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Review Article

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A Fundamental Approach on Sustained Drug Delivery System

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Abstract Now a day as very few drugs are coming out of research and development and already existing drugs are suffering the problem of resistance due to their irrational use specifically in case of drugs like antibiotics. Hence, change in the operation is a suitable and optimized way to make some drug more effective by slight alteration in the drug delivery. Sustained Release is also providing promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. This article contains the basic information regarding sustained-release formulation and also the different types of the same. All drug delivery systems, oral drug delivery remain the most preferred option for administration for various drugs. Sustained release is also providing promising way to decrease the side effects of drug by preventing the fluctuation of the therapeutic concentration of drugs in the body. The basic rationale of sustained drug delivery system optimizes of the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of a drug in such a way that utility is maximized, side effects are reduced and cure of the disease is achieved. This is improved patient compliance due to less frequent drug administration, reduction of fluctuation in steady state drug levels.

Keywords Research and development, Sustained release, Oral administration, Therapeutic concentrations

Introduction

Sustained Release drug delivery System

Simple definition of **sustained release drug system** as **"any drug or dosage form modification that prolongs the therapeutic activity of the drug."**

Ideally a sustained release oral dosage form is designed to release rapidly some pre- determined fraction of the total dose in to GI tract.

This fraction (loading dose) is an amount of drug, which will produce the desired pharmacological response as promptly as possible and the remaining fraction of the total dose (maintenance dose) is then release at a constant rate.

The rate of the drug absorption from the entire maintenance dose into the body should equal to the rate of the drug removal from the body by all the processes over the time for which the desired intensity of pharmacological response is required.

These dosage forms offer many advantages, such as

- Nearly constant drug level at the site of action.
- Prevention of peak-valley fluctuations.
- Reduction in dose of drug.
- Reduced dosage frequency.
- Avoidance of side effects.
- Improve patient compliance.

Mechanism of Sustained Release:

a) Diffusion.

b) Dissolution.

c) Osmosis: Placement of a semipermeable membrane around a tablet, particle, or drug solution, which allows creation of an osmotic pressure difference between the inside and outside of the tablet and hence "pumps" drug solution out of the tablet through a small orifice in the coat, can be used as a sustained release mechanism**.**

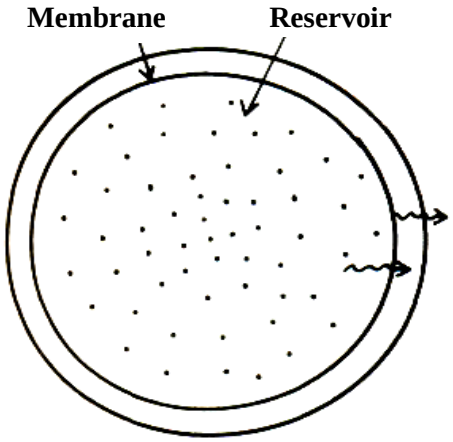

Figure 1: Diffusion control of drug release by a water insoluble polymer.

(Here, the polymer is water insoluble, so important factor is solubility of Drug in the membrane and so gives rise to the driving force for diffusion.**)**

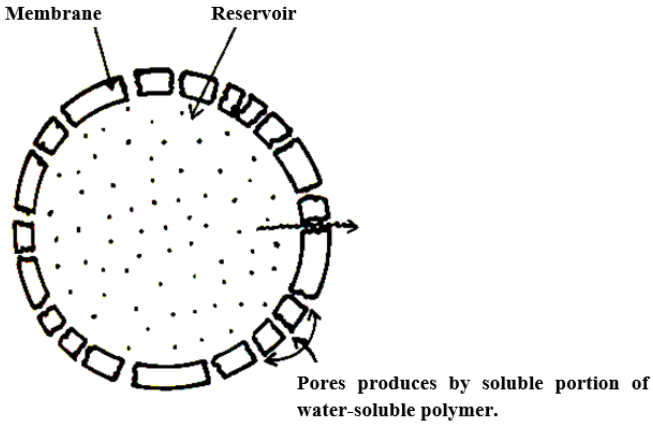

Figure 2: Diffusion control of drug release by a partially water soluble polymer.

