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SUSTAINED RELEASE DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT
In the recent years, various modified drug products have been developed to release the active drug at a controlled rate. Controlled release dosage forms cover a wide range of prolonged action formulations which provide continuous release of their active ingredients at a predetermined rate and for a predetermined time. A sustain release drug product is designed to deliver an initial therapeutic dose of the drug followed by a slower and constant release of drug. The rate of release of the maintenance dose is designed so that the amount of drug loss from the body by elimination is constantly replaced. With the sustain release product, a constant plasma drug concentration may be maintained with minimal fluctuation. This article provides information about the Sustain release formulation, Design and Fabrication of oral controlled release systems.
INTRODUCTION

Sustained release describes the release of drug substance from a dosage form or delivery system over an extended period of time. The basic goal of this system is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal.

Sustained release, sustained action, controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug therapy systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. In the case of injectable dosage forms, this period is measured in hours and critically depends on the residence time of the dosage form in the gastrointestinal tract. The term controlled release has become associated with those systems from which therapeutic agents may be automatically delivered at predetermined rates over a long period of time. Products of this type have been formulated for oral, injectable and topical use and inserts for placement in body cavities. Controlled release systems also denotes systems which can provide some control whether this be of a temporal or spatial nature or both, of drug release in the body. The system attempts to control drug concentrations in the target tissues or cells. Prolonged or sustained release systems only prolong therapeutic blood or tissue levels of the drug for an extended period of time.

Figure No. 1: A hypothetical Plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations
Terminology

Modified release delivery systems may be divided conveniently into four categories.

A) Delayed release
B) Sustained release
   i) Controlled release
   ii) Extended release
C) Site specific targeting
D) Receptor targeting

A) Delayed Release:
These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating.

B) Sustained release:
During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now-a-days the technology of sustained release is also being applied to veterinary products.

These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

i) Controlled Release: These systems include any drug delivery system that achieves slow release of drug over an extended period of time.

ii) Extended Release: Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds.

C) Site specific targeting:
These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.
D) Receptor targeting:
These systems refer to targeting of a drug directly to a certain biological location. In this case the
target is the particular receptor for a drug within an organ or tissue.
Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery
and are also considered to be sustained drug delivery systems.

Advantages\(^5,6\):
1. The frequency of drug administration is reduced.
2. Patient compliance can be improved.
3. Drug administration can be made more convenient.
4. The blood level oscillation characteristics of multiple dosing of conventional dosage form is
   reduced, because a more even blood level can be maintained.
5. Better control of drug absorption can be attained, since the high blood level peak that may be
   observed after administration in an extended action form.
6. The characteristic blood level variations due to multiple dosing of conventional dosage form
   can be reduced.
7. The total amount of drug administration can be reduced, thus
   a) Maximizing availability with minimum dose
   b) Minimize or eliminate local side effects
   c) Minimize or eliminate systemic side effects
   d) Minimize drug accumulation with chronic dosing
8. Safety margin of high potency drugs can be increased and the incidence of both local and
   systemic adverse side effects can be reduced in sensitive patients.
9. Improve efficacy in treatment
   a) Cure or control condition more promptly
   b) Improve/ control i.e. reduce fluctuation in drug level.
   c) Improve bioavailability of some drugs
   d) Make use of special effect e.g. sustained release aspirin for morning relief of arthritis by
dosing before bed time.
10. Economy

Disadvantages\(^5,6\):
1. Administration of sustained release medication does not permit prompt termination of therapy.
2. Flexibility in adjustment in dosage regimen is limited.

3. Controlled release forms are designed for normal population i.e., on the basis of average drug biological half lives.

4. Economy factors may also be assessed, since most costly process and equipment are involved in manufacturing so many controlled release dosage forms.

**Limitations**: 5, 6:

1. If the active compound has a long half-life (over six hours), it is sustained on its own.

2. If the pharmacological activity of the active compound is not related to its blood levels, slow releasing then 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.

