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## A comprehensive review on sustained release drug delivery systems

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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 optimising pharmacokinetic and pharmacodynamic properties of drug. The 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. These dosage forms are available in extended release, targeted release, delayed release, prolonged action dosage form. Some factors like molecular size, diffusivity, pKa-ionization constant, release rate, dose and stability, duration of action, absorption window, therapeutic index, protein binding, and metabolism affect the design of sustained release formulation. This article contains various types, evaluation and factors affecting the design of sustained release formulation.

**Key words:** sustained release system, controlled release system, delayed release etc.

### Introduction

Sustained release formulation maintains a uniform blood level of drug with better patient compliance as well as increased efficacy of drug. Release rate from sustained release dosage form is controlled mainly by type and proportion of various natural and synthetic polymer used in the formulation. Hydrophilic polymer matrix is widely used for formulating sustained release dosage form. There are certain considerations for the formation of sustained release formulation.

- If active compound has long half-life (over 6 hour) it is sustained its own.
- If the absorption of the active compound involves an active transport the development of time release product may be problematic.
- If the pharmacological activity of active compound is not related to its blood level, time releasing has on purpose.
- Finally if the active compound has short half-life it would require a large amount to maintain a prolonged effective dose. In this case a broad therapeutic window is necessary to avoid toxicity.

### Advantages of Sustained Release Drug Delivery System

1. Improved patient convenience and compliance due to less frequent drug administration.
2. Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local and systemic side effect.
3. Increased safety margin of high potency drug due to better control of plasma levels.
4. Maximum utilization of drug enabling reduction in total amount of dose administered.
5. Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing and reduction in personnel time to dispense, administer and monitor patients.

### Disadvantages of Sustained Release Drug Delivery System

1. Decreased systemic availability in comparison to immediate release, conventional dosage form; this may be due to incomplete release, increased first pass metabolism, increased instability, insufficient residence time for complete release site specific absorption.
2. Poor in vitro-in vivo correlation.
3. Possibility of dose dumping due to food or formulation variable or chewing of oral formulation by patient and thus, increased risk of toxicity.
4. Retrieval of drug is difficult in case of toxicity.

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5. Higher cost of formulation.
6. Reduced potential for dosage adjustment of drugs normally administered in varying strength.

### Classification of Sustained Release System

Oral controlled delivery system can be classified in to the following category based on their mechanism of drug release.

1. Dissolution controlled release
  - Encapsulation dissolution control
  - Matrix dissolution control
2. Diffusion controlled release
  - Reservoir devices
  - Matrix devices
3. Ion exchange resins
4. Osmotic controlled release
5. Gastro retentive system

**Dissolution Controlled Release:** Dissolution controlled release can be obtained by slowing the dissolution rate of a drug in the GIT medium, incorporating the drug in an insoluble polymer, and coating drug particle with polymeric material of varying thickness.

The rate of dissolution (dm/dt) can be shown by

$$Dm/dt = ADS/h$$

Where S is aqueous solubility of drug

A is surface area of tablet

D is diffusivity of drug

H is thickness of boundary layer

Example of drug with limited dissolution rate includes digoxin, griseofulvin, nifedipine, salicylamide.

**Encapsulation dissolution control:** Rate of dissolution achieved by encapsulation of drug polymer matrix with relatively insoluble polymeric membrane, the coated beads can be compressed in to tablet and granules with varying thickness can be employed to achieve sustained release of drug. Example of drug delivered in this manner is antispasmodic-sedative, combination, phenothiazine, anticholinestrase.

**Matrix dissolution control:** It involves the incorporation of drug in a hydrophobic matrix such as wax, polyethylene, polypropylene, ethyl cellulose or hydrophilic matrix such as Hydroxypropylcellulose, hydroxypropylmethylcellulose. The rate of drug availability is controlled by rate of penetration of dissolution fluid in to the matrix.

**Diffusion Control Release System:** It involve the diffusion of dissolved drug through polymeric barrier .the drug release rate is never zero order since the diffusional path length increases with time as the insoluble matrix gradually depleted of drug. The two type of diffusion controlled system

- a. Matrix system
- b. Reservoir system

**Matrix system:** In this drug is dispersed in a matrix of rigid non swellable hydrophobic material or swellable hydrophilic material. Materials used for rigid matrix are insoluble plastic such as polyvinylchloride and fatty material like stearic acid, bee wax etc. Swellable matrix system is popular for sustaining the release of highly water soluble drugs. The materials for such matrix are hydrophilic gum and may be of natural origin (guar gum, tragacanth). Semi synthetic (HPMC, CMC). The drug and the gum are granulated together with a solvent such

as alcohol and compressed in to a tablet.

