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Sustained release drug delivery systems: A review

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Abstract
The oral route is the most common route for drug administration, in part because it is simple to use and because gastrointestinal physiology allows for more design freedom in dosage forms than most other routes. Drug delivery systems that are intended to produce or increase therapeutic effect by continually releasing medication over a longer duration of time upon administration of a single dose are referred to as long-lasting release, prolonged release, modified release, extended release, or depot formulations. these dosage types are appealing for a number of reasons: reduces the variability of peak trough concentration, adverse effects, and frequency of administration to extend the duration of therapeutic blood levels. It also increases the bioavailability of the drug product. the most popular and practical method of drug administration is oral drug delivery because it offers the most active surface area of any drug delivery mechanism. for internal mode of treatment, oral drug delivery stays best and the most favored for delivery for various drugs. Sustained Release can be used to reduce a drug's adverse effects and boost its therapeutic effectiveness. due to knowledge of drug toxicity and ineffectiveness when administered orally using the conventional approach in the form of tablets and capsules, these dosage forms are more appealing.

Keywords: sustained release, controlled release, receptor targeting, polymers

Introduction

In the last 30 years, as the costs and difficulty of marketing novel drug entities have grown, the therapeutic benefits of long-lasting drug administration have also become more widely acknowledged. The creation of oral extended-release drug delivery devices is receiving more focus. Reducing dosage, dose frequency, and ensuring uniform drug delivery are the objectives of the creation of extended-release drug delivery systems. So, a dosage form known as "sustained release" administers one or more medications constantly and according to a preset schedule for a set amount of time, either systematically or locally to a specific target organ. Extended release dosage forms offer more consistent drug delivery, reduced dosage frequency, fewer side effects, and greater regulation of plasma drug levels. **(1)** One of the most reliable and frequently used oral dosage types is the tablet. Tablets have been widely used since the latter part of the nineteenth century, and their appeal has not diminished. Tablets are still a common dosage type because of the benefits they provide to both pharmaceutical companies and patients. They are blandness of flavor, ease of administration, accuracy of single dose regimen, stability and convenience of packing, ease of transport and dispensing, simplification and economy of preparation. By localizing the drug at the site of action, lowering the dosage needed, and ensuring uniform drug delivery, sustained as well as controlled delivery systems aim to decrease frequency of dosing or increase the efficacy of the drug. Imagine the perfect medication delivery system:**(2)** The treatment of rheumatoid arthritis must include the use of non-steroidal anti-inflammatory drugs (NSAIDs). (RA). The tumor necrosis factor-alpha (TNF-a) biologic agents, which are only recommended in a small percentage of patients with severe RA, can be treated successfully with methotrexate (MTX). The "anchor drug" for the management of RA is still MTX.
MTX-Cubosomes, a novel pharmaceutical medication delivery system, were created to enhance delivery [3].

The categorization of oral delivery systems with modified release as following:

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

A. Delayed release

One or more instant release units are combined into a single dosage form in these systems, which employ repetitive, irregular dosing of a medication. Repeat action tablets, capsules, and enteric-coated tablets, where timed release is accomplished by a barrier coating, are some instances of delayed release methods. B) Sustained release:
The interest in sustained release medication delivery systems has increased significantly over the past 20 years. The prohibitive cost of developing new drug entities, the expiration of current international patents, the discovery of new polymeric materials suitable for delaying the release of the drug, and the improvement in therapeutic efficacy and safety attained by these delivery systems are just a few of the factors that have contributed to this. Today, veterinary products are also using the technique of sustained release. products. These systems also offer a slow drug release over a longer period of time and have the ability to control drug release in the body, either spatially or temporally or both. In

summary, the system is effective at maintaining constant levels of drugs in the targeted area of tissue or cells.

1. Controlled release
Any method of drug delivery that accomplishes a slow release of the drug over a prolonged period of time is included in these systems.

2. Extended Release
The dosage forms of pharmaceuticals that release the medication at a preset rate but in a slower than usual manner must double the dosage frequency.

C. Site specific targeting
These methods speak of direct drug delivery to a specific biological site. In instance, the affected organ or tissue is nearby or contains the target.

