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Sustained Release Drug Delivery System: A Review

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ABSTRACT: Among all drug delivery system, oral drug delivery is the most preferred route for administration of various drugs. Sustained release products provide advantage over conventional dosage form by optimizing bio pharmaceutics, pharmacokinetics and pharmacokinetics properties of drug. Thus sustained release formulation provides important way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. The term "sustained release" is known to have existed in the medical and pharmaceutical literature for many decades. Oral drug delivery is the most preferred route for the various drug molecules among all other routes of drug delivery, because ease of administration which leads to better patient compliance. Sustained Release is also providing promising way to decrease the side effect ofdrugbypreventingthefluctuationofthetherapeuticc oncentrationofthedruginthe body.

Keywords: Sustained release Controlled release, Plasma concentration, Frequency of dosing.

I. INTRODUCTION

Oral route of drug delivery is the most preferred route of the various drug molecules among all other routes of drug delivery because of ease of administration, patient compliance, and flexible design of dosage form[1]. Drug release is the process by which a drug leaves a drug product and is subjected to absorption, distribution, metabolism and excretion, eventually to becoming available for pharmacological action[2]. Now a day's conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems. Amongst, these the controlled release/sustained release dosage forms have become extremely popular in modern therapeutics. Matrix system is the release system which prolongs and controls the release of the drug, which is dissolved or dispersed[3]. The conventional dosage forms are rapidly replaced by this novel controlled release techniques. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extendedperiodoftimeafteradministrationofasingled ose[4].

1.1 Sustained release dosageforms

Any drug or dosage form modification that prolongs the therapeutic activity of the drug**[5]**. The release of the drug is retarded for a delayed and prolonged period of time in the systemic circulation**[6]**. Sustained release formulation maintains a uniform blood level of drug with better patient compliance as well as increased efficacy of drug**[7]**. Sustained release tablets are generally taken once or twice a day during a course of treatment whereas in conventional dosage forms there is need to take 3-4 times dosage in a day to achieve the same therapeuticaction**[8]**.

1.1.1 Rational for developing ofSRDDS[9,10]

I. Formulation of SRDDS minimizes dosing frequency and sustained release provides availability of a drug at action site throughout the treatment to improve clinical efficiency of a drugmolecule.
II. To reduce cost of treatment by reducing number of dosage requirement.
III. To minimize toxicity due to overdose which is often in conventional dosagefrom.
IV. To enhance the activity duration of a drug possessing shorthalf-life.

1.1.2 Principle ofSRDDS[11,12]

The conventional dosage forms release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme. The absorption pool represents a solution of the drug at the site ofabsorption, Kr, Ka and Ke - first order rate-constant for drug release, absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that

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Kr>>>>Ka. For non-immediate release dosage forms, Kr<<<Ka i.e. the release of drug from the dosage form is the rate limiting step. The drug release from the dosage form should follows zero-order kinetics, as shown by the following equation:

Kr° = Rate In = Rate Out=Ke.Cd.Vd 1

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

1.2 Advantages ofSRDDS

Following are some advantages of SRDDS:

Clinical advantages[13,14,15,16]

I. Reduction in frequency of drugadministration
II. Improved patientcompliance
III. Reduction in drug level fluctuation inblood
IV. Reduction in total drug usage when compared with conventionaltherapy
V. Reduction in drug accumulation with chronictherapy
VI. Reduction in drug toxicity(local/systemic)
VII. Stabilization of medical condition (because of more uniform druglevels)
VIII. Improvement in bioavailability of some drugs because of spatialcontrol
IX. Economical to the health care providers and the patient.

Commercial advantages[17]

I. Product life-cycleextension
II. Productdifferentiation
III. Marketexpansion
IV. Patentextension

1.3 Disadvantages ofSRDDS [18, 19, 20, 21]

Following are some disadvantages ofSRDDS:

I. Delay in onset of drugaction.
II. Possibility of dose dumping in the case of a poor formulationstrategy.
III. Increased potential for first passmetabolism
IV. Greater dependence on GI residence time of dosage form.
V. Possibility of less accurate dose adjustment in some cases.
VI. Cost per unit dose is higher when compared with conventionaldoses.
VII. Not all drugs are suitable for formulating into ER dosage form.
VIII. Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stabilityetc.
IX. Poor In vitro – In vivocorrelation.
X. Retrieval of drug is difficult in case of toxicity, poisoning (or) hypersentivityreactions.
XI. Reduced potential for dose adjustment of drugs normally administered in varyingstrength.

Table 1: Advantages Sustained release dosage forms over Conventional dosage forms **[22]**

Sr. No.	Sustained releasedosage form	Conventional dosageforms
1.	The total dose of drug and dosing frequency is reduced by SRDF and therefore it improves patient compliance and efficiency of a treatment.	Dosing frequency is more in conventional dosage forms and requires large number of dosage and efficiency of a treatment is poor. The characteristic blood level variations due to multiple dosing
2.	The constant level of drug concentration in blood plasma is maintained and prolonged therapeutic action of a drug is achieved.	The characteristic blood level variations due to multiple dosing of conventional dosage forms prolonged action cannot be achieved.

