ABSTRACT
Now a day’s pharmaceutical industry focusing for development of sustained release oral dosage forms as it become an important tool in medical practice. These sustained release formulations are designed to release drug in pre-determined rate and able to maintained plasma drug concentration in therapeutic window with minimum side effects. The basic rational behind sustained release drug delivery is to alter biopharmaceutical, pharmacokinetic and pharmacodynamic of drug to reduce side effect, give patient compliance and cure the disease. Sustained release drug delivery is 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, reduction in healthcare costs through improved therapy and shorter treatment period. The principal goal of sustained release forms is the improvement of drug therapy assessed by the relationship between advantages and disadvantages of the use of sustained release system. This review article contained basic information of matrix type of sustained release drug delivery system.

KEY WORDS: sustained release, Matrix tablet, oral drug delivery system.

INTRODUCTION
The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The conventional dosage forms are rapidly replaced by this novel controlled release techniques. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by
continuously releasing medication over an extended period of time after administration of a single dose².

Matrix tablets is a promising approach for the establishment of extended-release drug therapy as tablets offer the lowest cost approach to sustained and controlled release solid dosage forms. Matrix tablets may be defined as the “oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serves as release rate retardants³”. These systems release drug in continuous manner by dissolution-controlled and diffusion-controlled mechanisms. Two different release mechanisms are operative, either of which is zero-order erosion and decreasing surface area, and dissolution of coated particles, but the overall tablet release profile comprising the two mechanisms in sequence is nearly linear for most of the dose in the tablet⁴.

**Advantages Sustained Release Drug Delivery System⁵**

**Clinical advantages**
1. Reduction in frequency of drug administration
2. Improved patient compliance
3. Reduction in drug level fluctuation in blood
4. Reduction in total drug usage when compared with conventional therapy
5. Reduction in drug accumulation with chronic therapy
6. Reduction in drug toxicity (local/systemic)
7. Stabilization of medical condition (because of more uniform drug levels)
8. Improvement in bioavailability of some drugs because of spatial control
9. Economical to the health care providers and the patient

**Commercial / Industrial advantages**
1. Product life-cycle extension
2. Product differentiation
3. Market expansion
4. Patent extension

**Disadvantages Sustained Release Drug Delivery System⁵**
1. Delay in onset of drug action.
2. Possibility of dose dumping in the case of a poor formulation strategy.
3. Increased potential for first pass metabolism.
4. Greater dependence on GI residence time of dosage form.
5. Possibility of less accurate dose adjustment in some cases.
6. Cost per unit dose is higher when compared with conventional doses.
7. Not all drugs are suitable for formulating into ER dosage form.

Certain Considerations For The Formation Of Sustained Release Formulation

1. If the active compound has a long half-life (over 6 hours), it is sustained on its own.
2. If the pharmacological activity of the active compound is not related to its blood levels, time releasing has no purpose.
3. If the absorption of the active compound involves an active transport, the development of a time-release product may be problematic.
4. Finally, if the active compound has a short half-life, it would require a large amount to maintain a prolonged effective dose. In this case, a broad therapeutic window is necessary to avoid toxicity; otherwise, the risk is unwarranted and another mode of administration would be recommended.

The Goal In Designing Delayed Release Sustained Or Controlled Delivery System

1. Reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery.
2. It would be a single dose for the duration of treatment whether it is for days or weeks, as with infection or for the life time of the patient, as in hypertension or diabetes.
3. It should deliver the active entity directly to the site of action, minimizing or eliminating side effects.
4. This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body.
5. The safety margin of high potency drug can be increase and the incidence of both local and systemic adverse side effects can be reduced in sensitive patient.

Modified Release Drug Delivery System

1. Extended release system
   The drug delivery system that allows at least two folds reduction in dosage frequency as compared to that drug presented as an immediate release system.

2. Sustained release system
   It includes any drug delivery system that achieves slow release of drugs over an extended period of time not particularly at pre-determined rate.
3. **Controlled release system**  
   It includes any drug delivery system from which the drug is delivered at a predetermined rate over a long period of time.

4. **Prolonged release system**  
   It is designed to release the drug slowly and to provide a continuous supply of drug over an extended period.

