (matrix) drug delivery over conventional dosage forms like improved patient compliance due to less frequent drug administration, reduction of fluctuation in steady-state drug levels, maximum utilization of the drug, increased safety margin of potent drug, Developing oral sustained release matrix tablet with constant release rate has always been a challenge to the pharmaceutical technologist. Most of drugs, if not formulated properly, may readily release the drug at a faster rate, and are likely to produce toxic concentration of the drug on oral administration.

KEY WORDS: ODDS, Sustain release, Matrix system

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INTRODUCTION:

A number of terms have been used to describe the oral dosage forms that represents modified release properties; which include delayed release, repeated action, prolonged release, sustained release, extended release and controlled release. Each drug delivery system is focused at eliminating the cyclical changes in plasma drug concentration seen after administration of conventional delivery systems. Modified release dosage forms are designed to provide quick achievement of a drug plasma level that remains constant at a value within the therapeutic range of a drug for a significant period of time or achievement of a plasma concentration of a drug that delivers at a slow rate (i.e. sustained release) that stays within the therapeutic range for a longer period of time.⁽¹⁾

Based on the assumption that a drug, which is to be incorporated into a modified release dosage form, confers upon the body characteristics of a one-compartment open model, then the basic kinetic design of such a product may be assumed to contain two portions, one that provides the initial loading dose, and one that provides the maintenance or sustained dose. To ensure that the therapeutic

concentration of the drug in the body remains constant, two conditions must be fulfilled, namely 1) The zero order rate of drug release must determine the absorption rate of the drug, and 2) The rate at which the drug is released from maintenance dose (and subsequently the absorption rate) should be equal to the rate of drug elimination at the required steady-state concentration a list of important terms that describe different modified release dosage forms are defined below.⁽²⁾

1. Modified release dosage forms

Those dosage forms whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic and/or convenience objectives not offered by conventional dosage forms.⁽³⁾

2. Controlled release

The drug is released at a constant (zero order) rate and the drug concentration obtained after administration is invariant with time.⁽⁴⁾

3. Delayed release

The drug is released at a time other than immediately after administration.⁽⁵⁾

4. Extended release

Slow release of the drug so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time usually between 8 and 12 hours.⁽⁶⁾

5. Prolonged release

The drug is provided for absorption over a longer period of time than from a conventional dosage form. However, there is an implication that onset is delayed because of an overall slower release rate from the dosage form.⁽⁷⁾

6. Repeat action

Indicates that an individual dose is released fairly soon after administration, and second or third doses are subsequently released at intermittent intervals.⁽⁸⁾

7. Sustained release

The drug is released slowly at a rate governed by the delivery system.

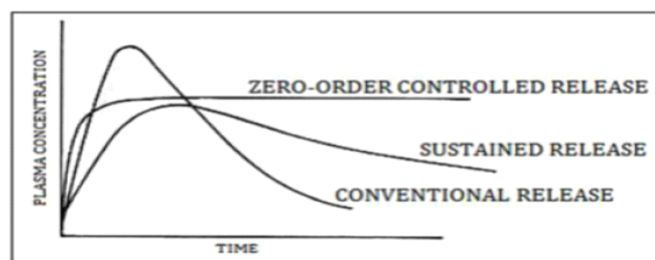
Oral Sustained Release dosage form:

Sustained release, sustained action, prolonged action, controlled release, extended action, depot are terms used to identify drug delivery systems that are designed to achieve prolonged

therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. In the case of orally administered this period is measured in hours while in the case of injectable this period varies from days to months. The oral route administration is mostly adopted because of its comfortable dosage form, design and patient care. Several parameters should be kept in mind before formulating sustained release dosage form which includes various pH in GIT, the gastrointestinal motility, the enzyme system and its effect on the dosage form and the drug. Most of sustained release dosage form follows the mechanism of diffusion, dissolution or combination of both, to produce slow release of drug at predetermined rate. Hypothetically, a sustained release dosage form should release the drug by a zero-order mechanism which maintains drug plasma level time similar to intravenous infusion. Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero order sustained release formulation are as follows in given Figure 1.⁽⁹⁾

Advantages of sustained release dosage forms:⁽¹⁰⁾

1. Control of drug therapy is achieved.
2. Rate and extent of drug absorption can be modified.
3. Frequency of drug administration is reduced.
4. Patient compliance can be improved.
5. Drug administration can be made convenient.
6. Maximizing the availability of drug with minimum dose.
7. The safety margin of high potency drug can be increased.



