

A NOVEL APPROACH: SUSTAINED/ CONTROLLED RELEASE DRUG DELIVERY SYSTEM

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ABSTRACT: Basic rationale of sustained release drug delivery system optimizes the pharmacokinetic, biopharmaceutical, and pharmacodynamic properties of a drug in such a way that its utility is maximized, side-effects are reduced & cure of the disease is achieved. 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. There are several advantages of sustained release technology over conventional dosage forms like improved patient compliance due to less frequent drug administration, maximum utilisation of the drug, reduction of fluctuation in steady-state drug levels, 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 main goal in designing sustained release delivery systems is to reduce frequency of dosing or to increase effectiveness of the drug by localization at the site of the action, reducing dose required or providing uniform drug delivery.

KEYWORDS: Sustained Release Drug Delivery, Controlled Release, Bilayer tablet, Continuous Release, Matrix Tablet

INTRODUCTION: [1-3]

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. Compared to investigate a new molecule, it is better to do the research and development of already existing molecules by solving the problem of confrontation due to their awkward use particularly in case of drugs like antibiotics.

Sustained release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of the single dose. The main aim of preparing sustained release formulations was intended to modify and improve the drug performance by increasing the duration of drug action, decreasing the frequency of dosing, decreasing the required dose employed and providing uniform drug delivery. Sustained release dosage forms are prepared by coating the tablets so that the rate of solubility is controlled or individually encapsulating micro particles of varying sizes so that the rate of dissolution can be controlled. Sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects. Localize drug action by spatial placement of a controlled release system usually rate controlled adjacent to or in the diseased tissue or organ. In short, Sustained release formulations (e.g., Dextrin SR & Aspirin SR) describe the slow release of a drug substance from a dosage form to maintain therapeutic response for extended period (i.e. 8-24 hours) of time. In oral form it is in hours, and in parenteral's it is in days and months.

Sustained release, sustained action, prolonged action controlled release, extended release, depot release these are the various terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over a long period of time after administration of a single dose of drug. The ideal drug delivery systems have two things would be required first it would be a single dose the duration of treatment whether it is for days or week, as with infection, or for the life time of the patient, as in hypertension or diabetes. Second it should deliver the active entity directly to the site of the action, thereby minimizing side effects.

DISADVANTAGES OF CONVENTIONAL DOSAGE FORMS: [1, 3, 4]

1. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
2. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
3. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.

ADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY: [3, 5]

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

DISADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY: [1, 6, 7]

1. Reduced potential for dose adjustment of drugs normally administered in varying strengths
2. Risk of side effects or toxicity upon rapid release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
3. Poor *in vitro* – *in vivo* correlation

4. Retrieval of drug is difficult in case of poisoning, toxicity or hypersensitivity reactions
5. Extra need for additional patient education and counseling related to dosage form

FACTORS AFFECTING SUSTAINED RELEASE DRUG DELIVERY SYSTEM: [3, 8, 9, 15]

A. Physicochemical factor:

1. **Dose size:** For the orally administered systems, there is an upper limit to the bulk size of the dose to be administered. A single dose which contains drug about 0.5-1.0g 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. Another consideration is the margin of safety involved in the administration of large amounts of a drug with narrow therapeutic range.
2. **Molecular Weight and Diffusivity:** Diffusivity is defined as the ability of a drug to diffuse through the membrane. Diffusivity depends on size and shape of the cavities of the membrane. The diffusion co-efficient of intermediate drug molecular weight is 100-400 Daltons; through flexible polymer range is 10^{-6} to 10^{-9} cm²/seconds. Molecular size or weight is indirectly proportional to the diffusibility. Drugs with larger molecular size are a poor candidate for oral SR system.
3. **Protein Binding:** It is well-known that many drugs bind to plasma proteins with concomitant influence on the duration of drug action. Since blood proteins are four the most part re-circulated and not eliminated, drug protein binding can serve as the depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs. The drug interaction and the period of binding with mucin-like protein also influence the rate and extent of oral absorption.
4. **Ionization, pka and aqueous solubility:** Most drugs are weak bases or acids. 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 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.
5. **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.
6. **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.

B. Biological factor:

1. **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 form 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.
2. **Side Effect:** The side effects of the some drugs are mainly developed due to fluctuation in the plasma concentrations. The incidences of side effects can be minimized by controlling the concentration within therapeutic range at any given time. The SR drug delivery is the most widely used to incidences of the GI (local) side effects rather than a systemic side effect of the drug. The drug properties which induce local or systemic side effect can be circumvented or modified by their incorporation in a suitable oral SR delivery system that employs a specific controlled release mechanism.
3. **Therapeutic index:** If the dose of a drug in the conventional dosage form is high, then it is less suitable candidates for sustained release drug delivery system as the size of a unit dose sustained release would become too big to administer.
4. **Disease State:** Disease state and circadian rhythm are not drug properties, but they are equally important as drug properties in considering a drug for SR.
For example:
 - a. Aspirin is a drug of choice for rheumatoid arthritis though it is not suitable for SR dosage form. Still, aspirin SR dosage form could be advantageous to maintain therapeutic concentrations, particularly throughout the night, thus alleviating morning stiffness.
 - b. Asthma attacks are commonly occurring before bedtime, due to a low cortisol level. The highest cortisol level occurred between 12 midnight and 4 a.m. These variations entail for the design an oral SR delivery in accordance to circadian rhythm

5. **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 sustained release drug delivery system.
6. **Plasma concentration response relationship:** 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 sustained release drug delivery system.
7. **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.