5. **Delayed release system**  
   This are the system which designed to release a discrete portion of drug at a time or other than promptly after administration, although one portion may be release promptly after administration of dosage form.

### Biological Factors Affecting Design Of Oral Sustained Release Dosage Form\(^{10,11}\)

1. **Biological half-life**  
   Drug with biological half-life of 2-8 hours are considered suitable candidate for sustain release dosage form, since this can reduce dosing frequency. However this is limited in that drugs with very short biological half lives may require excessive large amounts of drug in each dosage unit to maintain sustained effects, forcing the dosage form itself to become limitingly large. In general drug with short half life than 2 hr are poor candidates of sustained release systems.

2. **Absorption**  
   The rate, extent and uniformity of absorption of a drug are important factors when considering its formulation into an extended release system. The most critical in case of oral administration is $K_r << K_a$. Assuming that the transit time of drug through the absorptive area of gastrointestinal tract is between 9-12 hours, the maximum absorption half-life should be 3-4 hours. This corresponds to a minimum absorption rate constant $K_a$ value of 0.17-0.23/hr necessary for about 80-95% absorption over a 9-12 hr transit time. For the drugs with very slow rate of absorption ($K_a << 0.17/hr$), the first order release rate constant $K_r$ less than 0.17/hr results in unacceptably poor bioavailability in many patients. Therefore, slowly absorbed drug will be difficult to be formulated into extended release systems where the criterion $K_r << K_a$ must be met. If the drug absorbed by active transport or transport is limited to specific region of GIT this drug are poor candidates for sustained release systems.
3. Metabolism
Metabolism leads to either inactivation of an active drug moiety or activation of an inactivated drug molecule. Metabolic alteration of a drug mostly occurs in the liver. Metabolism is reflected in the elimination constant of a drug or by the appearance of metabolite, provided the rate and extent of metabolism are predictable, this property can be incorporated into the product design, although complex metabolic patterns make the design more difficult, particularly when biological activity is due to a metabolite. If the drug on chronic administration induces or exhibits enzyme synthesis, it will make a poor candidate for sustained release product because of difficulty of maintaining uniform blood level.

4. Therapeutic Index
It is most widely used to measure the margin of safety of a drug.

\[ TI = \frac{TD50}{ED50} \]

The longer the value of T.I the safer is the drug. Drugs with very small value of Therapeutic index are poor candidates for formulation into sustained release products. A drug is considered to be safe if its T.I value is greater than 10.

Physiological Factors Affecting Design Of Oral Sustained Release Dosage Form

1. Molecular Size and Diffusivity
For the drug absorption it required to diffuse through a variety of biological membranes during its time course in the body. In addition to diffusion through these biological membranes, drugs in many controlled-release systems must diffuse through a rate-controlling polymeric membrane or matrix. The drugs with molecular weight 150-400 are good candidates for sustained release dosage forms. For drugs with a molecular weight greater than 500Da, their diffusion coefficients in many polymers are frequently so small that they are difficult to quantify.

2. Dosage size
In general conventional dosage forms, dose size 500-1000 mg is maximum which is also applicable to sustained release dosage forms.

3. Aqueous Solubility
The fraction of drug absorbed into the blood is a function of the amount of drug in the solution in the G.I tract, i.e., the intrinsic permeability of the drug. For a drug to be absorbed, it must dissolve in the aqueous phase surrounding the site of administration and the partition into the absorbing membrane. Therefore, the aqueous solubility of a drug can be used as a
first approximation of its dissolution rate. Drugs with low aqueous solubility have low
dissolution rates and usually suffer oral bioavailability problems. The lower limit of solubility
of drug is 0.1 mg/ml for sustained releases system. Drugs with good aqueous solubility are
good candidates for oral sustained release formulation.

4. Partition coefficient (K)
Drugs with extremely large values of K are very oil-soluble and will partition into
membranes quite readily and localize in body for long period of time. The values of K larger
than the optimum result in poorer aqueous solubility but enhanced lipid solubility and the
drug will not partition out of the lipid membrane once it gets in. The value of K at which
optimum activity is observed is approximately 1000/1 in n-octanol /water. Drugs with a
partition coefficient that is higher or lower than the optimum are, in general, poor candidates
for formulation into extended release dosage form.