D. Receptor targeting
These methods speak of direct drug delivery to a specific biological site. In this instance, the target is a specific chemical receptor found in a tissue or organ. Systems for site-specific targeting and receptors. targeting are also thought of as continuous drug delivery methods because they meet the spatial requirement of drug delivery [4].

Classification of Modified Release Drug Delivery System
Some characteristics, such as dose maintenance, sustained release rate, and site targeting, are absent from the IR drug delivery system. Some possible benefits of oral sustained drug delivery include sustained release rate and plasma dose maintenance. The release rate is controlled by waxes, polymers that swell, or a combination of both in the SR formulas. The reservoir method is also effectively used. recognized for regulating discharge rate. demonstrates the relationship between plasma concentration and duration.

Advantages of Sustained/Controlled release drug delivery system over the conventional dosage form

1. Decreased regularity of dosing.
2. Lowering the dose.
3. Patient cooperation has improved.
4. Blood plasma drug content remains constant.
5. Reduced toxicity as a result of an excess.
6. Decreases the peak-to-valley concentration variation.
7. Dosing at night can be prevented [5].

Formulation strategy for oral SRDDS

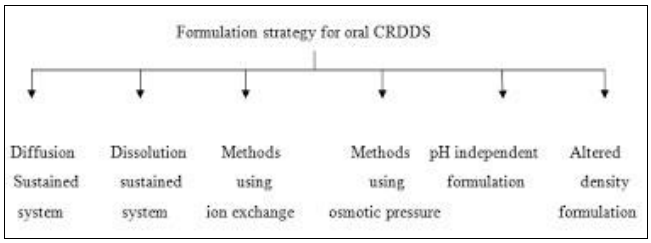


Fig 1: Formulation Strategy for Oral Sustained Release Drug Delivery System

1. Diffusion sustained system
Drug molecules move through the diffusion process from an area of higher concentration to another of lower concentration.

a. Diffusion reservoir system
In this system, the drug's core is covered by a polymeric substance that is insoluble in water. Drug will trade with the fluid associated with the particle or tablet after partitioning into the membrane. More medication will penetrate the polymer, move to the periphery, and interact with the media there. The diffusion process is used for drug release. demonstrates the dispersion type reservoir device.

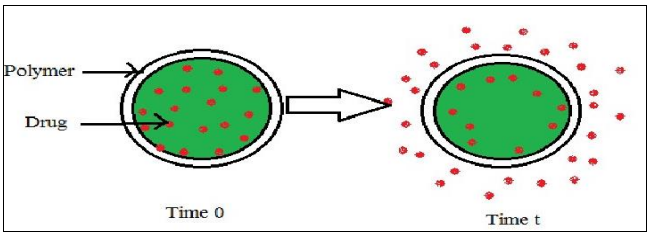


Fig 2: Schematic Representation of Diffusion Type Reservoir System

Advantages	Disadvantages
Zero order delivery is possible. Release rates can be modified with polymer type & concentration.	Difficult to deliver high molecular weight compound. Generally increased cost per dosage unit. Potential toxicity if dose dumping occurs.

b. Diffusion matrix system
The term "matrix system" refers to a thoroughly combined mixture of one or more medicines and a gelling agent, such as hydrophilic polymers.
The discharge rate is frequently sustained by matrix systems. The release mechanism is what delays and regulates the drug's dispersed or dissolved release. A solid drug is distributed in an insoluble matrix, and drug release is influenced by drug diffusion rate rather than solid dissolution rate.

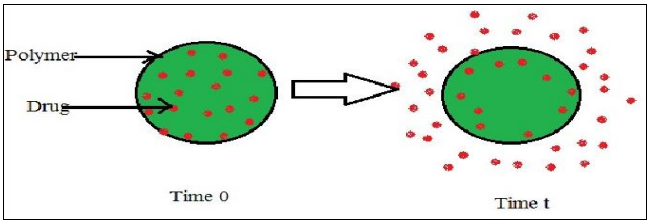


Fig 2: Schematic Representation of Diffusion Type Matrix System

Advantages	Disadvantages
Easier to produce than reservoir or encapsulated devices. Versatile, effective and low cost. Possible to formulate high molecular weight compounds. Increased the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract	The ghost matrix must be removed after the drug has been released. The release rates are affected by various factors such as, food and the rate transit through the gut. Cannot provide pure zero order release.