MAIN OBJECTIVES OF ORAL SUSTAINED RELEASED DRUG DELIVERY SYSTEM: ^[1,3]

1. The safety margin of potent drugs can be improved.
2. To maintain the concentration of drug at constant level for a preferred period of time.
3. Incidence of both local and systemic adverse side effects can be reduced in sensitive patient.
4. To reduce the frequency of doses administered as compared to conservative dosage form
5. It should deliver active entity directly to site of action, minimizing or eliminating side effects.
6. It may necessitate delivery to specific receptors or to localization to cells or to definite areas of the body.

CLASSIFICATION OF ORAL SUSTAINED OR CONTROLLED RELEASE SYSTEMS: ^[3,10]

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:

1. Continuous release systems
2. Delayed transit and continuous release systems
3. Delayed release systems

Continuous release systems:

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:

- A. Diffusion controlled release systems
- B. Dissolution controlled release systems
- C. Dissolution and diffusion controlled release systems
- D. Ion exchange resin- drug complexes
- E. pH-independent formulation

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 muco-adhesive systems and size based systems.

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.

- A. Known to cause gastric distress
- B. Destroyed in the stomach or by intestinal enzymes.
- C. Meant to extent local effect at a specific GI site
- D. Absorbed from a specific intestinal site

The two types of delayed release systems are:

1. Intestinal release systems
2. Colonic release systems

STRATEGY OF FORMULATION FOR ORAL SUSTAINED RELEASE SYSTEM: ^[1,3]

1. Dissolution Sustained System
2. Methods using ion exchange
3. Diffusion Sustained System
4. Altered density formulation
5. pH independent formulation
6. Methods using osmotic pressure

INTRODUCTION OF MATRIX TABLET: ^[1,3,11]

Sustained release has given a new breakthrough for novel drug delivery system in the field of pharmaceutical technology. Hydrophilic polymer matrix is extensively used for formulating a sustain release dosage form.

Advantages of Sustain Release Matrix Drug Delivery System:

1. Patient compliance can be enhanced.
2. The frequency of drug administration is reduced.
3. Drug administration can be made more suitable
4. Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduce.

5. The total amount of drug administered can be reduced, thus maximizing availability with minimum dose. Minimize or eliminate local side effects. Minimize or eradicate systemic side effect. Reduce drug accumulation with chronic dosing.
6. The characteristic blood level variations due to multiple dosing of conventional dosage forms can be reduced.

Disadvantages of Sustain Release Matrix Drug Delivery System:

1. Reduced potential for dose adjustment
2. Probability of dose dumping
3. Increase potential for first pass metabolism
4. Requirement for additional patient education for proper medication
5. Cost of single unit higher than predictable dosage forms.

INTRODUCTION OF BILAYER TABLET:^[1, 3,12, 13]

Most important aim of sustained drug delivery is to decrease frequency of dosing. The design of modified release drug product are to optimize a therapeutic regimen by providing slow and continuous delivery of drug over the partial dosing interval providing greater patient compliance and convenience. Bilayer the tablet is the new era for the successful growth of controlled release formulation. Bi-layer tablets suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is instantaneous release as initial dose and second layers is maintained dose there are various applications of the bi-layer tablets as it consists of monolithic partly coated or multilayered matrices. The main objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs.

Advantages of Bilayer Tablet:

1. Cost is lesser as compare to other dosage forms.
2. Suitable for large scale production.
3. Easy to swallowing with least tendency for hang up.
4. Superior chemical and microbial stability compared to other oral dosage forms.
5. Objectionable odor and taste can be masked by coating technologies.
6. It can be designed in such a manner as to modified discharge of the layers can be kept as extensive and the other as instant release.

Disadvantage of Bilayer Tablet:

1. Bitter testing drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen
2. May require encapsulation or coating.
3. Some drugs resist compression into impenetrable compacts, due to amorphous nature, low density nature.
4. Inaccurate individual layer weight control.
5. Insufficient hardness, layer separation reduced yield.
6. Bilayer rotary presses are expensive.

Various Approaches Used In the Bilayer Tablet:

1. Floating drug delivery system
2. Polymeric Bioadhesive system
3. Swelling system/unfolding system

Types of Bilayer Tablet Press

1. Single sided tablet press
2. Double sided tablet press
3. Bilayer tablet press with displacement monitoring.

MASRX AND COSRX SUSTAINED-RELEASE TECHNOLOGY:^[14]

A. MASRx Technology:

The main objective is to assess factors affecting drug release from guar-gum-based once-daily matrix sustained-release formulations (MASRx). Tablets were designed to hydrate completely into the tablet core. In the manufacturing process, the tablet core expanded & released the drug in a sustained release manner.

B. COSRx Technology:

The formulations base on constant sustained-release matrix (COSRx) technology can be developed using guar gum as a major rate-controlling polymeric material. Depending on the solubility of the drug, low or high-viscosity guar gum can be use. The formulation involves a guar-gum-base tablet & a combination of water-soluble and water-insoluble polymeric tablet coat. When the tablet is placed in a dissolution medium, there is slow diffusion of water through the polymeric wall leading to swelling and gelations of the guar gum/drug core. As the hydration a progress, the tablet continues to swell until the wall breaks, forming a sandwich-like structure. The release of drug proceeds primarily out of the sides of the tablet as it passes through the intestinal tract. The tablets provide a nearly zero-order drug release following a programmed period of delayed drug release.

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