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A REVIEW ON SUSTAINED RELEASE DRUG DELIVERY SYSTEM

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ABSTRACT

In all drug delivery system, Oral drug delivery remains the most preferred system for administration of various drugs. Sustained Release Drug Delivery System (SRDDS) is designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. The basic rationale of sustained release drug delivery system optimizes the biopharmaceutical, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximized, side-effects are reduced and cure of the disease is achieved. There are several advantages of sustained release drug delivery over conventional dosage forms like improved patient compliance due to less frequent drug administration, maximum utilization of the drug, increased safety margin of potent drug, reduction of fluctuation in steady-state drug levels, maximum utilization of the drug, increased safety margin of potent drug, reduction in healthcare costs through improved therapy and shorter treatment period. The present article contains brief review on various formulation approaches for Sustained release drug delivery system.

KEYWORDS: Sustained release drug delivery system, Extended release, Reservior system

INTRODUCTION[1,2,3]

The oral route of drug delivery is largest and oldest segment of the total drug delivery market. It is the fastest growing and most preferred route for drug administration of therapeutic agent, convenient method of effectively achieving both local and systemic effects and number of diseases which have been successfully treated. Oral dosage form and oral route are the most preferred route of administration for various drugs have limitations like first-pass

metabolism, psychiatric patients, bedridden and uncooperative patients. Many patients preferred oral dosage forms as well as advanced oral drug delivery systems over other dosage forms. Tablets are most popular oral formulation available in the market. Sustained release technology helps to maintain the therapeutic range of plasma drug concentration for prolong period of time. Therefore, we aimed to present a dual character of orodispersible as well as sustained release profile in order to enhance patient compliance. Moreover, the sustained or extended release technology offer potential drug delivery systems to provide optimum regimens of therapeutic value. Such dosage forms enhance the efficacy, reduce toxicity. Whereas, reduces frequency, shorten the half-lives and help to avoid the undesired troughs and peaks of plasma drug concentration to obtain the time variant efficacy associated with rapid drug release.

ADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY[1,4,5]

- Reduction in dosing frequency of intakes.
- Increased safety margin of potent drug.
- Uniform release of drug over time.
- Reduced fluctuation in steady-state drug levels.
- Maximum utilization of the drug.
- Reduce side effects.
- Better patient compliance.
- Minimize the fluctuations in plasma level.
- Drug administration can be made more convenient as well.
- To extend the duration of action of the drug.

DISADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY[5,6,7]

- Cost of the formulation is high.
- Toxicity due to dose dumping.
- Increased cost.
- Increase potential for first pass metabolism.
- Reduced potential for dose adjustment.
- Requirement for additional patient education for proper medication.
- Poor In vitro and In vivo correlations (IVIVC).

CLASSIFICATION[1,8,9]

The sustained release drug delivery system is achieving a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. The main aim of preparing sustained release formulations was intended to modify and improve the drug performance by increasing the duration of drug action, decreasing the required dose, decreasing the frequency of dosing employed and providing uniform drug delivery.

