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A REVIEW: SUSTAINED RELEASE DOSAGE FORM

***Suresh Choudhary, Santosh Waghmare and Hemant Kamble**

Loknete Shri Dadasaheb Pharate Patil College of Pharmacy, Mandavgoan Pharate, Tal-Shirur, Dist-Pune, Maharashtra.

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***Corresponding Author**
Suresh Choudhary
Loknete Shri Dadasaheb Pharate Patil College of Pharmacy, Mandavgoan Pharate, Tal-Shirur, Dist-Pune, Maharashtra.

ABSTRACT

The main goal of therapy for many drugs is to establish a steady-state blood or tissue level that is therapeutically efficacious and nontoxic over time. Sustain release systems are a better option for medications with short half-lives that require repeated dosing since they are simple to design and independent of the gastrointestinal tract's absorption process after oral administration. The primary goal of these dosage forms is to optimise drugs distribution in order to establish a measure of therapeutic effect control in the face of variable oscillations in the in vivo environment where drug release occurs. In comparison to conventional immediate release formulations of the same drug, advances in the formulation technology of modified release dosage form with sustained release oral dosage form has been widely accepted approach, which provides a prolong release of the drug over an extended period of time, resulting in better patient compliance and enhanced bioavailability and resulting blood concentration time profile of drugs that otherwise suffer from few limitations This article covers the fundamentals of sustained-release formulation.

KEYWORDS: Sustained release dosage form, Factors affecting the oral sustained release dosage form design, Evalution.

INTRODUCTION

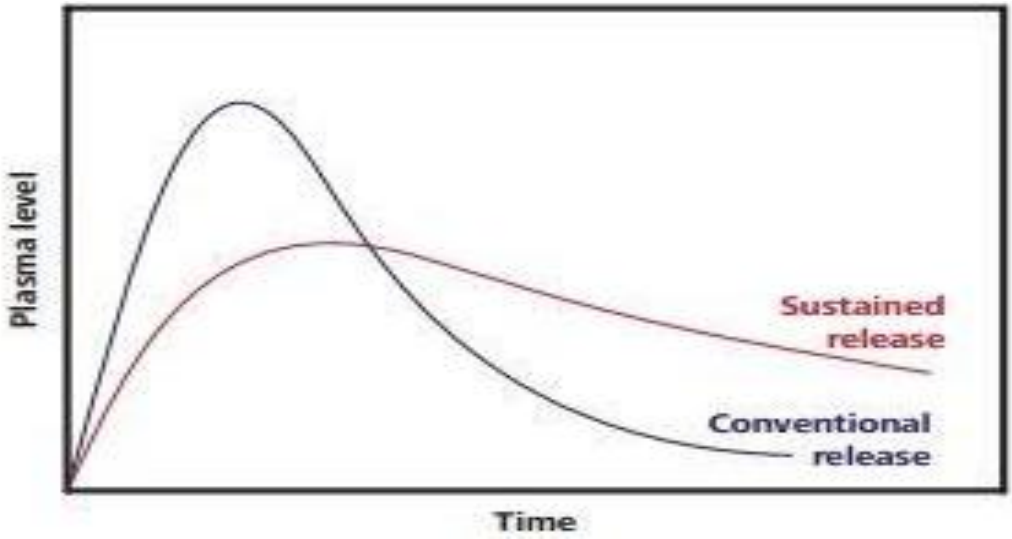
Sustained release doasage described as slow release of a drug from a dosage form to sustain therapeutic response over a prolonged length of time (8-12 hours) is referred to as SRFs. The length of time depends on the dose type. It is measured in hours in oral form and days and months in parenteral form. Ex- Dextrim SR, Aspirin SR.

Sustained release, sustained action, prolong action, controlled release, extended action, depot are terms used to identify drug delivery systems that are designed to achieve prolong therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. In the case of orally administer this period is measured in hours while in the case of injectables this period varies from days to months.

Ex- Dextrim SR, Aspirin SR.

Dosage form with a controlled release The rate or speed at which the medication is delivered is regulated in this method.

Ex -Dynacirc CR (Nifidipine), Adalat CR (Nifidipine) (Isradipine.)



ADVANTAGES AND DISADVANTAGES OF SUSTAINED RELEASE DOSAGE FORM

ADVANTAGES

- Patient compliance has improved.

