Sustained Release Oral Drug Delivery System: A Review

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Abstract- *The most popular and practical method for administering different medications is oral drug delivery since it offers the highest active surface area of any drug delivery mechanism. The popularity of these dosage forms stems from awareness of the toxicity and lack of efficacy of medications when taken orally using the traditional technique in the form of tablets and capsules. Typically, standard dose forms result in broad variations in drug concentration in the blood and tissues, which has an unfavorable impact on toxicity and ineffectiveness. For a treatment to be effective, the drug's plasma concentration must be kept within the therapeutic range. The idea of oral Sustained release drug delivery systems was developed in response to these factors, as well as factors including recurrent dosing and inconsistent absorption. The medication release rate is controlled by a variety of techniques used in sustained release drug delivery systems. For pharmaceutical technologists, creating oral sustained release matrix tablets for medications with steady release rates has always been a challenge. Water penetration, polymer swelling, drug dissolution, drug diffusion, and matrix erosion have all been used as formulation strategies to predict drug release through matrix systems. A concise overview of the various formulation strategies for sustained release drug delivery systems is provided in the current article.*

Keywords- Matrix system, oral release drug delivery system, reservoir system, sustained drug delivery system.

I. INTRODUCTION

The development of oral sustained release drug delivery systems has received more attention over the past 30 years as the cost and difficulty of selling new pharmacological entities have increased, along with knowledge of the therapeutic benefits of prolonged drug administration. Reducing dosage, dose frequency, and ensuring uniform drug administration are the objectives of the design of sustained release drug delivery systems. Therefore, a dosage form known as a sustained release dosage form is one that continuously delivers one or more medications in aprogrammed sequence for a set amount of time, either systemically or locally to a specific target organ. Sustained release dosage forms offer more consistent distribution, reduced dosing frequency, less adverse effects, and better control of plasma drug levels.[1-4]

The classification of modified release oral drug delivery system is shown in Figure 1.

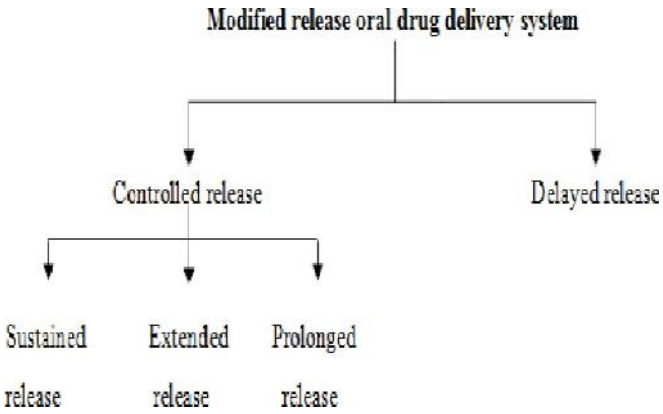

Figure 1: Classification of Modified release oral drug delivery system

For decades, oral drug delivery has been recognized as the most popular mode of administration among all those that have been investigated for the systemic distribution of medications via various pharmaceutical products of varied dose forms. Traditional drug delivery systems (DDS) are characterized by fast release and frequent dosing of the drug, which may increase the risk of dose variation. As a result, a formulation with controlled release is required to maintain a blood level that is almost constant or uniform. Therefore, the majority of pharmaceutical experts nowadays are working to create the optimal DDS.[5,6]

Goal: An SR dose form is intended to sustain therapeutic medication levels in the blood or tissuesfor an extended length of time. Typically, zero-order release from the dose form is attempted to achieve this. Medication release from the dosage form known as zero-order release is unaffected by the quantity of the drug in the delivery mechanism (i.e., a constant release rate). SR systems typically fail to achieve this form of release and instead attempt to imitate zero-order release by slowly delivering the drug in a first-order manner (i.e., concentration dependent).[7,8]

PRINCIPLE OF SRDDS: [9,10]

The active chemicals in conventional dose forms are promptly released into an absorption pool. The basic kinetic scheme that follows serves to explain this. The absorption pool represents a drug solution at the absorption site, with Kr, Ka, and Ke, respectively, representing first order rate constants for drug release, absorption, and total elimination. A traditional dose form's immediate medication release suggests that Kr>>>>Ka. The rate-limiting phase for non- immediate release dosage forms is Kr<<<Ka, or the drug release from the dosage form. The following equation illustrates how the drug release from the dose form should adhere to zero-order kinetics:

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 in litter.