**Reservoir system:** The systems are hollow containing an inner core of drug surrounded in a water insoluble polymer membrane. The polymer is applied by coating and microencapsulation techniques. The drug release across the membrane involve its partitioning in to membrane with release in to surrounding fluid by diffusion .the polymer commonly used in such devices are Hydroxypropylcellulose, ethyl cellulose and polyvinyl acetate.

**Ion Exchange Resin System:** Ion exchange resin complex which potentially can be prepared from both acidic and basic drugs have been more widely studied. Salts of cationic or anionic exchange resin are insoluble complexes in which drug release result from exchange of "bound" drug ions by ions present in GIT. Ion active sites are distributed through the resin structure. Variable relating to the resin are degree of cross linking, which determine the permeability of the resin, its swelling potential, and the excess of the exchange sites to the drug ion

**Osmotic Controlled Release System:** Osmotic system release a therapeutic agent at a predetermined, typically zero order, delivery rate is based on the principle of osmosis. Osmosis is the natural movement of solvent through a semi permeable membrane in to a solution of higher solute concentration to lower concentration, leading to equal concentration of solute on both sides of membrane. Osmosis system imbibes water from the body through a semi permeable membrane in to osmotic material, which swells, resulting in slow delivery of drug formulation. The osmotic pressure is the driving force for fluid transport through the semipermeable membrane. The greater the gradient in osmotic pressure, greater will be the rate of transport of solvent through membrane.

**Gastroretentive Drug Delivery System:** the control Release drug delivery system possessing the ability of being retained in the Stomach are called gastro retentive drug delivery system and they can help in optimising the oral controlled delivery of drug having absorption window by continuously releasing the drug prior to absorption window for prolonged period of time.

### Factor Governing the Design of Sustained Release Dosage Form

**Molecular Size and Diffusivity:** A drug must diffuse through a variety of biological membrane during its time course in the body. In addition to diffusion through these biological membranes, drugs in many extended release system must diffuse through a polymeric membrane or matrix. The ability of drug to diffuse in polymer so called diffusivity (diffusion coefficient D) is a function of its molecular size (molecular weight).

**pka – ionisation constant:** The pKa is a measure of the strength of acid or an base. The pKa allow determining the charge on drug molecule at any given pH. Drug molecule is active in only the undissociated state and also in unionised state. An unionised molecule crosses these lipodial membranes much more rapidly than ionised species. The amount of drug that exists in unionised form is a function of dissociation constant of a drug and Ph of fluid at absorption

site. For a drug to be absorbed, it must be in unionised form at the absorption site. Drugs which exist in ionised form at absorption site are poor candidate for sustained release/controlled release dosage form.

### Biological Factors

**Duration of Action:** Duration of action is the time period for which the blood Level remains above MEC and below MSC levels are more specifically with in therapeutic window. Drug acting for long duration are unsuitable candidate for formulation in to SR/CR forms. Receptor occupation, tissue binding, half life, metabolism, partition coefficient, irreversible binding to cells are some parameter which are responsible for long duration of action of drugs.

**Absorption Window:** Some drugs show region specific absorption which is related to differential drug solubility and stability in different regions of G.I.T. as a result of changes in environmental pH, degradation by enzyme, etc. These drugs represent absorption window, which signifies the region of G.I tract where absorption primarily occur. Drugs released from sustained/controlled release system, after absorption window goes waste with little absorption. Hence absorption window play major role in the development of sustained/controlled release drugs

**Therapeutic Index:** It is most widely used to measure the margin of safety of a drug.

$$TI = TD50 / ED50$$

Drugs with very small value of therapeutic index are poor candidates for formulation in to sustained release products. A drug is consider to be safe if its T.I value is greater than 10, that is longer the value of TI, the safer the drug.

