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An overview on basic fundamental approach of sustained release dosage form

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Abstract
Sustained release allows the delivery of a specific drug at a programmed rate that results in drug delivery over a longer period of time. Drug release approach is particularly useful for drugs that are metabolized too quickly and are eliminated from the body shortly after administration. For the internal route of administration, oral drug administration remains the best and most convenient for the administration of various drugs. Gradual release is also suitable for overcoming the side effects of the drug and also for increasing the therapeutic efficacy of the drug. A constant dose of a drug within a therapeutic window is beneficial, for example, in the treatment of cancer. When a drug is dissolved in an aqueous body fluid, it can be readily transported with the fluid to target receptors. Some studies have shown that one way to achieve sustained drug release is to prevent the drug molecules from fully entering the aqueous environment for a manageable amount of time. The basic concepts of a sustained drug delivery system optimize various parameters such as biopharmaceutical, pharmacokinetic and pharmacodynamic properties of a drug to maximize therapeutic efficacy.

Keywords: sustained release tablets, therapeutic efficacy, pharmacokinetics, pharmacodynamics

Introduction

1. Sustain Release Drug Delivery System

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. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels as shown in Figure 1.1 and 1.2 [1].

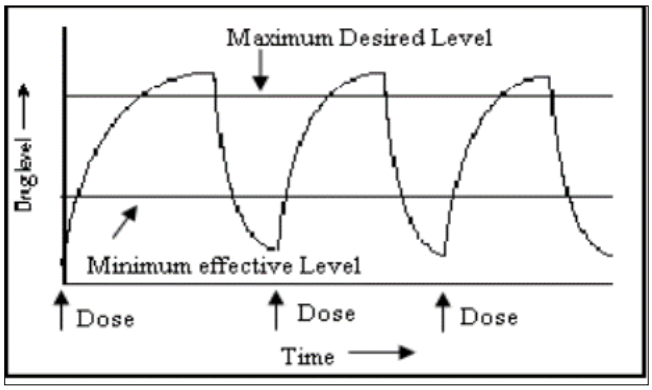


Fig 1: Drug levels in the blood with Conventional drug delivery Systems

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.

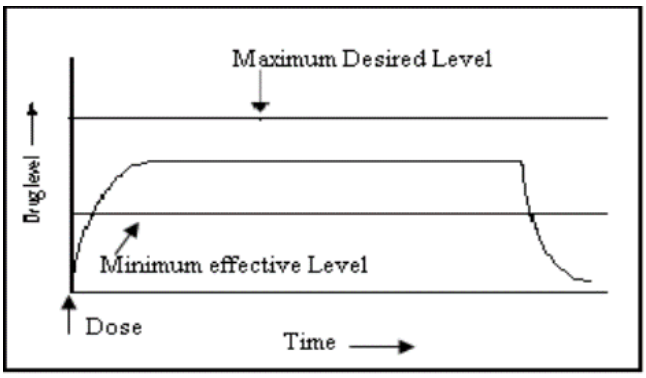
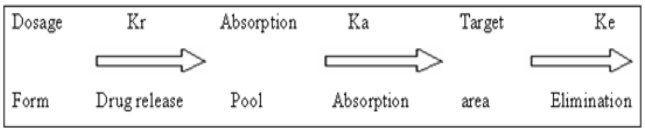


Fig 2: Drug levels in the blood with Controlled drug delivery Systems

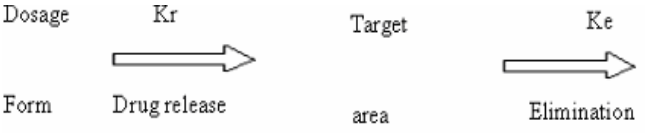
Simple definition of sustained release drug system is "any drug or dosage form modification that prolongs the therapeutic activity of the drug [1, 2]."
Ideally a sustained release oral dosage form is designed to release rapidly some pre determined fraction of the total dose in to GI tract. This fraction (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.

2. Principle of sustained release drug delivery

The conventional dosage forms release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetics scheme.



The absorption pool represents a solution of the drug at the site of absorption, and the term Kr, Ka and Ke are first order rate-constant for drug release, absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that Kr>>>>Ka. Alternatively speaking the absorption of drug across a biological membrane is the rate-limiting step. For non immediate release dosage forms, Kr<<<Ka i.e. the release of drug from the dosage Form is the rate limiting step.
This causes the above kinetic scheme to reduce to the following.



