WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 11, 236-248. Review Article ISSN 2277– 7105

ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEM –A REVIEW ARTICLE

Umesh Pant* and Dr. G. Gnanarajan

Shri Guru Ram Rai Institute of Technology & Science, Division of Pharmaceutical Sciences Patel Nagar, Dehradun, Uttarakhand.

Article Received on
09 April 2018,

Revised on 30 April 2018,
Accepted on 21 May 2018,

DOI: 10.20959/wjpr201811-12369

***Corresponding Author**
Umesh Pant
Shri Guru Ram Rai Institute of Technology & Science, Division of Pharmaceutical Sciences Patel Nagar, Dehradun, Uttarakhand.

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. Oral sustained release formulation have been developed in an attempt to release the drug slowly into the g.i.t. and maintain a constant drug concentration for long period of time. Sustained released drug delivery system optimize the biopharmaceutical, pharmacokinetic and pharmacodynamic properties of a drug in such a way that it utility is maximized side-effects are reduced and cure of the disease is achieved. 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 of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body.

KEYWORDS: Sustained release drug delivery system, Dose frequency, Biological half-life, Physicochemical properties of drugs.

INTRODUCTION

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate time and place of release of drug in the body. The earliest Sustained release drugs is associated with a patent in 1938 by Israel Lipowski, who coated pellets which led to coating particles. The science of controlled release developed further with more oral sustained-release products in the late 1940s and early 1950s, the development of controlled

release of marine anti-foulants in the 1950s and controlled release fertilizer in the 1970s where sustained and controlled delivery of nutrients following a single application to the soil.[1] [2]

Oral route of drug delivery is the most preferred rout of the various drug molecules among all other routes of drug delivary because of ease of administration, patient compliance, and flexible dosign of dosage form.[3] 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. The conventional dosage forms are rapidly replace by this noval controlled release technique. The terms sustained release, prolonged release, modified release, extended release or depot formulation are used to identify drug delivery system that are designed to achieved or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. 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.

Terminology

Modified release delivery system may be divided conveniently in to four categories.

- Delayed release.
- Sustained release.
- Controlled release.
- Extended released
- Site specific targeting.
- Receptor targeting.

Delayed released

A dosage form that released a discrete potion or portions of drug at a time or at time other than promptly after administration, although one portion may be released promptly after administration. Enteric – coated dosage forms are the most common delayed – released products.[4]

Sustained release

Sustained release dosage form are dosage forms designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects. This can be achieved through a various of formulation including liposomes and drug- polymer conjugates (an example Hydrogels) sustained release's definition is more akin to a "controlled release " rather than "sustained".

Extended

Release dosage consists of sustained release (SR) and controlled release (CR) dosage. SR maintains drug release over a sustained period but not at a constant rate. CR maintains drug release over a sustained period at a nearly constant rate.[5]

Objective of oral sustained released dosage form

- To maintain the concentration of drug at constant level for a desired period of time.
- To reduce the frequency of dosage administrated as compared to conventional dosage form.
- It should deliver active entity directly to site of action, minimizing or eliminating side effects.
- This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body.
- The safety margin of potent drugs can be increased.
- Incidence of both local and systemic adverse side effects can be reduced in sensitive patient.[6][7][8]

ADVANTAGES OF SR DDS[9]-[15]

- Improved patient compliance.
- A constant level of drug concentration in blood plasma.
- Reduced toxicity due to overdose.
- Reduces the fluctuation of peak-valley concentration.
- Night time dosing can be avoided.
- The total amount of drug administered can be reduced, thus:-
- Maximizing availability with minimum dose.
- Minimize or eliminate local side effects.
- Minimize or eliminate systemic side effects.

- Minimize drug accumulation with chronic dosing.

DISADVANTAGES OF SR DDS[16]

- Cost of single unit higher than conventional dosage forms.
- Increase potential for first-pass metabolism.
- The requirement for additional patient education for proper medication.
- Decreased systemic availability in comparison to immediate release conventional dosage forms.
- Poor *in vitro* and *in vivo* correlations.
- Probability of dose dumping.
- Reduced potential for dose adjustment.

DRUG SELECTION FOR ORAL SR DDS

The biopharmaceutical evaluation of a drug for potential use in SR DDS requires knowledge on the absorption mechanism of the drug form the gastrointestinal (GI) tract, the general absorbability, the drug's molecular weight, pKa, solubility at different pH, and apparent partition coefficient as shown in Table 1.

Similarly, there are some pharmacokinetic parameters for drug selection which includes drug's elimination half-life, total clearance, absolute bioavailability, possible first-pass effect, and the desired steady concentrations for peak and trough as shown in Table 2.

Table 1: Physicochemical parameters for drug selection.

Parameter	Preferred value
Molecular weight/size	<1000 Daltons
Solubility	>0.1 mg/ml for Ph 1-7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbility	Form all GI segments
Release	Should not be influenced by pH and enzymes

Table 2: Pharmacokinetic parameters for drug selection.

Parameter	Comment
Elimination half –life	Preferable between 2 and 8 hrs
Total clearance	Should not be dose dependent
Elimination rate constant	Required for design
Apparent volume of Distribution (Vd)	The larger Vd and MEC,the larger will be the required dose size
Absolute bioavilability	Should be 75% or more

Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration Css	The lower Css 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.