5. Not effectively absorbed in lower small intestine.

6. Large doses are required (more than 1 gm).

7. Drug with low therapeutic index.

8. Precise dose to individuals is required.

**Design and Fabrication of Oral Controlled Release Systems**: 2-5, 7-9:

The majority of oral controlled release systems depend on dissolution, diffusion, or a combination of both mechanisms, to generate slow release of drugs into gastrointestinal milieu. The following techniques are employed in the design and fabrication of oral sustained release dosage forms.

1) **Continuous Release Systems**

These systems release the drug for a prolonged period of time along the entire length of gastrointestinal tract with normal transit of the dosage form.

The various systems under this category are as follow,

A. **Dissolution Controlled Release Systems**

i) Matrix Dissolution Controlled Systems

ii) Encapsulation/Coating Dissolution Controlled Systems (Reservoir Devices)
B. Diffusion Controlled Release Systems
   i) Matrix Diffusion Controlled Systems
   ii) Reservoir Devices or Laminated Matrix Devices
C. Dissolution and Diffusion Controlled Release Systems
D. Ion-Exchange Resin-Drug Complexes
E. pH Dependent Formulations
F. Osmotic Pressure Controlled Systems
G. Hydrodynamic Pressure Controlled Systems

A. Dissolution Controlled Release Systems
These types of systems are easiest to design. The drug present in such system may be the one:
   • With inherently slow dissolution rate e.g. Griseofulvin and Digoxin.
   • That produces slow dissolving forms, when it comes in contact with GI fluids.
   • Having high aqueous solubility and dissolution rate.
Drugs having high aqueous solubility and dissolution rate, shows challenge in controlling their dissolution rate.
Dissolution-controlled release can be obtained 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 thickness. The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer. The rate of dissolution (dm/dt) can be approximated by Equation 1.

\[
\frac{dm}{dt} = \frac{A S D}{h} \quad -------- 1
\]

Where,
S = Aqueous solubility of the drug.
A = Surface area of the dissolving particle or tablet.
D = Diffusivity of the drug and
h = Thickness of the boundary layer.

i) Matrix (or Monolith) Dissolution Controlled Systems
As the drug is homogeneously dispersed throughout the rate controlling medium, this system is also called as monolith system. It is very common and employs waxes such as beeswax,
carnauba wax which control the drug release rate by controlling the rate of dissolution fluid penetration into the matrix by altering the porosity of tablet, decreasing its wettability or by itself getting dissolved at a slower rate. The drug release is often first order from such matrices.

Figure No. 2: Matrix (or Monolith) Dissolution Controlled Systems

ii) Encapsulation/Coating Dissolution Controlled Systems (Reservoir Devices)

In this type, the drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose and polyethylene glycol. The dissolution rate of coat depends upon the solubility and thickness of the coating.

Figure No. 3: Encapsulation/Coating Dissolution Controlled Systems (Reservoir Devices)
B. Diffusion Controlled Release Systems

In this type of systems, the diffusion of dissolved drug through a polymeric barrier is a rate limiting step. 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.

Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems. Similar to the dissolution-controlled systems, the diffusion-controlled devices are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix. Unlike the dissolution-controlled systems, the drug is made available as a result of partitioning through the polymer. In the case of a reservoir type diffusion controlled device, the rate of drug released (dm/dt) can be calculated using the following equation 2

\[
\frac{dm}{dt} = ADK \frac{\Delta C}{\ell} \quad \ldots \ldots 2
\]

Where,
A = Area,
D = Diffusion coefficient,
K = Partition coefficient of the drug between the drug core and the membrane,
\( \ell \) = Diffusion path length and
\( \Delta C \) = Concentration difference across the membrane.

In order to achieve a constant release rate, all of the terms on the right side of equation 2 must be held constant. It is very common for diffusion controlled devices to exhibit a non-zero-order release rate due to an increase in diffusional resistance and a decrease in effective diffusion area as the release proceeds.

