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SUSTAINED DRUG DELIVERY SYSTEM – A REVIEW

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ABSTRACT

Modified release drug delivery systems are those that release a drug over a long period of time. Israel Lipowski's 1938 patent for drug delivery dosage forms was a precursor to sustained release. The benefits of sustained release are to prolong the effects of a drug and to reduce the need for repeated dosing. Additionally, these candidates are unsuitable for SRDDS. Plasma concentration response relationship: In most situations, plasma drug concentration rather than dose is more essential for pharmacological activity. However, medicines with pharmacological activity unrelated to plasma concentrations are poor candidates for oral SR drug delivery systems. Concentration dependency on transfer of drug: Such drugs are poor candidates for oral SR delivery methods if the drug has been transferred from one compartment to another using a zero order kinetic process. It should be kinetically first order.

***KEYWORD-** Sustained Release, Polymers, Matrix, Drug Delivery.

INTRODUCTION

Any pharmaceutical product designed for systemic delivery via the oral route of administration, regardless of the mode of delivery (immediate, sustained, or controlled release), and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamics, and formulation design in order to achieve a systemic approach to the successful development of an oral pharmacology product.[1-5] The benefits of giving one dose of a drug that releases over a long period of time rather than many doses have been clear to the pharmaceutical industry for some time. Israel Lipowski's 1938 patent is where drug delivery dosage forms first appeared. This research focused on coated pallets for prolonged drug release and was probably a precursor to the early 1950s emergence of the coated particle method of sustained drug delivery.[6] By providing sustained, controlled delivery and/or directing the drug to the desired site, the novel drug delivery system provides a way to enhance the therapeutic benefit of the included drugs.[7] Any drug delivery system's objective is to rapidly and sustainably achieve the desired drug concentration by making a therapeutic quantity of the drug available to the body's appropriate site.[8] Any drug delivery system that achieves a slow release is considered a sustained release system. Release of drug distributed over a long period of time. A controlled-release system is a method that effectively keeps constant drug levels in the blood or the intended tissue.[9]

Terminology

Both controlled and sustained release have been implemented in a disorderly and disconcerting way. Both indicate different delivery processes. Any dosage form that provides medication over a prolonged period of time or indicates that the system is able to provide some actual therapeutic control, whether this is of a temporal, spatial, or both natures, is considered SR. Any drug delivery system that distributes medication over an extended period of time without regard to time has been included. A sustained dosage form is frequently made using a hydrophilic polymer matrix. The ideal drug delivery system's job is to keep the drug's therapeutic range in blood plasma by delivering the appropriate dose at the right site of action at the right time.[10,11]

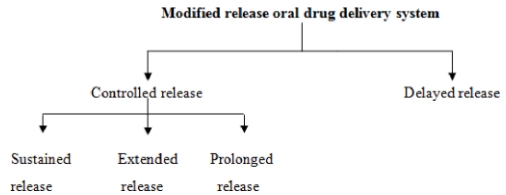


Figure 1: Classification of Modified Release Drug Delivery System.

The following are the rationale of developing SR[12,13,14]

1) To prolong the effects of the drug.
2) To lessen the frequency of dosing.
3) To reduce fluctuations in plasma level.
4) To improve drug absorption.
5) Less harmful effects.

Advantages of sustained release dosage forms[12,13,14]

1) Less medication is administered frequently.
2) It is possible to increase patient compliance.
3) It is also possible to improve the administration of medications.
4) There is a decrease in the oscillation in blood levels that multiple doses of conventional dosage forms are known for.
5) Since the high blood level peaks that may be observed following the administration of a dose of a high availability drug can be reduced, better control of drug absorption can be attained.
6) It is possible to reduce the typical blood level variations helped bring on by multiple doses of conventional dosage forms.
7) By reducing the total amount of medication given, it is possible to:
- Increase drug availability with the lowest dose.
- Reduce or eliminate drug accumulation with repeated dosing.
8) In sensitive patients, the frequency of both local and systemic adverse side effects can be reduced, and the safety margins of high potency drugs can be increased.
9) Increase therapeutic efficacy.
- Treat or manage condition more quickly
- Improved condition control and increased drug bioavailability
- Utilize special effects, such as sustained release aspirin for morning arthritis relief by taking a dose before bed.
10) Economy.

