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A BRIEF OVERVIEW OF SUSTAINED RELEASED DRUG DELIVERY SYSTEM

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ABSTRACT
The most popular and patient-friendly method of drug administration is often thought to be the oral route of administration. Compared to conventional release formulations, advancements in formulation technology, including modified release dosage forms or sustained release oral dosage forms, have been extensively accepted. A sustained release dosage form provides a prolonged release of the drug over an extended period, thereby giving better patient compliance and enhanced bioavailability. Sustain release systems are considered a wiser approach for drugs with short half-lives requiring repeated dosing. Sustained release drug delivery has a range of advantages over conventional dosage forms, including increased patient compliance due to less frequent drug administration, significantly reduced steady-state drug level fluctuations, maximum drug utilization, the increased safety margin of potent drugs, lower healthcare costs due to improved therapy, and shorter treatment times. The present review focuses on design, fabrication, and various factors that influence the performance of sustained-release dosage forms.

INTRODUCTION

Sustained release dosage forms are made to release medicine at a given rate while keeping the drug level constant for a defined period of time with the minimal adverse effects possible. The fundamental concept behind sustained-release drug delivery systems is to improve the patient's compliance though increasing the bioavailability and effectiveness of the medicines [1]. Sustained release with the introduction of extended release matrix tablet have proved to be an effective tool to control the release of drug without involving the complex production procedures [2]. Through localising the drug to the site of action, lowering the dosage needed, and ensuring uniform drug distribution, sustained or controlled delivery systems aim to boost drug effectiveness or decrease the frequency of dosing [3]. Numerous sustain release oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed. Intense research has recently focused on the designation of SR systems for poorly water soluble drugs [4]. However, designing such a system necessitates a number of factors, among which the half-life and pharmacological effect of the drug play an

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important role. Therefore, taking into account the shortcomings of the standard drug delivery system (repeated dosing and dose variability), the sustained release delivery supports in the accomplishment of the following objectives:

i) Uniform release of drug over prolong period of time.
ii) Reduced dosing frequency.
iii) Less fluctuating blood levels.

In many instances, conventional method is more preferred to deliver the drug, but some drugs are unstable and toxic by frequently dosing. These kinds of drug have narrow therapeutic range and face solubility difficulties. In such cases, sustained drug delivery system is used, which maintain the drug plasma level in the therapeutic index.

Problem occurs during multiple dosing [5,6]

1. If the dosing interval between the two doses is not proper according to the drug's biological half-life, than it may result in the fluctuation of the drug plasma concentration.
2. Drug plasma level will not remain in the therapeutic range due to inappropriate dosing, which may result in toxicity.
3. Inconvenient for the patient and can result in missed doses and noncompliance with the regimen.

Parameters for the drug to be formulated as sustained release dosage form [7,8]

There are some physicochemical parameters for the drug selection to be formulated in sustained release dosage form which mainly includes the knowledge on the absorption mechanism of the drug form the Gastro Intestinal (GI) tract, its general absorbability, the drug's molecular weight, solubility at different pH and apparent partition coefficient as shown in Table 1.

Table 1: Physicochemical parameters for drug selection

Parameter	Preferred value
Molecular weight/ size	< 1000 Daltons
Solubility	> 0.1 mg/ml for pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segments
Release	Should not be influenced by pH and enzymes

Similarly there are some pharmacokinetic parameters for drug selection which includes drug's elimination half- life, total clearance, absolute bioavailability, possible first-pass effect, and the desired steady concentrations for peak and trough as shown in Table 2.