(Here, polymer is partially soluble in water or mixture of water soluble and Water insoluble polymer is used. The water soluble polymer then dissolves Out of the film, giving rise to small channels through which the drug can diffuse.**)**

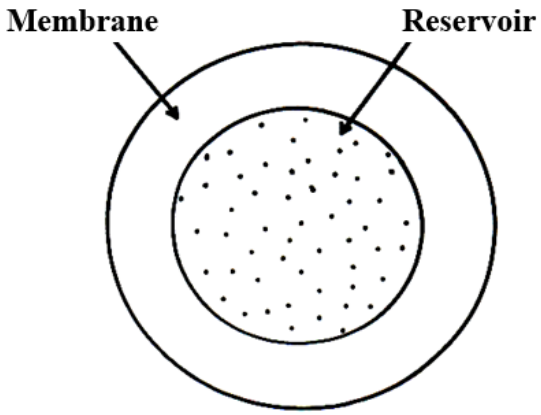

Figure 3: Dissolution control of drug release via thickness and Dissolution rate of the membrane barrier coat

(By varying the coating thickness, or layering concentric sphere of coating material and Drug reservoir material, gives rise to different release times, Producing the repeat action dosage form.**)**

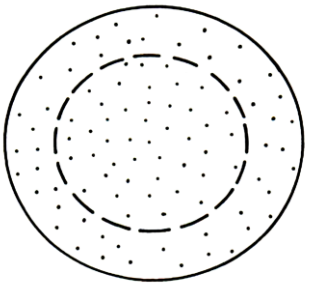

Figure 4: Dissolution control of drug release via polymer core Erosion or polymer-coating erosion

(Here, the drug is either embedded in a polymer or coated with a water soluble polymer, Which in turn is compressed into a slowly dissolving tablet. The release rate is Controlled by the dissolution rate of the polymer or tablet**)**

Table 1: Types & mechanisms of sustained release system

Types	**Mechanism**
Matrix	Diffusion
	Through a matrix or membrane
Reservoir	Chemical reaction – erosion or cleavage
(Hybrids)	
Osmotic Pumps	Solvent activation
	Osmotic pump or polymer swelling

Matrix diffusion controlled drug delivery system

In this type of controlled drug delivery system, the drug reservoir results from the homogeneous dispersion of the drug particles in either a lipophilic or a hydrophilic polymer matrix.

