A REVIEW ON SUSTAINED RELEASE ORAL DRUG DELIVERY SYSTEM

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ABSTRACT
Sustain release systems are thought to be a better approach for drugs with short half-life that require repeated dosing, they are simple to formulate and are not affected by the absorption process from the gastrointestinal tract after oral administration. The primary goal of sustained release forms is to improve drug therapy as measured by the relationship between the benefits and drawbacks of using a sustained release system. Factors Influencing Sustained Release Product Design and Performance. It involve Different types of polymer used for formulation of sustained release dosage form and different evaluation test for the sustained release dosage form.

KEYWORDS: Sustained formulation, polymer, factor for design, and mechanism of release.

INTRODUCTION
The oral route is the most often used mode of drug administration and gastrointestinal physiology offers extra flexibility in dosage form design in comparison to other routes. Any drug delivery system’s goal is to deliver a therapeutic amount of drug to a specific site in the body in order to attain and then maintain the appropriate drug concentration. The Important role of Sustained drug delivery system that improve the therapeutic effectiveness of incorporated drugs by ensuring sustained, controlled administration and/or delivering the drug...
to a specific location.

The primary goal of developing sustained release formulations was to modify and improve drug performance by increasing the duration of drug action, decreasing the frequency of dosing, lowering the required dose, and providing uniform drug delivery.\[3\]

Matrix tablets are commonly used for the long-term release of both water-soluble and insoluble drugs. The method entails directly compressing a mixture of drug, retardant material (polymer), and additives to develop a tablet in which the drug is uniformly dispersed throughout the polymeric matrix.\[4\]

Extensive Because of their known biocompatibility and biodegradability, biodegradable polymers have been widely used in biomedical applications. Polymers are commonly used as implants in the biomedical field and are expected to provide long-term service.\[5\]

1. **Limitations of conventional dosage form**
   - Short-half-life drugs need frequent administration, which increases the risk of skipping a dose, resulting in poor patient compliance.
   - The conventional peak-valley plasma concentration-time profile, making steady state conditions difficult to achieve.
   - Whenever overdose occurs, fluctuating drug levels may precipitate undesirable effects, especially when substance has a small therapeutic index.
   - Patient noncompliance: forget to take your medication.

2. **Advantages of sustain release dosage forms**
   - Reduction in frequency of dose intakes.
   - Side effects are minimised.
   - Drug release that is consistent across time.
   - Increased patient compliance.

3. **Disadvantages of sustained release drug delivery**
   - Increased cost.
   - Toxicity because of dose dumping.
   - When a drug is released quickly, there is a risk of adverse effects or toxicity.
   - There is a need for more patient education and counselling.
4. Characteristics of drugs unsuitable for oral sustained release forms

- Drug which are not well absorbed in the lower intestine e.g. riboflavin, ferrous salts.
- Drug having shorter biologic half-lives (< 1 hr > 12 hr.) e.g. diazepam, phenytoin
- Drug which required Large doses (> 1 g) e.g. Sulphonamides.
- Drugs having low therapeutic index e.g. phenobarbital, digitoxin.
- No advantage for formulating in to the sustained release formulation e.g. Griseofulvin

5. Factors influencing the Design and Performance of sustained release products

A. Physicochemical Properties of drugs

B. Biological Factors

A. Physicochemical properties of drugs

1. Dose size
The bulk size of the dose to be delivered has an upper limit for orally administered systems. A single dose of 0.5 to 1 gm is generally considered the maximum.

2. Ionization, pKa & Aqueous solubility
The pH Partition hypothesis basically suggests that a drug’s unchanged form will be absorbed preferentially by various human tissues. As a result, it’s crucial to understand the relationship between the compound's pKa and its absorptive environment.

3. Partition coefficient
Compounds having a high partition coefficient are mostly lipid soluble and permeate membranes easily, resulting in high bioavailability. Compounds with a low partition coefficient will have trouble passing through membranes, resulting in low bioavailability.

4. Drug stability
Drugs that are unstable in the stomach can be put in a slowly soluble form and released once they reach the small intestine.

5. Protein binding
Many drugs are known to bind to plasma proteins, which has an effect on the duration of pharmacological action. Proteins in the blood are primarily recirculated rather than removed. When a significant degree of drug binding occurs, drug protein binding might act as a depot for the drug, resulting in a sustained release profile.
B. Biological factors

1. Biological Half-Life
Compounds with a half-life shorter than 8 hours are ideal candidates for sustained release development.

2. Absorption
The absorption qualities of a drug can have a significant impact on its usefulness as a sustained release product. Drugs that are absorbed through a specialised transport method (carrier mediated) or at specific places in the gastrointestinal tract (Absorption Window) are not good candidates for sustained release.

3. Metabolism
When designing a sustained-release system for a drug, the metabolic conversion of that drug to another chemical form is taken into account.

Monolithic matrix system
In pharmaceutical SRDDS, matrix based systems are the most commonly used type of release controlling methodology owing to their simple manufacturing process. The preparation of a tablet with the matrix includes the direct compression of drug, release retardant, and other additive blends, with the drug being uniformly distributed throughout the matrix core of the release retardant.