Table 2: Pharmacokinetic parameters for drug selection

Parameter	Comment
Elimination half life	Preferably between 2 to 8 hrs
Total clearance	Should not be dose dependent
Elimination rate constant	Required for design
Apparent volume of distribution Vd	The larger V_d and MEC, the larger will be the required dose size.
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration C_{ss}	The lower C_{ss} and smaller Vd, the loss among of drug required
Toxic concentration	Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

Merits of Sustained release dosage form [9-12]:

Clinical Merits

1. Decreased local and systemic side effects:
- Reduced gastrointestinal irritation.

2. Better drug utilization:
- Reduction in total amount of drug used.
- Minimum drug accumulation on chronic dosing.

3. Improved efficiency in treatment:
- Optimized therapy.
- Less reduction in drug activity with chronic use.

4. Improved patient compliance:
- Less frequent dosing
- Reduced night-time dosing

5. Economical to the health care providers and the patients

Commercial Merits

1. Chances of Illustration of innovative/technological leadership
2. Extension of product life-cycle
3. Differentiation of product
4. Expansion of market
5. Extension of patent

Demerits of Conventional release dosage form [13, 14]:

1. If the drug has short half-life, it has to be administered frequently, so there are chances of missing the dose.

2. If the drug is not taken at periodic interval, peak valley plasma concentration time profile obtained is not steady.
3. The fluctuations of drug plasma level that occurs during conventional release may produce under medication or overmedication.
4. Poor patient compliance

Common terminology mostly used to express the drug release fashion:

1. **Sustained release:** These are drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose of drug [15].
2. **Controlled-release dosage forms:** They are class of pharmaceuticals or other biologically active products from which a drug is released from the delivery system in a planned, predictable, and slower-than-normal manner for longer period of time [16].
3. **Extended release:** Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds [4].
4. **Delayed release:** Delayed release systems are those systems that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form [5].
5. **Repeat action drug delivery system:** These are the alternative system of sustained release which multiple contains doses of drug within the dosage form, and each dose is released at regular intervals [17].
6. **Prolonged release system:** They are designed to release the drug slowly and to provide a continuous supply of drug over an extended period. They prevent very rapid absorption of the drug, which could result in extremely high peak plasma drug concentration [18].
7. **Timed release drug delivery system:** Timed release drug delivery system are used to obtain the drug release after a lag time of about 4-5 hrs. Enteric coated dosage forms of cellulose acetate phthalate are designed to provide protection in the stomach. Application of a thick coat causes a delay in the drug release in small intestine and delays the drug release. This time controlled drug release may be retarded up to 5 hrs this targets the drug to the colon [19].
8. **Site-specific and receptor release:** They are designed to target the drug directly to a certain biological location. In the case of site- specific release, the drug directly target to a certain organ or tissue, while in receptor release, the target on the particular receptor within an organ or tissue [5].

Factors affecting the oral sustained release dosage form design

1. Pharmacokinetic and Pharmacodynamic factors:

1. **Biological half-life:** Drug with biological half-life of 2-8 hours are considered suitable candidate for sustain release dosage form. However, drugs with very short biological half-life may not be a good candidate for sustained release dosages forms [17].
2. **Absorption:** Rate of absorption of a sustained formulating depends upon release rate constant of the drug from the dosage form, and for the drugs that are absorbed by active transport the absorption is limited to intestine.[18]
3. **Distribution:** The distribution of drugs into tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending n the time course of drug disposition. Thus for design of sustain release products, one must have information of disposition of drug.[19]
4. **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.[20]

2. Drug properties relevant to sustain release formulation:

1. **Dose size:** A dose size of 500-1000mg is considered maximal for a conventional dosage form. This also holds true for sustain release dosage forms. Since dose size consideration serves to be a parameter for the safety involved in administration of large amounts with narrow therapeutic range.[21]

2. **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.

3. **Partition coefficient:** Bioavailability of a drug is largely influenced by the partition coefficient, as the biological membrane is lipophilic in nature transport of drug across the membrane largely depends upon the partition coefficient of the drug. Drugs having low partition coefficient are considered as poor candidate for the sustain release formulation as it will be localized in the aqueous phase eg: Barbituric acid and vice a versa [22].

