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A Review on Sustained Release Drug Delivery and Sustained Release Matrix Tablets

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Abstract

Oral medication delivery is still the finest and most popular method for administering pharmaceuticals via the internal route. A Sustained Release is also a good option for reducing a drug's negative effects and boosting its therapeutic potency. The fundamental ideas of sustained drug delivery systems optimize a variety of factors, including a medication's biopharmaceutical, pharmacokinetic and Pharmacodynamic properties, such that therapeutic efficacy is increased, side effects are minimized, and disease treatment is made simple. The major methods of manufacturing sustained-release matrix tablets include wet granulation, direct compression, or dispersion of solid particles within solid particles within a porous matrix created by employing various polymers. The matrices employed might be mineral, hydrophilic, hydrophobic, or biodegradable in nature. Therefore, by lowering the overall dosage and dosing schedule, sustained-release matrix tablets may improve patient compliance, which is very beneficial for treating chronic diseases. Studies of in-vitro dissolution can be used to determine the medication release rate. The main objective of this study is to provide comprehensive information for sustained release matrix tablet dosage form.

1. Introduction

Sustained release dosage types are intended to achieve an extended therapeutic impact. The primary goal of creating sustained-release formulations was to improve and enhance the efficacy of drugs by prolonging their period of action, requiring less frequent dosing, using lower doses, and ensuring uniform drug delivery. There has been a notable rise in interest in sustained-release drug delivery systems over the last two to three decades. This is because of several factors, among other things, the high price for producing novel drug molecules, the expiration of current foreign patents, the development of new polymeric materials useful for delaying the release of drugs, and advancements made in therapeutic effectiveness & these delivery techniques deliver safety. (Wagner et al., 1973)

Sustained release dosage forms are designed to release medication at a specific rate and maintain a constant drug level for a specified amount of time with as minimal side effects as possible. The primary goal of sustained-release drug delivery systems is to increase the bioavailability and efficacy of the medicines. Sustained delivery systems aim to increase drug efficacy or decrease the dosage's frequency by localizing the drug to the action site, lowering the dosage frequency, and ensuring uniform drug distribution. (Lee et al., 1987) Many sustain-release oral dosage forms have been developed, including membrane-controlled systems, matrices with water-soluble/insoluble polymers or waxes, and osmotic systems.A recent intense study has concentrated on choosing SR systems for poorly water-soluble drugs. The drug's pharmacological effect and its half-life are two essential considerations when designing such a system. (Kumar et al., 2017)

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In light of these drawbacks of the conventional drug delivery method (repeated dosing and dose variability), sustained release delivery can help in the achievement of the following objectives:

I. Steady drug release for a longer time.

II. Less frequent dosage.

III. Less fluctuating elevation of blood pressure readings.

2. Terminology:

The terms controlled release and sustained release have both been used inconsistently and confusingly. Both signify different transportation processes. SR refers to any medication form that delivers medicine for a longer time or indicates that the system can offer some real therapeutic control, whether of a temporal, spatial, or both natures. The drug delivery system that dispenses medicine over a long period without regard to time is included. A sustained dose form is frequently created using a hydrophilic polymer matrix. The optimal drug delivery system's role is to keep the drug's therapeutic range in blood plasma by delivering the right dose at the right site of action at the appropriate moment. (Wani et al., 2008)

During the course of medical treatment, sustained-release tablets are typically taken once or twice daily, whereas

conventional dosage forms require three to four doses per day to have the same therapeutic effect.

Fig. 1: Plasma Drug Conc. Profiles for Conventional Tablet Formulation, a Sustained Release Formulation, and a Zero Order Controlled Release Formulation.

Principle of SRDDS (Bharagava et al., 2013) (Bhowmik et al., 2009)

The active ingredients in conventional dosage forms are instantly released into an absorption pool. This is illustrated in the following simple kinetic scheme The absorption pool represents a solution of the drug at the site of absorption, Kr, Ka, and Ke - first order rate-constant for drug release, absorption, and overall elimination respectively. Immediate drug release from a conventional dosage form denotes that Kr>>>>Ka. For dosage forms with a non-immediate release, Kr<<<Ka i.e. the release of the drug from the dosage form is the rate-limiting step. The dosage form should follow zero-order kinetics for drug release. as shown by the following equation:

$Kr° = Rate\ In = Rate\ Out = Ke.Cd.Vd$

Where, Kr°: Zero-order rate constant for drug release-Amount/time

Ke: First-order rate constant for overall drug elimination-time

Cd: Desired drug level in the body – Amount/volume

Vd: Volume space in which the drug is distributed

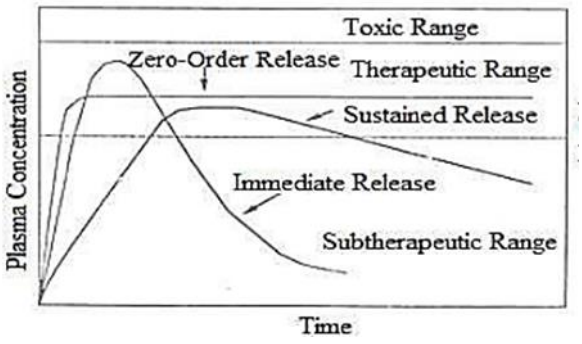

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Table 1: Advantages of Sustained release dosage forms over Conventional dosage forms (Bankar et al., 2012)

