Journal of Carcinogenesis
Covering Genesis to Therapeutics

Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 4s, https://carcinogenesis.com/

Sustained Release Oral Drug Delivery System

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ABSTRACT

Traditional drug delivery systems have been characterized by immediate release and repeated dosing of the drug which might lead to the risk of dose fluctuation, this raises the need for a formulation with control release that maintains a near-constant or uniform blood level. Sustain release systems are considered a wiser approach for drugs with short half-lives and which require repeated dosing, they are easy to formulate and are irrespective of the absorption process from the gastrointestinal tract after oral administration. The basic objective of these dosage forms is to optimize the delivery of medications to achieve a measure of control on therapeutic effect in the face of uncertain fluctuation in the in vivo environment in which drug release takes place. Sustained release systems include any drug-delivery system that achieves slow release of drugs over an extended period. Sustained release also provides a promising way to decrease the side effects of the drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. The basic rationale of a sustained drug delivery system optimize the biopharmaceutical, pharmacokinetic, and pharmacodynamic properties of the drug in such a way that utility is maximized, side effects are reduced and cure of the disease is achieved. The principal goal of sustained release forms is the improvements of drug therapy assessed by the relationship between the advantages and disadvantages of the use of sustained release systems.

How to Cite: S Muthukumar, S Rohini, Dharani Shree M, Kavin Raj M, Abinaya M, Chrisil Auxi N, S.Darshini , Kowsalya M, Mallika A, (2025) Sustained Release Oral Drug Delivery System, *Journal of Carcinogenesis*, *Vol.24, No.4s*, 652-658

1. INTRODUCTION

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of sustained drug delivery, greater attention has been paid to the development of oral sustained-release drug delivery systems. The goal in designing a sustained-release drug delivery system is to reduce the frequency of the dosing, reducing the dose & providing uniform drug delivery. So, a sustained release dosage form is a dosage form that releases one or more drugs continuously in a predetermined pattern for a fixed period, either systemically or locally to specified target organs 1-3. Sustained release dosage forms provide better control of plasma drug levels, less dosage frequency, fewer side effects, increased efficacy, and constant delivery.

2. SUSTAINED RELEASE DOSAGE FORMS

Any drug or dosage form modification that prolongs the therapeutic activity of the drug. The release of the drug is retarded for a delayed and prolonged period in the systemic circulation. Sustained release formulation maintains a uniform blood level of the drug with better patient compliance as well as increased efficacy of the drug. Sustained-release tablets are generally taken once or twice a day during a course of treatment whereas in conventional dosage forms, there is a need to take 3-4 times the dosage in a day to achieve the same therapeutic action.

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The rationale for developing seeds

a) Formulation of SRDDs minimizes dosing frequency, and sustained release provides the availability of a drug at the auction site throughout the treatment, improving the clinical efficiency of a drug molecule.

b) To reduce the cost of treatment by reducing the number of dosage requirements.

c) To minimize toxicity due to overdose which is often in conventional dosage form.

To enhance the activity duration of a drug possessing a short half-life.

Principle of seeds

The conventional dosage forms release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme. 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 the drug from the dosage form is the rate-limiting step. The drug release from the dosage form should follow 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

3. DISADVANTAGES OF CONVENTIONAL DOSAGE FORMS

1. Poor patient compliance, and increased chances of missing the dose of a drug with a short half-life for which frequent administration is necessary.

2. The unavoidable fluctuations of drug concentration may lead to under-medication or over-medication.

3. A typical peak-valley plasma concentration-time profile is obtained which makes the attainment of the steady-state condition difficult.

4. The fluctuations in drug levels may lead to the precipitation of adverse effects especially of a drug with a small therapeutic index whenever overmedication occurs.

Advantages of sustained-release dosage forms

1. Reduction in frequency of intakes.

2. Reduce side effects.

3. Uniform release of drugs over time.

4. Better patient compliance.

Disadvantages of sustained-release drug delivery

1. Increased cost.

2. Toxicity due to dose dumping.

3. Unpredictable and often poor in vitro-in vivo correlation.

4. Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).

5. Increased potential for first-pass clearance.

6. Need for additional patient education and counseling.

The characteristicthatmakesadrugunsuitableforextended-release formulation[5]

1. Shorteliminationhalf-life,<2hr
2. Longeliminationhalf-life,>8hr
3. Narrowtherapeuticindex
4. Largedoses
5. Poorabsorption
6. Lowor slowsolubility

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7. Extensivefirst-passclearance

Characteristics that make drugs suitable for extended-release-release formulation biological characteristics

1. Biologicalhalf-life
2. Absorption
3. Metabolism

Biologicalhalf-life

Theusualgoalofanoralsustained-releaseproductisto maintaintherapeuticbloodlevelsoveranextendedperiod. To achieve this, the drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life (t1/2). Each drug has its characteristic elimination rate, the sum of all elimination processes, including metabolism, urinary excretion, and all over processes that permanentlyremove the drugfrom thebloodstream. Therapeutic compounds with short half-lives (2-8 hr.) Are generally excellent candidates for sustained release formulation, as this canreducedosingfrequency.Ingeneral,drugswithhalf-lives shorter than 2hours such as furosemide or levodopa are poor candidatesforsustainedreleasepreparation.Compoundswith longhalf-lives, morethanhoursarealsogenerallynot usedin sustaining form, since their effect is already sustained. Digoxinandphenytoin areexamplesofdrugshaving a long life.