Disadvantages of sustained release dosage forms[12,13,14]

1) The possibility of dose dumping.
2) Lessened possibility of dose modification.
3) Single unit costs are higher than those of conventional dosage forms.
4) Enhance first pass metabolism potential.
5) The demand for more patient education regarding appropriate medication.
6) Lower systemic availability compared to conventional, immediate-release dosage forms.
7) Insufficient correlations in vitro and in vivo.

Theoretical Overview[15,16,17,18]

A steady-state blood or tissue level that is beneficial for the treatment and non - toxic for an extended period of time is the fundamental aim of therapy. It is simple to classify modified-release delivery systems into the four following groups:
1) Delayed release.
2) Sustain release.
3) Site-specific targeting.
4) Receptor targeting.

When one or more immediate-release components are combined into a single dose form, a drug is dosed repeatedly and intermittently using a delayed release system. Repeat action tablets, capsules, and enteric coated tablets are some examples of delayed release systems where timed release is achieved by barrier coating.

Any drug delivery system that achieves a slow release of drugs over an extended period is considered a sustain release system. A system is considered to be a controlled-release system if it is capable of controlling the release of a drug into to the body, whether this control is of a temporal, spatial, or both. In other words, the system is effective in maintaining constant drug levels in the target cells or tissues. Site-specific targeting is when a drug is directed specifically at a few specific biological sites. With site-specific release, the target is either near or inside the organ or tissue that is afflicted. Receptor targeting describes a drug's specific target receptor in a tissue or organ. These two systems are considered of as controlled drug delivery systems because both of them meet the requirements for drug delivery.

Drug Selection for Oral Sustained Release Drug Delivery System[19,20]

The biopharmaceutical estimation of a drug for potential use in a controlled release drug delivery because to comprehension of the drug's mechanism of absorption from the gastrointestinal tract, general absorbability, molecular weight, pKa, solubility at different pH levels, and apparent partition coefficient.[21]

Table 1: Parameter for Drug Selection.

Content	Preferred Value
Molecular Weight/Size	< 1000
Solubility	> 0.1 µg/ml for pH 1 to 7.8
Pka	Non ionized moiety > 0.1% at pH 1 to 7.8
Apparent Partition Coefficient	High
Absorption Mechanism	Diffusion
Absorbability From all G.I. segments	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 Vd 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 Cssav	The lower Cssav and smaller Vd, 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.

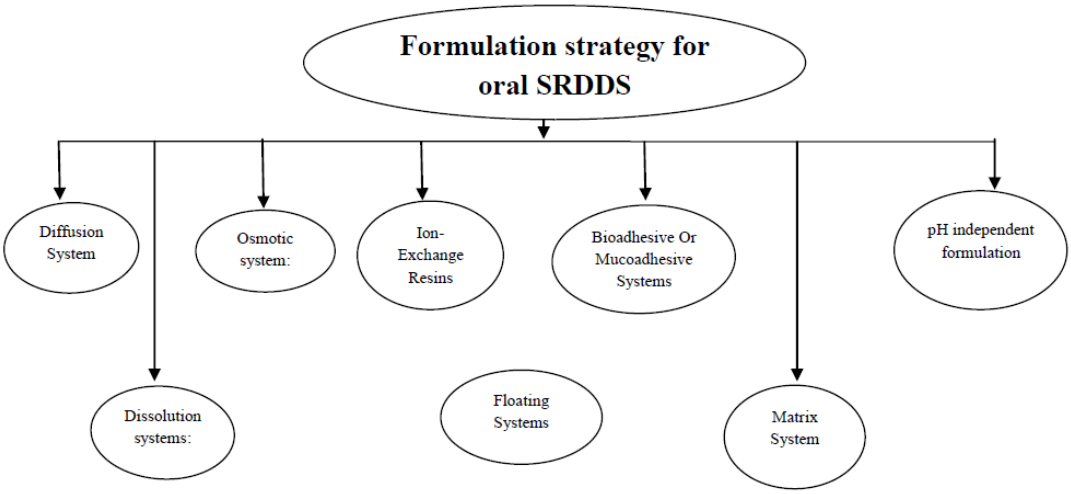


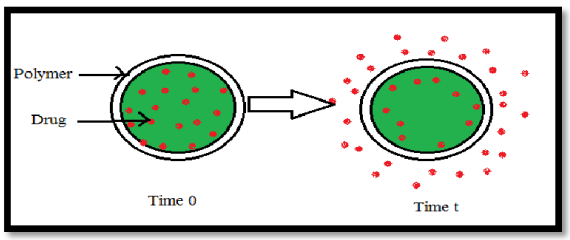
Figure 2: Formulation Strategy for Oral Sustained Release Drug Delivery System.