Sr. No	Sustained release dosage forms	Conventional dosage forms
	SRDF improves patient compliance and treatment effectiveness by reducing the overall dose of the drug and dosing frequency	The effectiveness of a treatment is poor because conventional dosage forms need more frequent dosing and a greater number of dosages.
	It is possible to keep a constant level of drug concentration in blood plasma and extend a drug's therapeutic effect	It is impossible to accomplish the characteristic blood level variations produced by multiple dosages of conventional dosage forms for prolonged action.
	The matrix system in the SRDF tablet prevents dosage dumping and reducing overdose-related toxicity	When a drug is released quickly in conventional dosage forms, the possibility of dose dumping increases; toxicity may result from an overdose
	Reduced dosage lowers treatment costs, but the cost of producing a single unit of SRDF is greater due to the need for expensive processes and machinery	Conventional dosage forms require fewer preparation costs, but sometimes the need for more dosages results in higher therapy costs overall.
	Comparing in-vitro and in-vivo correlations to standard dosage forms, they are outstanding.	Due to less flexible dose adjusting and dosage protocols, there are poor correlations between in vitro and in vivo results.

Advantages of SRDDS (Patel et al., 2014) (Pogula et al., 2010) (Parashar et al., 2013) (Patel et al., 2012) (Mamdouh et al., 2012)

I. Less frequent drug administration

II. Better patient compliance

III. Less fluctuating blood drug levels

IV. Less overall drug use compared to conventional treatment

V. Less drug accumulation with long-term therapy

VI. Reduction in systemic and local medication toxicity

VII. Stabilization of medical state (due to more consistent drug levels)

VIII. Enhanced bioavailability of some drugs due to spatial control

IX. Economical for both the patient and the healthcare professionals

Disadvantages of SRDDS (Parashar et al., 2013) (Wadher et al., 2013) (Kumar et al., 2010) (Bose et al., 2013)

I. A delayed onset of action of the drug.

II. If a formulation approach is poor, there may be a chance of dose dumping.

III. Enhanced first-pass metabolism capacity

IV. A greater reliance on the dosage form's GI residence duration.

V. In some situations, it may be possible to modify the dose less accurately may be possible dosage is higher compared to conventional doses.

VII. Not all medications can be made into ER dose forms.

VIII. Poor correlation between in vitro and in vivo.

IX. It can be challenging to retrieve a medication in cases of toxicity, poisoning, or hypersensitivity reactions.

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X. Reduced possibility for dose adjustments for medications that are typically given in different strengths

Ideal properties of the drug suitable for SRDDS (Misa et al., 2013)

I. It must be properly absorbed through the oral route and stable in GI fluid.

II. Drugs with short half-lives (2-4 hrs.) are excellent candidates to be formulated into SR dosage forms.

III. To develop SRDDS, the drug dose should not be less than 0.5 gm and should not exceed 1.0 gm.

IV. The drug's therapeutic range in SRDDS should be high and it should be sufficiently broad that variations in the release do not cause concentrations to rise above the minimally toxic values.

Challenges for the preparation of sustained release dosage form (Deore et al., 2010) (John et al., 2003)

i. A poor correlation between in vitro and in vivo

In dosage forms for sustained release, the rate of drug release is gradually decreased to achieve drug release, which may occur over a significant portion of the gastrointestinal tract. The "Absorption window," as it is known, therefore becomes crucial and contributes to inadequate drug absorption in-vivo despite great in-vitro release characteristics**.**

ii. Dose dumping

This could significantly increase a drug's body concentration, causing negative effects or even drug-induced poisoning. The relatively high amount of medicine in a formulation with sustained release delivery is released gradually when there is dose dumping. In the event of powerful drugs with a limited therapeutic index, such as phenobarbital, dose dumping might result in fatalities.

iii. Limited options for choosing the appropriate dose within the unit

The dose adjustments for conventional dosage forms are much simpler, for example, a tablet can be divided into two parts. Sustained release dosage types may make this seem to be more difficult. A fractured dosage form could result in the loss of the sustained release characteristic.

iv. Patient variation

Individuals may require a different amount of time for the dosage form-released medication to be absorbed. Different individuals respond differently to co-administration of other medications, food intake or lack of it, and gastrointestinal tract residence time. Additionally, it causes the patient's clinical responses to differ.

Criteria for the selection of the drug (Deore et al., 2010) (John et al., 2003)

i. Minimal dosage

In a conventional dosage form, a drug's potential as a contender for sustained release is severely unknown if the amount is large. This is significant because it would make a unit dosage sustained release formulation bigger and more challenging to deliver.

ii. Desirable properties for absorption and solubility

Drugs that are insufficiently soluble in water frequently have dissolution rate limitations when being absorbed. Therefore, it is unrealistic to include these types of compounds in sustained-release formulations, which could reduce overall absorption efficiency.

iii. Favorable half-life

A drug's half-life in the body has a residence time of index. The drug may be present in large amounts in the dosage form despite having a short half-life. The medicines remain in the bloodstream for a long enough time for their eight-hour elimination half-life.

iv. High Therapeutical Index

Low therapeutic index medications are inappropriate for inclusion in extended-release formulas. The failure of the body's systems can result in dose dumping, which can be fatal.