**Metabolism:** Drugs that are significantly metabolised before absorption either in the lumen or tissue of intestine can show decreased bioavailability. Most intestinal wall enzyme system is saturable. As the drug is released at a slower rate to these regions, less total drug is presented to enzymatic process during a specific period allowing more complete conversion of a drug to its metabolite.

**Protein Binding:** There are some drugs which having tendency to bind with Plasma protein (e.g. albumin) causes retention of drug in vascular space. The main force of attraction responsible for binding is Vander wall forces, hydrogen bonding, and electrostatic forces. In general charged compound have a greater tendency to bind a protein than uncharged compound, because of electrostatic effect.

**Absorption:** The rate, extent and uniformity of a drug are important factors when considering formulation in to a controlled-release system. Since the rate limiting step in drug delivery from a controlled release system is its release from a dosage form, rather than absorption of drug relative to its release is essential if the system is to be successful. Drugs which are absorbed by specialized transport process (carrier mediated) and drug absorption at special sites of gastrointestinal tract (absorption window) are poor candidate for sustained release.

### Evaluation of Sustained Release Dosage Form

Evaluation of these dosage form done by two ways

- Evaluation of granules

- Evaluation of tablets

### Future Prospective

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

**Particulate systems:** The microparticle 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 buccal 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

Development of sustained release oral dosage forms is important for optimal therapy regarding efficacy, safety, and patient compliance. In case of sustained release dosage forms the release of active substance, although is slower than in conventional formulation; however it is substantially affected by external environment in to which it is going to be released. From 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 also improving the patient compatibility. Some factors like absorption window, therapeutic index, pKa - ionisation constant, molecular size, tissue binding, are important in formulating effective sustained release product.

### Reference

1. Singhvi G, Singh M. In-vitro drug release characterization models. International journal of pharmaceutical studies and research, 2224-4619.
2. Modi SA, Gaikward PD, Banker VH, Pawar SP. Sustained release drug delivery system-review. International journal of pharma research and development 2011; 2(12):016.
3. Ratilal DA, Gaikward PD, Banker VH, Pawar SP. Review on sustained release technology. International journal of research and pharmaceutical science 2011; 2(6):1701-1708.
4. Brahmankar HA, Jaiswal SB. Biopharmaceutics and pharmacokinetics A Treatise. Vallab prakashan 2000, 337.
5. Allen LV, Popovich NG, Ansel HC. Pharmaceutical dosage form and drug delivery. Eight edition, 263-268.
6. Robinson RJ, Vincent HL. Controlled drug delivery and application. Second edition, 29:56.

7. Mamidala RK, Ramana V, Sandeep G, Lingam M, Gannu R, Yamsani MR. Factors Influencing the design and performance of oral sustained/controlled release dosage form. *International journal of pharmaceutical science and nanotechnology*, 2009; 2(3):583-594.
8. Bankar AU, Bankar VH, Gaikward PD, Pawar SP. A Review on sustained release drug delivery system. *International journal of research and pharmaceutical science*, 2011; 2049-2063.
9. Wise DL. *Handbook of pharmaceutical controlled release technology*, 435-436.
10. Lieberman HA, Lachman L, Kanic JL. *The theory and practice of industrial pharmacy*. Third edition, 450.
11. Jain NK. *Controlled and Novel drug delivery systems*. First edition. CBS publisher and distributors, 2002, 79-87.
12. Mamidala RK, Ramana V, Sandeep G, Lingam M, Gannu R, Yamsani MR. Factors influencing the design and performance of oral sustained/controlled release dosage form. *International journal of pharmaceutical science and nanotechnology*, 2009; 2(3):583-594.
13. Remington AR. *The science and practice of pharmacy*. 20th edition, 2002, 903-929.
14. Robinson JR, Vincent H, Lee L. *Controlled drug delivery fundamentals and application*. Marcel Dekker Inc., 2002, 3-61.
15. Swarkbrick J, Boylan JC. *Encyclopedia of pharmaceutical Technology*, 2007, 369-394.
16. Higuchi T. Mechanism of rate of sustained action medication. *Journal of pharmaceutical science*, 1963; 52:1145-1149.
17. Singh BN, Kwon KH. Drug delivery oral route. *Encyclopedia of pharmaceutical technology*, 2007; 1; 1242-1261.
18. Venkataraman Daar SN, Chester A, Kliener L. *An overview of controlled release system*. Marcel dekker Inc., 2000, 1-30.