- **Classification of SR Formulation**[22-24]

The following are the methods that are most commonly used to ensure that medications taken orally release their effects over time:

1) Diffusion systems: In a diffusion system, the drug's rate of release is determined by how rapidly it diffuses through an inert membrane barrier. This barrier generally consists of an insoluble polymer. In general, reservoir devices and matrix devices are identified as two types or subclasses of diffusional systems.

a) Reservoir Devices: Devices with a reservoir consist of a drug-filled core that is surrounded by a polymeric membrane, as the names indicate. The membrane's composition affects how quickly substances leave the body. Polymer coatings may also be used to achieve sustained release. Rather than dissolving for this purpose, the polymer must allow the drug to diffuse through the polymer membrane to the outside, or in the case of oral drug delivery, into the gastrointestinal tract.



4: Schematic Representation of Diffusion Type Reservoir

Figure 3: Schematic Representation of Diffusion Type Reservoir System.

b) Matrix Devices: As the name suggests, a matrix device contains drug that is distributed evenly throughout a matrix of polymeric materials. In the model, the drug first dissolves in the layer that is exposed to the showering solution before diffusing out of the matrix. In order for this system to be diffusion controlled, the rate of drug particle dissolution within the matrix must be much faster than the rate of diffusion of dissolved drug leaving the matrix. The above process will continue with the interaction between both the bathing solution and the solid drug moving towards the interior.

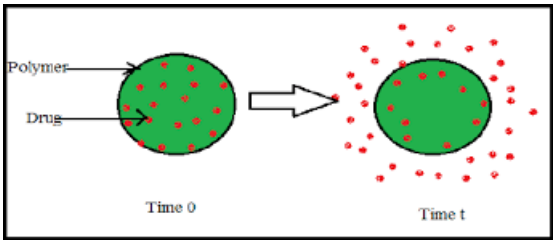


Figure 4: Schematic Representation of Diffusion Type Matrix System.

2) Dissolution systems: Because the dissolution rate will limit the amount of drug released, it seems obvious that a drug with a slow dissolution rate will display sustaining properties. Given this, drugs could be ready for sustained release by slowing their rate of dissolution. The methods to achieve this include making the suitable salts or derivatives, coating the medication with a material that dissolves slowly, or including the medication in a tablet that dissolves slowly.

3) Osmotic system: A constant release of the drug is generated using osmotic pressure as the driving force. Consider a semipermeable membrane that is drug as well as water impermeable. Due to the osmotic pressure difference, water will flow into the tablet whenever this device is exposed to water or any other biological fluids. There are typically two variations of these systems. The first contains an electrolyte that is dissolved by water coming and the drug as a solid core. The high osmotic pressure difference is provided by the electrolyte. The device's second system has the medication in solution inside of an impermeable membrane.

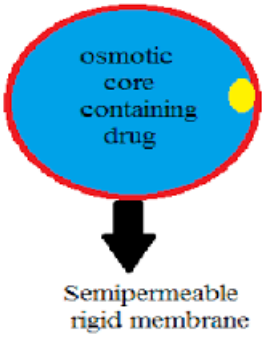


Figure 8: Type-A osmotic system

Figure 5: Type-A osmotic system.

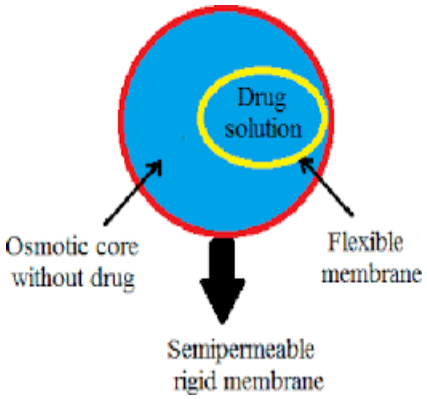


Figure 6: Type-B osmotic system.