4. **Drug stability:** When drugs are orally administered, they come across acid-base hydrolysis and enzymatic degradation. In this case, if the drug is unstable in stomach, drug release system which provides medication over extended period of time is preferred, whereas in contrast the drug unstable in intestine will face problem of less bioavailability.

Model of oral sustained release drug delivery system:

The oral route administration is mostly adopted route because of its comfortable dosage form, design and patient care. Several parameters should be kept in mind before formulating sustain release dosage form which includes various pH in GIT, the gastrointestinal motility, the enzyme system and its effect on the dosage form and the drug.

Most of sustained release dosage form follows the mechanism of diffusion, dissolution or combination of both, to produce slow release of drug at predetermined rate. Hypothetically, a sustained release dosage form should release the drug by a zero-order mechanism which maintains drug plasma level time similar to intravenous infusion. Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero order sustained release formulation are as follow in given figure.

Approaches to sustained release drug delivery system [21-27]:

1. Dissolution controlled release systems
2. Diffusion controlled release systems
3. Dissolution and diffusion controlled release systems
4. Ion exchange resin- drug complexes
5. pH dependent formulation
6. Osmotic pressure controlled systems

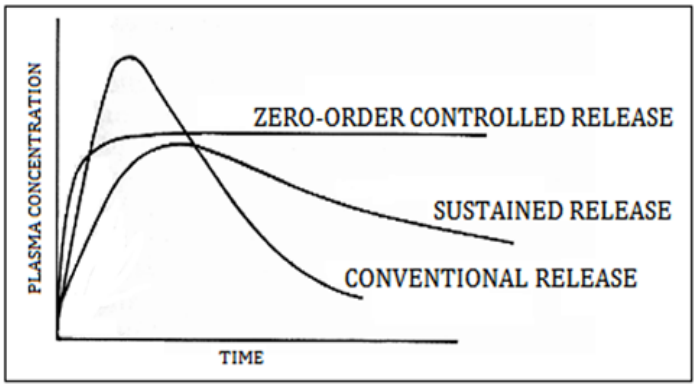

Figure 1: Plasma drug concentration profile for conventional release, a sustained release and zero order controlled release formulation

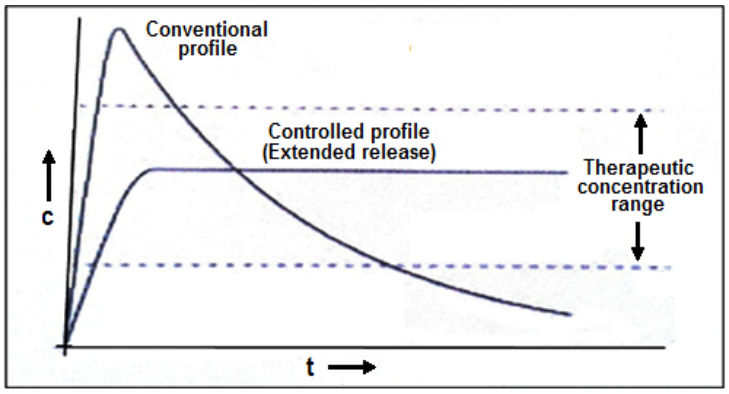

Figure 2: Comparison of conventional and controlled release profiles

1. Dissolution controlled release systems

These systems are easy to formulate. Drug which are formulated using system have slow dissolution rate, produce slow dissolving forms with gastric intestinal fluids and the drugs which are having high aqueous solubility and dissolution rate.

Dissolution controlled release system can be classified into two techniques:

A. **Matrix dissolution controlled release system:** Matrix dissolution system is known as monolithic because the drug present in the matrix is completely dissolved in the medium which controls the drug release. They are mostly made of waxes like beeswax, carnauba wax, hydrogenated castor oil, etc. and play important role to control the drug release rate by controlling the rate of dissolution fluid penetration into the matrix by altering the porosity of tablet, decreasing its wettability or by itself getting dissolved at a slower rate. The drug release generally follows first order kinetics from such matrices system.