Dosing less often

- Allows for complete coverage throughout the day.
- Local and systemic side effects were reduced.
- Irritation in the GI tract has decreased.
- Local inflammation was reduced.
- Improved drug utilisation.
- The overall amount of drug utilised reduced.
- On chronic dosage, there is a minimum amount of drug buildup.

- Treatment efficiency has improved.
- Blood and plasma concentrations are consistent.
- Reduced drug level volatility, implying a more consistent pharmacological response.
- Some medicines have a higher bioavailability.
- Added effects SR After waking up, aspirin provides symptoms relief in Arthritis.

DISADVATANGES

- Dumping DOSES Increased drug release leads to drug dumping, which in turn leads to toxicity.
- Potential for accurate dose adjustment has been reduced.
- It is impossible to provide a portion of the medicine.
- Additional patient education is required
- The dosage unit should not be crushed or chewed.
- Stools may contain tablet residue.
- Problems with stability because of the intricacy of SRFs, there will be a stability issue.
- Systemic availability is hard
- Example -Combinations of theophylline, procainamide, and vitamins

FACTORS AFFECTING THE ORAL SUSTAIN RELEASE DOASAGE FORM DESIGN

Pharmacokinetics and pharmacodynamics factor

A) Absorption.

B) Distribution.

C) Metabolism.

D) Biological half life.

Drug properties relevant to sustain release formulation:

Physicochemical properties-

A) Dosage size.

B) Drug stability.

C) Protein binding.

D) Ionization, Partition coefficient, Aqueous solubility

E) Aqueous solubility

- **Pharmacokinetics and Pharmcodynamics factors**

Absorption Before a medicine to reach the systemic circulation, it must dissolve in fluid. When examining the formulation of a controlled release system, the rate, extent, and consistency of medication absorption are critical factors to consider. Dissolution = absorption The features of a drug's absorption can have a significant impact on its suitability as a sustained release medication.

The release rate is substantially slower than the absorption rate. If the maximum half-life for absorption is less than 3-4 hours, the device will pass out of the potential absorptive zone before the drug is completely released. When creating a sustained release formulation, the rate, extent, and consistency of medication absorption are all crucial elements to consider.

Rather than absorption, the rate limiting step in drug administration from a sustained-release system is its release from a dosage form.

We suppose that medication transit time in the absorptive portions of the GI tract is between 8 and 12 hours.

It is difficult to produce a sustained release formulation if the rate of absorption is less than 0.17/hr and more than 0.23/hr.

Another significant criterion is drug via absorption in the GIT tract; drugs such as **Kanamycine** and **Gentamycine** exhibit absorption at diverse places, whereas **Riboflavin** is successfully absorbed like drug absorbed effectively by carrier transport and at upper part of GIT that make it preparation in SRDF difficult.

Distribution

Drug distribution into tissue can be a key element in overall drug elimination kinetics since it not only lowers circulating drug concentrations, but it can also be a rate limiting factor in equilibration with blood and extracellular fluid. The binding of the drug to tissue and proteins in the blood is one part of this distribution. The apparent volume of distribution of a medicine is commonly used to represent the size of distribution within the body, including binding.

Although it would be ideal to have as much information on drug disposition as possible when designing sustained/controlled release products, decisions are frequently made based on only a few pharmacokinetic parameters, one of which is apparent volume of distribution.

Metabolism

The metabolic conversion to 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.

Biological half life

The normal purpose of a sustained release product is to maintain a therapeutic blood level for an extended length of time; therefore, the medication must enter the circulation at a rate that is roughly equal to its elimination rate. The half-life (t1/2) describes the rate of elimination quantitatively.

Short-half-life therapeutic substances are ideal candidates for sustained release preparation because they reduce dose frequency.

Drugs with a shorter half-life than 2 hours. Sustained release formulations are difficult to achieve with drugs like furosemide and levodopa because they require high doses and l In addition, sustaining versions that last more than 8 hours are rarely used because their effect is already long-lasting.

For example, **digoxin, warfarin, and phenytoin**.
long half-life. In addition, forms that last more than 8 hours are rarely employed.

Drug properties relevant to sustain formulation

1. Dosage size

For a conventional dosage form, a single dose of 0.5-1.0 gm is recommended; this also applies to sustained release dosage forms.