4) Ion-exchange resins: Ion-exchange systems generally employ resins made of cross-linked, water-insoluble polymers. Salt-forming functional groups can be identified in these polymers at repeated locations along the polymer chain. By exchanging with appropriately charged ions in contact with the ion-exchange groups, the drug is bound to the resin and released. Resin+ - drug - + X - resin+ - = X - + drug – Conversely, Resin- - drug+ + Y + resin- - = Y + + drug+ The free drug diffuses out of the resin. The drug resin complex is prepared either by repeated exposure of the resin to the drug in a chromatography column, or by prolonged contact in solution.

5) Floating systems: The duration of time the drug is released before the stomach empties into the small intestine can be extended if the dosage form has a lower density than the gastric fluids and floats on top of the stomach's components. The density of the gastric fluid is around 1 gm/cm3. The dosage form will float on the gastric fluids if its density is lower than that. As stated above, these systems contact for the stomach to contain an adequate amount of fluid as well as food.

6) Bioadhesive or Mucoadhesive systems: To obtain gastric retention, it has also been recommended to use bioadhesive or mucoadhesive polymers such as polyacrylic acid and chitosen. The fundamental principle is that the dosage forms adhere to the mucus of the gastric wall due to the mucoadhesive or bioadhesive polymers. Due to the rapid turnover of the mucus in the stomach, the bioadhesive or mucoadhesive approach is reasonable for buccal or sublingual formulations, but it is not as simple for gastroretentive systems. The dosage forms may also contain magnetic materials as a final step. An external magnate can then be used to hold these systems in place, but doing so requires careful positioning and is not likely to result in high patient compliance.

7) Matrix systems: The direct compression of mixtures of drug, retardant, and additive materials to produce a tablet with the drug embedded in the matrix core of the retardant is one of the simplest methods for producing sustained release dosage forms. Retardant drug mixtures may also be granulated before compression.

Types of Matrix

Hydrophobic Matrices: In this technique, the drug is combined with an inert or hydrophobic polymer and compressed into a tablet to achieve and sustain release from an oral dosage form. The drug that's also dissolving has diffused through a network of channels that are present between compacted polymer particles, resulting in sustained release. The polymers and their co - polymers of polyethylene, polyvinyl chloride, ethyl cellulose, and acrylate have all been used as inert or hydrophobic matrices.

Lipid Matrices: These matrices have been formed using lipid waxes and related compounds. Drug release from these matrices occurs via pore diffusion as well as erosion. Therefore, release characteristics are more sensitive to digestive fluid composition than a polymer matrix that really is totally insoluble. For many sustained release formulations, carnauba wax is used as the retardant base in combination with stearyl alcohol or stearic acid.

Hydrophilic Matrices: A matrix is an extensively combined mixture of one or more drugs as well as a gelling agent (hydrophilic polymer). Swellable controlled release systems are what these systems have been known as. Three broad categories of polymers are used in the formation of hydrophilic matrices.

- Methylcellulose 400 and 4000cPs, hydroxyethylcellulose, hydroxypropylmethylcellulose (HPMC) 25, 100, 4000, and 15000cPs, and sodium carboxymethylcellulose are all cellulose derivatives.
- Agar-Agar, carob gum, alginates, molasses, polysaccharides of mannose and galactose, chitosan, and modified starches are examples of noncellulose natural or semi-synthetic polymers.

Biodegradable Matrices: These are composed of polymers with unstable backbone linkages made up of monomers linked to one another by functional groups. By means of enzymes produced by nearby living cells or through enzymatic and non - enzymatic processes, they are biologically eroded or degraded into oligomers and monomers that can be metabolised or excreted. Examples are including synthetic polymers such as aliphatic poly (esters) and poly anhydrides, as well as natural polymers such as proteins and polysaccharides, as well as modified natural polymers.

Mineral Matrices: These are made up of polymers that originate from various kinds of seaweed. An example of this is alginic acid, a hydrophilic carbohydrate that is made from brown seaweed species (Phaephyceae) using diluted alkali.

On the Basis of Porosity of Matrix: Matrix tablets can be divided in to 3 types.

•**Macro porous systems**: In these systems, drug diffusion takes place through pores in the matrix that range in size from 0.1 to 1 m. This pore size is bigger than the size of the diffusant molecule.

• **Micro porous system:** In this kind of system, diffusion takes place mainly through pores. Pore sizes in micro porous systems range from 50 to 200 A°, which is a little bigger than the size of diffusant molecules.

• **Non-porous system:** Molecules diffuse through the network meshes throughout non-porous systems because they lack pores. In this example, there is only the polymeric phase and no pore phase.