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3.	Use of matrix system in SRDF tablet eliminates dose dumping and reduces toxicity due to overdose	Forms upon fast release of drug; toxicity can be produced due to overdose
4.	The cost of treatment is reduced by reducing number of dosage but cost of production of single unit SRDF is higher due to requirement of costly processes and equipment's.	The cost of preparation is less in conventional dosage forms but number dosage requirement sometimes lead to increase in total cost of treatment

1.4 Ideal properties of drug suitable forSRDDS[23]

I. It should be effectively absorbed by oral route and stable in gastro-intestinal (GI)fluid.
II. Drugs that have short half-lives (2-4 hrs) are ideal drug candidate for formulation into SR dosage forms eg. Captopril, Salbutamolsulphate.
III. The dose of drug should not be less than 0.5gm and maximum dose of drug for designing SRDDS is 1.0 gm eg.Metronidazole.
IV. The therapeutic range of the drug should be high in SRDDS for drug should have wide therapeutic range enough such that variation in the release does not result in concentration beyond the minimum toxiclevels.

1.5 Challenges forSRRDS[24,25]

Dosedumping

This can greatly increase the concentration of a drug in the body and there by produce adverse effects or even drug- induced toxicity. Dose dumping means the relatively large quantity of medication in a sustained release formulation is slowly released. If the dose dumping can leads to fatalities in case of potent drug, which have a narrow therapeutic, index e.g. Phenobarbital.

Limited choice of selecting desired dose in the unit

In case of conventional dosage forms, the dose adjustments are much simple e.g. tablet can be divided into two portions. In case of sustained release dosage forms, this can appear to be much more complicated. Sustained release property may get lost, if dosage form isfractured.

Poor in-vitro – in-vivo correlation

In sustained release dosage form, the rate of drug release is slowly reduced to achieve drug release possibly over a large region of gastrointestinal tract. Hence it is so called as 'Absorption window' becomes important and give rise to unsatisfactory drug absorption in-vivo despite excellent in-vitro release characteristics.

Patient variation

The time period required for absorption of drug released from the dosage form may vary among individuals. The co- administration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among thepatient.

Criteria for selection of SRDDS[26,27] Following is the criteria of SRDDS;

Desirable half-life: The half- life time of a drug in the body has a residence time of index. Drug has a short half- life time in the dosage form may contain a large quantity of the drug. The drugs have elimination half-life of eight hours are sufficiently sustained in the body.

High therapeutic index

In the sustained release formulation drugs with low therapeutic index are unsuitable for incorporation. Dose dumping may occur due to the system fails in the body that leads tofatalities.
e.g. Digitoxin.

Small dose

In the conventional dosage form, if the dose of a drug is high then its suitability as a candidate for sustained release is seriously

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undetermined. This is important because the size of a unit dose sustained release formulation would become larger, to administer withoutdifficulty.

Desirable absorption and solubility characteristics

In the absorption of poor water soluble drug it is often dissolution rate limited. Incorporation of such type of compounds into sustained release formulations is therefore unrealistic and may decrease overall absorptionefficiency.

Desirable absorption window

Certain drugs when orally administered and absorbed only from a specific part of a body i.e. gastrointestinal tract. This body part is referred to as the 'absorption window'. There are some drugs such as thiazide diuretics, fluorouracil that are absorbed from an absorption window. If they formulated as sustained release dosage form then that are unsuitable dosageform.

First pass clearance

In sustained drug delivery system, delivery of the drug to the body in desired concentrations is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in sustained release form.

1.6 Formulation ofSRDDS [28,29,30]

There are no. of formulation are considered in-

Drug complexes: The principal advantage of preparing drug derivatives for sustained release is those materials can be formulated into diverse dosage forms. This approach has proven effective in the development of injectable depot forms, in which release profiles are not subject to the variability characteristics of the gastrointestinal tract. Sensitivity to in vivo variables is a definite disadvantage of per orally administered forms; in vivo studies may not consistently support sustained releaseclaims.

Encapsulated slow release granules

The first significant marketed sustained release dosage forms were encapsulated mixed slow release beads, to which was applied the barrier principles of controlling drug release, based on model D. For low milligram potency formulations, nonpareil seeds are initially coated with an adhesive followed by powdered drug, and the pellets are dried. This step is repeated until the desired amount of drug has been applied. The resultant granules are subsequently coated with a mixture of solid hydroxylated lipids such as hydrogenated castor oil or glyceryltrihydroxystearate mixed with modified celluloses. The thickness of the barrier was regulated by the no. of applied coatings to obtain the desired release characteristics. The original formulation utilised glycerol monosterate bees wax compositions, which tended to be physically unstable, showing altered release pattern onaging.

Tableted slow release granulation

Compression of time release granulations into tablets is an alternate to encapsulation. Such tablets should be designed to disintegrate in to stomach so as to stimulate the administration of a capsule form having the advantage associated with sustained release encapsulations, while retaining the advantage of the tablet dosage forms. Three examples, each utilizing a different process, illustrate this type of formulation. The first is a tabletted mixed release granulation in which binders with different retardant properties are used to prepare three different granulations, which are colour coated for identification, blended & tabletted. This first is a conventional non sustained release granulation prepared using gelatin as a binder, the uses vinyl acetate, and the third uses shellac as binders. Drug release is controlled by erosion of the granulation in intestinal fluid the vinyl acetate granulation disintegrates at a faster rate than the shellac granulation.

Controlled release technology

Controlled release dosage forms are designed to release drug in vivo according to predictable rates that can be verified by a vitro measurements. Of the many approaches to formulation of sustained release medication, those fabricated as insoluble matrix tablets come closest to realization of this objective, since release of water soluble drug from this forms should be independent of in vivo variables. Controlled release technology implies a quantitative understanding of the physicochemical mechanism of drug availability to the extent that the dosage forms release rate can be specified. Potential developments & new approaches to oral controlled release drug delivery include hydrodynamic pressure controlled systems, intragastric floating tablets, transmucosal tablets, and micro porous membrane coatedtablets.