v. Desirable properties for absorption and solubility

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Medications with poor water solubility frequently have dissolution rate limitations when being absorbed. Therefore, incorporating these kinds of compounds into formulations for sustained release is unrealistic and could reduce overall absorption effectiveness.

vi. Desirable absorption window

When taken orally, some medications are only absorbed from one area of the body, the gastrointestinal tract. The "absorption window" is the term used to describe this body part. Some medications, including thiazide diuretics and fluorouracil, are absorbed through an absorption window. They are an inappropriate dosage form if they were created as a formulation for sustained release delivery.

vii. First pass clearance

When drugs are administered in sustained release form but are subject to broad first-pass liver metabolism, the drug's ability to reach the body in the desired concentrations is severely hampered.

Manufacturing of SRDDS (Gautam et al., 2011) (Higuchi et al., 1963) (Korsmeyer et al ., 1983)

Numerous formulations are taken into consideration in-

i. Drug complexes

The ability to formulate materials into different dosage forms is the main benefit of creating drug derivatives for sustained release. This strategy has been successful during the development of injectable depot forms, in which release profiles are not impacted by the gastrointestinal tract's variability characteristics. A clear drawback of orally administered forms is their sensitivity to in vivo variables; in vivo, studies may not always support sustained release claims.

ii. Granules with encapsulation for slow release

Encapsulated mixed slow-release beads were the first significant sustained dosage types to be commercially available. To these beads, barrier principles for regulating drug release based on model D were applied. Nonpareil seeds are first coated with an adhesive for low milligram potency formulations, then the powdered medication, and finally the pellets are dried. Up until the desired dosage of the drug has been applied, this step is repeated. The resulting granules are then covered with a mixture of solid hydroxylated lipids, such as modified celluloses and hydrogenated castor oil or glyceryl trihydroxy stearate. To achieve the desired release characteristics, the number of applied coatings controlled the barrier's thickness.

iii. Granulation for slow-release tablets

An alternative to encapsulation is to compress time-release granulations into tablets. To encourage the administration of a capsule form with the advantage of sustained release encapsulations while maintaining the benefit of tablet dosage forms, such tablets should be made to dissolve in the stomach. This kind of formulation is demonstrated by three examples, each using a different method. The first is a mixed-release granulation that is tablet-formulated using binders with various retardant properties to create three distinct granulations that are color-coated for identification, blended, and tablet-formulated. Gelatin, vinyl acetate, and shellac were used as binders in the preparation of the first conventional non-sustained release granulation.

iv. Technology for controlled drug release

Formulations with a controlled-release drug are developed to release the medication in vivo at predetermined rates that can be measured in vitro. The formulation of insoluble matrix tablets is among the many methods used to create sustained-release drugs, and these are the ones that are nearest to achieving this goal because the release of water-soluble drugs from these forms should be unaffected by in vivo factors. To be able to specify the dosage forms release rate, controlled release technology requires a quantitative knowledge of the physicochemical mechanism of drug availability. Hydrodynamic pressure-controlled systems, intragastric floating tablets, transmucosal tablets, and microporous membrane-coated tablets are some potential innovations and fresh ideas for administering drugs with a regulated delivery orally.

Classification of SRDDS (Tripathi et al., 2003) (Rang et al., 2003) (Harsh et al., 2000)

The oral controlled delivery methods are primarily solids and dependent on diffusion, dissolution, or a mix of both processes in regulating the drug's release

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rate. Depending on the method of drug release, these systems are categorized as follows:

A. Continuous release systems

With Continuous release, methods release the drug over a prolonged period along with a regular journey of the dose from the full length of the gastrointestinal tract. These are the different methods that come under this category:

I. Diffusion-controlled release system

II. Dissolution-controlled release system

III. Dissolution and diffusion controlled-release system

IV. Complexes of drugs and ion exchange material

V. The formulation that is irrespective of pH

VI. Osmotic pressure controlled-system

I. Diffusion-controlled release system

The passage of dissolved substance through polymeric barriers rate-limiting process in these types of systems The drug release rate is never zero-order because the diffusional channel length expands with time as the insoluble matrix gradually loses its drug content. These controlled-drug delivery devices are based on drug molecules diffusing through polymeric membranes. The drug molecule is either enclosed in a polymeric membrane or dispersed in the polymeric matrix to create diffusion-controlled devices, which are similar to dissolution-controlled systems. The drug is made available as a consequence of partitioning through the polymer, as opposed to dissolution-controlled systems.

The diffusion-controlled release can take one of two forms:

i. Matrix diffusion-controlled system

ii. Reservoir devices

II. Dissolution-controlled release systems

The following components may be found in such a system:

i. Achieving high aqueous solubility and dissolution rates

ii. Having a naturally slow rate of dissolution

iii. whenever GI fluids get in touch with it, it produces slow-dissolving forms.

Slowing a drug's rate of dissolution in the GI medium, drug encapsulation in an insoluble polymer, and polymer coating of drugs granules or particles of varying thickness can all be used to achieve dissolution-controlled release. The diffusion across the aqueous boundary layer is the rate-limiting step for drug dissolution. The drug's solubility provides a source of energy for drug release for which the stagnant-fluid diffusional boundary layer acts as a block.