Modified release delivery system

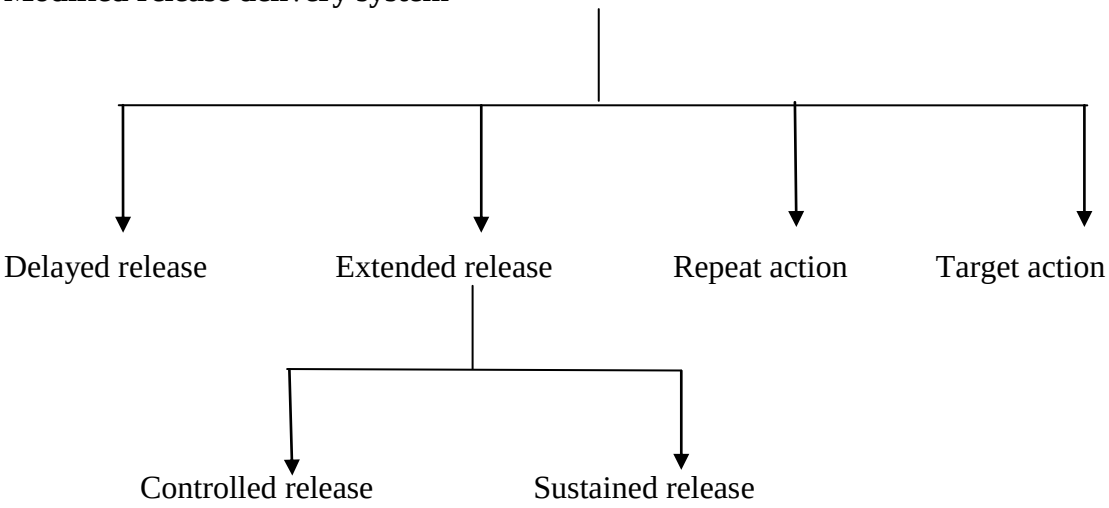

Figure No. 1: Flow chart of modified release delivery system.

Delayed release

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form.

Extended release

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds.

A. Controlled release

These systems which delivers the drug at predetermined rate, for locally r systematically, for a specified period of time. Continuous oral delivery of drugs at predictable ad reproducible kinetics for predetermined period throughout the GIT.

B. Sustained release

Sustained drug delivery may provide an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific period of time usually 8-12 hours.

Repeat action

These are dosage forms usually containing 2 single doses of medication, one foe immediate and the second for delayed release e.g. Bi-layered tablets.

Target action

Drug release that is directed towards isolating or concentrating a drug in a body region, tissue, or site for absorption or drug action.

DRUG SELECTION FOR SUSTAINED RELEASE DRUG DELIVERY SYSTEM[1,10,6]

There are some physiochemical parameters for the drug selection to be formulated in sustained release dosage form.

Table No. 1: Physicochemical parameters of drug Selection.

Parameter	Preferred Value
Molecular Weight	<1000 Daltons
Solubility	>0.1 mg/ml for pH 1 to pH 7.8
Apparent Partition Coefficient	High
Absorption Mechanism	Diffusion
General Absorbability	From all GI segment
Release	Should not be influenced by pH and Enzymes

Table No. 2: pharmacokinetic parameters for drug selection.

Parameters	Comment
Elimination half-life	Preferably between 2 to 8
Total clearance	should not be dose dependent
Elimination rate constant	Required for design
Apparent volume distribution (Veda)	The larger Veda and MEC, the larger will be the required dose size
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration	The lower C_{uss} and smaller Veda loss among the dose required
Toxic concentration	Apart the values of MTC and MEC, safe the dosage form. Also Suitable for drugs with very short half life

DESIGN AND FORMULATION OF ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEM[1,9,11,12,13,18]

a) Diffusion sustained system

I. Reservoir type

II. Matrix type

b) Dissolution sustained system

I. Reservoir type

II. Matrix type

c) Methods using Ion-exchange

d) Methods using osmotic pressure

e) pH independent formulations

f) Altered density formulations

a. Diffusion sustained system

Diffusion is process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. Drug across a membrane in the direction of decreasing concentration is given by Fick's law.

I. Reservoir type

In diffusion reservoir system, a water insoluble polymeric material covers a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media. The drug release takes place by diffusion mechanism**.**

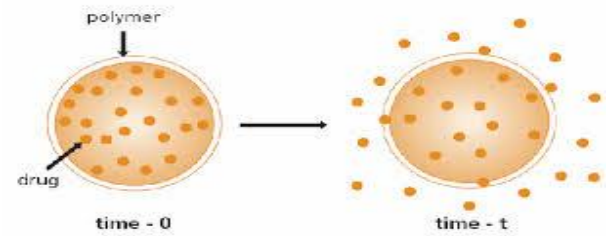

Figure No. 2 Schematic Representation of Diffusion Type Reservoir System.

II. Matrix type

A solid drug is dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution. It consists of drug dispersed homogenously in a matrix.