CHARACTERISTIC THAT MAKES A DRUG UNSUITABLE FOR SR FORMULATION

- Short elimination half-life, i.e., t1/2 <2 hrs
- Long elimination half-life, i.e., t1/2 >8 hrs
- Narrow therapeutic index
- Large doses
- Poor absorption
- Low or slow solubility
- Extensive first-pass clearance.

Site specific targeting

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

Receptor targeting

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue.

Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be sustained drug delivery systems.

FACTORS AFFECTING SUSTAINED RELEASE DRUG DELIVERY SYSTEM:-

1. **Physicochemical factor.**
2. **Biological factor.**

1. **Physicochemical factor**[17]

- **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.

2. Biological factor[18]

- **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**

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 sustaining effect.

- **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.

Classification of SRDDS

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[19][20][21]

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:

1. Diffusion controlled release systems
2. Dissolution controlled release systems
3. Dissolution and diffusion controlled release systems
4. Ion exchange resin- drug complexes
5. pH-independent formulation
6. Osmotic pressure controlled systems

Diffusion controlled release systems

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-zeroorder 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 controlled systems

II. Reservoir devices

1. Dissolution-controlled release systems

The drug present in such system may be the one:

I. Having high aqueous solubility and dissolution rate

II. With inherently slow dissolution rate e.g. Griseofulvin and Digoxin

III. That produces slow dissolving forms, when it comes in contact with GI fluids 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 boundary layer

The two types of dissolution-controlled release are:

I. Matrix (or monolith) dissolution controlled systems

II. Reservoir dissolution controlled systems

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

3. 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 polymer chain.

4. 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 with appropriate 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 drug release.

5. 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 systems are:

I. Type 1 contains an osmotic core with drug

II. Type 2 contains the drug in flexible bag with osmotic core surrounding.

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

6. 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 based systems.

7. 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 that are:

I. Known to cause gastric distress

II. Destroyed in the stomach or by intestinal enzymes.

III. Meant to extent local effect at a specific GI site

IV. Absorbed from a specific intestinal site

The two types of delayed release systems are:

I. Intestinal release systems

II. Colonic release systems

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.

REFERENCE

1. Lee VHL, controlled drug delivery fundamentals and application: introduction, marcel dekker, (2nd ed) INC, New York, 1987; 29.
2. Banker GS and Anderson NR. The theory and practice of industrial pharmacy : tablet.
3. Kamboj. S, saroha K, foel M, madhu C., sustained release drug delivery system : An overview, journal of pharmaceutics, 2013; 1: 169-181.
4. w.w.w. pharmamirror .com /knowledge – base / pharmaceutical – dictionary / delayed – release drug delivery 20 november 2013.
5. Pharmaceutics: drug delivery and targeting, 7- 13.
6. Bechgaard H, Nielson GH. Controlled release multiple units and single unit dosage. Drug Dev & Ind Pharm, 1978; 4(1): 53-67.
7. Qiu Y, Zhang G, Wise DL. Handbook of pharmaceutical controlled release technology. New York: Marcell Dekke, 3rd edition 2000.
8. Chugh I, Seth N, Rana AC, Gupta S. Oral sustained release drug delivery system: anoverview. International research journal of pharmacy 2012; 3(5): 57-62.
9. Wani MS, Controlled release system-A. Rev 2008; 6(1). www.pharmainfo.net/review. Available from: http://www.pharmainfo.net/reviews/controlled-released system-review.
10. Bechgaard H, Nielson GH. Controlled release multiple units and single unit dosage. Drug Dev Ind Pharm, 1978; 4(1): 53-67.
11. Bhowmik D, Kumar KP, Dutta A, Paswan S. Trends in scope and opportunities of control release oral drug delivery systems. Crit Rev Pharm Sci, 2012; 1: 20-33.
12. Patel H, Panchal DR, Patel U, Brahmbhatt T. Matrix type drug delivery system: A review. J Pharm Sci Biosci Res, 2011; 1(3): 143-51.
13. Dixit N, Maurya SD, Bhanu PS. Sustained release drug delivery system. Indian J Res Pharm Biotechnol, 2013; 1: 305-10.

14. Kola R, Kumar BP. A detailed description of synthetic and natural polymers which are used in the formulation of sustained release drug delivery system: A review. J Chem Pharm Sci, 2013; 6: 161-9.
15. Ratnaparkhi MP, Gupta JP. Sustained release oral drug delivery system – An overview. Int J Pharm Res Rev, 2013; 2: 11-21.
16. Chein YW. Novel Drug Delivery System. Revised and Expanded. 2nd ed. New York: Marcel Dekker; 2005.
17. Robinson JR, Lee VH. Controlled drug delivery. 2nd ed. Marcel Dekker, 1987; 4 -15.
18. Devraj, Bhatt DC. Studies on enteric coated sustained timed-release tablets of Metronidazole. J. Chem. Pharm. Res, 2010; 2(2): 226-232.
19. Tripathi KD., Antihypertensive Drugs In: Essentials of Medical Pharmacology, 5th edition, Jaypee Brothers Medical Publishers, 2003; 115-120.
20. Rang HP., Dale MM., The Vascular System. In: Pharmacology, Churchill Living Stone, International Journal of Clinical Pharmacology, 2003; 1, 2003: 298-302.
21. Harsh M., The Kidney and Lower Urinary Tract. In: Textbook of Pathology, 6th edition Jaypee Brothers Medical Publishers, 2000; 2: 649-654.