IJMPR 2021, 5(1), 71-76

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article

SJIF Impact Factor: 5.273

SUSTAINED RELEASE DRUG DELIVERY SYSTEM: A REVIEW OF NOVEL APPROACH.

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Received on: 09/12/2020
Revised on: 29/12/2020
Accepted on: 19/01/2021

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ABSTRACT

Drug absorption in the gastrointestinal tract is a highly variable process and prolonging gastric retention of the dosage form extends the time for drug absorption. Novel drug delivery system overcomes the physiological problems of short gastric retention through various approaches including floating drug delivery systems (FDDS), these systems float due to bulk density less than gastric fluids and so, remain buoyant in the stomach for a prolonged period of time, releases the drug slowly at the desired rate from the system and increase the bioavailability of narrow absorption window drugs. This review entitles the applications of sustained release floating tablets, suitable for sustained release of those drugs incompatible with floating constituents over an extended period of time for better patient compliance and acceptability. The purpose of this paper is to review the principle of sustained release drug delivery system, current technology used in the development of same as well as summarizes the applications, advantages, methodology, evaluation methods and future potential for sustained release drug delivery systems.

KEYWORDS: Drug Delivery Systems, Sustained DDS, Floating DDS, Novel DDS.

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. 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. 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 extended period of time after administration of a single dose.[2]

Sustained release dosage forms

Any drug or dosage form modification that prolongs the therapeutic activity of the drug.[3] The release of the drug is retarded for a delayed and prolonged period of time in the systemic circulation. Sustained release formulation maintains a uniform blood level of drug with better patient compliance as well as increased efficacy of drug. 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 therapeutic action.

Rational for developing of SRDDS

- 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 drug molecule.[4]
- To reduce cost of treatment by reducing number of dosage requirement.
- To minimize toxicity due to overdose which is often in conventional dosage from.
- To enhance the activity duration of a drug possessing short half-life.

Principle of SRDDS

The conventional dosage forms release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme.[5] The absorption pool represents a solution of the drug at the site of absorption, Kr, Ka and Ke - first order rate-constant for drug release, absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that 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

Advantages of SRDDS

Following are some advantages of SRDDS:

Clinical advantages.[6]

- Reduction in frequency of drug administration
- Improved patient compliance
- Reduction in drug level fluctuation in blood
- Reduction in total drug usage when compared with conventional therapy
- Reduction in drug accumulation with chronic therapy
- Reduction in drug toxicity (local/systemic)
- Stabilization of medical condition (because of more uniform drug levels)
- Improvement in bioavailability of some drugs because of spatial control
- Economical to the health care providers and the patient

Commercial advantages.[7]

- Product life-cycle extension
- Product differentiation
- Market expansion
- Patent extension

Disadvantages of SRDDS.[8]

Following are some disadvantages of SRDDS

- Delay in onset of drug action.
- Possibility of dose dumping in the case of a poor formulation strategy.
- Increased potential for first pass metabolism
- Greater dependence on GI residence time of dosage form.
- Possibility of less accurate dose adjustment in some cases.
- Cost per unit dose is higher when compared with conventional doses.
- Not all drugs are suitable for formulating into ER dosage form.
- 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 stability etc.
- Poor In vitro – In vivo correlation.
- Retrieval of drug is difficult in case of toxicity, poisoning (or) hypersentivity reactions.
- Reduced potential for dose adjustment of drugs normally administered in varying strength.

Ideal properties of drug suitable for SRDDS

- It should be effectively absorbed by oral route and stable in gastro-intestinal (GI) fluid.
- Drugs that have short half-lives (2-4 hrs) are ideal drug candidate for formulation into SR dosage forms eg. Captopril, Salbutamol sulphate.
- 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.
- 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 toxic levels.

Challenges for SRRDS[9]

Dose dumping

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 is fractured.

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 coadministration 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 the patient.

Formulation of SRDDS[10]

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 release claims. 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 on aging. 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[11]

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 coated tablets.

Classification of SRDDS[12]

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

Continuous release systems[13]

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 as follow:

- Diffusion controlled release systems
- Dissolution controlled release systems
- Dissolution and diffusion controlled release systems
- Ion exchange resin- drug complexes
- pH-independent formulation
- Osmotic pressure controlled systems

Diffusion controlled release systems[14]

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 following equation:

$Dm / dt = ADK \Delta C/L$

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:

- Matrix diffusion controlled systems
- Reservoir devices

Novel trends in SRDDS[15]

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 as follows.

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 into tablets.

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 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 the drug from thedevice. Mucoadhesive system is suitable to increase the contact time of drug with absorbing membrane and localization of delivery of drug at targeted sites.

Factors affecting SRDDS[16,17]

Two types of factors involved

- Physicochemical factor
- Biological Factor
- Physicochemical factor

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 dosage form.

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 aqueous phase.

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 is required.[18]

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 delivery for 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 delivery system.[19]

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 and peptides.

Dose size

For oral administration of drugs in the upper limit of the bulk size of the dose to be administered. In general, a single 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 liquid systems

II. Biological factors

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.

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.

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 delivery system.

Goals in designing SRDDS[20]

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 drug delivery.
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.[21]
III. It should deliver the active entity directly to the site of action, minimizing or eliminating side effects.
IV. This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body.
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 sensitive patient.

Future prospects[22]

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 growth patterns.

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.

CONCLUSION

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. 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 optimal therapy 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.

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