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A BRIEF OVERVIEW OF SUSTAINED RELEASED DRUG DELIVERY SYSTEM

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ABSTRACT

Since the quick release and repeated dosing of the drug in traditional drug delivery systems may increase the danger of dose variation, a formulation with regulated release that maintains a nearly constant or uniform blood level is required. For medications that have short half-lives and need to be taken repeatedly, sustained release systems are thought to be a better option because they are simple to make and do not depend on the gastrointestinal tract's absorption process following oral administration. The fundamental goal of these dosage forms is to maximize drug delivery in order to attain a measure of therapeutic effect control in the face of unpredictable fluctuations in the in vivo environment where drug release occurs. Any medication delivery method that distributes the drug gradually over a long period of time is considered a sustained release system. Because sustained release keeps the therapeutic concentration of the medicine from changing in the body, it also offers a promising means of reducing the drug's negative effects. In order to increase usefulness, minimize side effects, and treat the disease, the sustained drug delivery system's underlying logic optimizes the drug's biopharmaceutical, pharmacokinetic, and pharmacodynamic properties. Improvements in drug therapy as determined by the balance between the benefits and drawbacks of using sustained release systems are the main objective of sustained release forms.

Keywords: Sustained Release, Dose Frequency, Physicochemical Properties Of Drugs, Biological Half Life.

I. INTRODUCTION

Among all the methods that have been investigated for the systemic distribution of pharmaceuticals via diverse pharmaceutical products of the different dosage form, oral drug delivery has long been recognized as the most popular method of administration. A formulation with regulated release that maintains a nearly constant or uniform blood level is required since traditional drug delivery systems (DDS) are characterized by fast release and frequent dosing of the medication, which may increase the danger of dose fluctuation. As a result, the majority of pharmaceutical scientists today work on creating the perfect DDS. The benefit of a single dose for the length of treatment and controlled drug delivery at a specific place are features of the ideal system [1,2]. In order to achieve greater predictability and reproducibility, the primary objectives of oral sustain DDS design should be to control drug concentration in the target tissue and optimize the therapeutic effect of a drug by controlling its release in the body with a lower and less frequent dose [3].

The objective of constructing sustained or sustained delivery systems is to either provide uniform drug distribution, decrease the frequency of dosing, or increase the medication's effectiveness by localizing at the site of action and lowering the dose needed. Accordingly, a sustained release (SR) dosage form is one that delivers one or more medications systemically or to a designated target organ over a predetermined amount of time in a continuous pattern [4,5].

II. DRAWBACK OF CONVENTIONAL DOSAGE FORM

1. Low patient compliance: The possibility of skipping a medication dose.
2. The inevitable variations in medication focus could result in taking too little medication or over-medication.
3. A normal plasma concentration-time peak-valley profile is acquired, which facilitates the achievement of disadvantage of the traditional dose form.
4. The variations in medication levels that result in onset of negative consequences primarily the medication which has a low Therapeutic Index whenever an overdose of medicine occurs.[6,7,8]

III. PRINCIPLE OF SRDDS

Traditional dose formulations instantly release their active components into an absorption pool. The following basic kinetic scheme serves as an illustration of this. Kr, Ka, and Ke are the first order rate-constants for drug release, absorption, and total elimination, respectively, and the absorption pool is a solution of the drug at the

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site of absorption. A traditional dose form's instantaneous medication release suggests that Kr>>>>Ka. The release of the medication from the dosage form, or Kr<<<Ka, is the rate limiting step for non-immediate release dosage forms. According to the following equation, the drug release from the dose form should follow zero-order kinetics:

$$\text{Rate In} = \text{Rate Out} = Ke.Cd.Vd = Kr° \text{----------1.}$$

Where ,

Kr° is the zero-order rate constant for the amount/time of medication release.

Ke: First-order rate constant for the total amount of time needed to eliminate drugs.

Cd: The body's desired drug level, expressed as volume or amount.