5. Drug Stability
For those drugs that are unstable in the stomach the most appropriate controlling unit would
be one that releases its contents only in the intestine. The release in the case for those drugs
that are unstable in the environment of the intestine, the most appropriate controlling such as
in this case would be one that releases its contents, only in the stomach. So, drugs with
significant stability problems in any particular area of the G.I. tract are less suitable for
formulation into controlled release systems that deliver the contents uniformly over the length
of GIT.

Physicochemical Parameters For Drug Selection

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Preferred value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight/ size</td>
<td>&lt; 1000</td>
</tr>
<tr>
<td>Solubility</td>
<td>&gt; 0.1 µg/ml for pH 1 to pH 7.8</td>
</tr>
<tr>
<td>Apparent partition coefficient</td>
<td>High</td>
</tr>
<tr>
<td>General absorbability</td>
<td>From all GI segments</td>
</tr>
<tr>
<td>Release</td>
<td>Should not be influenced by pH and enzymes</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>Preferably between 0.5 - 8 hours</td>
</tr>
<tr>
<td>Total clearance</td>
<td>Should not be dose-dependent</td>
</tr>
<tr>
<td>Apparent volume of distribution Vd</td>
<td>The larger Vd and MEC, the larger will be the required dose size.</td>
</tr>
<tr>
<td>Absolute bioavailability</td>
<td>Should be 75 % or more</td>
</tr>
<tr>
<td>Intrinsic absorption rate</td>
<td>Must be greater than release rate</td>
</tr>
<tr>
<td>Dose size</td>
<td>0.5-1gm</td>
</tr>
<tr>
<td>Partition Coefficient</td>
<td>High partition coefficient</td>
</tr>
<tr>
<td>Stability</td>
<td>Drug should be stable in intestine</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Drug should not undergo First pass metabolism</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Therapeutic Index</td>
<td>Should have wide range of Therapeutic index</td>
</tr>
<tr>
<td>BCS Class</td>
<td>BCS Class I and II are suitable for CR/ SR formulation development</td>
</tr>
</tbody>
</table>

**Matrix Type Of Sustained Release Drug Delivery System**

The system in which molecules of drug are dissolved or dispersed in a biocompatible polymer, producing a homogeneous device with drug molecules uniformly dispersed throughout the material. In this case, the drug molecules are released by diffusing through the polymer to the surface of the device, from which they are released into the external environment.

![Diagram of matrix-type systems for controlled drug delivery](attachment:image)

**Fig. 1:** Schematic of matrix-type systems for controlled drug delivery. Matrix delivery systems can be constructed with drug dissolved in the matrix material (a) or Particles of drug dispersed to form a composite material (b and c).

**Advantages of Matrix System**

1. Their manufacturing is cost-effective and does not require any special infrastructure.
2. The drug can be protected from the acidic environment of gastrointestinal tract thereby increasing its stability.
3. Improvement in patient compliance by reducing the dosing frequency
4. Minimizing the drug accumulation and associated side-effects

**Disadvantages of Matrix System**

1. Zero-order release of the drug is often difficult to achieve.
2. The drug release can be affected by physiological factors, presence of food, gastric emptying time and intestinal transit.
Classification of matrix tablets

On The Basis Of Retardant Material Used: 13-16

1. Hydrophobic Matrices (Plastic 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 into 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. The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

2. 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. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

3. Hydrophilic Matrices

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release. Infect 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 into three broad groups,

1. Cellulose derivatives

Methylcellulose 400 and 4000cPs, Hydroxy ethyl cellulose; Hydroxypropyl methyl cellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxy methyl cellulose.
2. **Non cellulose natural or semi synthetic polymers**
Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches.

3. **Polymers of acrylic acid**
Carbopol-934, the most used variety.

4. **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 non enzymatic process into 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.

5. **Mineral Matrices**
These consist of polymers which are obtained from various species of seaweeds. E.g. 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 system can also be classified according to their porosity and consequently, Macro porous; Micro porous and Non-porous systems can be identified

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

3. **Micro porous System**
Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50–200 A°, which is slightly larger than diffusant molecules size.