8) pH Independent Formulations: Most substances are weak bases or weak acids. Sustained release formulations' release is pH-dependent. Buffers, however, such as phthalic acid, citric acid, and amino acid salts The formulation can be enhanced with phosphoric acid or tartaric acid to help maintain the pH stable and enable pH independent drug release. A basic or acidic drug is combined with one or more buffering agents to create a buffered formulation. The mixture is then granulated with the proper pharmaceutical excipients and coated with a gastrointestinal fluid permeable film forming polymer. The buffering agents adjust the fluid inside to a suitable constant pH when gastrointestinal fluid permeates through the membrane, resulting in a constant rate of drug release.[25,26]

- **Factors Affecting Sustained Release Drug Delivery System**

1) Physicochemical factor[26]

- Dose Size: For a conventional dosage form, a single dose that contains between 500mg and 1.0g of a drug is widely considered as the maximum. compounds with large doses that occasionally can be administered in multiple doses or are formulated into liquid systems The same standards apply to sustained release dosage forms.

- Ionization, pka and aqueous solubility: Most drugs are primarily weak bases or acids. Since unchanged drugs can pass through lipid membranes, the relationship between the compound's pka and the absorptive environment is crucial. The solubility of the drug in aqueous media will be equally important to delivery systems that depend on diffusion or dissolution. These dosage forms must work in a pH-changing environment, with the small intestine being more neutral and the stomach being more acidic. The effect of the release process must also be defined. Low soluble compounds (0.01 mg/ml) are inherently sustained because the drug's dissolution will limit their release over the course of a dosage form in the GI tract.

- Partition Coefficient: When a drug is administered to the GI tract, it must cross a variety of biological membranes in order to have a therapeutic effect in another area of the body. The partition coefficient of oil soluble drugs is significant in determining the efficiency of membrane barrier penetration because it is common to

assume that these membranes are lipidic. Compounds with high partition coefficients that are lipophilic in nature are poorly soluble in water and stay in the lipophilic tissue for a longer period of time. When a substance has a very low partition coefficient, it is extremely difficult for it to cross the membrane, which leads to a low level of bioavailability.

- Stability: The drugs that are administered orally are subjected to both enzymatic and acid-base hydrolysis. This is the preferred composition of delivery for problematic cases because a drug's degradation will proceed at a slower rate in the solid state. Systems that prolong delivery over the entire course of transit in the GI tract are beneficial for dosage forms that are unstable in the stomach. This holds true even for systems that hold off on releasing the medication until the dosage form reaches the small intestine. When taken from a sustaining dosage form, substances that are unstable in the small intestine may exhibit decreased bioavailability. This is due to the small intestine's increased drug delivery and the drugs' vulnerability to degradation.

2) Biological Factor[27]

- Half-life: A drug's half-life is a measure of how long it stays in the body. A prohibitively high concentration of the drug may be present in the dosage form if the drug has a short half-life (less than 2 hours). Particularly in comparison, medications with an elimination half-life of at least 8 hours are sufficiently controlled in the body when taken in conventional dosages, necessitating the absence of a sustained release drug delivery system in these circumstances. For the creation of a drug delivery system, the drug should ideally have a half-life of 3–4 hours.

- Therapeutic index: A drug's dose in its standard dosage form helps determine whether or not it is a suitable candidate for SRDDS. This is because the size of a unit dose of a sustained release oral formulation to become too large to administer appropriately.

- Absorption window: When taken orally, a few medications are only absorbed from a particular region of the gastrointestinal tract. The "absorption window" is the name given to this area. Additionally, these candidates are unsuitable for SRDDS.

- Plasma concentration response relationship: In most situations, plasma drug concentration rather than dose is more essential for pharmacological activity. However, medicines with pharmacological activity unrelated to plasma concentrations are poor candidates for oral SR drug delivery systems.

- **Concentration dependency on transfer of drug:** Such drugs are poor candidates for oral SR delivery methods if the drug has been transferred from one compartment to another using a zero order kinetic process. It should be kinetically first order.

CONCLUSION

As per literature survey it was conclude that the use of Sustained Release Dosage Form was really helpful to overcome the patient compliance problems which are associated with the conventional Dosage Form. The advantage of Sustained Release Formulation are that they can often be taken less frequently than instant formulation of the same drug and that they keeps steadier levels of drug in blood stream. They are economic as compare to oral conventional dosage form.

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