2. Dissolution sustained systems
Drugs that are naturally sustained and those with a high water solubility can have their dissolution rate reduced by the creation of the proper salts or derivatives. Enteric

covered dosage forms are most frequently produced using these methods.

A coating that dissolved in pure or alkaline solutions is used to shield the stomach from the effects of medications like aspirin. As a result, drug release from the dosage form is delayed until it hits the higher pH of the intestine. Most of the time, enteric covered medication forms are not genuinely supporting in nature, but they do serve a useful purpose in guiding drug release to a specific site. Compounds that degrade due to the harsh surroundings found in the gastrointestinal area can be treated using the same method.

a. Soluble reservoir system

This method coats the medication with a coating of a specific thickness, which is then gradually dissolved in the contents of the gastrointestinal tract. Drug layers are alternated with rate-regulating coverings as demonstrated

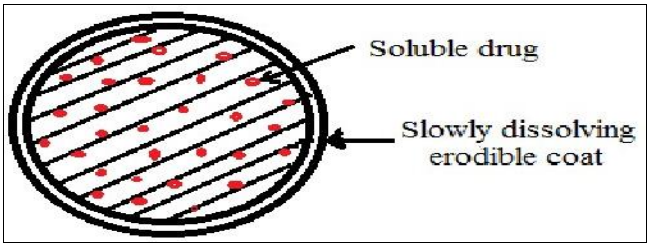


Fig 3: Schematic Representation of Dissolution of Reservoir System

accomplished. Initial drug levels in the body can be quickly set with pulsed intervals. The biological effects may be comparable, despite the fact that this is not a true longlasting release system. An alternative way is to administer the medication as a collection of beads with varying coatings.

The beads' release happens gradually because of the various coating thicknesses. The original dose will be given by those with the thinnest layers. Thicker coating can be used to deliver the drug's maintenance dosage. The spansule capsule operates on a similar premise.

For pills containing acetyl salicylic acid, the nitrate of cellulose phthalate was created to serve as a coating agent.

b. Soluble matrix system

It could either be a drug-impregnated spheroid or a drug-impregnated tablet, and both will slowly erode. The more prevalent kind of sustained-dissolution dose form as shown down

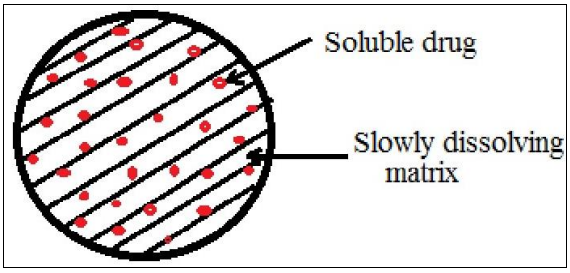


Fig 4: Schematic Representation of Dissolution Matrix System

c. Dissolution- sustained pulsed delivery system

Due to the following benefits, hydrophilic matrix technological advances is the most popular among sustained release formulas.

- provide a broad range of therapeutic drug categories, drugs, and solubility the desired release profiles.
- Manufacturing is straightforward, economical, and durable.
- approval by patients
- Drug control is made simple through level, polymeric system selection, and function coating.

An excipient mixture of drug, polymer, and excipients (filler/diluents and other excipients) made by hydrophilic polymers in the matrix makes up a hydrophilic matrix tablet. Formulators frequently select from a variety of hydrophilic polymers as stand-alone or in conjunction with other polymers for control of release rate.