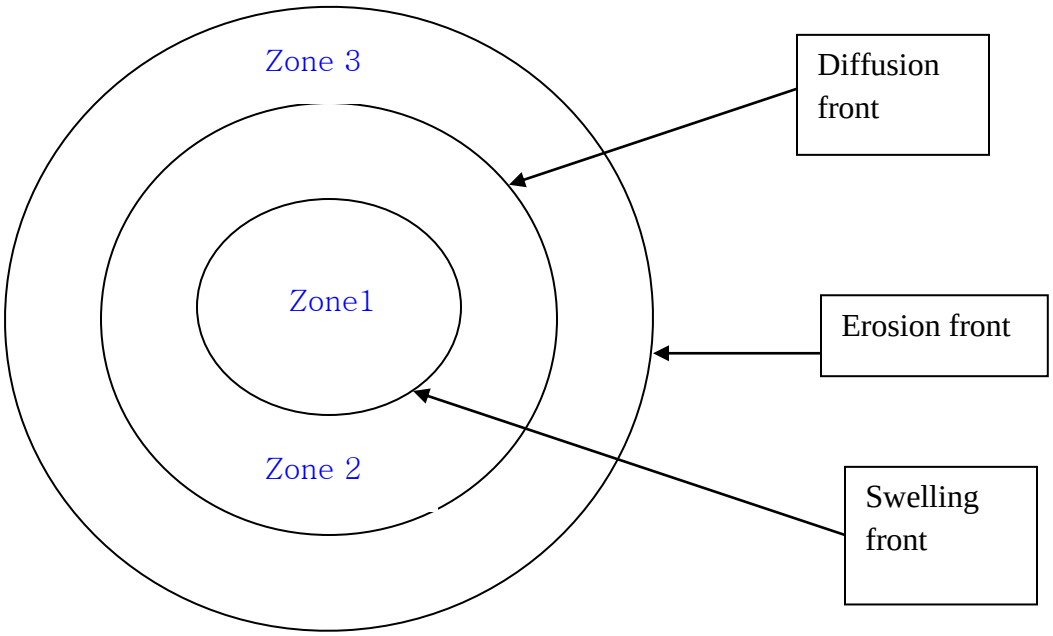

Figure: 4 Matrix Diffusion Controlled Drug Delivery System

Zone 1: Undissolved drug, glassy polymer.

Zone 2: Undissolved drug, gel layer.

Gel layer thickness = Difference between erosion and swelling front position

The rate of drug release from the system is time dependent and is given by,

$$dQ/dt = (ACrDp/2t)^{1/2}$$

Where dQ /dt is rate of drug release,

A is loading dose

Cr is drug solubility in polymer

T is the time

Dp is drug diffusivity in the polymer.

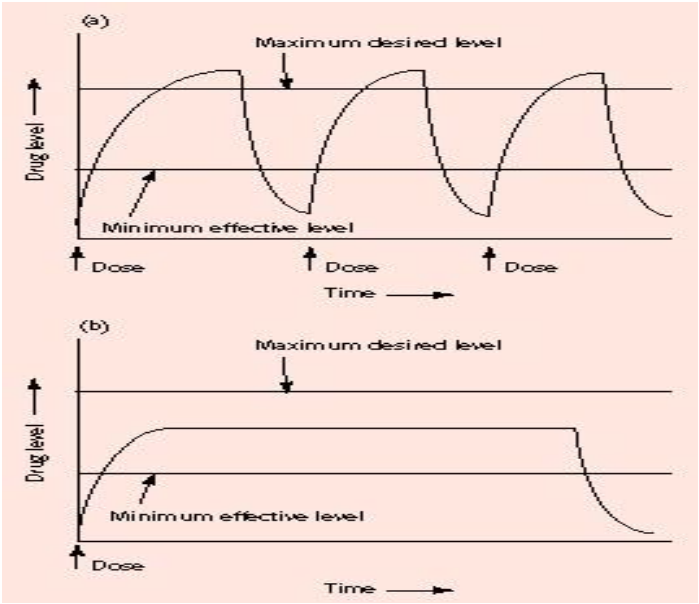

Figure 5: Drug levels in the blood with

The treatment of acute diseases or chronic illnesses has been achieved by delivery of drugs to the patients for many years. These drug delivery systems include tablets, injectables, suspensions, creams, ointments, liquids, and aerosols. Today these conventional drug delivery systems are widely used. The term **drug delivery** can be defined as techniques that are used to get the therapeutic agents inside the human body.

Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems.

a) Traditional drug dose systems and b) Controlled drug delivery dose systems.

To overcome these problems, controlled drug delivery systems were introduced three decades ago. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity, and improved patient convenience. The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies.

Controlled drug delivery is delivery of drug at a rate or at a location determined by needs of body or disease state over a specified period of time. Ideally two main objectives exist for these systems. These are spatial delivery, which is related to the control over the location of drug release, temporal drug delivery, in which the drug is delivered over an extended period of time during treatment.

The oral controlled-release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time **(sustained release),** thereby ensuring sustained therapeutic action. Thus, the release commences as soon as the dosage form is administered as in the case of conventional dosage forms.

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates.