B. **Reservoir dissolution controlled release system:** In reservoir system, the drug particles are coated or encapsulated with one of the several microencapsulation techniques using slowly dissolving materials like cellulose, polyethylene glycol and waxes. This unit can be encapsulated in capsules or may be compressed into tablets Solubility and thickness of the coating play important role in dissolution rate of drug [22].

2. Diffusion controlled release systems

In diffusion release models, the diffusion of dissolved drug through a polymeric membrane is a rate limiting step. In this system, the drug release rate never follows zero-order kinetics, because the diffusional path length increases with time as the insoluble matrix is drug depleted [23].

The mechanism of diffusion process shows the movement of drug molecules from a region of a higher concentration to region of lower concentration. The flux of the drug J (in amount / area -time), across a membrane in the direction of decreasing concentration is given by Fick's law.

$$J = - D \, dc/dx$$

where, J = flux of the drug across a membrane in the direction of decreasing conc., D = Diffusion coefficient of the drug, and dc /dx = Change in the concentration of the drug in the membrane, Whereas when drug present in a water insoluble membrane, it must diffuse through the membrane.

The drug release rate dm/ dt is given by

$$dm/dt = ADK\Delta C/L$$

where,

A = Area, K = Partition coefficient of drug between the membrane and drug core, L = Diffusion path length (i.e. thickness of coat), ΔC = Concentration difference across the membrane [24].

3. Dissolution and diffusion controlled release systems

In this kind of system, the drug is enclosed in a membrane which is partially water soluble. The dissolution of the membrane take place due to which pores are formed and these pores allows aqueous medium to enter in the membrane. This results in the dissolution of the drug in membrane followed by the diffusion of the dissolved drug from the system. Example of such coating is combination of ethyl cellulose with PVP or methyl cellulose [25].

4. Ion exchange resin- drug complexes

Resins are the materials which are insoluble in water. Resin contains anionic groups such as amino or quaternary ammonium groups and cationic groups such as carboxylic groups, or sulfonic groups in repeating positions on the chain. A drug–resin complex is formed by prolonged exposure of drug to the resin. The drug from these complexes gets exchanged in gastrointestinal tract and later they are released with excess of Na^+ and Cl^- present in gastrointestinal tract.

$$Resin^+ – Drug^– + Cl^– \text{ ---------> } resin^+ Cl^– + Drug^–$$

where x^- is Cl^- conversely

$$Resin^– – Drug^+ + Na^+ \text{ ----------> } resin^– Na^+ + Drug$$

Water insoluble cross linked polymer compounds are used for this system [22,26,27].

5. pH dependent formulation

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. Osmotic pressure controlled systems

These types of system are also known as oros, which follows the mechanism of osmotic pressure where the drug is released at constant zero order rate. The reservoir is made up of the drug and osmotic agent like mannitol or KCl, which is surrounded by semipermeable membrane. A small orifice is present in the dosage form, which allows the entry of water in the reservoir and helps the dissolved drug to pump out at the determined rate due to osmotic pressure. The release of the drug from the reservoir is unaffected by the conditions of the GIT. The release of drug is depended on factors like size of orifice, thickness of semipermeable membrane, permeability of membrane, osmotic properties of core and stability of the drug [20, 22].

CONCLUSION

From the above discussion, it can be concluded that the sustained release dosage form are drug delivery system which by virtue of its design, release drug in a slow and steady manner. Drug release can either be delayed or extended in nature. When

compared to conventional dosage forms, it improves patient compliance and is a useful tool for drugs that are not necessarily long-lasting and require numerous daily doses to get the necessary therapeutic benefits. Hence, the future of sustained release drug delivery system is having a huge prospect in the health care system.

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CONFLICT OF INTEREST
The authors declare no conflict of interest

AUTHOR CONTRIBUTION
Priyanka Prajapat designed the entire work. Gaurav Bhaduka and Dilip Agrawal contribute in making necessary correction and revision of the manuscript. The final draft was checked by all the authors.

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