Vd: The amount of area in which the medication is dispersed in litter.[9,10]

IV. RATIONAL FOR DEVELOPMENT OF SRDDS

1. To increase a drug molecule's therapeutic effectiveness, SRDDS formulations reduce the frequency of doses and offer sustained release, which keeps the medication available at the site of action throughout the course of treatment.
2. To reduce the number of dosages required in order to reduce treatment costs.
3. To reduce toxicity from overdosing, which is frequently the case with traditional dosage forms?
4. To extend a medication's duration of action when it has a short half-life. [11,12]

V. TERMINOLOGY

According to the broad consensus, controlled release refers to systems that can offer some control over the body's release of drugs, whether that control is geographical, temporal, or both. In other words, the system aims to regulate the amount of medicine present in the target cells or tissue. Accordingly, sustained release or prolonged release systems that simply maintain therapeutic drug levels in the blood or tissues for a long time cannot be classified as controlled release systems. On the basis of straightforward in vitro testing, they can accurately specify the release rate and duration in vivo, which sets them apart from rate-controlled drug delivery systems.

However, because drug targeting manipulates the location of drug release within the body, it might be seen as a type of controlled release. Generally speaking, regulated delivery aims to:

- Maintain a reasonably steady, effective drug level in the body while simultaneously minimizing unwanted side effects linked to a saw tooth kinetic pattern to sustain drug action at a predetermined rate.
- By placing a controlled release system—typically rate-controlled—next to or inside the afflicted tissue or organ, you can localize the drug's action.
- Target drug action involves delivering the drug to a specific "target" cell type through the use of carriers or chemical derivatization.

Very few of the applied systems in use actually incorporate all of these activities. Most of the time, the release systems produce a steady drug concentration in the body over a long period of time. It is presumed that there is a correlation between the steady state medication levels in plasma and the target tissue or cells. Positioning the medicine at the target—whether it is a tissue, a population of cells, or receptors—while leaving the rest of the body free of the drug is ideal. Naturally, this would be quite challenging, particularly if the target is protected from systemic circulation by a number of barriers. For example, the blood-brain barrier's selectivity significantly restricts the ability to deliver drugs to the brain through systemic administration. In Figures 1 and 2, blood level profiles from conventional, controlled, and sustained release dose forms are compared. A single, brief dose of medication is all that is provided by a typical tablet or capsule. Pharmacological effects occur when the dosage of the medicine is within the therapeutic range. When the peak concentration falls or rises above this range, it might cause issues, particularly for medications with limited therapeutic windows. Infact, because prolonged release dosage forms slow down the rate of drug release, they also minimize volatility in plasma drug levels.

The phrase "sustained release" has been used in pharmaceutical and medical literature for a known time for many years. The term has been used consistently to refer to a pharmacological dosage form that has been

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created to postpone the release of the medicinal substance so that its presence in the bloodstream is Its plasma profile is sustained over time and can be either delayed or protracted.

However, "controlled release" has a definition that extends beyond the parameters of long-lasting pharmacological activity. It also suggests that the medication release kinetics are predictable and repeatable. This indicates that a controlled release drug delivery system releases its medication at a rate profile that is reproducible across units but not kinetically predictable.

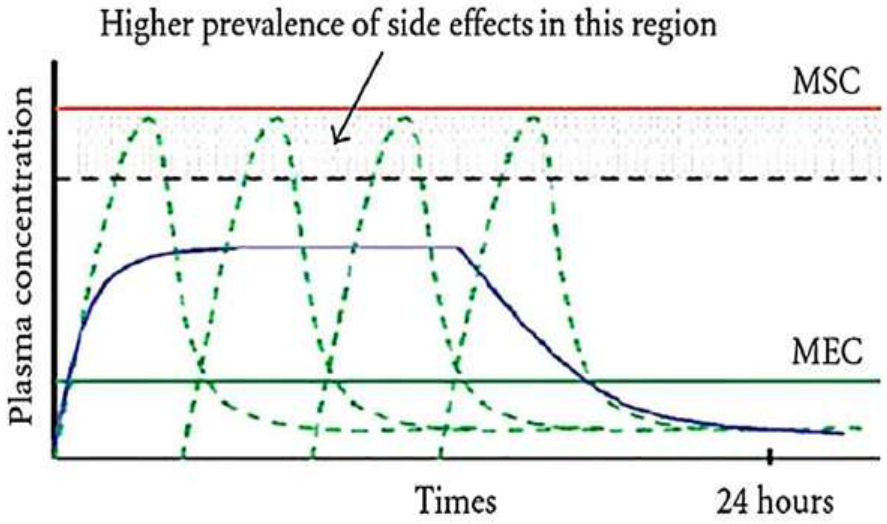

Figure 1: Plasma drug concentration profiles for conventional tablet formulation, sustained release formulation and a zero order controlled release formulation.