Disadvantages of Conventional Drug Delivery System

- Inconvenient
- Difficult to monitor
- Careful calculation necessary to prevent overdosing
- Large amounts of drug can be “lost” when they don’t get to the target organ
- Drug goes to non-target cells and can cause damage
- Expensive (using more drug than necessary)

Advantages of Controlled Drug Delivery System

- Avoid patient compliance problems.
- Employ less total drug.
- Minimize or eliminate local rate effects.
- Minimize or eliminate systemic side effects.
- Obtain less potentiation or reduction in drug activity with chronic use.

Disadvantages of Controlled Drug Delivery System

1. Decreased systemic availability in comparison to immediate release conventional dosage forms.
2. Poor in vitro and in vivo correlation.
3. Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient.
4. Increased risk of toxicity.
5. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
6. Higher cost of formulation.

Challenges to Controlled Release

- Cost of formulation – preparation and processing
- Fate of controlled release system if not biodegradable
- Biocompatibility
- Fate of polymer additives, e.g., plasticizers, stabilizers, antioxidants, fillers

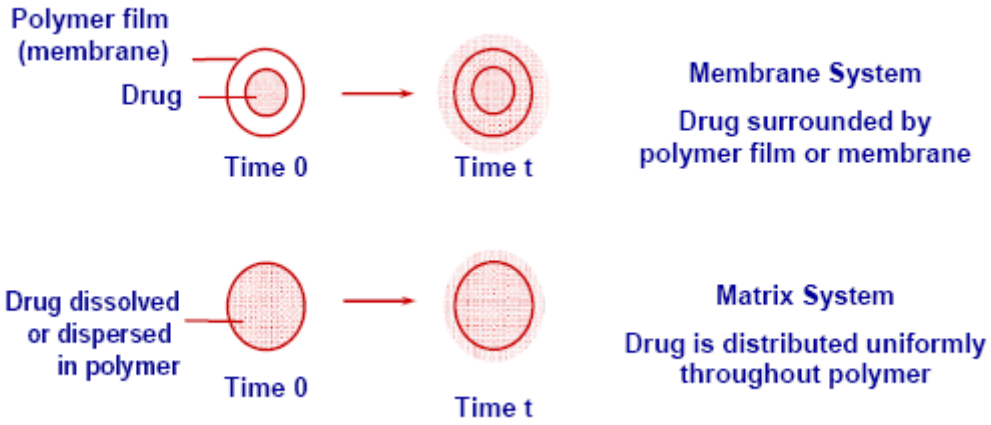

Figure 6: Reservoir devices and matrix devices

To obtain a constant rate of drug release maintaining constant area of diffusion, path length, concentration and diffusion coefficient is necessary. This does not always happen in real practice as one or more terms change and sometime nonzero order release of drugs is possible. Common methods used to develop reservoir type devices are microencapsulation and press coating of tablets containing a drug core. Drug release from these types of systems is usually a combination of diffusion and dissolution. Materials, which are commonly used, include gelatin, methyl or ethyl cellulose and various waxes.

In the matrix devices, solid drug is assumed to dissolve in the surface layer first. When this layer becomes exhausted, the next starts depleting. Three major types of materials are used for the preparation of these devices. These are insoluble plastics, hydrophilic polymers and fatty compounds. In the dissolution systems, a drug with a slow dissolution rate can provide sustained drug levels. This makes possible preparation of good controlled release products by controlling the dissolution rate of drugs that are highly water-soluble. This can be done by preparing a suitable salt or by coating the drug with a slowly soluble material. The dissolution system can be considered diffusion-layer controlled, where the rate of diffusion from the solid surface to the bulk solution through an unstirred liquid film is the rate-determining step. In such case, the dissolution process at steady state is described by the Noyes-Whitney equation-

$$dc/dt = K_d A (Cs - C) \quad (2)$$
$$= (D/h) A (Cs - C)$$

Where dc/dt = Dissolution rate,

K_d = Dissolution rate constant,

A = Surface area,

Cs = Saturation solubility of the solid, and is the concentration of solute in the bulk solution.

h = Thickness of the diffusion layer.