3. Ion exchange resins sustained release

Cross-linked, water-insoluble polymers with ionisable functional groups are ion exchange resins. The resins were previously used in a variety of pharmaceutical applications, mainly for controlled release mechanisms and taste masking. Ionic exchange resins were previously used as a disintegrate in tablet formulas because of their capacity to swell. Upon extended exposure of the medication to the resin, it creates an irreversible complex with ionisable drugs. When the right ions come into touch with the ion-exchanged groups, the resin-bound drug is released. The quantity of cross-linked polymer within the resin moiety, the area as well as length of the diffusion pathway, and the rate of drug absorption are all controlled by these factors. Ion exchange resin with a drug that has the opposite charge has been discovered to have an impact in a matrix system, according to Sriwongjanya *et al*. Following their research, they came to the conclusion that the incorporation of ion exchange resins to HPMC matrices caused the release of drugs with opposite charges to be delayed due to the formation of a complex between the drugs and resin.

4. Methods using osmotic pressure

The osmotic pressure differential between inside the compartment and the outside environment must be optimized in this technique to control release. The most straightforward and predictable method to maintain a constant osmotic pressure in a container is to keep an osmotic agent solution saturated in the compartment. With the help of this technology, hydrophilic medicines can be released with zero order. A drug may join with an osmotically active salt, such as NaCl, or be osmotically active on its own. The hydrostatic pressure created by a liquid in a space divided by a semipermeable membrane as a result of a variation in solute concentration is known as osmotic pressure. Osmosis is the process by which fluid diffuses through a semipermeable membrane from a low concentration of solute solution to a solution with a greater solute concentration solution until there is a comparable amount of fluid on each side of the membrane. A tablet, particle, or drug solution is enclosed in a semi-permeable membrane that permits the passage of water into the tablet and eventually the pumping of the drug fluid out of the tablet by a tiny delivery aperture in the tablet coating. Type-A and Type-B are the two main categories into which the osmosis systems fall.

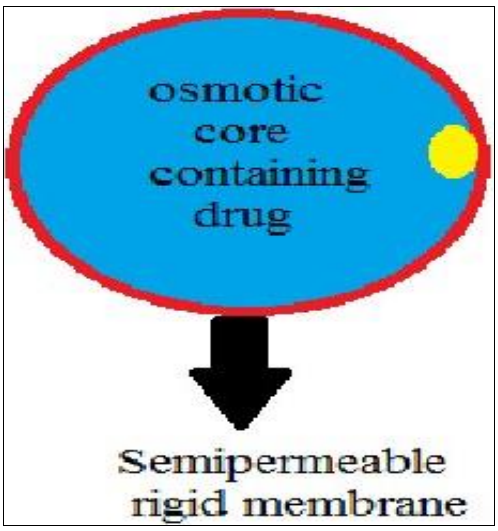
Drugs and electrolytes are both present in the type-A system's centre. The electrolytes sustain the rate of release of drugs and supply osmotic pressure.

In a semi-permeable membrane encircled by electrolytes, the drug fluid is present in a Type-B system. The two methods are depicted in:

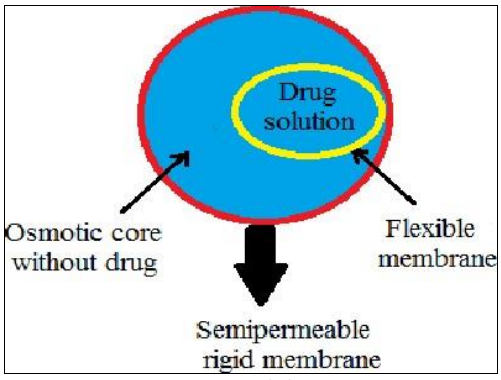
A. Single chamber osmotic pump:
- Elementary osmotic pump (EOP) Ø

B. Multi chamber osmotic pump
- Push pull osmotic pump.
- Osmotic pump with non-expanding second chamber.

C. Specific types
- Controlled porosity osmotic pump.
- Monolithic osmotic systems.
- Osmotic bursting osmotic pump.
- OROS – CT Multi particulate delayed release systems (MPDRS)
- Liquid Oral Osmotic System (L-OROS)



Type(A)



Type(B)

5. pH Independent formulations

The majority of medicines are either weak bases or weak acids. Sustained release formulations' discharge is pH-dependent. However, buffers can be added into the formulation to help keep a constant pH, resulting in pH separate from drug release. Examples of these buffers include derivatives of amino acids such as citric acid, phthalic acid, phosphoric acid, or tartaric acid. A basic or acidic medication 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 producing polymer. The buffering agents adjust the fluid inside to an appropriate constant pH when gastrointestinal fluid permeates by the membrane, resulting in a constant rate of drug release.