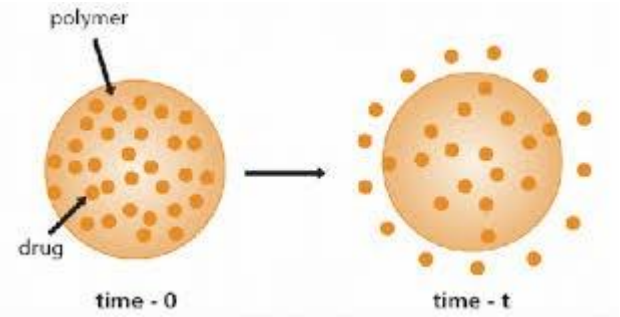

Figure No. 3 Schematic Representation of Diffusion Type Matrix System.

b. Dissolution sustained system

In dissolution sustained system is a drug with a slow dissolution rate is inherently sustained and for those drugs with high water solubility, one can decrease dissolution through appropriate salt or derivative formation. These systems are most commonly employed in the production of enteric coated dosage forms. This inhibits release of drug from the dosage form until it reaches the higher pH of the intestine.

I. Reservoir type

In reservoir dissolution system is coated with a given thickness coating, which is slowly dissolved in the contents of gastrointestinal tract by alternating layers of drug with the rate controlling coats.

II. Matrix type

The dissolution matrix systems it can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion.

c. Methods using Ion-exchange

Ion exchange resins are cross-linked water-insoluble polymers carrying ionizable functional groups. The resins have been used in various pharmaceutical applications, primarily for taste masking and controlled release systems. In tablet formulations, ion exchange resins have been used as disintegrate, because of their swelling ability. It forms irreversible complex with ionizable drugs upon prolonged exposure of the drug to the resin. A resin bound drug is removed when appropriate ions are in contact with ion-exchanged groups. The area and length of diffusion pathway and the amount of cross-linked polymer in the resin moiety governs the rate of drug release.

d. Methods using osmotic pressure

In this method, the release controlling factor that must be optimized is the osmotic pressure gradient between inside the compartment and the external environment. The simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the compartment. This technology provides zero order release used for hydrophilic drugs. Drug may be osmotically active or combine with osmotically active salt e.g. NaCl. A semi permeable membrane is placed around a tablet, particle or drug solution that allows transport of water into the tablet with eventual pumping of drug solution out of the tablet through a small delivery aperture in tablet coating. The osmotic systems are classified in major two types, Type A contains an osmotic core with drug Type B contains the drug in flexible bag with osmotic core surrounding.

e. pH independent formulations

Most drugs are either weak acids or weak bases. The release from Sustained release formulations is pH dependent. However; buffers such as salts of amino acids, citric acid, phthalic acid, phosphoric acid or tartaric acid can be added to the formulation to help to maintain a constant pH thereby rendering pH independent drug release. A buffered formulation is prepared by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH thereby rendering a constant rate of drug release.

f. Altered density formulations

Several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract. The delivery system remains in the vicinity of the absorption site until most, if not all of its drug contents is released. In high density approach, the density of the pellets must exceed that of normal stomach content and should therefore be at least 1-4g/cm3. In low density approach, the globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug for sustained release purpose. There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product. This system is generally used when, the single dose for the duration of treatment whether for days or weeks as with infection, diabetes or hypertension is required.

FACTORS INFLUENCING DESIGN OF SUSTAINED RELEASE DOSAGE FORMS[1,6,7]

The therapeutic efficacy of drug under clinical conditions is not simply a function of its intrinsic pharmacological activity but also depends upon the path of the drug molecule from the site of administration to the target site. Different conditions encountered by the drug molecule while traversing the path of distribution may alter either the effectiveness of the drug or affect the amount of the drug reaching the receptor site.

✓ **Pharmaceutics**

This refers to the development/manufacturing of an efficient delivery system in which the drug has maximum physiological stability and optimum bioavailability.