A constant dissolution rate can be obtained if all the terms in the above equation are held constant. This is not possible in practice. All parameters may change as the dissolution proceeds, especially surface area. Two main types

of systems exist in which dissolution determines the rate of release of the drug. These are encapsulated dissolution systems and matrix dissolution systems. Encapsulated systems can be prepared either by coating the particles or granules of drug with varying thicknesses of slowly soluble polymers or by micro encapsulation.

Criteria to be met by drug proposed to be formulated in sustained release dosage forms.

a) Desirable half-life. b) High therapeutic index c) Small dose d) Desirable absorption and solubility characteristics. **e) Desirable absorption window. f) First past clearance**.

a) Desirable half-life

The half-life of a drug is an index of its residence time in the body. If the drug has a 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 eight hours or more are sufficiently sustained inthe body, when administered in conventional dosage from, and sustained release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of three to four hours.

b) High therapeutic index

Drugs with low therapeutic index are unsuitable for incorporation in sustained release formulations. If the system fails in the body, dose dumping may occur, leading to fatalities e.g. Digitoxin.

c) Small dose

If the dose of a drug in the conventional dosage form is high, its suitability as a candidate for sustained release is seriously undetermined. This is chiefly because the size of a unit dose sustained release formulation would become too big, to administer without difficulty.

d) Desirable absorption and solubility characteristics

Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such Compounds into sustained release formulations is therefore unrealistic and may reduce overall Absorption efficiency.

e) Desirable 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'. Drugs exhibiting an Absorption window like fluorouracil, thiazide diuretics, if formulated as sustained release dosage forms are unsuitable.

f) First pass clearance

As discussed earlier in disadvantages of sustained delivery system, delivery of the drug to the body in desired concentrations is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in sustained release forms.

Classification of Sustained Release System

The controlled release system 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 three systems are classified as follows:

1. Continuous Release systems
2. Delayed transit and controlled release systems
3. Delayed release system

Continuous release system

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 system under this category are as follow:

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

F. Osmotic pressure-controlled systems

Diffusion controlled release system

In this type of systems, the diffusion of dissolved drug through a polymeric barrier is a rate limiting step. The drug release rate is never zero order since the diffusional path length increase with time as the insoluble matrix is gradually depleted of drug. Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery system. The two types of diffusion-controlled release are: 1. Matrix diffusion-controlled systems 2. Reservoir devices

Dissolution-controlled release systems

The drug present in such system may be the one: a) Having high aqueous solubility and dissolution rate b) With inherently slow dissolution rate e.g. Grisofulvin and digoxin c) That produces slow dissolving forms, when it comes in contact with GI fluids. Dissolution-controlled release can be obtained by slowing the dissolution rate of drug in GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules, with polymeric material of varying thickness. Dissolution and diffusion controlled release systems In such systems the drug core is encased in a partially soluble membrane. Pores are thus created due to dissolution of parts of membrane which permit entry of aqueous medium into the core and hence drug diffusion of dissolved drug out of the system.

Ion exchange resin-drug complexes

It is based on formulation of drug resin complex formed when ionic solution is kept in contact with ionic resins. The drug from this complex gets exchanges in gastrointestinal tract and release with excess of Na+ and Clpresent in gastrointestinal tract. This system generally utilize resin compound of insoluble cross linked polymer. They contain salt forming function group is repeating position on a polymer chain.

pH independent formulation

Most of the drug are either weak acid or weak base, the release from sustain release formulation is pH dependent. However buffer such as salt of citric acid, amino acid, tartaric acid can be added to the formulation to help to maintain to constant pH thereby retarding pH independent drug release. A buffer sustain release formulation is prepared by mixing a basic or acidic drug one or more buffering agent, granulating with appropriate excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane the buffering agent adjust the fluid inside to suitable constant pH thereby rendering a constant rate of drug release.

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