Another configuration of diffusion-controlled systems includes matrix devices, which are very common because of ease of fabrication. Diffusion control involves dispersion of drug in either a water-insoluble or a hydrophilic polymer.

The release rate is dependent on the rate of drug diffusion through the matrix but not on the rate of solid dissolution. Equation 3 describes the amount of drug released from the systems as derived by Higuchi,

\[
Q = \frac{D\varepsilon}{\tau} [(2C_0 \varepsilon S_0 \tau)^{1/2} \quad \ldots \ldots 3
\]
Where,
\( Q \) = Amount of drug released per unit surface area,
\( D \) = Diffusion coefficient of the drug in the release media,
\( \varepsilon \) = Porosity,
\( \tau \) = Tortuosity of the matrix,
\( S \) = Solubility of the drug in the release media and
\( C \) = Concentration of the drug in the tablet.

The two types of diffusion controlled systems are,

**i) Matrix Diffusion Controlled Systems**

In this type, the drug is dispersed in an insoluble matrix of rigid, non-swellable hydrophobic material or swellable hydrophilic substances. Materials used for rigid matrix are insoluble plastics such as Poly-vinyl chloride and Stearic acid. With the plastic materials, the drug is generally kneaded with the solution of Poly-vinyl chloride in an organic solvent and then granulated. The granules are then compressed into tablets, swellable matrix systems are popular for sustaining the release of highly water soluble drugs. The materials for such matrices are,

- Hydrophilic gums: Guar gum, Tragacanth
- Synthetic: Polyacrylamides
- Semi-synthetic: Hydroxypropylmethyl cellulose, Carboxyl methyl cellulose

The drug release in this type of controlled release systems follows Fickian first order diffusion under equilibrium condition.
Matrix Tablet

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant.

Alternatively drug and retardant blend may be granulated prior to compression. The materials most widely used in preparing matrix systems are shown in Table No. 1, which includes both hydrophilic and hydrophobic polymers.

Commonly available hydrophilic polymers include Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose (HPC), Hydroxyethylcellulose (HEC), Xanthan gum, Sodium alginate, Poly (ethylene oxide) and crosslinked homopolymers and copolymers of Acrylic acid. It is usually supplied in micronized forms because small particle size is critical to the rapid formation of gelatinous layer on the tablet surface.

Table No. 1: Examples of Two Classes of Retardant Material used to Formulate Matrix Tablet

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Matrix Characteristics</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Insoluble, inert</td>
<td>Polyethylene, Polyvinyl chloride, Ethyl cellulose</td>
</tr>
<tr>
<td>2.</td>
<td>Insoluble, erodible</td>
<td>Carnauba wax, Stearic acid, Polyethylene glycol</td>
</tr>
</tbody>
</table>

Matrix Tablets can be classified as,

a) Hydrophilic Matrix Tablet

Hydrophilic matrix can be utilized as a means to control the drug release rate. The matrix may be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix materials. The hydrophilic matrix requires water to activate the release mechanism and explore several advantages, including ease of manufacture and excellent uniformity of matrix tablets. Upon immersion in drug release is controlled by a gel diffusion barrier that is formed and tablet erosion. The effect of formulation and processing variables on drug release behavior from compressed hydrophilic matrices has been studied by number of investigators. The matrix building material with fast polymer hydration capability is the best choice to use in a hydrophilic matrix tablet formulation. An inadequate polymer hydration rate may cause premature diffusion of the drug and disintegration of the tablet owing to fast penetration of water. It is particularly true for formulation of water soluble drug. The polymers used in the preparation of hydrophilic matrices are divided into three broad groups as follow,
- **Cellulose derivatives**
  Hydroxyethylcellulose, Hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000 cps, Sodium carboxymethylcellulose and Methylcellulose 400 and 4000 cps.

- **Non-cellulose natural or Semi-synthetic polymers**
  Agar-agar, Carob Gum, Alginates, Molasses, Polysaccharides of mannose and Galactose, Chitosan and Modified starches.