RATIONALE FOR DEVELOPING SUSTAINED RELEASE OF DRUG DELIVERY SYSTEM:[11]

- To prolong the drug's period of action.
- To decrease the dosage's frequency.
- In order to reduce plasma level fluctuations.
- Less side effects.

ADVANTAGES OF SRDDS: *Clinical advantages:* [12,13,14,15]

- Less frequent medication delivery
- Better patient compliance
- Less fluctuating blood drug levels
- Less overall drug use compared to conventional therapy
- Less frequent medication delivery
- Reduction in systemic and local drug toxicity
- Stabilization of health condition (due to more consistent drug levels)
- Enhanced bioavailability of some drugs due to spatial control
- Stabilization of health condition (due to more consistent drug levels)*Commercial benefits:*[16]
- Extension of the product life cycle,
- Product Differentiation
- Market growth
- Extension of a patent

DISADVANTAGES OF SRDDS:[17,18,19,20]

The following list of SRDDS drawbacks is provided:

- A delayed beginning of the drug's effects.
- The potential for dosage dumping in cases of subpar formulation techniques
- Enhanced first pass metabolism potential
- A greater reliance on the dose form's GI residence duration.
- In some situations, it may be possible to alter the dose less precisely.
- The price per dose is higher compared to standard doses.
- Not all medications can be made into ER dose forms.
- Less systemic availability compared to immediate release conventional dosage forms, which may be brought on by insufficient release, increased first-pass metabolism, increased instability, insufficient residence time for full release, site-specific absorption, pH-dependent stability, etc.
- Insufficient in vitro to in vivo connection.

IDEAL PROPERTIES OF SRDDS:[21]

- It must be properly absorbed through the oral route and stable in GI fluid.
- Medicines with short half-lives (2-4 hrs) make excellent candidates for formulation into SR dosage forms, such as captopril and salbutamol sulphate.
- The drug dose should not be less than 0.5 gm, and the maximum dose for SRDDS design is1.0 gm, for example, metronidazole.
- The drug's therapeutic range must be sufficiently broad in SRDDS to ensure that variations in release do not cause concentrations to rise above the minimal hazardous values.

DRUG'S UNSUITABILITY FOR SR FORMULATION IS CAUSED BY THE FOLLOWING FEATURES:[22]

- A high elimination half-life, or t1/2 2 hrs.
- Long half-life of elimination, i.e., t1/2 > 8 hours
- Broad therapeutic index
- High dosages
- Inadequate absorption,
- Poor solubility
- Significant first-pass clearance.

TERMINOLOGY:

SUSTAINED RELEASE:

These drug delivery systems are created to achieve prolonged therapeutic impact by continually releasing

medication over a lengthy period of time following administration of the drug's single dose.[23]

EXTENDED RELEASE:

Reduce the dosing frequency by twofold and release the medication at a rate that is slower than usual.[24]

CONTROLLED RELEASE:

The medicine is released from the delivery mechanism over a longer length of time in a planned, predictable, slower than usual manner.[25]

CLASSIFICATION OF SUSTAINED RELEASE DRUG DELIVERY SYSTEM:[24]

1. Diffusion sustained system
    a. Reservoir type
    b. Matrix type
2. Dissolution sustained system
    a. Reservoir type
    b. Matrix type
3. Methods using Ion-exchange
4. Methods using osmotic pressure
5. pH-independent formulation
6. Altered density formulation

DIFFUSION SUSTAINED SYSTEM:[24,26]

In a diffusion system, a drug's rate of release is governed by how quickly it diffuses past an inert membrane barrier. The diffusion process essentially depicts the transfer of drug molecules from an area of higher concentration to one of lower concentration. Fick's law determines the flow of the drug J (in amount/area time) across a membrane in the direction of decreasing concentration.

$$J = -Ddc / dxL$$

Where,
D = diffusion coefficient in area/time
dc/dx = change of concentration “c” with distance “x”

DISSOLUTION SUSTAINED SYSTEM:[26]

A drug with a slow rate of dissolution will exhibit sustaining features since the rate of dissolution will limit the medication's release. Drugs could be prepared for SR by slowing down their rate of disintegration. The methods for accomplishing this include making the right salts or derivatives, coating the medications with ingredients that dissolve slowly, or adding it to a tablet with a slowly dissolving carrier. Different methods can be used to create a sustained system for dissolution.

ION-EXCHANGE METHODS:[26]

Ion-exchange systems typically employ resins made of cross-linked, water-insoluble polymers. Salt-forming functional groups can be found in these polymers at repeated locations along the polymer chain. By exchanging with properly charged ions in contact with the ion-exchange groups, the medication is attached to the resin and released.

