Sustained release drug delivery system: review

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ABSTRACT

Sustained release dosage forms are 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, 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.

Drug release through matrix system is determined by Water penetration, Polymer swelling, Drug dissolution, Drug diffusion, Matrix erosion have been utilized as formulation approaches. The present article contains brief review on various formulation approaches for Sustained release drug delivery system

Keywords: sustained release system, Matrix tablet, Half-life, Matrix type system, reservoir system.

INTRODUCTION

Oral drug delivery is the most preferred and convenient option as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs because of certain advantages such as unit dosage form, low cost, cheapest for packaging. Tablets are one of the most stable and commonly administered oral dosage forms. Tablets remain popular as dosage form because of the advantages afforded both to the pharmaceutical manufacturers and patient.

The goal in designing sustained or controlled delivery systems is to reduce frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, providing uniform drug delivery. Sustained release system is a type of modified drug delivery system that can be used as an alternative to conventional drug delivery system. These systems sustain the release of drug and maintain the plasma drug concentration in therapeutic window except any fluctuation and increase the therapeutic efficacy of drug. They show their action by avoiding peak and trough in dosing and show constant plasma drug concentration in therapeutic window. Sustained release system have benefits like patient compliance, avoid multiple dosing, increase the plasma drug concentration, avoid side effects and overcome the problems associated with conventional system

Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed, for sustained release systems, oral route of administration has received most of the attention with respect to research on physiological and drug constraints as well as design and testing of products [1, 3].

Terminology: Controlled and Sustained Release, both have been used in inconsistent and confusing manner. Both represent separate delivery process. SR constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both. It includes any drug delivery system achieves release of drug over an extended period of time, which not depend on time. Hydrophilic polymer matrix is widely used for formulating a Sustained dosage form. The role of ideal drug delivery system is to provide proper amount of drug at regular time interval & at right site of action to maintain therapeutic range of drug in blood plasma [2, 3].

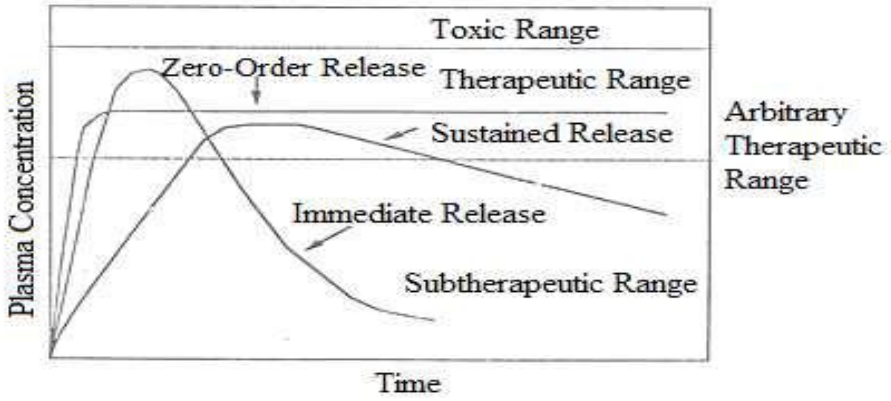

Figure 1. Plasma Drug Concentration Profiles for Conventional Tablet Formulation, a Sustained Release Formulation and a Zero Order Controlled Release Formulation

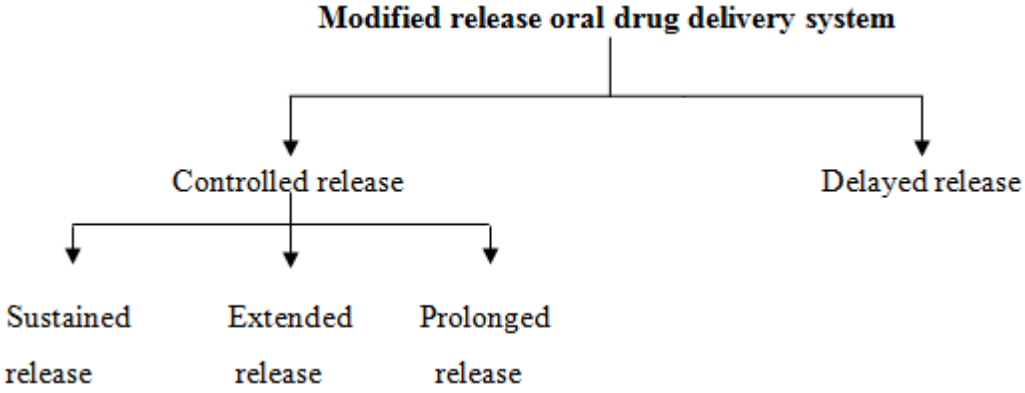

Figure.2.Classification of Modified Release Drug Delivery System

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Drug selection for oral sustained release drug delivery systems: the absorption mechanism of the drug form the G. I. tract, the general absorbability, the drug's molecular weight, pKa, solubility at different pH and apparent partition coefficient [4, 5]

Table.1. Parameter for drug selection

Parameter	Preferred value
Molecular weight/ size	< 1000
Solubility	> 0.1 µg/ml for pH 1 to pH 7.8
Pka	Non ionized moiety > 0.1% at pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segments
Release	Should not be influenced by pH and enzymes

The pharmacokinetic evaluation requires knowledge on a drug's elimination half- life, total clearance, absolute bioavailability, possible first- pass effect, and the desired steady concentrations for peak and trough.