If an oral product has a dose size more than 500mg, it is not a good option for a sustained release system, because adding a sustaining dose and possibly a sustaining mechanism will, in most situations, result in a huge volume product that is unacceptably.

2. Drug stability

Acid-base hydrolysis and enzymatic breakdown of medicines taken orally are also possible outcomes. Drugs in the solid state degrade at a slower rate, hence this is the preferable delivery method in issue situations. Methods that prolong delivery over the whole course of GI tract transits, as well as systems that postpone release until the dosage form reaches the

small intestine, are advantageous for medications that are unstable in the stomach. When administered from a sustaining dose form, a compound that is unstable in the small intestine may have reduced bioavailability. This is due to the fact that more medications are administered in the small intestine, which results in a lower drug concentration.
Eg. Nitroglycerine

3. Protein binding

A long half life of elimination for medications with extensive binding to plasma proteins will be evident, and such drugs will almost always require a sustained release dosage form. Drugs with a high affinity for plasma proteins, on the other hand, may bind to biopolymers in the gastrointestinal system, affecting drug delivery over time. The inclusion of a hydrophobic moiety on a pharmacological molecule boosts its binding ability.

Drug binding to plasma proteins (e.g., **Albumin**) results in drug retention in the vascular space, and the drug protein complex can act as a reservoir in the vascular space for prolonged drug release to extravascular tissue, but only for medications with a high degree of binding.

Wander-vals forces, hydrogen binding, and electrostatic binding are the major forces of attraction.

Due to the electrostatic effect, charged compounds have a higher potential to bind proteins than uncharged compounds.

Amitryptline, cumarin, diazepam, digoxide, dicaumarol, and novobiocin are only a few examples.

4. Ionization, pka and aqueous solubility

Most drugs are weak acids or bases and in order for a drug to get absorbed, it must dissolve in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane.

5. Aqueous solubility

Compounds with very low solubility (less than 0.01 mg/ml) are naturally sustained, as dissolving of the medication will limit their release during the period of a dosage form's time in the GI tract. The lower limit for a drug's solubility in a sustained-release system has been reported to be 0.1 mg/ml, therefore it's clear that the compound's solubility will limit the

mechanism that can be used in a sustained-release system. Because the driving force for diffusion, which is the drug's concentration in solution, will be low, diffusional systems will be poor alternatives for slightly soluble medicines.

METHODS TO MAINTAIN THE RELEASE DRUG DELIVERY SYSTEM

1. Dissolution-controlled release mechanisms.
2. Release mechanisms that are regulated. by diffusion.
3. Controlled release methods based on dissolution and diffusion.
4. Drug compounds made with ion exchange resin.
5. A formulation that is pH dependant.
6. Systems that are controlled by osmotic pressure.

1. Dissolution-controlled release mechanisms

These systems are simple to create. Medications designed using the system have a slow dissolve rate and produce slow dissolving forms in stomach and intestinal fluids, as do drugs with a high aqueous solubility and dissolution rate. There are two approaches for a dissolution controlled release mechanism.

A. Matrix dissolution system with controlled release

Because the drug in the matrix is entirely dissolved in the medium that controls drug release, the matrix dissolving system is referred to as monolithic. They are mostly made of waxes such as beeswax, carnauba wax, hydrogenated castor oil, and so on, and they play an important role in controlling the drug release rate by controlling the rate of dissolution fluid penetration into the matrix by altering the porosity of the tablet, decreasing its wettability, or by themselves dissolving at a slower rate. The drug release from such matrix systems usually follows first order kinetics.

B. Controlled release mechanism for reservoir dissolution

The drug particles are coated or encased in the reservoir system using one of several microencapsulation processes that use slowly dissolving materials such as cellulose, polyethylene glycol, and waxes. This unit can be compacted into tablets or encapsulated in capsules. The solubility of the medicine and the thickness of the coating both play a role in its dissolving rate.

2. Release mechanisms that are regulated by diffusion

The diffusion of dissolved drug through a polymeric membrane is a rate-limiting phase in diffusion release models. Because the diffusion path length increases with time as the insoluble matrix is drug depleted, the drug release rate in this system never follows zero-order kinetics. The transfer of drug molecules from an area of higher concentration to a region of lower concentration is depicted by the mechanism of diffusion.

Fick's law describes the flow of the drug J (in amount / area -time) across a membrane in the direction of decreasing concentration.