Resin+ Drug - + x- = Resin+ x- + drug- Resin - Drug + + y+ = Resin- x+ + Drug+ Where;
x- and y+ are Ions in GI tract.

SR FORMULATION BASED ON OSMOTIC PRESSURE:[23]

The release-controlling process in this system uses the flow of liquid into the release unit, which is fueled by a differential in osmotic pressure between the inside and exterior of the release unit. In osmosis SR system, the following sequences of stages are engaged in the release process:

- Liquid entering the release unit through osmotic transport.
- The medication dissolving inside the release unit.
- Pumping a saturated medication solution through a single orifice or pores in a semi-permeable membrane to transport it by convection.

PH INDEPENDENT FORMULATION:[24]

The release from SR formulations is pH-dependent because the majority of medicines are either weak bases or weak acids. However, buffers can be added to the formulation to help maintain a consistent pH, resulting in pH-independent drug release. These buffers include salts of amino acids, citric acid, phthalic acid, phosphoric acid, and tartaric acid. A basic or acidic medicine is combined with one or more buffering agents to create a buffered SR formulation. The mixture is then granulated with the proper pharmaceutical excipients and coated with a GI fluid permeable film generating a polymer. The buffering agents modify the fluid inside to an appropriate constant pH as GI fluid seeps through the membrane, resulting in a consistent rate of medication release.

ALTERED DENSITY FORMULATIONS:[24,27]

It is logical to assume that a delivery system would be of little use unless it stayed close to the absorption site until most, if not all, of its medication contents were discharged. In order to do this, a number of strategies have been devised to extend DDS's time spent in the GI tract.

FACTORS AFFECTING THE FORMULATION OF ORAL SR DDS

There are two major factors that affect the release rate from the DDS. They are:

1. Physicochemical factors
2. Biological factors.

PHYSICOCHEMICAL FACTORS

a. Aqueous solubility
b. Partition coefficient (P [O/W])
c. Drug pKa and ionization at physiological pH
d. Drug stability
e. Molecular weight and diffusivity
f. Protein binding
g. Dose size.

AQUEOUS SOLUBILITY:[2,4]

The majority of medications are weak bases or weak acids. It will be challenging to include drugs with limited water solubility into the SR mechanism. It can be challenging to slow the dissolving rate of a medication with a high solubility and quick dissolution rate. When compared to a drug that is less soluble in water, a drug with a high water-solubility readily dissolves in water or GI fluid, tends to release its dosage form all at once, and is absorbed quickly. This causes the blood drug concentration to rise sharply. When the dose is high, it is frequently challenging to combine a highly water-soluble medicine in the dosage form and delay the drug release.

PARTITION COEFFICIENT: [4]

The partition coefficient is the ratio of the drug concentration in the oil phase to that in the adjacent aqueous phase. Between the time a drug is administered and when it is eliminated from the body,it must diffuse through a variety of biological membranes, many of which act primarily as lipid-like barriers. Partition coefficient influences both the permeation of the drug across the biological membranes and diffusion across the rate controlling membrane or matrix. The apparent oil or water partition coefficient, which is defined as, is a key factor in determining whether a medicine may pass through these lipid membranes.

DRUG PKa AND IONISATION: [2,28]

Oral SR DDS is not a good option for medications that are primarily in ionised form. Because ionised medications are absorbed 3–4 times less quickly than unionised drugs, their diffusion into the body is far less than that of unionised drugs. The best pKa ranges for optimum positive absorption are 3.0-7.5 for acidic drugs whose ionisation is pH sensitive and 7.0-11.0 for basic drugs whose ionisation is pH sensitive. Drug must be unionised at the facility to a degree of 0.1% to 5%.

DRUG'S STABILITY:[7,29]

When taken orally, drugs are subject to enzymatic and acid/base hydrolysis deterioration. Drug release can be postponed until the dosage form reaches the intestine for medications whose pH stability in the stomach can be addressed by developing slow release dosage forms. Drugs that undergo gut wall metabolism and exhibit small intestine instability are not appropriate for the SR system. In this situation, either a different route of administration should be chosen or the drug can be chemically altered to create prodrugs, which may have different physicochemical properties.

BIOLOGICAL FACTORS:

a. Absorption
b. Distribution
c. Metabolism
d. Biological half-life

ABSORPTION:

A sustained system should be able to discharge all of the absorbed energy. Rapid absorption relative to drug release is always anticipated, therefore it appears that the drug's release from the body is the rate-limiting stage.