6. Altered density formulations

To extend the residence time of a method of drug delivery in the gastrointestinal tract, various strategies have been devised. The delivery mechanism waits until a majority of the drug in it has been released before moving away from the absorption site. When using a high density method, the pellets' density must be greater than that of the contents of a typical stomach and must therefore be between 1-4g/cm3. The perceived density of the globular shells in low density approaches a drug carrier with a pH level that is lower than the gastric juice can be used for prolonged release purposes. These dosage types are appealing for a number of reasons: gives the medicinal product's bioavailability a boost. This method is typically used when a single dose is needed for the entire course of treatment, whether it lasts for weeks or days, as is the case with infections, diabetes, or hypertension [6].

Methods to achieve oral sustained drug delivery

The creation of orally sustained release delivery systems uses a variety of techniques. Ritschel has provided a thorough report on these methods. These are listed below.

a. Hydrophilic matrix
b. Plastic matrix
c. Barrier resin beads
d. Fat embedment
e. Repeat action
f. Ion exchange resin
g. Soft gelatin depot capsules
h. Drug complexes

Hydrophilic matrix system

Natural gums, polyethylene oxide, polyvinyl-107, Molidones, Hydroxymethyl cellulose, Carboxymethyl cellulose sodium, polyethylene oxide, and matrix components. The active component and specific hydrophilic carriers may be directly compressed to form the matrix, or the drug and hydrophilic matrix material may be combined in a wet granulation.

The hydrophilic matrix quickly creates a gel coating around the tablet after submersion in water. A gel-like diffusional barrier and/or tablet erosion maintain drug release.

Requirements of matrix materials

The following requirements must be met by the matrix materials:

1. They must be entirely neutral towards the medication and tablet ingredients.
2. When crushed, either directly or more frequently as granules made by adding a binding agent, they should be able to form a robust and strong matrix. 3) They must be harmless [7].

Polymers

Polymers' enhanced pharmacokinetic properties have made them a crucial component of drug delivery devices. Since they circulate more quickly than traditional tiny drug molecules, they more effectively target tissue. In the fields of polymer therapies and Nano medicines, polymers have

been used extensively. In reservoir-based drug delivery systems, polymers have made significant advancements in the shape of hydrogels as well and liposomes [8]. molecules with a constant carbon backbone. Monomers are the tiny, unique repeating elements or molecules. A copolymer or Homopolymer is a polymer made up of two distinct molecules. Low density, excellent corrosion resistance, affordability, poor resistance to temperature change, and transparency or in colors are just a few of its qualities. For many years, polymers have been employed as excipients in traditional dosage forms that are taken orally for rapid release.

Prior to the tablet, polymers like polyvinyl pyrrolidone and HPMC are used as binders to help create granules that enhance the flow and practical properties of tablet formulations. To prevent a drug from degrading, hide the flavour of an unpleasant medication or excipients, or improve the formulation's visual appeal without slowing the drug's release rate, dosage forms occasionally need to be coated with a "nonfunctional" polymeric film [9]

Some of polymers used in sustained release

Type of polymers	Example
1. Natural polymers	Aloe Vera, Calcium Hydroxide, Gelatin, Gum Tragacanth, Xanathan gum, Bees wax, Acacia gum
2. Synthetic polymer	HPMC K100M, Carbopal974p, HPMCk4m, Ethyl cellulose, Polyvinyl acetate

Conclusion

The current review demonstrates of Sustained Release Drug Delivery System (SRDDS) one of the common techniques in the world of pharmaceutical sciences. It is characterized by being used once at a long time. It does not need to take the medicine more than once, because the medication lasts up to eight hours by release it in small doses for long-term therapy. Polymers help for that technique which is responsible for controlling of the drug release.

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