Essentially, the absorptive phase of the kinetic scheme become insignificant Compared to the drug release phase. Thus, the effort to develop a non immediate release delivery system must be directed primarily at altering the release rate [4, 6].

The main objective in designing a sustained release delivery system is to deliver drug at a rate necessary to achieve and maintain a constant drug blood level. This rate should be analogous to that achieved by continuous intravenous infusion where a drug is provided to the patient at a constant rate. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time.

3. Classification of Sustained Release Systems

"OR" The various sustained release polymeric system can be classified depending upon the mechanism controlling the drug release, as follows [8].

Table 1: Various Types of Sustained Release System:

Type of system	Rate-control mechanism
Diffusion controlled Reservoir system Monolithic system	Diffusion through membrane
Water penetration controlled Osmotic system Swelling system	Transport of water through semipermeable membrane Water penetration into glossy polymer
Chemical controlled Monolithic system Pendant system Ion exchange resins	Surface erosion or bulk erosion Hydrolysis of pendent group and diffusion from bulk polymer Exchange of acidic or basic drugs with the ions

3.1 Chemically Controlled System
3.2 Diffusion Controlled Systems
(A) Membrane Reservoir Systems
(B) Matrix Systems: Matrix System can be classified based on mechanism of controlling the drug release as follows:
1. Matrix diffusion
2. Polymer erosion
3. Polymer swelling
4. Geometry factors

3.3 Dissolution Controlled Systems
(A) Encapsulation
(B) Matrix Systems

3.4 Chemically Controlled System
- Bioerosion control
- Drug attached to a polymer backbone
- Drug in a biodegradable core
- Drug dispersed in a bioerodible matrix
- Diffusion controlled
- Erosion controlled
- Regulated Systems
- Release varies with environment
- Externally regulated
- Ultrasound
- Heat
- Magnetic
- Pumps
- Self regulated
- pH changes
- Bonding to specific lectins
- Triggered devices

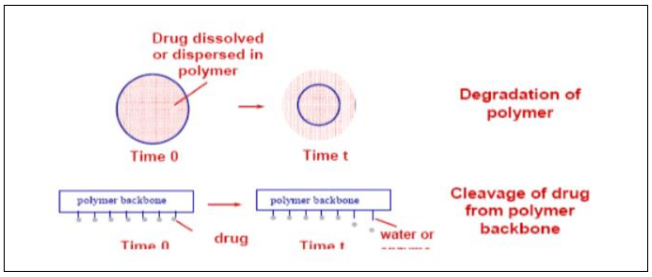


Fig 3: Rate control: Chemical Reaction

3.5 Diffusion Controlled Systems
(A) Membrane Reservoir System
The kinetics of drug release from membrane reservoir systems generally follows either a solution diffusion mechanism or an osmotic pumping mechanism.
In the solution diffusion mechanism, the drug transport occurs by first dissolving in the reservoir membrane at one interface followed by diffusion down a chemical potential gradient across the membrane and eventually released from the second interface into the external medium, such solution diffusion mechanism is typically observed in a non porous membranes.
In the pumping mechanism, a semi permeable membrane is utilized to regulate the osmotic permeation of water/GI fluid. The rate of osmotic water influx and therefore the rate of drug delivery will be constant as long as a constant thermodynamic activity gradient is maintained across the membrane. The delivery rate from such devices is generally regulated by osmotic pressure of the drug core formulation and by the water permeability of the semi permeable membrane [8, 9].

(B) Matrix Systems (Monolithic system or device)
Monolithic (matrix) devices are possibly the most common of the devices for controlling the release of drugs. This is possibly because they are relatively easy to fabricate, compared to reservoir devices, and there is not the danger of

an accidental high dosage that could result from the rupture of the membrane of a reservoir device. In such a device the active agent is present as dispersion within the polymer matrix, and they are typically formed by the compression of a polymer/drug mixture or by dissolution or melting.
The dosage release properties of monolithic devices may be dependent upon the solubility of the drug in the polymer matrix or, in the case of porous matrixes, the solubility in the sink solution within the particle's pore network, and also the tortuosity of the network (to a greater extent than the permeability of the film), dependent on whether the drug is dispersed in the polymer or dissolved in the polymer [11,12].
• Diffusion controlled by Fick's law.

$$J = -D\frac{dC_m}{dx}$$

Where,
J = flux of the drug across a membrane in the direction of decreasing conc.
D = Diffusion coefficient of the drug, and
dCm /dx = Change in the concentration of the drug in the membrane.