✓ **Biopharmaceutics / pharmacokinetics**

This involves the study of absorption, distribution, metabolism and excretion of the drug, before and after reaching the target site and evaluation of the relationship between delivery system and therapeutic response.

✓ **Pharmacodynamics/ Clinical Pharmacology**

It is the study of the mechanism of action and clinical efficacy of a drug administered in dosage form in terms of onset, intensity and duration of pharmacological activity.

CHARACTERIZATION OF SUSTAINED RELEASE TABLET[1,14,15,16,17]

Before marketing a sustained release product, it is must to assure the strength, safety, stability and reliability of a product by forming In-vitro and In-vivo analysis and correlation between the two. Various authors have discussed the evaluating parameters and procedures for sustained release formulations.

a) Pre-Compression evaluation

Angle of repose (θ)

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by the angle of repose.

$\tan\theta = h / r$

$\theta = \tan^{-1} (h/r)$

Where, θis the angle of Repose

his height of pile

r is radius of the base of the pile

Different ranges of flowability in terms of angle of repose are given below.

Bulk density

Bulk density is defined as the mass of a powder, divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

$$\text{LBD} = \frac{\text{Weight of the powder}}{\text{Volume of the packing}}$$

Where, LBD is loose bulk density

Tapped density

$$\text{TBD} = \frac{\text{Weight of the powder}}{\text{Tapped volume of packing}}$$

Where, TBD is tapped density

Hausner's ratio

Hausner's ratio is an indirect index of ease of power flow.

$$\text{Hausner's ratio} = \frac{\rho_t}{\rho_d}$$

Where ρ_t is tapped density and ρ_d is bulk density. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones. (>1.25) indicates poor flow.

Carr's compressibility index

The compressibility index of the granules was determined by the Carr's compressibility index. (%) Carr's Index can be calculated by using the following formula.

$$\text{Carr's Index (\%)} = \frac{\text{TBD - LBD}}{\text{TBD}} \text{ x } 100$$

b) Post-Compression parameters

1. Hardness test

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling during manufacture, packaging and shipping. The hardness of the tablets was determined using Digital Hardness tester. It is expressed in

Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

2. Friability test

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition.

The friability of tablets was determined by using Electro lab, USP EF 2 friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 RPM for 4 minutes. The tablets were weighed again (W_{final}). The percentage friability was then calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100$$

% Friability of tablets less than 1% is considered acceptable.

3. Weight variation test

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

Table No. 3: Percentage deviation in weight variation.

Average weight of a tablet	Percentage deviation
200mg or less	10
More than 190 mg and less than 200 mg	7.5
200 or more	5

4. Uniformity of thickness

In all the formulations the tablet weight was more than 190 mg, hence 5% maximum difference allowed.

The thickness of individual tablet may be measured with a digital vernier calliper, which permits accurate measurements and provides information on the variation between tablets.

5. Disintegration test

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in-vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P.

The test was carried out on 6 tablets using the apparatus specified in I.P.-1996 distilled water at 37°C ± 2°C was used as a disintegration media and the time in second is taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

6. Drug content

Take the powder of 20 tablets. Weighed a quantity of powder containing 0.1gm of verapamil hydrochloride with 150ml of phosphate buffer pH6.8 for 10 minutes, add sufficient phosphate buffer pH6.8 to produce 200ml and filter. Dilute 10 ml of filtrate to 100ml with water and measure the absorbance at 278nm.

7. *In vitro* drug release

Drug release study is generally determined in Rotating Paddles apparatus. Mainly buffer is used as a dissolution medium. The temperature of the bath maintained at 37°C and required sample of the dissolution medium in which drug is release is taken at a regular interval and the same quantity of the medium is replace. The amounts of the drug released is determined using an UV spectrophotometer a Drug dissolved at specified time period is plot as percent release versus time.

Stability studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The ability of a pharmaceutical product to retain its chemical, physical, microbiological and biopharmaceutical properties within specified limits throughout its shelf life and recommended storage conditions.

CONCLUSION

The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. The design of oral sustained release delivery systems is subject to several inter related variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug.

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