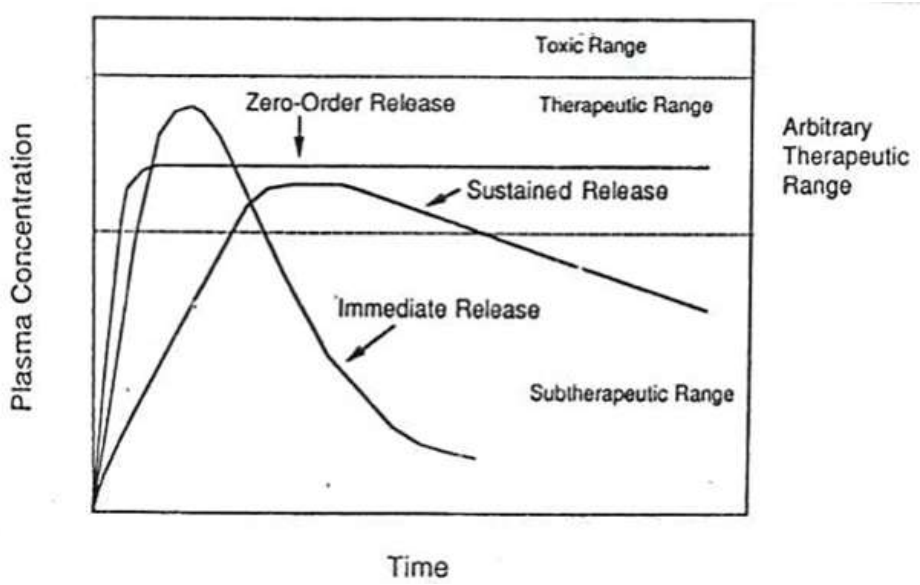

Figure 2: Drug level vs. time profile showing the relationship between sustained release and conventional release. [13,14]

VI. ADVANTAGES OF SRDDS

1. Compliance of the patient:

Since the effectiveness of medication therapy depends on the patient's capacity to adhere to the drug treatment, noncompliance is typically seen in chronic diseases that require long-term care. Patient understanding of a rigorous treatment regimen, patient faith in treatment, and knowledge of the illness process are some of the elements that influence patient compliance. Additionally, the local or systemic adverse effects of the dosage type, the expense of therapy, and the complexity of treatment regimens. Using a sustained release drug delivery mechanism can help to mitigate this issue to some degree.

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2. Less' see-saw' fluctuation:

When a drug is administered in a standard dose form, the' see-saw' pattern in drug concentration in the systemic circulation and tissue compartments occurs often. The magnitudes of these variations are mostly determined by drug kinetics, including dosage intervals, distribution, elimination, and absorption rates. Since recommended dose intervals are rarely fewer than four hours, the "see-saw" pattern is more noticeable only for medications with biological half-lives less than four hours. In addition to maintaining a constant medication concentration in the bloodstream and target tissue cells, a well-designed sustained release drug delivery system can significantly lower the frequency of drug dosage.

3. Total dose reduction:

In sustained release drug delivery systems, a smaller quantity of the entire drug is used to treat a sick condition. There is a reduction in systemic or local side effects when the overall dosage of the medication is decreased. More economic growth would result from this as well.

4. Enhancement of treatment deficiencies:

The best possible treatment of a disease necessitates the efficient delivery of active medications to the tissues and organs that demand attention. To obtain the required therapeutically effective concentration, it is frequently essential to deliver doses that are far higher than those needed in the cells. Unfortunately, this could cause immunological, toxicological, and unintended effects in non-target tissue. The acute or chronic medical condition is better managed with a sustained release dose type.