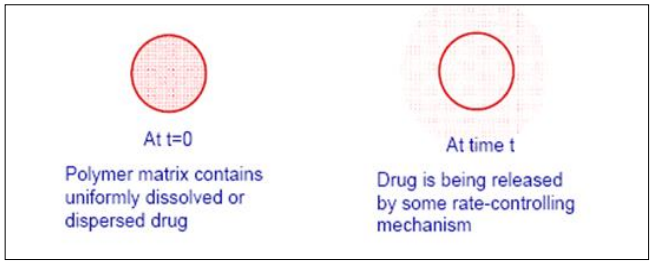


Fig 4: Rate Control: Matrix System

Matrix System can be classified based on mechanism of controlling the drug release as follows:

(a) Matrix diffusion
Historically, the most popular diffusion controlled delivery system has been the matrix system. However, the inherent drawback of the matrix system is its first order release behavior with continuously diminishing release rate. This is a result of the increasing diffusional resistance and decreasing area at the penetrating diffusion front.
The kinetics of drug release from homogenous dispersed drug matrix devices (which act as a diffusional medium) can be given by T. Higuchi's as equation.

$Q = [DT (2A-C_S) C_S]_1^{/2}$

Where,
Q = amount of drug released after time t
D= Diffusivity of the drug in the homogenous matrix media
C_S= the solubility of the drug in the matrix substance
A= surface area of the drug particle

(b) Polymer erosion
The release of a dissolved drug or dispersed drug from an erodible polymer matrix can be controlled by a variety of mechanism ranging from hydrolysis/enzymatic cleavage to swelling and dissolution the situation where polymer erodes by a purely heterogeneous process, viz. surface erosion, is of special interest because the drug release from such devices having constant geometry will be a constant rate.

(c) Polymer swelling
Swelling phenomena are generally encountered in both the hydrophilic and hydrophobic polymer matrices during the release of entrapped water soluble drug in an aqueous environment.

(d) Geometry factors
To overcome the inherent first order release behavior with continuously diminishing release rate from matrix system, geometry system have been utilized to compensate for the increasing diffusional distance and decreasing area at theenetrating diffusion front generally encountered in matrix systems [13].

Mechanisms of Drug Release from Matrix Systems
The release of drug from controlled devices is via dissolution or diffusion or a combination of the two mechanisms.

3.6 Dissolution Controlled Systems
A drug with slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by the rate of dissolution. In principle, it would seem possible to prepare extended release products by decreasing the dissolution rate of drugs that are highly water-soluble. This can be done by:

- Preparing an appropriate salt or derivative.
- Coating the drug with a slowly dissolving material – encapsulation dissolution control.
- Incorporating the drug into a tablet with a slowly dissolving carrier – matrix dissolution control (a major disadvantage is that the drug release rate continuously decreases with time).

The dissolution process 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.
The dissolution process at steady-state is described by the Noyes-Whitney equation:

$$\frac{dC}{dt} = \frac{DA(C_s - C)}{h}$$

Where, dC / dt = dissolution rate
D = the dissolution rate constant (equivalent to the diffusion coefficient divided by the thickness of the diffusion layer D/h)
Co = saturation solubility of the solid
C = concentration of solute in the bulk solution
A = Surface area
h = Diffusion layer thickness
Equation predicts that the rate of release can be constant only if the following parameters are held constant:

- Surface area
- Diffusion coefficient
- Diffusion layer thickness
- Concentration difference.

These parameters, however, are not easily maintained constant, especially surface area, and this is the case for combination diffusion and dissolution systems[14,15].

3.7 Diffusion controlled systems

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier. Usually, this barrier is an insoluble polymer. In general, two types or subclasses of diffusional systems are recognized: reservoir devices and matrix devices. It is very common for the diffusion-controlled devices to exhibit a non-zero order release rate due to an increase in diffusional resistance and a decrease in effective diffusion area as the release proceeds.

In a hydrophilic matrix, there are two competing mechanisms involved in the drug release: Fickian diffusional release and relaxation release. Diffusion is not the only pathway by which a drug is released from the matrix; the erosion of the matrix following polymer relaxation contributes to the overall release. The relative contribution of each component to the total release is primarily dependent on the properties of a given drug [14].