Disadvantages of sustained release dosage forms: -

1. It does not permit prompt termination of therapy.
2. Less flexibility in dose adjustment.
3. These dosage forms are designed on the basis of average biological half-life.
4. They are costly.

Drug Selection for Oral Sustained Release Drug Delivery System:

The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge

on the absorption mechanism of the drug from the G. I. tract, the general absorbability, the drug's molecular weight, pKa, solubility at different pH and apparent partition coefficient. ⁽¹¹⁾

Table 1: Parameter for Drug Selection

	Preferred Value
Molecular Weight/Size	< 1000
Solubility	> 0.1 µg/ml for pH 1 to 7.8
Pk _a	Non ionized moiety > 0.1% at pH 1 to 7.8
Apparent Partition Coefficient	High
Absorption Mechanism	Diffusion
Absorbability	From all G.I. segments
Release	Should not be influenced by pH and Enzyme

Table 2: Pharmacokinetic parameter for drug selection

Parameter	Preferred Value
Elimination half life	Preferably between 0.5 and 8 h
Total clearance	Should not be dose dependent
Elimination rate constant	Required for design
Apparent volume of distribution V _d	The larger V _d and MEC, the larger will be the required dose size.
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration C _{ssav}	The lower C _{ssav} and smaller V _d , the loss among of drug required
Toxic concentration	Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

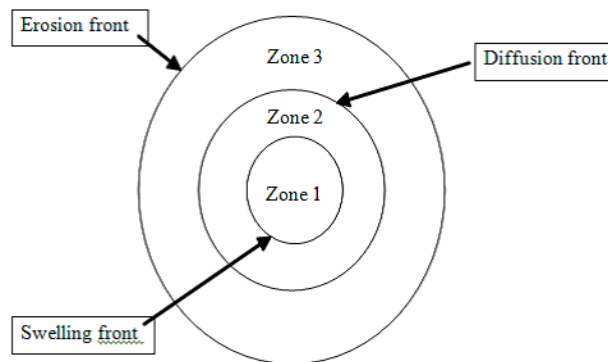
Classification of SR Formulation:

The most common methods used to achieve sustained release of orally administered drugs are as follows: (12)

- Diffusion System
 - Reservoir Device
 - Matrix Device
- Dissolution System
- Osmotic System
- Ion-exchange Resin
- Swelling and Expansion System
- Floating System
- Bioadhesive or Mucoadhesive system

Matrix System: ⁽¹³⁾

A matrix device, as the name implies, consist of drug dispersed homogeneously throughout a polymer matrix. In the model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving towards the interior, obviously, for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster that the diffusion ate of dissolved drug leaving the matrix. (Figure 2)



Advantages of Matrix system: (14)

- 1) Maintains therapeutic concentrations over prolonged periods.
- 2) Avoids the high blood concentration.
- 3) Reduction in toxicity by slowing drug absorption.
- 4) Minimize the local and systemic side effects.
- 5) Improvement in treatment efficacy.
- 6) Better drug utilization.
- 7) Minimize drug accumulation with chronic dosing.
- 8) Can be made to release high molecular weight compounds.
- 9) Increase the stability by protecting the drug from hydrolysis or other derivative changes in GIT.
- 10) Reduction in health care cost.
- 11) Usage of less total drug.
- 12) Improvement of the ability to provide special effects. Ex: Morning relief of arthritis through bed time dosing.
- 13) Improved patient compliance.

Disadvantages of Matrix system:

- 1) The remaining matrix must be removed after the drug has been released.
- 2) Greater dependence on GI residence time of dosage form.
- 3) Increased potential for first-pass metabolism.

Types of Matrix: ⁽¹⁵⁾

- Hydrophobic Matrices

In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers.

- Lipid matrices

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnuba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

- Hydrophilic matrices

A matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems. The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups,

- Cellulose derivatives

Methylcellulose 400 and 4000cPs, Hydroxyethylcellulose; Hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxymethylcellulose.

- 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 consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by nonenzymetic process in to oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

- Mineral Matrices

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaeophyceae) by the use of dilute alkali. On the Basis of Porosity of Matrix: Matrix tablets can be divided in to 3 types.

- Macro porous systems

In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm . This pore size is larger than diffusant molecule size.

- Micro porous system

Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 \AA , which is slightly larger than diffusant molecules size.