It takes the GI tract 8 to 12 hours to absorb food.

The recommended maximum half-life for absorption is 3 to 4 hours.

DISTRIBUTION:

The drug's binding to blood and tissue proteins is a part of the distribution process.

A high level of protein binding results in sustained therapeutic action even though medication molecules that are protein bound are thought to be inert and unable to penetrate cellular membranes**.**

METABOLISM:

Drugs that can stimulate or inhibit the production of enzymes are poor candidates for continuous release delivery systems since it is difficult to maintain consistent blood levels with them.

Drugs with variable bioavailability because of the first pass effect should not be delivered via a sustained release approach.

HALF-LIFE:

For the development of a drug delivery system, the drug should have a half-life of 3 to 4 hours.

METHODS FOR PREPARATION:

DIRECT COMPRESSION:

Powdered materials are directly compressed without affecting their physical or chemical characteristics, such as those of a medication.

WET GRANULATION:

An adequate amount of granulating agent is combined with weighed amounts of the medication and polymer in the wet granulation process.

Screening of wet mass comes when sufficient cohesion has been created.

After being dried and screened for dry granules, the granules are blended with lubricant.

Using a single-punch tablet compression machine, the powder is compressed.

MELT GRANULATION:

A substance melts during this process at a relatively low temperature.

This chemical can be added to a substrate that has been heated past its melting point in molten form.

Utilizing the melt granulation process, various lipophilic binders were tested.

HOT-MELT EXTRUSION PROCESS:

The thermoplastic polymers are mixed with the active ingredients and fed into the barrel of the extruder through the hopper during the hot-melt extrusion process.

A spinning screw moves the materials into the heated barrel.

The materials melt at a high temperature, and the bulk of molten material is continually fed through the barrel's associated die.

EVALUATION OF ORAL SUSTAINED RELEASE TABLETS:

Tablet thickness:

A micrometre screw gauge is used to measure tablet thickness. Twenty tablets are tested at random, and the average results are computed.

Tablet hardness:

The Monsanto hardness tester measures the tablet hardness of each batch, and average values are computed.

Weight uniformity:

20 tablets are chosen at random, weighed separately and collectively, and an average weight is computed.

% of weight variation= (Individual Weight- Average weight/Average Weight) × 100

Uniformity of content:

In order to ensure that every tablet contains the same amount of the active component with little to no fluctuation within a batch, this test is performed for uniformity of content. 30 tablets are chosen for the content uniformity test, and 10 of them are individually tested. At least nine must assay between 15% and not more than 25% of the specified potency.

Friability:

20 pills are weighed and put in the friability machine. The tablets are withdrawn from the chamber and weighed once more after it has been rotating for 4 minutes at a speed of 25 rpm. Weight loss is a sign of friability. When there is a weight loss of less than 0.8%, the tablets are deemed to be of high quality.

In vitro dissolution studies:

Studies on in vitro dissolution are performed to determine how long it takes for a specific amount of medication to dissolve in a solution under particular test circumstances. As stated in the monograph for a certain medicine or in accordance with pharmacopoeial standards, rotating paddle type and rotating basket type apparatus can be employed.[32]

If the amount of active ingredient in solution for each of the five tablets is greater than or equal to the amount mentioned in the monograph of the API in the pharmacopoeia, the test is considered successful.[30,31]

II. DISCUSSION

The sustained release matrix tablet is the main subject of the current article. The use of matrix tablets made it simple and efficient to determine the desired sustained release. In comparison to their conventional counterparts, matrix tablets improve patient compliance, maintain a stable plasma drug concentration level, lower the risk of toxicity, and lower overall treatment costs through once-daily medication administration. Maintaining drug concentrations within therapeutic range aids in the management of chronic diseases and reduces the irrational use of pharmaceuticals, particularly antibiotics. Additionally, it is a practical financial strategy.

III. CONCLUSION

The sustained release drug delivery system is particularly beneficial for improving patientcompliance, dose efficiency, and dose safety. Due to its increased flexibility, decreased dose frequency, and improved patient compliance, the oral route of administration for Sustained release drug delivery systems has recently attracted considerable interest. The design of an oral sustained release drug delivery system is influenced by a number of variables, including the drug's physicochemical properties, the type of delivery system used, the disease being treated, the patient's condition, the length of the treatment, the presence of food, gastrointestinal motility, and the coadministration of other medications. We may infer from the explanation above that the affordable price of oral sustained release drug delivery systems has made it easier for them to replace oral conventional drug delivery systems in the market.

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