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1.7 Classification ofSRDDS [31,32, 33]

The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanismsinthecontrolofreleaserateofdrug.Depending upon the manner of drug release, these systems are classified as follows:

Continuous release systems [31,32]

Continuous release systems release the drug for a prolonged period of time along the entire length of gastrointestinal tract with normal transit of the dosage form. The various systems under this category are asfollow:

I. Diffusion controlled releasesystems
II. Dissolution controlled releasesystems
III. Dissolution and diffusion controlled releasesystems
IV. Ion exchange resin- drugcomplexes
V. pH-independentformulation
VI. Osmotic pressure controlledsystems

Diffusion controlled release systems [31,33]

In this type of systems, the diffusion of dissolved drug through a polymeric barrier is a rate limiting step. The drug release rate is never zero-order since the diffusional path length increases with time as the insoluble matrix is gradually depleted of drug. Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems. Similar to the dissolution-controlled systems, the diffusions controlled devices are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix. Unlike the dissolution-controlled systems, the drug is made available as a result of partitioning through the polymer. In the case of a reservoir type diffusion controlled device, the rate of drug released (dm/dt) can be calculated using the followingequation:

dm/dt = ADK ΔC/L Where, A = Area
D = Diffusion coefficient
K = Partition coefficient of the drug between the drug core and the membrane
L = Diffusion path length and
C = Concentration difference across the membrane

In order to achieve a constant release rate, all of the terms on the right side of equation must be held constant. It is very common for diffusion controlled devices to exhibit a non-zero- order release rate due to an increase in diffusional resistance and a decrease in effective diffusion area as the release proceeds. Another configuration of diffusion-controlled systems includes matrix devices, which are very common because of ease of fabrication. Diffusion control involves dispersion of drug in either a water-insoluble or a hydrophilic polymer. The release rate is dependent on the rate of drug diffusion through the matrix but not on the rate of solid dissolution.

The two types of diffusion-controlled release are:

I. Matrix diffusion controlledsystems
II. Reservoirdevices

Dissolution-controlled releasesystems [31,32,33]

Thedrugpresentinsuchsystemmaybetheone:

I. Having high aqueous solubility and dissolutionrate
II. With inherently slow dissolution rate e.g. Griseofulvin andDigoxin
III. That produces slow dissolving forms, when it comes in contact with GIfluids

Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer. The rate of dissolution (dm/dt) can be approximated by following equation:

dm/dt =ADS/h Where,
A = Surface area of the dissolving particle or tablet
D = Diffusivity of the drug
S = Aqueous solubility of the drug h = Thickness of the boundarylayer

The two types of dissolution-controlled release are:

I. Matrix (or monolith) dissolution controlledsystems
II. Reservoir dissolution controlledsystems

Dissolution and diffusion controlled release systems

In such systems, the drug core is encased in a partially soluble membrane. Pores are thus created due to dissolution of parts of the membrane

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which permit entry of aqueous medium into the core and hence drug dissolution and allow diffusion of dissolved drug out of thesystem.

Ion exchange resin-drug complexes

It is based on formulation of drug resin complex formed when ionic solution is kept in contact with ionic resins. The drug from this complex gets exchanged in gastrointestinal tract and released with excess of Na^+ and Cl^- present in gastrointestinal tract. This system generally utilize resin compound of insoluble cross linked polymer. They contain salt forming function group in repeating position on a polymerchain.

pH-independent formulation

Most of the drug are either weak acid or weak base, the release from sustain release formulation is pH dependent. However, buffer such as salt of citric acid, amino acid, tartaric acid can be added to the formulation, to help to maintain to constant pH their by retarding pH independent drug release. A buffer sustain release formulation is prepared by mixing a basic or acidic drug one or more buffering agent, granulating withappropriate excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agent adjusts the fluid inside to suitable constant pH there by rendering a constant rate of drugrelease.

Osmotic pressure controlled systems

A semi permeable membrane is placed around the tablet, particle or drug solution that allows transport of water into tablet with eventual pumping of drug solution out of the tablet through the small delivery aperture in tablet core. Two types of osmotic pressure controlled systemsare:

I. **Type 1 contains an osmotic core withdrug**
II. **Type 2 contains the drug in flexible bag with osmotic coresurrounding**

By optimizing formulation and processing factor, it is possible to develop osmotic system to deliver the drug of diverse nature at pre-programmedrate.

Delayed transit and continuous release systems

These systems are designed to prolong their residence in the GI tract along with their release. Often the dosage form is fabricated to detain in the stomach and hence the drug present therein should be stable to gastric pH. Systems included in this category are mucoadhesive systems and size basedsystems.

Delayed release systems

The design of such systems involves release of drug only at specific site in the GIT. The drugs contained in such a system are those thatare:

I. Known to cause gastricdistress
II. Destroyed in the stomach or by intestinalenzymes.
III. Meant to extent local effect at a specific GIsite
IV. Absorbed from a specific intestinal site The two types of delayed release systemsare:

I. Intestinal releasesystems
II. Colonic releasesystems

1.8 Novel trends inSRDDS [34,35,36]

For orally administered dosage forms, sustained drug action is achieved by affecting the rate at which the drug is released from the dosage form and or by slowing the transit time of dosage form through the gastrointestinal tract. Zahirul Khan has classified the sustained release dosage form on the basis of its structural and physical appearance as, single unit dosage form, and multiple unit dosage form and mucoadhesive delivery systems.