- **Polymers of acrylic acid**
  Polymers which are used in acrylic acid category is Carbopol 934. Other hydrophilic materials used for preparation of matrix tablet are Alginic acid, Gelatin and Natural gums.

b) **Fat-wax Matrix Tablet**
The drug can be incorporated into fat-wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray-drying techniques. In the bulk congealing method, a suspension of drug and melted fat-wax is allowed to solidify and is then comminuted for sustained-release granulations. The mixture of active ingredients, waxy materials and fillers also can be converted into granules by compacting with roller compactor, heating in a suitable mixture such as fluidized-bed and steam jacketed blender or granulating with a solution of waxy material or other binders.

The drug embedded into a melt of fats and waxes is released by leaching and/ or hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the gastrointestinal tract. The addition of surfactants to the formulation can also influence both the drug release rate and the proportion of total drug that can be incorporated into a matrix.

c) **Plastic Matrix Tablet (Hydrophobic matrices)**
The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. Sustained release tablets based upon an inert compressed plastic matrix have been used extensively. Release is usually delayed because the dissolved drug has to diffuse through capillary network between the compacted polymer particles. Plastic matrix tablets, in which the active ingredient is embedded in a tablet with coherent and porous skeletal structure, can be easily prepared by direct compression of drug with plastic materials provided the plastic material can be comminuted or granulated to desired particle size to facilitate mixing with the drug particle. In order to granulate for compression into tablets, the embedding process may be accomplished by,
1. The solid drug and the plastic powder can be mixed and kneaded with a solution of the same plastic material or other binding agent in an organic solvent and then granulated.
2. The drug can be dissolved in the plastic by using an organic solvent and granulated upon evaporation of the solvent.
3. Using latex or pseudo latex as granulating fluid to granulate the drug and plastic masses.
For example: Polyvinyl chloride, Ethyl cellulose, Cellulose acetate and Polystyrene.

**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. It is biologically degraded or eroded by enzymes generated by surrounding living cells or by nonenzymetic process into oligomers and monomers that can be metabolised or excreted. Examples are natural polymers such as proteins, polysaccharides and 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.

Matrix system can also be classified according to their porosity and consequently, macroporous, microporous and non-porous systems can be identified as,

**i) Macroporous 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.

**ii) Microporous System**

Diffusion in this type of system occurs essentially through pores. For microporous systems, pore size ranges between 50-200 Å, which is slightly larger than diffusant molecules size.

**iii) 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. Different drugs and polymers used in sustained-release based on matrix table is given in the following table.
Table No. 2: Different Drugs and Polymers Used in Sustained-Release Based on Matrix Tablet

<table>
<thead>
<tr>
<th>Drug</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopramide Hydrochloride</td>
<td>Hydroxy Propyl Methyl Cellulose (HPMC), Carboxymethylcellulose (CMC), Ethyl Cellulose (EC)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Ethyl cellulose, Cellulose acetate phthalate</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>HPMC K100M, Xanthan gum</td>
</tr>
<tr>
<td>Ambroxol Hydrochloride</td>
<td>HPMC</td>
</tr>
<tr>
<td>Tramadol Hydrochloride</td>
<td>Xanthan gum, Guar gum.</td>
</tr>
<tr>
<td>Tramadol Hydrochloride</td>
<td>Carrageenan gum, Karaya gum, HPMC K15 .</td>
</tr>
<tr>
<td>Aceclofenac</td>
<td>Carbopol 971P, Carbopol 974P</td>
</tr>
</tbody>
</table>

**Drug Release from Matrix Systems:**

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 toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following assumptions:

a) A pseudo-steady state is maintained during drug release,

b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix,

d) The bathing solution provides sink conditions at all times.