5. Economy:

Because sustained release medications contain unique chemicals, their initial unit cost is typically higher than that of standard dosage forms; However, crucially, the average cost of treatment over an extended period of time may be lower.[15,16,17]

VII. DISADVANTAGES OF SRDDS

1. Dose dumping: This can be caused by inaccurate formulation.
2. Less chance of dosage modification.
3. It is more expensive than a traditional dose form.
4. Boost the possibility of first-pass metabolism.
5. Proper treatment requires patient education.
6. The systemic availability may be reduced.
7. Poor relationships between in vitro and in vivo.[18,19,20]

Table 1: Characteristics of drug for Paroral sustained release forms*:*

Sr.No	Characteristic	Drugs
1.	Not effectively absorbed in the lower intestine.	Riboflavin, ferrous Salt.
2.	Absorbed and excreted rapidly, short biological half-lives (<1 hr).	Penicillin G, Furosemide.
3.	Long biologic half- lives(>12h) .	Diazepam, phenytoin.
4.	Large doses required(>1g).	Sulfonamides.
5.	Cumulative action and undesirable side effects; drugs with low therapeutic indices.	Phenobarbital, digitoxin.
6.	Precise dosage titrated to individual is required.	Anticoagulants, cardiac glycosides
7.	No clear advantages for sustained released formulation.	Grisofulvin. [21,22]

VIII. CRITERIA TO BE MET TO INCORPORATE THE DRUG INTO SUSTAINED RELEASE DOSAGE FORM

A number of physicochemical factors, primarily related to the drug's absorption mechanism from the gastrointestinal (G.I.) tract, are taken into consideration when choosing which medication to construct in a sustained release dosage form.

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Table 2: Physicochemical parameter for drug selection

Sr.No	Parameters	Criteria
1.	Molecular size	<1000 Daltons
2.	Aqueous Solubility	More than 0.1 mg/ml for pH 1 to pH 7.8
3.	Apparent partition coefficient	High
4.	Absorption mechanism	Diffusion
5.	General absorbability from all GI segments	Release should not be influenced by pH and enzyme

Table 3: Pharmacokinetic parameter for drug selection

Sr.No	Parameters	Comments
1.	Elimination half-life	Between 2 to 8 hrs
2.	Absolute bioavailability	Should be 75% or more
3.	Absorption rate constant(K_a)	Must be higher than release rate
4.	Apparent volume of distribution(V_d)	Larger V_d and MEC, larger will be the required dose
5.	Total clearance	Not dependent on dose
6.	Elimination rate constant	Required for design
7.	Therapeutic concentration(C_{ss})	The lower C_{ss} and smaller V_d , the less amount of drug required
8.	Toxic concentration	Apart the value of MTC and MEC safer the dosage form.[23,24]

IX. CLASSIFICATION OF SUSTAINED RELEASE DRUG DELEVERY SYSTEM

1. Matrix Systems :

In matrix systems, the medication is evenly dispersed across a polymer or other material matrix. The matrix regulates drug release through dissolution, swelling, or diffusion.

- Types :

a) Hydrophilic Matrix Systems
b) Fat-Wax Matrix Systems.

2. Reservoir Systems :

A membrane that regulates the release surrounds the core of the reservoir system, which holds the medication. Diffusion across the membrane causes the release to happen.

- Types :

a) Coated Reservoir Systems
b) Osmotic Pump Systems.

3. Diffusion-Controlled Systems :

Through a matrix or membrane, the medication diffuses out of the system. Both the system's diffusion characteristics and the drug's concentration gradient affect the release rate.

- Types:

a) Monolithic Diffusion Systems
b) Membrane-Controlled Diffusion Systems.

4. Ion-Exchange Systems :

In ion-exchange systems, the medication and resins combine to produce complexes. Ions from the gastrointestinal tract displace the medication, causing the release.

- Types :

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a) Polymeric Ion-Exchange Systems.

5. Erodible or Biodegradable Systems :

As the matrix material deteriorates or erodes over time, frequently through hydrolysis or enzymatic degradation, these systems release the medication.

- Types :

a) Erodible Matrices
b) Biodegradable Polymers.

6. Lipid-Based Systems :

By solubilizing the medicine in lipids (fats or oils), lipid matrices regulate drug release. As the fat dissolves in the digestive system, the medication is gradually released.

- Types:

a) Microspheres of Lipids
b) Nanoparticles of Lipid.