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 can be classified asfollows

Complex reservoir system or coated tablets or multi-layered system

The core material which typically, the drug alone or blended with hydrophobic or hydrophilic Inert material and it is compressed intotablets.

Hydrophobic/Swellable tablets

Optimum alkaloid such as morphine salts homogenized with its salt and fatty acid or any ethylene vinyl acetate copolymer (hydrophobic filler) and then compressed into tablets.

Semisolid matrix systems

In this system drug is incorporated in an oily "semisolid" hydrophobic carrier, and finally mass is typically filled into a gelatin capsule to prepare dosage form.

Ion exchange resins

A drug–resin complex is formed by

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prolonged exposure of drug to the resin. The drug from these complexes gets exchanged in gastrointestinal tract and later they are released with excess of Na^+ and Cl^- present in gastrointestinal tract.

Osmotic pump

The system is composed of a core tablet surrounded by a semipermeable membrane coating having a 0.4mm diameter hole produced by laser beam 16. The tablet, particle or drug solution that allows transport of water into tablet with eventual pumping of drug solution out of the tablet through the small delivery aperture in tablet coating.30. E.g. Glucotrol XL (glipizide) tablets (Pfizer), Covera – HS ® (verapamil HCl) tabs.(Searle)

Multiple Unit Dosage Forms

It represents a mixture of the dosage form, the source of which may either be homogenous or heterogeneous. The various forms which are available are Multitablet system Small spheroids compressed tablets 3 to 4 mm in diameter may be prepared to have varying drug release characteristics. They them may be placed in gelatin capsule shells to provide the desired pattern of drug release Coated Beads, granules& Microsphere In these systems, the drug is distributed on to beads, pellets, granules, or other particulate systems. Using conventional pan coating or air suspension coating, a solution of the drug substance is placed on small inert nonpareil seeds or beads made of sugar and starch or on microcrystalline cellulose spheres. Pellets prepared by coating inert drug pellet with film forming polymers. The drug release depends upon coating composition of polymers and amount of coatings. Microencapsulation is a process by which solids, liquids, or even gases may be enclosed in microscopic particles by formation of thin coatings of wall material around the substance. Mucoadhesive Delivery System. It utilizes principle of bioadhesion for optimum delivery of thedrug from the device. Mucoadhesive system is suitable to increase the contact time of drug with absorbing membrane and localization of delivery of drug at targeted sites.

2.0 Factors affecting SRDDS[37,38,39]

Two types of factorsinvolved

I. Physicochemicalfactor
II. BiologicalFactor

I. Physicochemicalfactor

Aqueous Solubility

The drug of good aqueous solubility and pH independent solubility are most desirable candidate for SRDDS. Poor aqueous solubility possess oral bioavailability problem and drug which having extreme aqueous solubility are unsuitable for sustained release because it is difficult task to control the release of drug from the dosageform.

Partition coefficient

Also called as distribution coefficient; the bioavailability of a drug is greatly influenced by the partition coefficient, as the biological membrane is lipophilic in nature transport of drug across the membrane is depends upon the partition coefficient of the drug. The drugs having low partition coefficient are considered as poor candidate for the sustained release formulation in the aqueousphase.

Drug Stability

SRDDS is designed to control release of a drug over the length of the gastrointestinal tract (GIT); hence high stability of drug in GI environment isrequired.

Protein Binding

Proteins binding of drug play a key role in its therapeutic. Pharmacological activity of a drug depends on unbound concentration of a drug rather than total concentration. The drugs which bound to some extent of a plasma and tissue proteins enhances the biological half-life of a drug. Release of such drug extended over a period of time and therefore no need to develop extended release drug deliveryfor this type of drug.

Drug pKa & Ionization at Physiological pH

If the unionized drug is absorbed and permeation of ionized drug is negligible, but the rate of absorption is 3 to 4 times is less than that of the unionized drug. Since the drug shall be unionized at the site to an extent 0.1 to 5%. Drugs existing largely in ionized form are poor candidates for oral SR drug delivery system. e.g.Hexamethonium.

Mechanism and Site of Absorption

Drug absorption by carrier mediated transport system and those absorbed through a window are poor candidate for oral SR drug delivery system. Drugs absorbed by passive diffusion, pore transport and over the entire length of GIT are suitable candidates for oral SR drug deliverysystem.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 953-966 www.ijprajournal.com ISSN: 2249-7781

Molecular size and diffusivity

Diffusivity depends on size & shape of the cavities of the membrane. The diffusion coefficient of intermediate molecular weight drug is 100 to 400 Dalton. For drugs having molecular weight > 500 Daltons, the diffusion coefficient in many polymers is very less. e.g. Proteins andpeptides.

Dose size

For oral administration of drugs in the upper limit of the bulk size of the dose to be administered. In general, asingle dose of 0.5 to 1.0g is considered maximal for a conventional dosage form. This also depends on sustained release dosage form. Compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquidsystems.

II. BIOLOGICALFACTORS

Absorption

To maintain the constant uniform blood or tissue level of drug, it must be uniformly released from the sustained release system & then uniformly absorbed in the body. Since the purpose of forming a SR product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours; otherwise, the device will pass out of the potential absorptive regions before drug release is complete. Thus corresponds to a minimum apparent absorption rate constant of 0.17-0.23 h-1 to give 80-95% over this time period. Hence, it assumes that the absorption of the drug should occur at a relatively uniform rate over the entire length of small intestine. For many compounds this is not true. If a drug is absorbed by active transport or transport is limited to a specific region of intestine, SR preparation may be disadvantageous to absorption. One method to provide sustaining mechanisms of delivery for compounds tries to maintain them within the stomach. This allows slow release of the drug, which then travels to the absorptive site. These methods have been developed as a consequence of the observation that co- administration results in sustainingeffect.