III . Dissolution and diffusion controlled-release system

As a result of the partially soluble membrane surrounding the drug core in these systems dissolving in some places, pores are formed that permit the entry of aqueous media into the core, causing drug dissolution, and allowing dissolved drugs to escape from the system.

IV . Complexes of drugs with ion exchange resin

Its foundation is the formulation of the drug resin complex created when ionic solution and ionic resins come into contact. The medication from this compound is released along with an excess of Na+ and Cl- after being exchanged in the digestive system. The resin compound of an insoluble cross-linked polymer is typically used in this system. They have a repeating salt-forming function group on a chain of polymers.

V. The formulation that is irrespective of pH

Most of the drugs have pH-dependent releases because they are either weak bases or weak acids. However, by delaying pH-dependent medication release, a buffer can be added to the formulation to assist maintain a constant pH, such as tartaric acid, amino acids, or citric acid salt. Combining a basic or acidic drug with one or more buffering agents, then granulated with the proper excipients to generate buffer sustained release formulation, the material is

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coated with gastrointestinal fluid permeable film-forming polymer. The buffering agent changes the internal fluid to a suitable constant pH at the time gastric fluid crosses the membrane, resulting releasing drugs at a constant rate.

VI. Osmotic pressure controlled-system

The tablet is surrounded by a semi-permeable membrane to pump the medication solution out of the tablet via the tiny delivery opening in the tablet core, particle, or drug solution. There are two different osmotic pressure-controlled systems**:**

i. Type 1 has a drug-filled osmotic core in it.

ii. Type 2 drug is enclosed in a flexible bag with an osmotic core all around

It is possible to develop an osmotic system to deliver drugs of various kinds at pre-programmed rates by optimizing the processing and formulation variables.

B. Delayed transit and continuous release system

The purpose of these systems is to delay both their release and residence time in the GI tract. The drug contained inside the dose form needs to be stable in stomach pH. because it is frequently designed to be retained in the stomach. Mucoadhesive and size-based systems are incorporated into this category.

C. Delayed release systems

These systems limit the drug's release to a specific GIT area. These drugs are among those that are kept in such a system:

I. known to induce gastrointestinal discomfort.

II. Digested by digestive enzymes

III. Intended to have a more local impact at a specific GI location

IV. Absorbed from a particular digestive location

There are two different delayed-release systems:

I. Intestinal release systems

II. Colonic release systems

Novel trends in SRDDS (Mahesh et al., 2011) (Gwen et al., 2002) (Leon et al., 2004)

For dosage forms that are taken orally, sustained drug action is achieved by changing the rate at which the drug is discharged from the dosing form or by slowing the dosage form's passage through the digestive system. Based on its structural and outward appearance, Zahirul Khan has split up the sustained release dosage form into three categories: single unit dosage form, multiple unit dosage form, and mucoadhesive delivery systems.

i.Single Unit Dosage Forms

This refers to diffusion controlled system where the therapeutic agent is evenly distributed (Dispersed /dissolved) throughout the solid matrix. This system is categorized as follows.

ii. Complex reservoir system or coated tablets or multi-layered system

The substance that makes up a tablet is usually the drug, either by itself or combined with hydrophobic or hydrophilic inert material.

iii. Hydrophobic tablets

Tablets made from optimal alkaloids, such as morphine salts homogenized with their salt and fatty acid or any ethylene vinyl acetate copolymer (hydrophobic filler), are then compressed.

iv. Semisolid matrix systems

To prepare a dosage form, the drug is first mixed with an oily "semisolid" hydrophobic carrier. After that, the mass is typically placed inside a gelatin capsule.

v. Ion exchange resins

Prolonged drug contact with resin results in the formation of a drug-resin complex. As more Na+ and Clare found in the digestive tract, drugs are derived from these complexes are exchanged there before being released.

vi. Osmotic pump

A semipermeable membrane surrounds a core tablet in the system. Coating with a hole that is 0.4 millimeters in diameter and was created by laser beam 16. The

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tablet, component, or medicine permits water to enter the tablet and eventually pump the drug solution out through the tablet's tiny delivery aperture.30

vii. Multiple Unit Dosage Form

It combines two different dose forms, whose source may be homogeneous or heterogeneous. The different available forms include multiple-tablet setups. Compressed tiny spheroids are feasible to prepare with a diameter of 3 to 4 mm that have different drug-release properties. To achieve the desired pattern of drug release, they can be put inside gelatin capsule shells. Microspheres, granules, and coated beads The drug is dispersed on beads, pellets, granules, or other particulate systems in these systems. A solution of the drug substance is applied to small, inert nonpareil seeds, beads made of sugar and starch, or microcrystalline cellulose spheres using the traditional pan coating or air suspension coating methods. Pellets were developed by adding film-forming polymers to inert drug pellets. Drug release is influenced by coating polymer composition and coating quantity. By forming thin wall coatings all around the substance, solids, liquids, or even gases can be microencapsulated and contained in microscopic particles. System for delivering mucoadhesive. It makes use of the adhesion principle to ensure the best possible drug delivery from the device. Increased drug contact time with absorbing membranes and localized drug delivery to specific sites are both possible with mucoadhesive systems.