Absorption

Sincethepurpose of forming a sustained-releaseproduct is to place control on the delivery system, the rate of release must be much slower than the rate of absorption. If we assume that the transit time of most drugs in theabsorptive areas of the gastrointestinal 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. This corresponds to a minimum apparent absorptionrateconstant of0.17-0.23h-1togive80-95%over this period. Hence, it assumes that the absorption of the drug should occur at a relatively uniform rate over the entire length of the 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 the intestine, sustained release preparation may be disadvantageous to absorption. One method to provide sustaining mechanisms of delivery for compounds is 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. One such attempt is to formulate low density pellet or capsule. Another approach is that of bio-adhesive materials.

Metabolism

Drugs that are significantly metabolized before absorption, eitherinthelumenorthetissueof theintestine,canshow decreased bioavailability from the slower-releasing dosage form.

Physicochemical factor:

Aqueous solubility

Drugs with good aqueous solubility and pH-independent solubility are the most desirable candidates for SRDDs. Poor aqueous solubility possesses oral bioavailability problems, and drugs with extreme aqueous solubility are unsuitable for sustained release because it is difficult to control the release of drugs 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 the drug across the membrane depends upon the partition coefficient of the drug. The drugs having low partition coefficients are considered poor candidates for the sustained release formulation in the aqueous phase.

Drug stability

Srdds is designed to control the release of a drug over the length of the gastrointestinal tract (git); hence high stability of the drug in the gi environment is required.

Protein binding

Protein binding of drugs plays a key role in their therapeutic. The pharmacological activity of a drug depends on the unbound concentration of a drug rather than the total concentration. The drugs that bind to some extent plasma and tissue proteins enhance the biological half-life of a drug. The release of such drugs is extended over some time and therefore no need to develop extended-release drug delivery for this type of drug.

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Drug PKA & ionization at physiological ph

If the unionized drug is absorbed and permeation of the ionized drug is negligible, the rate of absorption is 3 to 4 times less than that of the unionized drug. Since the drug shall be unionized at the site to an extent of 0.1 to 5%. Drugs existing largely in the ionized form are poor candidates for oral SR drug delivery systems. E.g. hexamethonium.

Mechanism and site of absorption

Drug absorption by carrier-mediated transport systems and those absorbed through a window are poor candidates for oral SR drug delivery systems. Drugs absorbed by passive diffusion, pore transport, and over the entire length of git are suitable candidates for oral SR drug delivery systems.

Molecular size and diffusivity diffusivity

Depends on the size & shape of the cavities of the membrane. The diffusion coefficient of an intermediate molecular weight drug is 100 to 400 dalton. For drugs having molecular weight > 500 daltons, the diffusion coefficient in many polymers is much less. E.g. proteins and peptides.

Does 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 the sustained release dosage form. Compounds that require large dosing sizes can sometimes be given in multiple amounts or formulated into liquid systems.

4. CHARACTERISTICS OF THE DRUG SUITABLE FOR SUSTAINED RELEASE TABLETS PARAMETERS

The ideal physiochemical and pharmacokinetic properties of drugs suitable for sustained-release tablets are:

Table 1: physiochemical properties for drug selection

Parameters	Criteria
Molecular size	<1000daltons
Aqueous solubility	More than 0.1 mg/ml for pH 1 to 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability from g.i. segments	Release should not be affected by pH and enzymes.

Table 2: pharmacokinetic properties for drug selection

Parameters	Criteria
Elimination half-life	**Between 2 to 8 hrs**
Absolute bioavailability	**It should be 75 % or more.**
Absorption rate constant (ka)	**It must be higher than the release rate**
The apparent volume of distribution (vd)	**Larger vd and mec, larger dose required**
Total clearance	**It does not depend on the dose.**
Elimination rate constant	**Required for design**
Therapeutic concentration (CSS)	**Lower cs and vd, less amt. Of drug Required**
Toxic concentration	**Apart from the value of mtc and mec the dosage form.**

Mechanisms of drug release of seeds [7]

Diffusion is rate-limiting

diffusion is the driving force where the movement of drug molecules occurs from a high concentration in the tablet to a lower concentration in gastrointestinal fluids. This movement depends on the surface area exposed to gastric fluid, diffusion pathway, drug concentration gradient, and diffusion coefficient of the system. In practice, we can follow either of the two methods,

1. The drug is formulated in an insoluble matrix; the gastric fluid penetrates the dosage form dissolves the medicament and releases the drug through diffusion.
2. The drug particles are coated with a polymer of defined thickness so that the portion of the drug slowly diffuses through the polymer to maintain a constant drug level in blood.