Distribution

Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug, are poor for oral SR drug delivery system e.g.Chloroquine.

Metabolism

The metabolic conversion of a drug is to be considered before converting into another form. Since as long as the location, rate, and extent of metabolism are known a successful sustain release product can be developed. Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage form. Even a drug that is poorly water soluble can be formulated in SR dosage form. For the same, the solubility of the drug should be increased by the suitable system and later on that is formulated in the SR dosage form. But during this the crystallization of the drug, that is taking place as the drug is entering in the systemic circulation, should be prevented and one should be cautious for the prevention of the same.

Half-life of Drug

The drug having short biological half-life between <5 but drugs is soluble in water. The drugs should have larger therapeutic window absorbed in GIT. The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life (t1/2). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove drug from the bloodstream.

Margin of safety

As we know that larger the value of therapeutic index safer is the drug. Drugs with less therapeutic index usually poor candidate for formulation of oral SR drug deliverysystem.

2.1 Mechanisms of drug release ofSRDDS[40,41]

Diffusion is rate limiting

Diffusion is driving force where the movement of drug molecules occurs from high concentration in the tablet to lower concentration in gastro intestinal fluids. This movement depends on surface area exposed to gastric fluid, diffusion

International Journal of Pharmaceutical Research and Applications
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pathway, drug concentration gradient and diffusion coefficient of the system. In practice we can follow either of the two methods,

I. The drug is formulated in an insoluble matrix; the gastric fluid penetrates the dosage form and dissolves the medicament and release the drug throughdiffusion.

II. The drug particles are coated with polymer of defined thickness so as the portion of drug slowly diffuse through the polymer to maintain constant drug level in blood.

Dissolution is rate limiting

The drugs with poor water solubility (BCS class 2 and 4) are inherently sustained release forms. While for water-soluble drugs, it's possible to incorporate a water insoluble carrier to reducedissolutionofthedrugparticlesarecoatedwiththistype of materials e.g. Polyethylene Glycol. One may skip the use of disintegrating agent to promote delayed release.

Osmotic pressure is rate limiting

Osmosis is a phenomenon in which the flow of liquid occurs from lower concentration to higher concentration through a semi permeable membrane which allows transfer of liquid only. The whole drug is coated with a semi permeable membrane with a hole on one end of tablet made by a laser beam. The gastric fluid penetrates through the membrane, solubilizes the drug and increases the internal pressure which pumps the drug solution out of the aperture and releases the drug environment. The delivery rate is constant provided that the excess of drug present inside the tablet. But, it declines tozero.

Release is controlled by ion exchange

Ion exchangers are water insoluble resinous materials containing salt forming anionic or cationic groups. While manufacturing, the drug solution is mixed with resin and dried to form beads which are tableted. The drug release depends upon high concentration of charged ions in gastro intestinal tract where, the drug molecules are exchanged and diffused out of the resin into the surrounding fluid. This mechanism relies upon the environment of resin and not pH or enzyme on absorptionsite**[41,42]**.

2.2 Goals in designingSRDDS[42]

I. Reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drugdelivery**[43,44]**.
II. It would be a single dose for the duration of treatment whether it is for days or weeks, as with infection or for the life time of the patient, as in hypertension or diabetes**[43]**.
III. It should deliver the active entity directly to the site of action, minimizing or eliminating sideeffects**[45]**.
IV. This may necessitate delivery to specific receptors or to localization to cells or to specific areas of thebody.
V. The safety margin of high potency drug can be increase and the incidence of both local and systemic adverse side effects can be reduced in sensitivepatient**[46].**

2.3 Evaluation forSRDDS

Evaluation of these dosage form done by two ways:

I. Evaluation ofgranules
II. Evaluation oftablets

I. Evaluation of granules involve followingtest

Angle of repose[47]

The angle of repose was determined using the funnel method. A funnel was secured on a stand at a fixed height h) above a graph paper placed on a horizontal surface. The sample was poured until the apex of the conical pile touched the tip offunnel.

The radius of the conical pile was measured and the angle of repose calculated as follows:

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

Bulk density[48]

The bulk density was calculated using equation:

$$\mathbf{\rho b = MV}$$

Where ρb = Bulk density,
M = Mass of the granules in gm
V = Final untapped volume of granules in ml.

True density[49]

The true density was measured using equation;

$$\mathbf{\rho t = M/VP}$$

Where,
ρ t = true density

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Volume 6, Issue 4 July-Aug 2021, pp: 953-966 www.ijprajournal.com ISSN: 2249-7781

M =Mass of granules in gm.,
VP = Final tapped volume of granules in ml.

Loss on drying (LOD)[50]

The moisture content of the lubricated granules was analysed by using IR moisture analyser. 5.0 gm. or more quantity of granules was heated at 1050c until the change in weight was no more observed by the instrument. The % loss in weight was recorded.

Compressibility index[51]

This was measured for the property of a powder to be compressed; as such they are measured for relative importance of inter-particulate interactions. Compressibility index was determined by followingequation.

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

Hausner ratio[52]

It was calculated by following equation.

Hausner ratio = Dt / Do

Where, Dt = Tapped density, Do = Bulk density

II. Evaluation of SR tablets involve followingtest

Weight variation[53]

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (citizen India) and test was performed according to official method Friability**[54]**

In this twenty tablets were weight and placed in the Roche friabilator and apparatus was rotated at 25rpm for 4min. After revolution the tablet were dusted and weight.