The release behavior for the system can be mathematically described by the following equation,

\[
\frac{dM}{dh} = \frac{Co \cdot dh - Cs}{2} \quad \ldots \ldots 4
\]

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,
\[ dM = \frac{(Dm \cdot Ca)}{h} \cdot dt \]  \hspace{1cm} \ldots \ldots 5

- \( dM \) = 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,
\[ dM = \frac{(Dm \cdot Cs)}{h} \cdot dt \]  \hspace{1cm} \ldots \ldots 5

- \( Dm \) = Diffusion coefficient in the matrix.
- \( h \) = Thickness of the drug-depleted matrix
- \( dt \) = Change in time

By combining equation 4 and 5 and integrating
\[ M = [Cs \cdot Dm \cdot (2Co - Cs \cdot t)]^{1/2} \]  \hspace{1cm} \ldots \ldots 6

When the amount of drug is in excess of the saturation concentration, then
\[ M = [Cs \cdot Dm \cdot Co \cdot t]^{1/2} \]  \hspace{1cm} \ldots \ldots 7

Equation 6 and 7 indicates the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores. The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix,
\[ M = [2D \cdot Ca \cdot p / T \cdot (2CO - p \cdot Ca)]^{1/2} \]  \hspace{1cm} \ldots \ldots 8

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 pathlength

For pseudo steady state, the equation can be written as,
The total porosity of the matrix can be calculated with the following equation,

\[ p = p_a + \frac{Ca}{\rho} + \frac{Cex}{\rho_{ex}} \]  

Where, \( p \) = Porosity, \( \rho \) = Drug density

\( p_a \) = Porosity due to air pockets in the matrix

\( \rho_{ex} \) = Density of the water soluble excipients

\( Cex \) = Concentration of water soluble excipients

For the purpose of data treatment, Equation 10 can be reduced to,

\[ M = k \cdot t^{1/2} \]  

Where \( k \) is 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. In this case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters,

- Initial concentration of drug in the matrix
- Porosity
- Tortuosity
- Polymer system forming the matrix
- Solubility of the drug

**ii) Reservoir Devices or Laminated Matrix Devices**

These systems are hollow containing an inner core of the drug surrounded in the water insoluble polymer membrane. The polymer can be applied by coating or microencapsulation techniques. The drug release mechanism across the membrane involves its partitioning into the membrane with subsequent release into the surrounding fluid by diffusion. The polymers commonly used in such devices are Ethyl cellulose and Poly-vinyl acetate. The disadvantage of reservoir devices over matrix diffusion controlled system is a chance of sudden drug dumping.

![Figure No. 5: Reservoir Devices or Laminated Matrix Devices](image)
C. Dissolution and Diffusion Controlled Release Systems
In such systems, the drug core is encased in a partially soluble membrane. Pores are thus created due to dissolution of parts of the membrane which permit entry of aqueous medium into the core and hence drug dissolution and allow diffusion of dissolved drug out of the system.

![Image](image.jpg)

Figure No. 6: Dissolution and Diffusion Controlled Release Systems

2. Delayed Transit and Continuous Release Systems
These systems are designed to prolong their residence in the GI tract along with their release. Often the dosage form is fabricated to detain in the stomach and hence the drug present therein should be stable to gastric pH. Systems included in this category are:
A. Altered density systems
B. Mucoadhesive systems
C. Size based systems.

3. Delayed Release Systems
The design of such systems involves release of drug only at specific site in the GIT. The drugs contained in such a system are those that are:
- Destroyed in the stomach or by intestinal enzymes
- Known to cause gastric distress
- Absorbed from a specific intestinal site
- Meant to extent local effect at a specific GI site
The two types of delayed release systems are:
A. Intestinal release systems
B. Colonic release systems

**Design of Sustained Release Dosage Forms**

The objective in designing a sustained release forms is to deliver drug at a rate necessary to achieve and maintain a constant drug blood level. This is usually accomplished by attempting to obtain zero order release from dosage forms. Zero order release constitutes drug release from dosage form that is independent of the amount of drug in the delivery system.