7. pH-Dependent Systems:

Targeted drug delivery to certain regions, such as the small intestine, is made possible by these systems, which are made to release the medication at particular pH levels in the gastrointestinal tract.

- Types:

a) pH-Sensitive Polymers.[25,26,27]

X. FORMULATION OF SUSTAINED RELEASE DRUG DELEVERY SYSTEM

1. Diffusion Sustained System
2. Dissolution Sustained System
3. Method Using Ion Exchange
4. Method Using Osmotic Pressure
5. pH Independent Formulation
6. Altered Density System

1. Diffusion Sustained System :

The diffusion process demonstrates how drug molecules migrate from an area with a higher concentration to one with a lower concentration. Fick's law determines the drug J's flux (in amount/area-time) across a membrane in the direction of decreasing concentration.

J=- D dc/dx

D = area/time diffusion coefficient

dc/dx = change of concentration 'c' with distance 'x' In a typical form, a drug must diffuse across a water-insoluble membrane that encloses its core; the drug release rate, dm/dt, is determined by

C/L = ADK. dm/dt

where

A = equivalent to area.

K = the drug's partition coefficient between its membrane and core.

L = Diffusion path length, or, in the best scenario, coat thickness

C= stands for concentration differential across the membrane.

a) System of diffusion reservoirs:

A polymeric substance that is insoluble in water envelops the drug's core in this arrangement. The medication will separate into the membrane and exchange the particle or tablet with the surrounding fluid. More medication will diffuse to the periphery, enter the polymer, and interact with the surrounding medium. Diffusion is the mechanism by which the medication is released.

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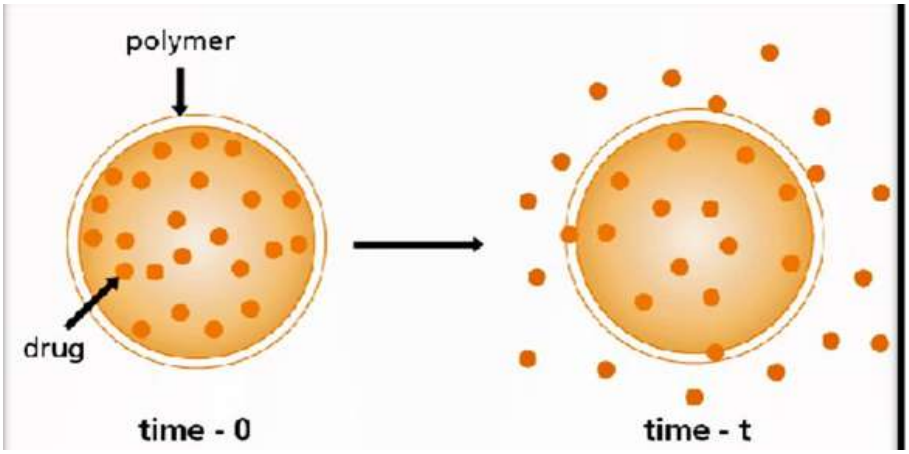

Figure 3: Diffusion Type Reservoir System diagrammatic representation

b) Diffusion Matrix Type:

A solid drug is dispersed throughout an insoluble matrix, and the drug's release rate is typically determined by both the solid dissolution rate and the drug diffusion rate. The suitable drug release equation for this system has been determined by Higuchi.

Q = D/T [2A–Cs] Cst ½

Where,

Q = the weight in grams of medication delivered per unit surface area at time t.

D = the drug's diffusion coefficient in the release medium.

ε = the matrix's porosity.

Cs= the drug solubility in the release media.

T = The matrix's tortuosity.

A = the tablet's medication concentration, expressed in grams per milliliter.