% friability = Wo - W/Wo × 100

Where, Wo = Initial weight of twenty tablet W = weight of 20 tablet after 100 revolution.

Hardness[55]

Tablet hardness was measured by using Monsanto hardness tester from each batch six tablets were measured for the hardness and an average of six values was noted along with and an average of six values was noted along with standard deviation.

Thickness[56]

Twenty tablets from the sample were randomly taken and individual tablet thickness was measured using digital Vernier calliper. Average thickness and standard deviation values were calculated.

In-vitro drug release rate[57]

Formulated tablet were subjected to invitro dissolution study using USP type I / II apparatus (paddle) at 100 rpm with temperature of water bath maintain at 37±0.5oc. Dissolution was carried in 900 ml simulated gastric fluid for 2 hrs and for further 8 hrs in simulated intestinal fluid. The release of different drugs at different time interval was measured at particular wavelength by U.V-visiblespectrophotometer

2.3. Future prospects[58,59,60]

The future of sustained-release products is promising, especially in the following areas that present high promise and acceptability:

Particulate systems

The micro particle and Nanoparticle approach that involves biodegradable polymers in which intact drug-loaded particles via the Peyer's patches in the small intestine could be useful for delivery of peptide drugs that cannot, in general, be given orally.

Chronopharmacokinetic systems

Oral sustained drug delivery with a pulsatile release regimen could effectively deliver drugs where need exists to counter naturally occurring processes such as bacterial/parasitical growthpatterns.

Targeted drug delivery

Oral controlled drug delivery that targets regions in the GI tract and releases drugs only upon reaching that site could offer effective treatment for certain disease states (e.g. colon-targeted delivery of Antineoplastics in the treatment of colon cancer).

Mucoadhesive delivery

This is a promising technique for buckle and sublingual drug delivery, which can offer rapid onset of action and superior bioavailability compared with simple oral delivery because it bypasses first-pass metabolism in the liver.

III. CONCLUSION:

The oral route of administration for Sustained release drug delivery system has received more attention due to its more flexibility,

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reduced dosing frequency and better patient compliance. The micro particles offers a variety of opportunities such as protection and masking, better processability, improved bioavailability, decreasing dosing frequency, improve stability, reduced dissolution rate, facilitation of handling, and spatial targeting of the active ingredient. Development of sustained release oral dosage forms is beneficial for optimaltherapy regarding efficacy, safety and patient compliance. Nowadays, the oral route of administration for Sustained release drug delivery system has received more attention due to its more flexibility, reduced dosing frequency and better patient compliance. By the above discussion, it can be easily concluded that sustained release formulation are helpful in increasing the efficiency of the dose as well as they are also improving the patient's compatibility.

REFERENCES

[1]. **[1].** Kamboj S., Saroha K., Goel M., Madhu C., Sustained Release Drug Delivery System: An Overview, Journal of Pharmaceutics2013;1:169-181.

[2]. **[2].** Zameerudin M., Namdev H., Jhadav SB., Kadam VS., Bade A., Recent Advances of Sustained Release Oral Drug Delivery System: A Review, International Journal of Pharmaceutical Sciences and Biomedical Sciences 2014;3:1479-1489.

[3]. **[3].** Ratilal D., Gaikwad Priti D., An Overview on Sustained Release Drug Delivery System, International Journal of Research and Applied Pharmaceutics 2011;1701-1708.

[4]. **[4].** Patil K., Patel Mehul S., Bhatt Narayana S., Patel L., An Overview on Extended Release Matrix Technology, Journal of Pharmaceutics2013;828-842.

[5]. **[5].** Gandhi A., Kumar SL., Recent Trends in Sustained Release Drug Delivery System, International Journal of Applied Pharmaceutics 2014;1:122-134.

[6]. **[6].** Bhankar SK., Chaudhari AV., Mahale NB., Chaudhari SR., A Review on Oral Dispersible Tablets Prepared Using Sustained Release Microparticles, Journal of Advanced Release Drug Delivery System 2014;1:2014,82-95.

[7]. **[7].** Semwal A., Singh R., Kakar S., Drug Release Characteristics of Dosage Forms: A Review, Journal of Coastal Life Medicine2014;332-336.

[8]. **[8].** Kumar P., Kijjal R., Novel Oral Sustained Release Drug Technology: A Concise Review, International Journal of Research and Development Pharmaceutical Sciences 2013;2:262-269.

[9]. **[9].** Phad Anil B., Mahale NB., Chaudhari SK., Salunke SK., A Sustained Release Drug Delivery System, World Journal of Pharmaceutical Research 2014;3:5:1377-1390.

[10]. **[10].** Nagarani B., Ashwin Kumar K., Julapally D., A Review on Controlled Drug Delivery System, International Journal of Applied Pharmaceutics 2014;2:1555-1586.

[11]. **[11].** Bharagava A., Rathore RPS., Tanwar YS., Gupta S., Oral sustained release dosage form: An opportunity to prolong the release of drug, International Journal of Applied Pharmaceutics and Biomedical Sciences2013;3:7-14.

[12]. **[12].** Bhowmik D., Matrix Drug Delivery System, Recent trends in Sustained release matrix drug delivery system-An Overview, Journal of Pharmaceutics2009;20-28.

[13]. **[13].** Patel Chirag J., Satyanand T., Novel Sustained Release Drug Delivery: A Modern Review, International Journal of Applied Pharmaceutics2014;1:115-119.

[14]. **[14].** Pogula M., Nazeer S., Extended Release Formulation, International Journal of Pharmacy & Technology 2010;2:625-684.