Factors affecting SRDDS (Brahmankar et al., 2009) (Khyati et al., 2012) (Nicholas et al., 1987)

Two types of factors involved

I. Physicochemical factor

II. Biological Factor

I. Physicochemical factor

i. Dose capacity

For oral administration of medications in the maximum bulk size of the prescribed dosage. For a usual dosage form, one dosage of 0.5 to 1.0g is typically regarded as the maximum. The dosage form for continuous release also affects this. Compounds that need large doses of medication can occasionally be administered in multiple doses or as liquid systems.

ii. Solubility in Water

The drug is well-soluble in water and pH-independent. The ideal prospect for SRDDS is solubility. Poor an issue with oral bioavailability is present in aqueous solubility. Unsuitable drugs include those with extremely high water solubility. Considering continuous release because controlling the drug discharge derived from the dose form

iii. Partition coefficient

The partition coefficient, which is also known as the distribution coefficient, has a significant impact on a drug's bioavailability because a drug's ability to cross a biological membrane relies on the partition coefficient. Drugs with low partition coefficients are thought to be bad candidates for formulations with sustained release when in the aqueous phase.

iv. Stability of Drugs

High drug stability in the GI environment is necessary because SRDDS is intended to control drug release gradually over time in the gastrointestinal tract (GIT).

v. Protein Binding

Drug-binding proteins are essential to their medicinal effects. Unbound drug concentration, not total concentration, determines a drug's pharmacological action. The biological half-life of the drug is extended by medications that are somewhat attached to tissue and plasma proteins. Since the release of such a drug was prolonged over time, it was unnecessary to create extended-release drug delivery for this kind of medication.

vi. Ionization and Drug pKa at Physiological pH

In the case that the unionized drug is taken and the permeation of the ionized drug is minimal3–4 times less absorption will occur compared with the unionized drugs. Given that the medication must be unionized at the location to a degree of 0.1 to 5%. The oral SR drug delivery system is not a good fit for drugs that are primarily in an ionized state.

vii. Mechanism and Absorption Site

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Poor candidates for oral SR drug delivery systems include drugs taken through windows or carrier-mediated transport systems. Drugs that are absorbed through pore transport, passive diffusion, and the full GIT length are good prospects for the oral SR drug delivery system.

viii. Diffusivity and molecular structure

The size & structure of the membrane's cavities affects diffusivity. The range of the diffusion index for drugs with intermediate molecular weights is 100 to 400 Dalton. The diffusion rate in many polymers is very low for pharmaceuticals with molecular weights greater than 500 Daltons. for example, proteins and peptides.

ix. Dose size

For oral administration of drugs in the maximum bulk size of the prescribed dosage. For a usual dosage form, a single dose of 0.5 to 1.0g is typically regarded as the maximum. The dosage form for continuous release also affects this. Compounds that need large doses of the drug can occasionally be administered in multiple doses or as liquid systems.

II. Biological factors

i. Absorption

The drug must be released from the sustained release device uniformly and then uniformly absorbed in the body to keep a constant, homogeneous tissue or blood level. The rate of release must be significantly slower than the rate of absorption because the formation of an SR product is intended to give the user control over the distribution system. The maximum half-life for absorption should be around 3–4 hours if we believe that the majority of drugs take 8–12 hours to travel through the GI tract's absorptive regions. Otherwise, the device will exit these areas before The drug has been released.

ii. Distribution

Drugs with a large apparent volume of distribution are the difficult fact that they impact the drug's rate of excretion and oral SR drug delivery systems.

iii. Metabolism

Before modifying a drug's shape, one must take into account its metabolic conversion. A successful sustain is possible if the location, rate, and breadth of metabolism are known.

iv. Drug's Half-Life

Although the drug has a short biological half-life of only 5 minutes, it is water-soluble. The therapeutic window of the drugs should be more widely absorbed in the GIT. prolonging the maintenance of therapeutic blood levels is typically the aim of an oral SR product. Drugs must reach circulation at nearly the same rate as they are eliminated to accomplish this. The half-life (t1/2) numerically describes the elimination rate. The total of all elimination processes, such as urine excretion, metabolism, and all other processes that completely remove drugs from the bloodstream, determines each drug's unique characteristic elimination rate.

v. Safety margin

As is well-known, a drug is safer with a higher therapeutic index number. Drugs with a lower therapeutic value are typically not good candidates for oral SR drug delivery systems.

Drug delivery mechanisms for SRDDS(Fincher et al.,1968) (Chien et al., (1990)

i. Rate limiting is osmotic pressure.

Osmosis is a process in which only liquid can pass through a semipermeable membrane as it moves from a lower concentration to a higher concentration. With a hole created by a laser beam on one end of the tablet, the entire drug is covered in a semi-permeable membrane. The drug solution is pumped out of the opening and into the drug environment when gastric fluid passes through the membrane, solubilizes the drug, and raises internal pressure. As long as there is enough drug in the tablet, the delivery rate remains consistent. However, it decreases to zero.

ii. Dissolution is rate limiting

The BCS classes 2 and 4 drugs, which have low water solubility, naturally come in sustained release forms. For drugs that dissolve in water, it is possible to use a carrier that is insoluble in water to slow the dissolution of the drug particles, such as polyethylene

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glycol. To encourage delayed release, disintegrating agent usage is optional.

iii. Diffusion is rate limiting

The movement of drug molecules from a high concentration in the tablet to a reduced concentration in gastrointestinal fluids is caused by a process called diffusion. This movement is influenced by the system's diffusion coefficient, drug concentration gradient, diffusion route, and surface area exposed to gastric fluid. In actuality, we can use either of the two approaches,

1. The drug is enclosed in an insoluble matrix, which is penetrated by gastric juice, which dissolves the medication and causes it to diffuse out of the dosage form.