The following formula can be used ”o determine the release rate:

Release rate = AD/ L = [C1-C2]

Where,

A= area

D = diffusion coefficient

C1 = The core’s drug concentration

C2 = The amount of drug present in the surrounding medium

L = length of the diffusion path

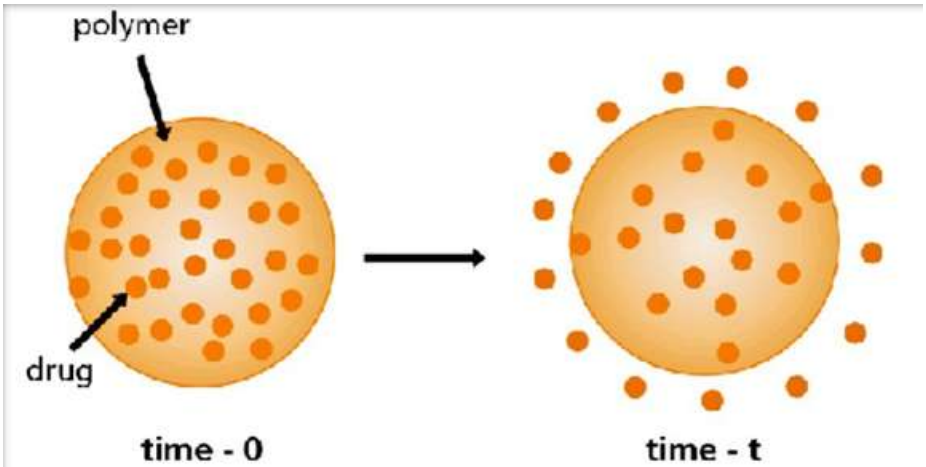

Figure 4: Diagrammatic representation of diffusion Sustained drug release: matrix system.

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2. Dissolution sustained systems:

Medications with a slow rate of dissolution are naturally maintained, while medications with a high water solubility can be made to dissolve more slowly by forming the proper salt or derivative. These systems are typically used in the production of enteric-coated dosage forms. A coating that dissolves in natural or alkaline media is used to protect the stomach from the effects of medications like aspirin. This prevents the medicine from escaping the dose form until it reaches the intestinal pH, which is higher.

a. System of soluble reservoir:

The medicine in this method is coated with an erodible coat that is gradually dissolved in the GI tract's contents by alternating drug layers with coats that control the pace of dissolution.

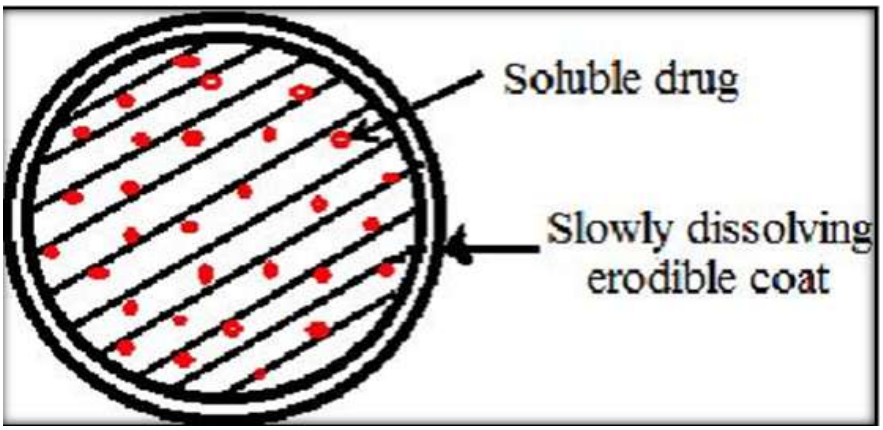

Figure 5: Diagrammatic representation of soluble Reservoir system

b. System of soluble matrix:

It will undergo gradual erosion and can be either a drug-impregnated tablet or a drug-impregnated spherical.