When a drug is present in a water insoluble membrane, it must diffuse through it.

J = -D dc/dx, where J = flow of the drug across a membrane in the direction of decreasing concentration, D = Diffusion coefficient of the drug, and dc /dx = Change in the concentration of the drug in the membrane. dm = ADK gives the drug release rate dm/ dt. C/dt L = C/dt L = C/dt L = C/dt L = C/dt L = C/d K is the drug's partition coefficient between the membrane and the drug core.

L is the length of the diffusion path (i.e. thickness of coat). C=Difference in concentration across the membrane.

3. Controlled release methods based on dissolution and diffusion

The medicine is encased in a membrane that is slightly water soluble in this arrangement. The membrane dissolves, causing pores to develop, which allow aqueous medium to penetrate the membrane. This causes the drug to dissolve in the membrane, and then the dissolved drug to diffuse out of the system. Combination of ethyl **cellulose** with **PVP** or **methyl cellulose** is an example of such a coating.

4. Drug compounds made with ion exchange resins

Resins are materials that are water insoluble. In repeating points on the chain, resin contains anionic groups such as amino or quaternary ammonium groups, as well as cationic groups such as carboxylic or sulfonic groups. A drug–resin complex is created when the drug is exposed to the resin for an extended period of time. The drug in these complexes is exchanged in the gastrointestinal tract before being released with an excess of Na+ and Cl- in the gastrointestinal system.

Resin+ – Drug– + Cl– ———————————————————————————————— Where x- is Cl and vice versa, resin+ Cl– + Drug– – – – – – – – – – – – – – > >> ———————————————————————————— a resin containing Na+ and a drug

This technique makes use of water-insoluble cross-linked polymer molecules.

5. A formulation that is ph dependant

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.

6. Systems that are controlled by osmotic pressure

These systems are also known as oros, because they use the osmotic pressure mechanism to deliver the drug at a constant zero order rate. The drug plus an osmotic agent such as mannitol or KCl make up the reservoir, which is surrounded by a semipermeable membrane. The dosage form has a small opening that admits water into the reservoir and helps the dissolved drug to be pumped out at the desired rate due to osmotic pressure. The GIT's circumstances have no effect on the drug's release from the reservoir.

Evaluation of sustained release tablet dosage form

1. Weight variation: Twenty tablets were randomly selected from each batch individually weigh, the average weight and standard deviation of 20 tablets calculated.

2. Thickness: The thickness of the tablet was measured by using digital venire caliper, twenty tablets from each batch were randomly selected and thickness was measured.

3. Hardness: Hardness was measured using Pfizer hardness tester, for each batch three tablet were tested.

4. Friability: Twenty tablets were weight and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 min. After revolution the tablets were dusted weight.

5. Drug content uniformity: - It is determined by means of the Assay procedures.

6. In-Vitro Dissolution Study: -These studies vary according to the drug employed in the formulation this example is of Nicorandil sustained release matrix tablet. The study was carried out using 0.1NHcl andphosphate buffer 7.4 using the USP apparatus types II, the

dissolution medium 900 ml maintained at 37oc ±0.5oc, the absorbance was measured at 262nm, thedissolution study were carried out for 24 hrs.

COMPOSITION	PRODUCT NAME	MANUFACTURER
TABLET		
DICLOFENAC SODIUM	NAC-SR	SYSTOPIC
DIAZEPAM	DILZEM SR	TORRENT
CAPSULES		
NIFEDIPINE	INDOCAP	J.B.CHEMICALS AND PHARMACEUTICALS
FLURBIPROFEN	ARFLUR SR	FDC

CONCLUSION

Sustain release systems are a better option for medications with short half-lives that require repeated dosing since they are simple to design and independent of the gastrointestinal tract's absorption process after oral administration. Good process development is required for the formulation of sustained release dosage forms. Aside from their obvious advantages over traditional dose forms, they have limitations such as limited dosage adjustment flexibility, high cost, and inability to terminate therapy quickly. This concept, however, requires accurate adjustment of the physicochemical parameters of core material, coating formulation and tableting excipients. Many drugs are formulated as sustained release dosage form to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose of drug. Hence, sustained release drug delivery system is the preferred dosage form for the drugs having short half-life, so as to maintain the drug plasma level in therapeutic index for prolonged period of time.

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