[15]. **[15].** Parashar T., Soniya S., Singh V., Novel oral sustained release technology: A Concise Review, International Journal of Research and Development in Pharmacy and Life Sciences2013;262-269.

[16]. **[16].** Patel Kundan K., Patel Mehul S., Bhatt Nayana M., An Overview: Extended Release Matrix Technology, International Journal of Pharmaceutical and Chemical Sciences 2012;112-115.

[17]. **[17].** Mamdouh G., Elsayed K., Marima K and Shadeed G., Formulation, Characterization and Comparative in-vitro, in-vivo evaluation of Sustained Release theophylline tablets, International Journal of Pharmacy and Pharmaceutical Sciences2012;721-728.

[18]. **[18].** Rao Raghavendra NG., Raj Prasanna Richard K., Nayak S., Review on Matrix Tablet as Sustained Release, International Journal of Pharmaceutical Research & Allied Sciences2013;2:1700-1717.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 953-966 www.ijprajournal.com ISSN: 2249-7781

[19]. **[19].** Wadher G., Satish B., Tukaram MK., Recent (Aspects) trend on Sustained drug delivery system, International Journal of Chemical and Pharmaceutical Sciences 2013;4:1-7.
[20]. **[20].** Kumar Sampath KP., Bhowmik D., Srivastava S., Sustained release drug delivery system potentials, International Journal of Pharmaceutics2010;2:751-754.
[21]. **[21].** Bose S., Kaur A., Sharma SK., A Review on Sustained release drug delivery system, International Research Journal of pharmacy2013;149-515.
[22]. **[22].** Bankar AU, Bankar VH. Gaikwad PD., A Review on Sustained release drug delivery system, An International Journal of pharmaceutical sciences 2012;3:2049-2063.
[23]. **[23].** Misa R., Waghmare A., Aqueel S., Matrix tablet: A Promising Technique for Controlled drug delivery, Indo American Journal of Pharmaceutical Research 2013;3:2013:3791-3805.
[24]. **[24].** Deore KR., Kuncha K and Theetha GT., Preparation and evaluation of sustained release matrix tablets of tramadol hydrochloride using Glycerol Palmitostearate, Tropical Journal of Pharmaceutical Research 2010;275-281.
[25]. **[25].** John C., Chris M., Modified–Release Peoral Dosage Form. In: M.E.Aluton's Pharmaceutics – The Science of Dosage Form Design, International Journal of Pharmaceutics 2003;296-298.
[26]. **[26].** Jun C., Haesun P., and Kinam P., Superporous Hydrogels as a Platform for Oral Controlled Drug Delivery,Hand Book of Pharmaceutical Controlled Release Technology 2000;211-216.
[27]. **[27].** Suvakanta D., Padala Narasimha M., Lilakanta N., Prasanta C., Drug Release From Controlled Drug Delivery Systems, Acta Poloniae Pharmaceuticals – Drug Research 2010; 217-223.
[28]. **[28].** Gautam S. and Mahveer S., Review: In-vitro Drug Release Characterization Models, International Journal of Pharmaceutical Studies and Research 2011;2:77-84.
[29]. **[29].** Higuchi T., Mechanism of sustained action medication, theoretical analysis of rate of release of solid drugs dispersed in solid matrices, Journal of Pharmaceutical Sciences1963;1145-1149.
[30]. **[30].** Korsmeyer RW., Gurny R., Doelker E., Buri P. Peppas NA., Mechanisms of solute release from porous hydrophilic polymers, International Journal of Pharmaceutics1983;2:25-35.
[31]. **[31].** Tripathi KD., Antihypertensive Drugs In: Essentials of Medical Pharmacology, 5th edition, Jaypee Brothers Medical Publishers2003;115-120.
[32]. **[32].** Rang HP., Dale MM., The Vascular System. In: Pharmacology, Churchill Living Stone, International Journal of Clinical Pharmacology2003;1,2003:298-302.
[33]. **[33].** Harsh M., The Kidney and Lower Urinary Tract. In: Textbook of Pathology, 6th edition Jaypee Brothers Medical Publishers2000;2:649-654.
[34]. **[34].** Mahesh H., Upendra P., Ghanshyam P., Dhiren D., Amarish S., Bhavin B., Matrix Tablets: A Tool of Controlled Drug Delivery, American Journal of Pharmaceutical Technology Research2011;1;127-143.
[35]. **[35].** Gwen MJ. and Joseph R., Sustained and Controlled Release Drug Delivery System, Modern Pharmaceutics Journal of Applied Sciences2002;507-510.
[36]. **[36].** Leon S., Susanna W., Andrew BC., Modified-Release Drug Products, In: Applied Biopharmaceutics & Pharmacokinetics, International Journal of Sustained Release Delivery System2004;223-228.
[37]. **[37].** Brahmankar DM., Sunil B., Controlled Release Medication. In: Biopharmaceutics and Pharmacokinetics, International Journal of Pharmaceutics2009:400-406.
[38]. **[38].** Khyati P., Upendra P., Bhavin B., Ghansyam P., Dhiren D., Extended Release Oral Drug Delivery System, International Journal of Pharmaceutical Research and Biomedical Sciences2012;2,1-26.
[39]. **[39].** Nicholas G., Sustained Release Dosage Forms. In: The theory and Practice of Industrial Pharmacy,International Journal of Pharmacy and Pharmaceutical Sciences 1987;3:430-476.
[40]. **[40].** Fincher JH., Particle size of drugs and its relation to absorption and activity, Journal of Pharmaceutical Sciences1968;1825-1835.
[41]. **[41].** Chien YW., Controlled and modulated-release drug delivery systems, In: Swarbrick J, Balyan JC. Encyclopedia of

Pharmaceutical Technology, New York: Informa Health Care1990;281-313.