Dissolution is rate-limiting.

The drugs with poor water solubility (bcs class 2 and 4) are inherently sustained release forms. For water-soluble drugs, it's possible to incorporate a water-insoluble carrier to reduce the dissolution of the drug particles coated with this type of material e.g. polyethylene glycol. One may skip the use of disintegrating agents to promote delayed release.

Osmotic pressure is rate-limiting

Osmosis is a phenomenon in which the flow of liquid occurs from lower concentration to higher concentration through a semi-permeable membrane which allows transfer of liquid only. The whole drug is coated with a semi-permeable membrane with a hole on one end of the tablet made by a laser beam. The gastric fluid penetrates through the membrane, solubilizes the drug, and increases the internal pressure which pumps the drug solution out of the aperture and releases the drug environment. The delivery rate is constant provided that the excess drug is present inside the tablet. But, it declines to zero.

The release is controlled by ion exchange.

Ion exchangers are water-insoluble resinous materials containing salt forming anionic or cationic groups. While manufacturing, the drug solution is mixed with resin and dried to form beads which are tableted. The drug release depends upon a high concentration of charged ions in the gastrointestinal tract where the drug molecules are exchanged and diffused out of the resin into the surrounding fluid. This mechanism relies upon the environment of resin and not pH or enzyme on the absorption site.

Evaluation for seeds

Evaluation of these dosage forms is done in two ways:

1. Evaluation of granules
2. Evaluation of tablets

I. Evaluation of granules involves following the test

Angle of repose

The angle of repose was determined using the funnel method. A funnel was secured on a stand at a fixed height h) above a graph paper placed on a horizontal surface. The sample was poured until the apex of the conical pile touched the tip of the funnel. The radius of the conical pile was measured and the angle of repose was calculated as follows:

$V = \tan^{-1} (h/r)$

Bulk density

the bulk density was calculated using the equation:

$\rho b = mv$

Where ρb = bulk density,

M = mass of the granules in gm

V = final untapped volume of granules in ml.

True density

The true density was measured using the equation;

$\rho t = m/vp$

Where, ρ t = true density

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M =mass of granules in gm.,

vp = final tapped volume of granules in ml.

Loss on drying (old)

The moisture content of the lubricated granules was analyzed by using a moisture analyzer. 5.0 gm. Or more quantity of granules was heated at 1050c until the change in weight was no more observed by the instrument. The % loss in weight was recorded.

Compressibility index

This was measured for the property of a powder to be compressed; as such they are measured for the relative importance of inter-particulate interactions. The compressibility index was determined by the following equation.

Compressibility index = (dt – db) × 100

Where, dt = tapped density,

Db = bulk density

Hausner ratio

It was calculated by following the equation.

hausner ratio = dt / do

Where, dt = tapped density,

Do = bulk density

II. Evaluation of SR tablets involves following the test

weight variation

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (citizen India) and the test was performed according to the official method.

Friability

Twenty tablets were weighed and placed in the Roche friability and the apparatus was rotated at 25rpm for 4min. After the revolution, the tablets were dusted and weighed.

% friability = wo - w/wo × 100

Where, wo = initial weight of twenty tablet

w = weight of 20 tablets after 100 revolutions.

Hardness

Tablet hardness was measured using a Monsanto hardness tester. Six tablets from each batch were measured for hardness, and the average of the six values and the standard deviation were noted.

Thickness

Twenty tablets from the sample were randomly taken and individual tablet thickness was measured using a digital vernier caliper. Average thickness and standard deviation values were calculated.

In-vitro drug release rate

Formulated tablets were subjected to an invitro dissolution study using usp type i / ii apparatus (paddle) at 100 rpm with a temperature of the water bath maintained at 37±0.5oc. Dissolution was carried in 900 ml simulated gastric fluid for 2 hrs and for a further 8 hrs in simulated intestinal fluid. The release of different drugs at different time intervals was measured at particular wavelengths by a UV-visible spectrophotometer.

5. CONCLUSION

The oral route of administration for sustained-release drug delivery systems has received more attention due to its flexibility, reduced dosing frequency, and better patient compliance. The microparticles offer a variety of opportunities such as protection and masking, better processability, improved bioavailability, decreased dosing frequency, improved stability, reduced dissolution rate, facilitation of handling, and spatial targeting of the active ingredient. The 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 systems has received more attention due to its flexibility, reduced dosing frequency, and better patient compliance. By the above discussion, it canbe easily concluded

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that sustained-release formulations help increase the efficiency of the dose as well as they are also improving the patient's compatibility.

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