- Non-porous system

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

Methods of preparation ⁽¹⁶⁾**Direct Compression**

In this process powdered materials are compressed directly without changing the properties of the drug like physical and chemical properties.

Wet Granulation

In this method weighed quantities of drug and polymer are mixed with sufficient volume of granulating agent. After enough cohesiveness was obtained, then screening of wet mass. The granules are dried and screening of dry granules, then blending with lubricant and disintegrant to produce "running powder" tablets are compressed using a single-punch tablet compression machine.³⁴

Melt Granulation

In this process use of a substance, which melts at relatively low temperature. This substance can be added in the molten form over the substrate, which is then heated above its melting point. Different lipophilic binders were tried by using melt granulation technique.

Hot-Melt Extrusion Process

In the hot-melt extrusion process, a mixture of the active ingredients, the thermoplastic polymers and other processing

aids is fed into the barrel of the extruder through the hopper. The materials are transferred inside the heated barrel by a rotating screw.

The materials melt at elevated temperatures and the molten mass is continuously pumped through the die attached at the end of the barrel. Depending upon the dimensions of the die cylinders, films can also be produced from the extruder.

Effect of Release limiting factor on drug release (17)

- Polymer hydration:
- Drug solubility
- Solution solubility
- Polymer diffusivity
- Thickness of polymer diffusional path
- Thickness of hydrodynamic diffusion layer
- Drug loading dose
- Surface area and volume
- Diluent's effect
- Additives

Polymers used in Matrix tablets (18,19)

a) Hydrogels

Polyhydroxyethylmethacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Crosslinked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Polyacrylamide (PA).

b) Soluble polymers

Polyethylene glycol (PEG), polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC).

c) Biodegradable polymers

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

d) Non-biodegradable polymers

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

e) Mucoadhesive polymers

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

f) Natural polymers in sustained release drug delivery

Xanthan Gum, Guar Gum, Sodium Alginate, Pectin, Chitosan

Table 3: Different drugs and polymers used in sustained-release MATRIX tablets

Drug	Polymer
Metoclopramide Hydrochloride	Hydroxy Propyl Methyl Cellulose (HPMC), Carboxymethylcellulose (CMC), Ethyl Cellulose (EC)
Ibuprofen	Ethyl cellulose, Cellulose acetate phthallate
Metoprolol succinate	HPMC K100M, Xanthan gum
Ambroxol Hydrochloride	HPMC
Tramadol Hydrochloride	Xanthan gum, Guar gum.
Tramadol Hydrochloride	Carrageenan gum, Karaya gum, HPMC K15 .
Aceclofenac	Carbopol 971P, Carbopol

Evaluation of Sustained release Matrix tablets: ^(20,21)

Before marketing a sustained release product, it is must to assure the strength, safety, stability and reliability of a product by forming in-vitro and in vivo analysis and correlation between the two. Various authors have discussed the evaluating parameters and procedures for sustained release formulations

- **Weight Variation:** Twenty tablets were weighed individually and then collectively, average weight of the tablets was calculated.
- **Hardness:** Hardness test was conducted for tablets from each batch using Monsanto hardness tester and average values were calculated.
- **Friability:** The tablets were tested for friability testing using Roche friabilator, which revolves at 25rpm for 4min.
- **Thickness:** The thicknesses of tablets were determined using micrometer screw gauge.
- **Content Uniformity:** Using UV Visible spectrophotometer found the amount of the drug using the calibration curve method.
- **Kinetic Studies**
- **In Vitro Dissolution Study:** Drug release study is generally determined in Rotating Paddles apparatus. Mainly buffer is used as a dissolution medium. The temperature of the bath maintained at 37°C and required sample of the dissolution medium in which drug is release is taken at a regular interval and the same quantity of the medium is replace. The amounts of the drug released is determined using an UV spectrophotometer a Drug dissolved at

- specified time period is plot as percent release versus time.
- **Stability Studies:** Short Term Stability Study: To determine change in vitro release profile on storage, a short term stability study of the optimal batch.
- **In-Vivo Methods** Once the satisfactory in-vitro profile is achieved, it becomes necessary to conduct in-vivo evaluation and establish 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 techniques

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 system. Above discussion concludes that matrix tablets are helpful to overcome the patient compliance and efficiency of dosage form in eliciting desired therapeutic response related problems associated with the conventional dosage forms. Cost effectiveness and once-daily dose are the plus points along with other benefits. Hence, sustained-release matrix tablets trends towards the optimization of the dosage form design.

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