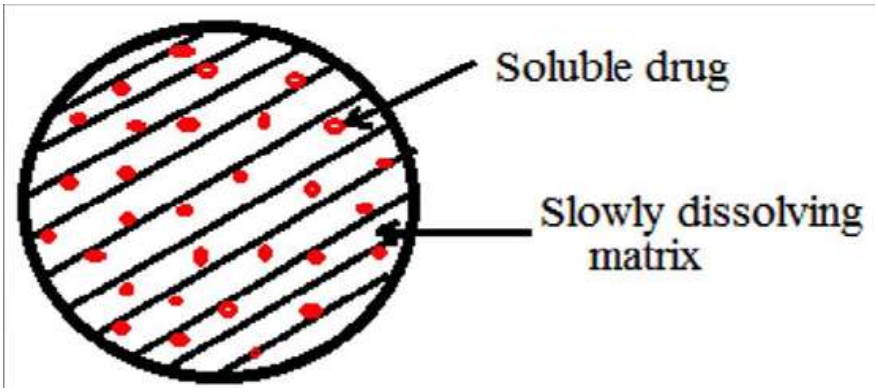

Figure 6: Diagrammatic representation of soluble Matrix system

3. Methods using Ion Exchange:

Ion exchange resin is a desirable technique for long-term drug delivery because its drug release properties primarily rely on the ionic environment of the resins containing the drug and are less sensitive to environmental factors like pH and enzyme concentrations at the absorption site zero order release. With this method, kinetic can be achieved to a satisfactory degree.

For a medicine that is extremely vulnerable to enzymatic degradation, an ion exchange-based delivery method is a superior option. There are various varieties of ion exchange resin, including:

a) Resin for Cation Exchange:

b) Resin for anion exchange:

a) **Cationic exchange resin:**

Has an acidic functional group in it. Polysteryne polymers having either phenolic carboxylic phenolic groups are typically present in them.

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b) **Resin for anion exchange:**

Involved a fundamental functional group with the ability to remove anions from an acidic solution based on the idea that a drug's negatively or positively charged moiety combines with the right resin to produce insoluble poly salts, ion exchange resins are used to prolong the effects of drugs.

Where as H N-A and HOOC-B indicate basic and acidic drugs, respectively, R-SO-H and R-NH–OH represent cationic and anionic resin. When resins that are taken orally come into touch with acidic fluids that contain 1.2 pH HCl, the following reaction occurs:

R-SO3-H^++ H2N-A = R-$SO3^-$+ H3N+-A

R-N^+H3OH^- + HOOC-B = R-N^+H3-00C-B+ H^2O

Subsequently when the system reaches to intestine Where it is exposed to a fluid of slightly alkaline pH.

Following reaction occurs:

- R-SO^3-H3N^{+-}A + HCl = R-SO_3-H^++A-$N^+H_3Cl^-$
- R-N^+H_3-OOC-B + HCl = R-$N^+H_3Cl^-$+ B-COOH
- R-SO_3-H_3N^+-A + NaCl = R-SO3-Na^++ A-$N^+H_3Cl^-$
- R-N^+H3-OOC-B + NaCl = R-$N^+H_3Cl^-$+ B-COO^-Na^+

➢ **These are some type of resins:**

Table 3:

Resin type	Chemical constituent
Strong acidic cationic exchanger	Sulfonic acid group attached to astyrene and divinyl benzene copolymer.
Weak acidic cationic exchanger	Carboxylic acid group linked to an acrylic acid and divinyl benzene copolymer.
Strong basic anion exchanger.	Quarternary ammonium groups attach to astyrene and divinyl benzene copolymer.
Weak basic anion exchanger	Polyalkylamine copolymer group linked to astyrene and divinyl benzene copolymer

4. pH-Independent formulations:

Unwanted characteristics of the oral mode of administration include a longer transit time through the GI tract, which limits the length of prolonging. In addition, the chemical environment along the entire GI tract limits the design of dosage forms. Given that the majority of medications are weak bases or acids, the drug release from pH affects formulations with sustained release. pH-independent drug release buffers, such as salts of amino acids, citric acid, phthalic acid, phosphoric acid, or tartaric acid added to the formulation, are made possible by keeping a steady pH . A basic or acidic medication is typically combined with one or more buffering agents to create a buffered sustained release formulation, which is then granulated using the proper pharmaceutical excipients and coated with gastrointestinal fluid. Polymer that forms permeable films. When gastrointestinal fluid passes across the membrane, the buffering agents bring the fluid's pH down to a stable level, resulting in a steady drug release rate.