[42]. **[42].** Harnish P., Dhrupesh RP., Upendra P., Jushar B., Mayur S., Matrix Type Drug Delivery System: A Review, Journal of Pharmaceutical Sciences Research and Bioscientific Research2011;1:143-151.

[43]. **[43].** Tapaswi R., Pankaj V., Matrix Tablets: An Approach towards Oral Extended Release Drug Delivery, International Journal of Pharmaceutical Research and Review2013;2:12-24.

[44]. **[44].** Loyd A., Nicholos G., Popvich Howard C., Solid Oral Modified-Release Dosage Forms and Drug Delivery System, In: Ansel's Pharmaceutical Dosage Forms and Drug Delivery System, International Journal of Pharmaceutics2009;257-270.

[45]. **[45].** Vinay K., Prajapati SK., Girish C., Mahendra S., Neeraj K., Sustained Release Matrix Type Drug Delivery System: A Review, World Journal of Pharmacy and Pharmaceutical Sciences 2012;1:934-960.

[46]. **[46].** Kumar V., Prajapati SK., Soni GC., Singh M., Neeraj K., Sustained release matrix type drug delivery system: a Review, World Journal of Pharmaceutics& Science 2012;1:934-960.

[47]. **[47].** Tripathi KD., Essentials of Medical Pharmacology. New Delhi: Jaypee Brothers Medical Publishers 2008; 196-197.

[48]. **[48].** Harish J., The U.S. Pharmacopeia Convention, The United States pharmacopoeia. Rockville: United States Pharmacopoeia Convention 2004;155-160.

[49]. **[49].** Collet J., Moreton C., Modified-release per oral dosage forms, In: Alton ME, editor. Pharmaceutics: science of dosage form design. United Kingdom: Churchill Livingstone; International Journal of Pharmaceutics, 2002;1:665-669.

[50]. **[50].** Forbes Z., Magnet is able implants for targeted drug delivery, USA: Drexel University; Journal of Pharmaceutics2005;222-225.

[51]. **[51].** Reddy KR., Mutalik S., Reddy S., Once-daily sustained- release matrix tablets of nicorandil: formulation and in vitro evaluation, Journal of Pharmaceutical Science & Technology2003;4:480-488.

[52]. **[52].** Satinder K., Batra D., Singh R., Preparation and evaluation of magnetic microspheres of mesalamine (5-aminosalicyclic acid) for colon drug delivery, International Journal of Pharmaceutics2013;2:226-231.

[53]. **[53].** Koëter GH., Jonkman JH., Vries K., Schoenmaker R., Greving JE., Zeeuw RA., Extended release theophylline alternative in vitro dissolution methods, Journal of Clinical Pharmacology 1981;2:647-651.

[54]. **[54].** Krishna KV., Reddy CH., Srikanth S., A review on microsphere for novel drug delivery system, International Journal of Research Pharmaceutical Chemistry 2013;763- 767.

[55]. **[55].** Costa P., Sousa Lobo JM., Modeling and comparison of dissolution profiles, Journal of Pharmaceutical Science 2001;123-133.

[56]. **[56].** Cohen DS., Erneaux T., Free boundary problems in controlled release pharmaceuticals, Journal of Applied Mathematics 1988;1451-1465.

[57]. **[57].** Varelas CG., Dixon DG., Steiner CA., Zero-order release from biphasic polymer hydrogels, Journal of Control Release1995;1;185-192.

[58]. **[58].** Ahmed I., Roni MA., Kibria G., Islam MR., Jalil R., In- vitro release kinetics study of ambroxol hydrochloride pellets developed by extrusion spheronisation technique followed by acrylic polymer coating, Dhaka University Journal Pharmaceutical Science2008;1:75-81.

[59]. **[59].** Arjun S., Ritika S., Faraz J., Sustained release drug delivery system: A Review, International Research Journal of Pharmaceutics2012-2013;1:21-24.

[60]. **[60].** Korsmeyer RW., Lustig SR., Peppas NA., Solute and penetrant diffusion in sellable polymers, Mathematical modelling, Journal of Polymer Science and Bioscience Polymer Physics 1986;3:395-408.

[61]. **[61].** Khodaverdi E., Tekie FS., Mohajeri SA., Ganji F., Zohuri G., Hadizadeh F., Preparation and investigation of sustained drug delivery systems using an injectable, thermosensitive, In-situ forming hydrogel compose of PLGA-PEG-PLGA, Journal of pharmaceutics 2012;2:590- 600

[62]. **[62].** Liberman HA., Lachmann L., Shwartz JB., Pharmaceutical Dosage Forms: Tablets, Journal of Pharmaceutics 1990;1: 285-327.

[63]. **[63].** Gupta AK., Mittal A., Jha KK., Fast Dissolving Tablet- A Review, The Pharmaceutical Innovation, International Journal of Biomedical Sciences 2012;1:1-7.

[64]. **[64].** Kaur .T, Gill B., Kumar .S, Gupta GD., Mouth Dissolving Tablets: A Novel Approach to Drug Delivery, International Journal of Current Pharmaceutical Research 2011; 2:1-7.

[65]. **[65].** Prasanth VV. Chakraborthy A., Moy., Sam., Mathew T., Mathapan R., Microspheres an Overview, International Journal of Research in Pharmaceutical and Biomedical Sciences 2011;2:332-338.