2. To keep the drug level in circulation constant, the drug particles are coated with a polymer of a specific thickness so that the drug portion gently diffuses through the polymer.

iv. Ion exchange regulates release.

Ion exchangers are resinous compounds metabolism, excretion of urine, and all other processes water and contain anionic or cationic salt-forming groups. The drug solution is combined with resin during production and dried to create pellets that are tabulated. The amount of charged ions in the gastrointestinal system, where the drug molecules are exchanged and dispersed into the fluid around it from the resin. determines how quickly the drug is released. This process is dependent on the resin's environment rather than the pH or an enzyme at the absorption site.

Objectives for developing the SRDDS (Harnish et al., 2011)

I. Decrease dosage frequency or enhance drug efficacy by localizing at the site of action, lowering the dosage necessary, or ensuring uniform drug delivery (Tapaswi et al., 2013) (Loyd et al, 2009)

II. There would be a single dose administered for the course of therapy, whether it lasted a few days or a few weeks as in the case of an infection or the patient's lifetime as in the case of diabetes or hypertension. (Tapaswi et al., 2013)

III. It should minimize or completely eradicate side effects by delivering the active ingredient to the location of the action. (Vinay et al., 2012)

IV. This may require delivery to particular receptors, localization to cells, or particular areas of the body.

V. High-potency medications carry a potential risk of both local and systemic severe side effects in susceptible patients.

(Kumar et al.,2012)

3. Matrix Tablets

Active and inactive components are uniformly combined and diffused in the dosage form to form a matrix system. The success of the matrix systems may be attributed to several variables, making it by far the most widely utilized oral prolonged-release technique. The release from matrix-type formulations is governed by Fick's first law of diffusion. A matrix method disperses the drug as solid particles inside a porous matrix made of a hydrophobic polymer like wax, polyethylene, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, sodium carboxymethylcellulose, alginates, and scleroglucan are examples of hydrophilic polymers. In this context, the term "matrix" refers to the three-dimensional network that holds the drug as well as other components like excipients and solvents needed for the particular preparation. The drug is continuously released via matrix drug delivery devices. These release the medication through diffusion- and dissolution-controlled processes, respectively. Medication molecules on the surface of the release unit will first disintegrate, causing a fast release of the medication. The drug particles will then disintegrate and diffuse through the pores of the release unit to the outside at gradually greater distances from the surface of the release unit. In this approach, the drug reservoir is generated by uniformly distributing drug particles inside a matrix of rate-regulating polymers made of either hydrophilic or lipophilic polymers. (Borguist et al., 2006)

Matrix system's limitations

The limits of matrix systems are the same as those of any technology. First, matrix methods are not adaptable enough to change dose amounts as needed by clinical trial results. When a new dose strength is

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judged required, a new formulation and hence extra resources are often anticipated. Additionally, more complicated matrix-based technologies such as multilayer tablets are needed for specific goods that need distinct release patterns (dual release or delayed + prolonged release).

Drugs or other active ingredients are encapsulated in insoluble excipients in matrix formulations, which enable continual leaching of the drug from the inert matrix core to achieve release.

There are three different categories of matrix systems:

1. Solvent-activated matrix tablets

2. Gel-forming hydrophilic matrix tablet

3. Tablets made of an erodible (hydrophobic) matrix

1. Solid matrix tablets

The most straightforward way of acquiring the inclusion of medication in inert matrix results in the prolonged release of the drug from an oral dosage form. In this context, inert denotes a lack of interaction with biological fluids. Its key benefit is the independence of medication release from polymer matrix tablets from the pH and viscosity of the digestive juices, which can vary greatly between inter and intra-patient.

The porous matrix tablet does not break down as regular tablets do after digestion; instead, it stays whole, and the skeleton can be found in the feces. Most of the components utilized to create these inert matrices are lipophilic chemicals and (insoluble) polymers. Initially, (semi) synthetic polymers including polyethylene, polyvinyl chloride, polymathic methacrylate, polystyrene, polyvinyl acetate, cellulose acetate, and ethyl cellulose were utilized to create matrix tablets. Carnauba wax, hydrogenated castor oil, and tristearin were the fat ingredients utilized. The primary drawbacks of the majority of inert polymeric matrix tablets were their poor direct compression characteristics, inherent first-order drug release characteristics, and difficult cleaning of the agglomeration equipment needed to produce agglomerates with the necessary compression characteristics. (Rao et al., 2013)

2. Gel-forming hydrophilic matrix tablet

The drug is distributed in a swellable hydrophilic polymer in homogeneous or heterogeneous systems known as gel-forming hydrophilic or swellable matrix systems. Since these systems provide the opportunity to establish a consistent dose over an extended period, researchers have extensively investigated them. The properties of the polymer influence drug release.