Generally sustain release system do not attain this type of release and try to mimic zero order release by providing drug in slow first order fashion as shown by following equation.

\[
\text{Rate in} = \text{Rate out} = K.C_d.V_d
\]

Where,

\( C_d \) = Desired drug level

\( V_d \) = Volume of distribution

\( K \) = elimination rate constant

**Figure No. 7: Design of Sustained Release Dosage Forms**
Factors Influencing Design of Sustained Release Dosage Forms $^{3,4,6}$:
The therapeutic efficacy of drug under clinical conditions is not simply a function of its intrinsic pharmacological activity but also depends upon the path of the drug molecule from the site of administration to the target site. Different conditions encountered by the drug molecule while traversing the path of distribution may alter either the effectiveness of the drug or affect the amount of the drug reaching the receptor site.

A. Pharmaceutics: This refers to the development/manufacturing of an efficient delivery system in which the drug has maximum physiological stability and optimum bioavailability.

B. Biopharmaceutics/pharmacokinetics: This involves the study of absorption, distribution, metabolism and excretion of the drug, before and after reaching the target site and evaluation of the relationship between delivery system and therapeutic response.

C. Pharmacodynamics/Clinical Pharmacology: It is the study of the mechanism of action and clinical efficacy of a drug administered in dosage form in terms of onset, intensity and duration of pharmacological activity.

Drug Properties Influencing the Design of Sustained Release Drug Delivery System are classified as $^{1,3,10,11}$:

A. Physicochemical Properties of the Drug

i) Aqueous Solubility:
   - A drug with good aqueous solubility, especially if pH independent, serves as a good candidate.
   - Drug to be absorbed it first must dissolve in the aqueous phase surrounding the site of administration and then partition into absorbing membrane.

ii) Partition Coefficient:
   - Between the time a drug is administered and is eliminated from the body, it must diffuse through a variety of biological membranes.
   - The ability of drug particles to penetrate through these membranes is given by Partition coefficient.

iii) Drug stability:
   - Drug for sustain release should not have a high degradation rate in GI track.
   - Drugs with stability problems are poor candidates.
Localized delivery can be attained by bioadhesive drug delivery systems and can act as reservoir of drugs, thus enhancing their bioavailability.

iv) Protein Binding:
- Most part of the blood protein are re-circulated and are not eliminated, drug-protein binding can serve as a depot.
- In general charged compounds have a greater tendency to bind a protein.
- Example: 95% PPB drugs are Diazepam, Dicoumarol, Novobiocin.

v) Dose size:
- For oral dosage form a dose size of 0.5 to 1.0 gm is considered maximum.
- Higher doses have to be given as liquids.
- Drugs with low therapeutic index needs to given additional core if dose size is high.

B. Biological Properties of the Drug:

i) Absorption:
- The rate-limiting step in drug delivery from a sustained release product is release, from the dosage form rather than absorption.
- A high absorption rate is advantageous for sustain drug release.
- The rate, extent and uniformity of absorption is an important factor, as here Kr<<Ka.

ii) Distribution:
- It not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibration with blood and extracellular fluid.
- The Vd and the ratio of drug in tissue to that of plasma at steady state is an important parameters to be considered in determining the release rate.

iii) Metabolism:
- Metabolism to other active form can also be considered as sustained effect.
- The extent of metabolism should be identical and predictable when the drug is administered by different routes.
- If a drug, upon chronic administration, is capable of either inducing or inhibiting enzyme synthesis, it will be poor candidate.

iv) Elimination Half Life:
- Smaller the t½, larger the amount of drug to be incorporated in the sustained release dosage form.
• Drug with the half life in the range of 2 to 4 hours make good candidate for such a system. e.g. Propranolol.

• Drugs with long half-life need not be presented in such a formulation e.g. Amlodipine.

v) Side Effect:

• The incident of side effects can be minimized by controlling the concentration at which the drug exists in plasma at any given time.

• Hence sustained release formulation appears to offer a solution to this problem.

CONCLUSION
Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue it is considered as controlled release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered a prolonged release system. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. The design of oral sustained release delivery systems is subject to several inter related variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug.

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