5. Altered density formulations:

Its use is limited if the entire dosage form is not released in the gastrointestinal tract. In order to do this, a number of strategies have been created to extend the drug delivery system's residence time in the digestive system.

a) High-density strategy:

With this method, the pellets' density should be at least 1-4 grams per centimeter, which is greater than the stomach's typical content. The medicine can be coated on a heavy core or combined with heavy inert materials as zinc oxide, titanium dioxide, barium sulfate, and iron powder to create such a formulation.

b) Low density approach:

Polystyrol, pop rice, and popcorn are all utilized as drug carriers for sustained release since their globular shells have a density lower than that of gastric fluid. Sugar or polymeric materials like cellulose acetate phthalate and

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methacrylic polymer are applied underneath the surface of these empty shells. A drug mixture containing polymers such hydroxy propyl and ethyl cellulose is then applied to the undercoated shell. As a result, the finished product floats on the stomach juice for a long time while the medicine releases gradually.[28,29,30,31]

XI. FACTORS AFFECTING SUSTAINED RELEASE DRUG DELIVERY SYSTEM

A. Physicochemical factor:

1. Dose size :

A single dose of approximately 500 mg 10 1.0 g of the medication is typically considered the limit for a regular dosage form. Substance with massive dosage amounts that can occasionally be mixed into liquid formulations or given in many doses The same criteria are met by the sustained release dosage form.

2. Ionization, pka and aqueous solubility:

Most drugs are weak acids or bases. Since pharmaceuticals can traverse lipid membranes in their unmodified form, the connection between the compound's pka and the absorptive environment is essential. The solubility of the drug in aqueous fluids will have an impact on diffusion or dissolution-based delivery systems. Because the small intestine is more neutral and the stomach is acidic, these dose forms need to function in a pH-changing environment. Furthermore, the effect of the phone release mechanism must be described.

3. The partition coefficient:

To have a therapeutic effect in another area of the body, a drug administered to the GI system must cross multiple biological membranes. The partition coefficient of oil-soluble compounds is a crucial metric in evaluating the effectiveness of drug penetration via membrane barriers because these membranes are commonly conceived of as lipidic. Long-lasting retention in lipophilic tissues is a characteristic of lipophilic substances having a high partition coefficient, which are poorly soluble in water. A medication with a very low partition coefficient has poor bioavailability because the component finds it very difficult to pass the membrane.

4. Stability:

Drugs taken orally are susceptible to acid-base hydrolysis as well as enzymatic breakdown. In challenging scenarios, this is the recommended delivery composition since the breakdown of a medicine in a solid state will occur more slowly. For dose forms that are unstable in the stomach, systems that distribute the medication throughout the whole GI tract's transit are beneficial. This also includes systems that delay the release of the dosage form until it reaches the small intestine. When administered in a prolonged dosage form, substances that show modest intestinal instability may have decreased bioavailability. This is because the small intestine is where more drugs are absorbed and where they also degrade.

B. The biological factor :

1. Half-life:

The half-life of a drug is a measure of how long it remains in the body. The dosage form may contain an unreasonably high amount of the drug if the half-life of the medication is short (less than two hours). On the other hand, when taken as directed, medications with an elimination half-life of eight hours or more are well-regulated in the body; in these cases, a sustained release drug delivery device is typically not necessary. The drug's half-life should preferably be three to four hours when designing a medicine delivery system.

2. Therapeutic index:

If a drug has a high dose in its regular dosage form, it is a worse choice for SRDDS. This is because the size of a unit dose sustained release oral formulation would increase to the point where delivery would be impossible.

3. Absorption window:

There are several drugs that only absorb from one portion of the digestive tract when taken orally. The term “absorption window” refers to this portion. Furthermore, these candidates are not suitable for SRDDS.

4. Relationship between plasma concentration and response:

In general, plasma drug concentration has a greater influence on pharmacological activity than dose. Oral SR drug delivery systems, however, are not suitable for drugs whose pharmacological action is independent of plasma concentrations.

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5. Dependency of concentration on drug transfer :

An oral SR delivery system is not a good fit for a medicine that is moved from one compartment to another utilizing a zero order kinetic process. First-order kinetics should be used.[32,33,34]

XII. CONCLUSION

It is clear from the explanation above that one of the most efficient dosage forms is sustained release. It enhances therapy effectiveness and helps to improve patient compliance. Certain parameters like molecular size, water solubility must be met to incorporate the medicine in sustained release dosage form. Certain methods are used in sustained release dose forms to release the medication. Before creating a drug's sustained release dosage, a number of pharmacokinetic and pharmacodynamic parameters should be taken into account.

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