The hydrophilic polymer is plasticized by the aqueous gastrointestinal system upon ingestion of gel-forming hydrophilic matrix tablets, resulting in macromolecular chain relaxation and volume expansion. As a result, when the gastrointestinal fluids penetrate the drug, a distinct front may be seen that divides the dry, glassy core from the hydrated, rubbery gel layer. The release is controlled by the drug's diffusion through the swelling gel layer, and it often exhibits a burst effect due to the dissolving and leaching of drug particles that were at the surface before the release-controlling gel was formed. (Brazel et al., 1999)

The rate at which the drug penetrates the tablet, the drug's diffusion coefficient, the erosion rate of the gel, and the relative location of the rubber glass contact all affect how the drug is released from swellable devices. When the drug's rate of diffusion through the swelling gel layer is higher than the rate of penetration, the drug's rate of diffusion through the gel layer controls release, and a diffusion-controlled (Fickian) release mechanism is shown. Release of the integrated drug is controlled by the interface penetration rate and zero order drug release with a constant release rate may be obtained if drug diffusion through the gel layer is quick compared to the water penetration rate. (Brazel et al., 2000)

3. Tablets made of an erodible (hydrophobic) matrix

Polyanhydrides, an erodible polymer, provide another fascinating material platform for zero-order drug release. Similar to some HPMC grades, polyanhydrides generate a gel layer upon water entry that erodes at a predetermined rate. The correct polymer composition may be used to ensure that the gel layer's thickness stays consistent throughout time, maintaining a constant release rate up to the point of drug depletion. (Modi et al., 2011)

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Matrix tablet classification: (Patil et al., 2014)

There are five different types of matrix tablets based on the retardant material used.

1. Hydrophobic Matrices

Inert or hydrophobic materials were initially proposed as matrix materials in 1959. Using this technique, a medication is combined with an inert or hydrophobic polymer and crushed into a tablet for prolonged release from an oral dosage form. The medication that is dissolving has diffused through a network of channels that are present between compressed polymer particles, resulting in sustained release. The polymers and their copolymers of polyethylene, polyvinyl chloride, ethyl cellulose, and acrylate have all been employed as inert or hydrophobic matrices. In these formulations, liquid penetration into the matrix serves as the rate-controlling step. Diffusion is a potential medication release mechanism in these types of tablets. Diffusion is a potential drug release mechanism in these types of tablets. In the presence of water and digestive fluid, certain types of matrix tablets become inactive.

2. Lipid Matrices

These matrices have been designed using lipid waxes and associated substances. Drug release from these matrices comes via pore diffusion as well as erosion. Therefore, release properties are more sensitive to the nature of the digestive fluid than they are to a completely insoluble polymer matrix. For several sustained-release formulations, carnauba wax has been used as the retardant base in conjunction with stearyl alcohol or stearic acid.

3. Hydrophilic Matrices

Due to versatility in achieving a desired drug release profile, economic effectiveness, and widespread regulatory acceptability, hydrophilic polymer matrix systems are often utilized in oral controlled drug delivery. In the realm of controlled release, there is special interest in the formulation of pharmaceuticals in gelatinous capsules or, more commonly, tablets utilizing hydrophilic polymers with high gelling capabilities as base excipients. A well-mixed mixture of one or more drugs and a gelling agent (hydrophilic polymer) is described as infecting a matrix. Swellable controlled release systems are what these systems are known as. Three major categories of polymers are employed in the creation of hydrophilic matrices

4. Biodegradable Matrices

These are composed of polymers with unstable backbone linkages made up of monomers connected by functional groups. By enzymes produced by nearby live cells or by non-enzymatic processes, they are physiologically eroded or destroyed into oligomers and monomers that can be metabolized or expelled. Examples consist of synthetic polymers such as aliphatic poly (esters) and poly anhydrides, as well as natural polymers like proteins and polysaccharides, as well as modified natural polymers.

5. Mineral Matrices

These are made up of polymers that come from different kinds of seaweed. A prime example of this is alginic acid, a hydrophilic carbohydrate that may be produced from brown seaweed species (Phaephyceae) using diluted alkali.

Polymers used in matrix tablets (Kumar et al., 2022)

1. Hydrogels:

Cross-linked polyvinyl alcohol (PVA), Polyhydroxyethylemethylacrylate (PHEMA), Polyvinyl pyrrolidone (PVP), Polyethylene-oxide (PEO), and Polyacrylamide (PA).

2. Soluble polymers

PVA (polyvinyl alcohol), PVP (polyvinylpyrrolidone), PEG (polyethyleneglycol), and Hydroxypropylmethylcellulose (HPMC).

3. Biodegradable polymers

polycaprolactone (PCL), Polyglycolic acid (PGA), polyanhydrides, and polyorthoesters are examples.

4. Non-biodegradable polymers:

Cellulose acetate (CA), Polyvinyl chloride (PVC), Polyether urethane (PEU), Polydimethylsiloxane (PDS), Polyethylene vinyl acetate (PVA), and Ethyl cellulose (EC).

5. Mucoadhesive polymers

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Tragacanth, Methylcellulose, Polycarbophil, Sodium carboxy methyl cellulose, Polyacrylic Acid, Guar gum, Karaya gum, Xanthan gum, and locust bean gum.