Table.2. Pharmacokinetic parameter for drug selection

Parameter	Comment
Total clearance	Should not be dose dependent
Elimination rate constant	Required for design
Elimination half life	Preferably between 0.5 and 8 h
Apparent volume of distribution Vd	The larger Vd and MEC, the larger will be the required dose size
Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration Css av	The lower Css av and smaller Vd, the loss among of drug required
Toxic concentration	Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life

ADVANTAGES

1. Reduction in frequency of intake
2. Uniform release of drug substance over time
3. Dose reduction
4. Increase patient compliance.

DISADVANTAGES

1. Poor *in vitro – in vivo* correlation
2. Reduced potential for dose adjustment of drugs normally administered in varying strengths
3. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.[6, 8]

CLASSIFICATION OF ORAL SUSTAINED/CONTROLLED RELEASE SYSTEMS

Diffusion sustained system: Diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration.

Diffusion reservoir system: A core of drug (reservoir) surrounded by a polymeric membrane characterizes them. The nature of the membrane determines the rate of drug release. The characteristics of reservoir diffusion systems are: Zero order drug release is possible. The release rate is dependent on the type of polymer. High molecular weight compounds are difficult to deliver through the device.

Matrix devices: It consists of drug dispersed homogenously in a matrix. The characteristics of matrix diffusion systems are: Zero order release cannot be obtained. Easy to produce than reservoir devices. High molecular weight compounds are delivered through the device.

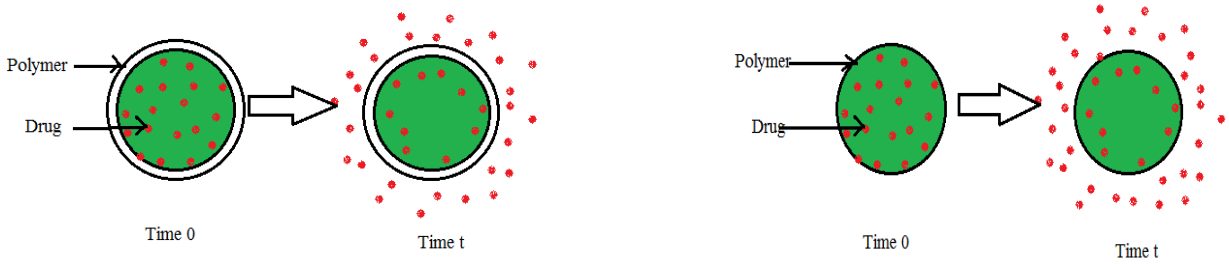

Figure.3.Schematic Representation of Diffusion Type Matrix System

Types of diffusion matrix system [9]

Hydrophobic matrix system: This is the only system where the use of polymer is not essential to provide Sustained drug release, although insoluble polymers can been used. As the term suggests, the primary rate controlling components of hydrophobic matrix are water insoluble in nature. These ingredients include waxes glycerides fatty acids, and polymeric materials such as ethyl cellulose, methyl cellulose and acrylate copolymer.

Hydrophilic matrix system: The primary rate limiting ingredients of hydrophilic matrix are polymers that would swell when in contact with aqueous solution and form a gel layer on the surface of the system. When the release medium is thermodynamically compatible with a polymer, the solvent penetrates into the free spaces between macromolecular chains. The polymer may undergo a relaxation process due to the stress of the penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allows the

encapsulated drug to diffuse more rapidly out of the matrix. The main polymers used in hydrophilic matrices are hydroxy propyl methyl cellulose (HPMC) and Hydroxy propyl cellulose (HPC), Xanthan gum, Carbopol and Alginates.

Fat-wax matrix system: The drug can be incorporated into fat wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray-drying techniques. In the bulk congealing method, a suspension of drug and melted fat-wax is allowed to solidify and is then comminuted for sustained release granulations.

Dissolution controlled release systems: These systems are easy to formulate. Drug which are formulated using system have slow dissolution rate, produce slow dissolving forms with gastric intestinal fluids and the drugs which are having high aqueous solubility and dissolution rate. Dissolution controlled release system can be classified into two techniques:

Matrix dissolution controlled release system: Matrix dissolution system is known as monolithic because the drug present in the matrix is completely dissolved in the medium which controls the drug release. They are mostly made of waxes like beeswax, carnauba wax, hydrogenated castor oil, etc. and play important role to control the drug release rate by controlling the rate of dissolution fluid penetration into the matrix by altering the porosity of tablet, decreasing its wettability or by itself getting dissolved at a slower rate