For example, the release of a sparingly soluble drug from hydrophilic matrices involves the simultaneous absorption of water and desorption of drug via a swelling-controlled diffusion mechanism. As water penetrates into a glassy polymeric matrix, the polymer swells and its glass transition temperature is lowered. At the same time, the dissolved drug diffuses through this swollen rubbery region into the external releasing medium.

This type of diffusion and swelling does not generally follow a Fickian diffusion Mechanism. The semi-empirical equation to describe drug release behavior from hydrophilic matrix systems.

$$Q = k\,t^{n} \ldots\ldots\ldots\ldots\ldots\ldots \quad (2.4)$$

Where,

Q = fraction of drug released in time t,

k = rate constant incorporating characteristics of the macromolecular network system and the drug

n = the diffusional exponent. It has been shown that the value of n is indicative of the drug release mechanism.

For n=0.5, drug release follows a Fickian diffusion mechanism that is driven by a chemical potential gradient. For n=1 drug release occurs via the relaxational transport that is associated with stresses and phase transition in hydrated polymers. For 0.5<n<1 non-Fickian diffusion is often observed as a result of the contributions from diffusion and polymer erosion [24].

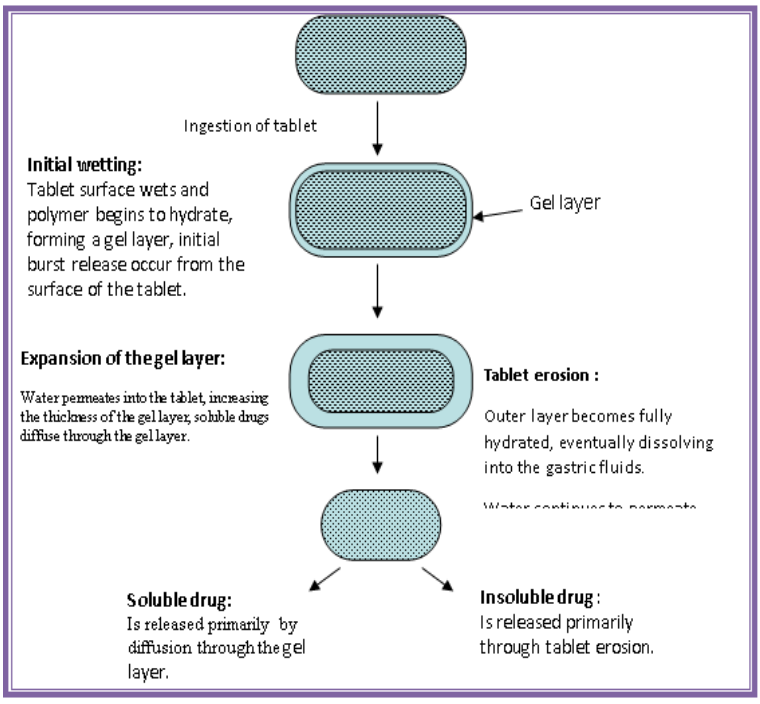


Fig 5: Drug Release from Hydrophilic Matrix Tablet

The hydrophilic polymers can be arranged into three broad categories

(A) Non-cellulose Natural or Semi Synthetic Polymer

These are products of vegetable origin and are generally used as such. Agar, alginate, guar gum, chitosan, modified starches, are commonly used polymer.

(B) Polymers of Acrylic Acid

These are arranged in carbomer group and commercialized under the name of carbopol. The major disadvantage of this type of polymer is its pH dependent gelling characteristics.

(C) Cellulose Ether

This group of semi-synthetic cellulose derivatives is the most widely used group of polymer. Non-ionic such as Hydroxypropylmethylcellulose (HPMC) of different viscosity grades are widely used group of polymers. Non-ionic such as HPMC of different viscosity grades is widely used.

4. Bioerodible and Combination of Diffusion and Dissolution Systems

Strictly speaking, therapeutic systems will never be dependent on dissolution or diffusion only. In practice, the dominant mechanism for release will overshadow other processes enough to allow classification as either dissolution rate-limited or diffusion-controlled release.

As a further complication these systems can combine diffusion and dissolution of both the drug and the matrix material. Drugs not only can diffuse out of the dosage form,

as with some previously described matrix systems, but also the matrix itself undergoes a dissolution process. The complexity of the system arises from the fact that as the polymer dissolves the diffusional path length for the drug may change. This usually results in a moving boundary diffusion system. Zero-order release is possible only if surface erosion occurs and surface area does not change with time.