Methods of preparation of matrix tablet (Rao et al., 2013) (Deepika et al., 2018)

1) Wet granulation method

1. Milling and gravitational mixing of excipients, polymer, and drug.

2. Preparing the binder solution

3. Adding a binder solution or granulating solvent to the wet mass

4. The filtration of moist matter.

5. The wet granules are dried.

6. Dry granules are screened

7. Combining with disintegrants and lubricants to form "running powder"

8. Tablet compression.

2) Dry granulation method

1. Gravitational milling and mixing of excipient, polymer, and drug

2. Compression into slugs

3. Slugs and compacted powder milling and screening

4. Blending with disintegrants and lubricants

5. Compression of the tablet.

3) The Sintering Method

1. Sintering is the process of using heat to crush or fuse neighboring particle surfaces into a mass of powder.

2. Conventional sintering entails heating a compact in a controlled environment with air pressure at a temperature below the melting point of the solid ingredients.

3. The effects of sintering on the hardness and rate of disintegration of tablets held at high temperatures were reported.

4. To stabilize and delay the release of the medicament, sustained-release matrix tablets have been developed through the sintering technique.

Evaluation tests for sustained release matrix tablet

These dosage forms were evaluated in two different methods.

I. Evaluation of granules

II. Evaluation of tablets

I. Evaluation of granules

i. Angle of repose (Tripathi et al.,2004)

The funnel technique was used to calculate the angle of repose. A funnel was attached to a platform at a predetermined height h) above graph paper that was laid out horizontally. The test was spilled. until the funnel's point reached the summit of the conical bulk**.**

Following measurements of the cone pile's radius and a calculation of its angle of repose

$\Theta = Tan^{-1} (h/r)$

ii. Bulk density (Collet et al., 2002)

The equation was used to establish the bulk density.

$\rho b = MV$, Where ρb = Bulk density, M = Mass of the granules in gm V = Final untapped volume of granules in ml.

iii. Tapped density (Forbes et al., 2005)

The tapped density was measured using the equation

$\rho t = M/VP$

Where, ρ t = true density

M =Mass of granules in gm.

VP = Final tapped volume of granules in ml.

iv. Compressibility index (Reddy et al., 2003)

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The capacity of powder to be compacted was evaluated; consequently, the proportional significance of inter-particulate interactions was observed. The following equation was used to calculate the compressibility index.

Compressibility index = (Dt – Db) × 100 Where,

Dt = Tapped density,

Db = Bulk density

v. Hauser's ratio (Satinder et al., 2012)

It was calculated by the following equation.

Hauser's ratio = Dt / Do

Where, Dt = Tapped density,

Do = Bulk density

Evaluation of tablets

i. Weight variation test (Koëter et al.,1981)

Using an electronic scale, 20 tablets of each formulation were measured to investigate weight variance, and the test was carried out by the recommended procedure.

ii. Friability test (Krishna et al., 2013)

Twenty pills were weighed and included in the Roche friabilator, which was then spun at a speed of 25 revolutions per minute for four minutes. The tablet was weighed and cleaned after the revolt.

% friability = Wo - W/Wo × 100

Where,

Wo = Initial weight of twenty tablet

W = weight of 20 tablets after 100 revolutions.

iii. Hardness test (Costa et al., 2001)

Using a Monsanto hardness tester, six tablets were examined for hardness from each batch. An average of six values was recorded along with the standard variation for each batch, as well as the hardness of the individual tablets.

iv. Thickness test (Cohen et al., 1988)

Twenty tablets were randomly chosen from the collection, and each tablet's thickness was Six tablets from each batch were inspected. Values for the average width and standard variation were computed.

v. In-vitro drug release (Varelas et al., 1995)

Formulated tablets were put through an in vitro dissolving test using a paddle-style USP type I / device running at 100 revolutions per minute and maintaining a 37°C water bath. Dissolution was maintained in 900 ccs of simulated stomach fluid for two hours and in simulated intestinal fluid for an additional eight hours. A UV-visible spectrophotometer was used to detect the emission of various medications at specific wavelengths over time.

4. Conclusion

Due to its greater freedom, decreased dosing frequency, and improved involvement of patients, the oral mode of administration for Drug delivery systems with sustained release has drawn more focus. The use of microparticles can help with the handling, protection, and masking of the active ingredient, greater processability, improved bioavailability, lowering the frequency of dosage, improving stability, and geographic targeting of an active ingredient. The formulation of oral dosage forms with sustained release is advantageous for the best possible treatment in terms of effectiveness, patient compliance, and safety. Due to its increased versatility, decreased dosing frequency, and improved patient cooperation, the oral mode of administration for Sustained-release drug delivery systems has recently drawn more focus. The previously mentioned discussion makes it clear that sustained-release formulations are beneficial for increasing dosage effectiveness and for increasing patient compatibility by decreasing the rate of dose consumption.

5. Future scope

The Sustained release dosage forms can increase the bioavailability and half-life of medications while providing effective therapeutic results. Due to these, the frequency of dosing will also reduce and improve patient compliance. Pharmaceutical companies are now utilizing sustained-release dosage forms advantages and growing acceptance by formulating

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various active pharmaceutical ingredients (APIs) as sustained-release matrix tablets to enhance patient outcomes. Considering the future, more drugs are being loaded with sustained-release matrix tablets.

Conflict of interest

None

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