➢ Advantages of matrix tablet
- Easy to manufacture.
- Versatile and low-cost
- Compounds with a high molecular weight can be released.
- Sustained release formulations may be able to maintain therapeutic concentrations for extended periods of time.
- The use of sustained release formulations eliminates the high blood concentrations.
- Sustain release formulations improve patient compliance.
- Slowing drug absorption reduces toxicity.
- Reduce the probability of local and systemic adverse effects.

➢ Disadvantages of matrix tablet
- After the drug has been released, the remaining matrix must be removed.
- Food and the rate of transit through the gut are two factors that influence releaserates.
Matrix tablet generally classified into different types

A. Hydrophilic matrix tablet

A hydrophilic matrix is commonly used to control the rate of drug release. The matrix can be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix materials. Water is required for the hydrophilic matrix to activate the release mechanism and explore several advantages, which includes simplicity of manufacture and excellent uniformity of matrix tablets. The formulation of a hydrophilic matrix tablet, the use of matrix building materials with fast polymer hydration capability is the best option. Due to the rapid penetration of water, an insufficient polymer hydration rate may result in premature drug diffusion and tablet disintegration... It is suitable for formulation of water soluble drug.

B. Fat-wax matrix tablet

Various techniques for incorporating drugs into fat wax granulation that involve spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray drying Technique. Bulk congealing method, a suspension of drug and melted fat wax is allowed to solidify and then comminute for sustained-release granulations. Mixing of active ingredients waxy materials and fillers when the mixing is over this mixture converted into granule by compacting with s compactor, heating in a suitable mixture such as fluidized-bed and steam jacketed blender or granulating with a solution of waxy material. The drug which is embedded into a melt of fats and wax released by leaching and hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the GI tract. Addition of various surfactants to the formulation can also influence both the release rate of drug and the total drug proportion that can be incorporated into a matrix.

C. Plastic matrix tablet (Hydrophobic matrices)

Sustained release tablets with an inert compressed plastic matrix are widely used. Because the dissolved drug must diffuse through the capillary network between the compacted polymer particles, release is usually delayed. Plastic matrix tablets, in which the active ingredient is embedded in a tablet with a coherent and porous skeletal structure, can be easily prepared by direct compression of the drug with plastic materials if the plastic material can be comminute or granulated to the desired particle size to facilitate mixing with the drug particle.

D. Biodegradable matrices

These are polymers made up of monomers linked together by functional groups and with an
unstable linkage in the backbone. It is biologically degraded or eroded into oligomers and monomers that can be metabolised or excreted by enzymes produced by surrounding living cells or by non-enzymatic processes. Natural polymers like proteins, polysaccharides, and modified natural polymers are examples, as are synthetic polymers like aliphatic poly (esters) and poly anhydrides.

E. Mineral matrices

Mineral matrices are made up of polymers derived from various seaweed species. For example, Alginic acid, is a hydrophilic carbohydrate extracted from brown seaweeds (Phaeophyceae) using dilute alkali.

- Polymers used in matrix tablet
  - Hydrogels
    Polyhydroxyethylmethacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Polyacrylamide (PA)
  - Soluble polymers
    Polyethyleneglycol (PEG), polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC)
  - Biodegradable polymers
    Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters.
  - Non-biodegradable polymers
    Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC)

- Mechanism of drug release from matrix tablets

In erodible matrices, drug release is determined by polymer erosion from the matrix's surface; in hydrophilic matrices, drug release is determined by the formation of the gel layer and its dynamics as a function of time. The distance between the diffusion and erosion fronts corresponds to the thickness of the gel layer, which determines the drug's diffusion path length. The gel layer gradually thickens as the swelling process progresses, resulting in progressively slower drug-release rates; however, due to continuous hydration, polymer disentanglement occurs from the matrix's surface, resulting in a gradually decreasing depletion zone and an increased dissolution rate.
Evaluation test for sustained release tablets

- **Weight variation:** Twenty tablets were weighed individually and then collectively, average weight of the tablets was calculated.
- **Hardness:** Hardness test was conducted for tablets from each batch using Monsanto hardness tester and average values were calculated.
- **Friability:** The tablets were tested for friability testing using Roche friabilator, which revolves at 25rpm for 4min.
- **Thickness:** The thicknesses of tablets were determined using micrometre screw gauge.
- **Content uniformity:** Using UV Visible spectrophotometer found the amount of the drug using the calibration curve method.
- **In vitro dissolution study:** Drug release study is generally determined in Rotating Paddles apparatus. Mainly buffer is used as a dissolution medium. The temperature of the bath maintained at 370C and required sample of the dissolution medium in which drug is release is taken at a regular interval and the same quantity of the medium is replace. The amounts of the drug released is determined using an UV spectrophotometer a Drug dissolved at specified time period is plot as percent release versus time. Short Term Stability Study: To determine change in vitro release profile on storage, a short term stability study of the optimal batch.

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