This system usually minimizes burst effects, as rapid polymer swelling occurs before drug release With regards to swellable matrix systems, different models have been proposed to describe the diffusion, swelling and dissolution processes involved in the drug release mechanism. However the key element of the drug release mechanism is the forming of a gel layer around the matrix, capable of preventing matrix disintegration and further
rapid water penetration [15, 17].

The result is an anomalous non-Fickian transport of the drug, owing to the polymer-chain relaxation behind the swelling position. This, in turn, creates osmotic stresses and convective transport effects.The gel strength is important in the matrix performance and is controlled by the concentration, viscosity and chemical structure of the rubbery polymer. This restricts the suitability of the hydrophilic polymers for preparation of swellable matrices. Polymers such as carboxymethyl cellulose, hydroxypropyl cellulose or tragacanth gum, do not form the gel layer quickly. Consequently, they are not recommended as excipients to be used alone in swellable matrices.

5. Factors influencing

5.1 Factor Influencing Oral Sustained Release Dosage form Design

5.1.1 Biological Factor

A. Biological half-life

Therapeutic compounds with short half-lives are excellent candidates for sustained-release preparations, since this can reduce dosing frequency.

B. Absorption

The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. If a drug is absorbed by active transport, or transport is limited to a specific region of the intestine, sustained-release preparations may be disadvantageous to absorptions.

C. Metabolism

Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during a specific period, allowing more complete conversion of the drug to its metabolite.

D. Dosage form Index

It is defined as the ratio of $C_{ss,max}$ to $C_{ss,min}$. Since the goal of controlled release formulation is to improve therapy by reducing the dosage form index while maintaining the plasma drug levels within the therapeutic window, ideally its value should be as close to one as possible [24].

5.1.2 Physicochemical Factors

A. Dose Size

In general, single dose of 0.5 – 1.0 g is considered maximal for a conventional dosage form. This also holds true for sustained-release dosage forms. Another consideration is the margin of safety involved in administration of large amounts of drug with a narrow therapeutic range.

B. Ionization, pKa and Aqueous Solubility

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pKa of the compound and the absorptive environment. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of drug in the aqueous media. For dissolution or diffusion sustaining forms, much of the drug will arrive in the small intestine in solid form, meaning that the solubility of the drug may change several orders of magnitude during its release. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1 mg/ml.

C. Partition Coefficient

Compounds with a relatively high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility. Furthermore these compounds can usually persist in the body for long periods, because they can localize in the lipid membranes of cells.

D. Stability

Orally administered drugs can be subjected to both acid-base hydrolysis and enzymatic degradation. For drugs that are unstable in the stomach, systems that prolong delivery over the entire course of transit in the GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form [14, 23].

5.2 Factors Influencing *In Vivo* Performance of Sustained Release Dosage Formulations

There are various factors that can influence the performance of a sustained release product. The physiological, biochemical, and pharmacological factors listed below can complicate the evaluation of the suitability of a sustained release dosage formulation.

A. Physiological

- Prolonged drug absorption
- Variability in GI emptying and motility
- Gastrointestinal blood flow
- Influence of feeding on drug absorption

B. Pharmacokinetic/ Biochemical

- Dose dumping
- First- pass metabolism
- Variability in urinary pH; effect on drug elimination
- Enzyme induction/ inhibition upon multiple dosing

C. Pharmacological

- Changes in drug effect upon multiple dosing
- Sensitization/ tolerance

Drug Selection for Oral Sustained Release Drug Delivery Systems

The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug form the Gastro Intestinal (G. I.) tract, the general absorbability, the drug's molecular weight, solubility at different pH and apparent partition coefficient [20].

Table 2: 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

The pharmacokinetic evaluation requires knowledge on a drug's elimination half- life, total clearance, absolute bioavailability, possible first- pass effect, and the desired steady concentrations for peak and trough.

Table 3: Pharmacokinetic Parameters for Drug Selection

Parameter	Comment
Elimination half life	Preferably between 5 and 11 h
Total clearance	Should not be dose dependent
Elimination rate constant	Required for design
Apparent volume of distribution V_d	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 conc. Css av.	The lower Css av and smaller V_d, the loss among of drug required

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Conflict of interest

The Author declare no conflict of interest

Author contribution

Priyanka designed the work and Dr. Gaurav Bhaduka and Dr. Dilip Agrawal necessary correction made and revises in the manuscript.

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