Reservoir dissolution controlled release system: In reservoir system, the drug particles are coated or encapsulated with one of the several microencapsulation techniques using slowly dissolving materials like cellulose, polyethylene glycol and waxes. This unit can be encapsulated in capsules or may be compressed into tablets Solubility and thickness of the coating play important role in dissolution rate of drug.[10]

Dissolution and diffusion controlled release systems: In this kind of system, the drug is enclosed in a membrane which is partially water soluble. The dissolution of the membrane take place due to which pores are formed and these pores allows aqueous medium to enter in the membrane. This results in the dissolution of the drug in membrane followed by the diffusion of the dissolved drug from the system. Example of such coating is combination of ethyl cellulose with PVP or methyl cellulose. [11]

Ion exchange resin- drug complexes: Resins are the materials which are insoluble in water. Resin contains anionic groups such as amino or quaternary ammonium groups and cationic groups such as carboxylic groups, or sulfonic groups in repeating positions on the chain. 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. Resin+ – Drug– + Cl– ---------- > > resin+ Cl– + Drug– where x- is Cl- conversely Resin– – Drug+ + Na+ ---------- > > resin– Na+ + Drug Water insoluble cross linked polymer compounds are used for this system. [12, 13]

pH dependent formulation: Some drugs on dissolution and absorption in GIT, changes the pH present in the gastrointestinal tract, so dosage forms are formulated using sufficient amount of buffering agent like salt of phosphoric ,citric or tartaric acids. These salts adjust the pH to the desired value when dosage form move across the gastrointestinal tract. Permeable coating agents are used to coat the drug and buffer present in the dosage form, which allows the aqueous medium to enter in it and prevents the dispersion of the tablets. [14]

Osmotic pressure controlled systems: These types of system are also known as oros, which follows the mechanism of osmotic pressure where the drug is released at constant zero order rate. The reservoir is made up of the drug and osmotic agent like mannitol or KCl, which is surrounded by semipermeable membrane. A small orifice is present in the dosage form, which allows the entry of water in the reservoir and helps the dissolved drug to pump out at the determined rate due to osmotic pressure. The release of the drug from the reservoir is unaffected by the conditions of the GIT. The release of drug is depended on factors like size of orifice, thickness of semipermeable membrane, permeability of membrane, osmotic properties of core and stability of the drug. [11, 15]

FACTORS AFFECTING SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Physicochemical factor: [14]

Dose size: In general, a single dose which contains drug about 500mg-1.0g is considered maximal for a conventional dosage form Compounds which having large dosing size that can sometimes be given in multiple amounts or formulated into liquid systems Same criteria also hold for sustained release dosage form.

Ionization, pka and aqueous solubility: Most drugs are weak acids or bases. While the drugs which are in unchanged form permeate across lipid membranes, therefore pka of the compound and absorptive environment relationship is important Delivery systems that are dependent on diffusion or dissolution will equally be dependent on the solubility of the drug in aqueous

media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of Phone the release process must be defined. Low soluble Compounds (<0.01mg/ml) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug.

Partition Coefficient: To produce therapeutic effect in another area of body, when a drug is administered to the GI tract, it must cross a variety of biological membranes. It is common to consider that these membranes are lipidic; therefore the partition coefficient of oil soluble drugs is important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer time. In case of compounds with very low partition coefficient, it is very difficult to penetrate the membrane in case of the compound which having very low partition coefficient, resulting in poor bioavailability.

Stability: The drugs which are orally administered subjected to both acid base hydrolysis and enzymatic degradation. For a drug in solid state degradation will continue at a reduced rate thus, this is the preferred composition of delivery for problem cases. For the dosage forms that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial. This is also true for systems that delay release until the dosage form reaches the small intestine. Compounds which are unstable in small intestine may show decreased in bioavailability when administered from a sustaining dosage form. This is because more drugs are delivered in the small intestine and these drugs are subjected to degradation.

Biological factor [15]:

Half-life: The half-life of a drug is an index of its residence time in the body. If the drug has short half-life (less than 2 hours) the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug with elimination half-life of 8 hours or more are sufficiently controlled in the body, when administered in conventional dosage from and Sustained release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of 3-4 hours for formulation of drug delivery system.

Therapeutic index: If the dose of a drug in the conventional dosage form is high, then it is less suitable candidates for SRDDS. This is because the size of a unit dose Sustained release oral formulation would become too big to administer without difficulty.

Absorption window: Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the *'absorption window'.* These candidates are also not suitable for SRDDS.

Plasma concentration response relationship: Generally, plasma drug concentration is more responsible for pharmacological activity rather than dose. But the drug having pharmacological activity independent of plasma concentrations, are poor candidate for oral SR drug delivery system.

Concentration dependency on transfer of drug: Transfer of drug from one compartment to other, if follows zero order kinetic process then such drugs are poor candidate for oral SR delivery system. It should be of first order kinetics.

CONCLUSION

It can be easily concluded, by the above discussion these dosage forms: provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug. If one were to develop an ideal drug delivery system. More over all these comes with reasonable cost. The dosage form is easy to optimize and very helpful in case of the antibiotics in which irrational use of the same may result in resistance.

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