4. **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.
Polymers Used In Matrix Tablet

Table 2: Polymers Use for Sustained Release Tablet

<table>
<thead>
<tr>
<th>Hydrophilic Polymers</th>
<th>Non Cellulosic</th>
<th>Non-Cellulosic (others)</th>
<th>Water-Insoluble and Hydrophobic</th>
<th>Fatty Acids /Alcohols /Waxes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulosic</td>
<td>Non Cellulosic</td>
<td>Non-Cellulosic (others)</td>
<td>Ethyl cellulose</td>
<td>Bees’ wax</td>
</tr>
<tr>
<td>Methylcellulose</td>
<td>Sodium alginate</td>
<td>Polyethylene oxide</td>
<td>Hypermellose acetate succinate</td>
<td>Carnauba wax</td>
</tr>
<tr>
<td>HPC</td>
<td>Xanthan gum</td>
<td>Homopolymers and copolymers of acrylic acid</td>
<td>Cellulose acetate</td>
<td>Candelilla wax</td>
</tr>
<tr>
<td>HPMC</td>
<td>Carrageenan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEC</td>
<td>Guar gum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na-CMC</td>
<td>Locust bean gum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chitosan</td>
<td></td>
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</tr>
</tbody>
</table>

Mechanism Of Drug Release From Matrix System

There are many types of commercial extended release preparation are available, none works by a single drug release mechanism. The drug release from controlled devices is via dissolution or diffusion or a combination of the two mechanisms or erosion controlled system.

Diffusion controlled system

In this type of system the rate controlling step is not the dissolution rate but the diffusion of dissolved drug through the polymeric barrier. The drug release rate is never zero order since the diffusional path length increases with time as the insoluble matrix is gradually depleted of drug. The two types of diffusion controlled systems are:

(a) Matrix diffusion controlled system.

(b) Reservoir devices.

In a matrix system the drug is dispersed as solid particles within a porous matrix formed of a water insoluble polymer, such as polyvinyl chloride. Initially drug particles located at the surface of the release unit will be dissolve and the drug release rapidly. Thereafter, drug particles at successively increasing distance from the surface of the releasing unit will be dissolved and released by diffusion in the pores to the exterior of the release unit. This process continues with the interface between the bathing solution and the solid drug moving towards the interior.
Fig. 2: Schematic for mechanism of drug release from a diffusion based matrix tablet.
It follows obviously that for this system to be diffusion controlled, the rate of dissolution of drug particle within the matrix must faster than the diffusion rate of dissolved drug leaving the matrix.

**Dissolution Controlled system**

A drug with slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by the rate of dissolution. In principle, it would seem possible to prepared extended release product by decreasing the dissolution rate of drugs that are highly water soluble. This can be done by

1. Preparing an appropriate salts or derivatives.
2. Coating the drug with a slowly dissolving material–encapsulation dissolution control.
3. Incorporating the drug into tablet with a slowly dissolving carrier–matrix dissolution control. (A major disadvantage is that drug release rate is continuously decreases with time.)
Erosion controlled systems
In erosion controlled extended release system the rate of drug release is controlled by the erosion of a matrix in which the drug is dispersed. The erosion in its simplest form can be described as a continuous liberation of matrix material (both drug and excipients) from the surface of the tablet i.e. surface erosion. The drug is subsequently exposed to the gastrointestinal fluid and mixed with (if the drug is dissolved in matrix) or dissolved in (if the drug is suspended in matrix) the fluid. This drug release scheme is in practice a simplification, as erosion system may combine different mechanism for drug release. For example, the drug may be release by both erosion and by diffusion within the matrix. However drug release can often approximate zero-order for a significant part of the total release time. The eroding matrix can be formed from different substances. One example is lipids or waxes, in which the drug is dispersed. Another example is polymer that gel in contact with water (e.g. Hydroxyethyl cellulose). The gel will subsequently erode and release the drug which is dissolved or dispersed in gel.

Fig. 4: Schematic illustration of mechanism of drug release from an erosion tablet.

REFERENCES


