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Review Article

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A Detailed Review on Sustained Release Drug Delivery System

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ABSTRACT

Now a days 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. An appropriately designated controlled release drug delivery system can be are major advance toward solving problems concerning targeting of a drug to a specific organ or a tissue and controlling the rate of a drug delivery to the target site. Developing oral sustained release matrix tablet with constant release rate has always been a challenge to the pharmaceutical technologist. Most of drugs, if not formulated properly, may readily release the drug at a faster rate, and are likely to produce toxic concentration of the drug on oral administration. The basic rationale of sustained release drug delivery system optimizes the biopharmaceutical, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximized, side-effects are reduced and cure of the disease is achieved. There are several advantages of sustained release drug delivery over conventional dosage forms like improved patient compliance due to less frequent drug administration, reduction of fluctuation in steady-state drug levels, maximum utilization of the drug, increased safety margin of potent drug, reduction in healthcare costs through improved therapy and shorter treatment period. This article contains the basic information regarding sustained-release formulation and also the different types of the same.

Key words: Sustained-release, Conventional tablet, Oral Sustained release Matrix tablet, Target site.

INTRODUCTION

Introduction to Drug Delivery

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily. In fact, the development of a pharmaceutical product for oral delivery, irrespective of its physical form involves varying extents of optimization of dosage form characteristics within the inherent constraints of GI physiology. Therefore a fundamental understanding of various disciplines, including GI physiology, pharmacokinetics, pharmacodynamic and formulation design are essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form. The more sophisticated a delivery system, the greater is the complexity of these various disciplines involved in the design and optimization of the system. In any case, the scientific framework required for the successful development of an oral drug delivery system consists of a basic understanding of the following three aspects:

A. Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug.
B. The anatomic and physiologic characteristics of the GIT,
C. Physicochemical characteristics and the drug delivery mode of the dosage form to be designed [1]

Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed, for sustained-release systems, the oral route of administration has by far received the most attention with respect to research on physiological and drug constraints as well as design and testing of products. This is because there is more flexibility in dosage form design for the oral route than there is for the parenteral route [2]. Over the past 30 years, as the expense and complications involved in marketing new drugs entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. There are several reasons for the attractiveness of these dosage forms. The goal in designing sustained or controlled-delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery [3]. The enormous problem of patient compliance as well as the therapeutic desirability of controlled tissue drug levels over the time course of therapy is sufficiently compelling reasons to warrant placement of drugs in a sustained form of drug delivery [4]. In the past, many of the terms used to refer to therapeutic systems of controlled and sustained release have been used in an inconsistent and confusing manner [4]. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot, and repository dosage forms are terms used to identify 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 a single dose [5].

Various Terminologies for controlled drug delivery [6-10]

The conventional dosage forms are immediate release type. Non-immediate release delivery systems may be divided conveniently into three categories:

1 Delayed Release
2 Sustained Release
  a. Controlled Release
  b. Prolonged Release
3 Site-specific and Receptor release
  a. Organ targeting
  b. Cellular targeting
  c. Sub cellular targeting

1. 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. Examples of delayed release system include repeat

action tablets and capsules. A delayed release dosage form does not produce or maintain uniform drug blood levels within the therapeutic range.

2. Sustained Release System

It includes any drug delivery system that achieves slow release of drug over an extended period of time.

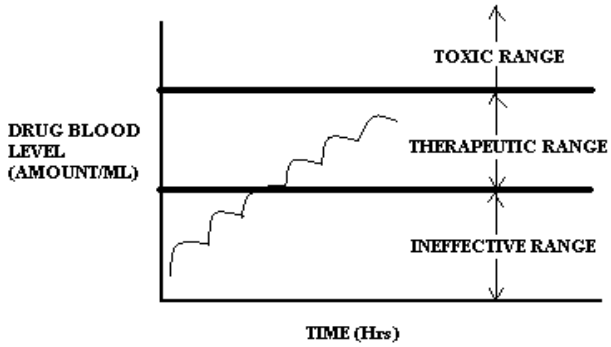


Figure 1: Typical drug blood level time profiles for delayed release drug delivery by repeat action dosage form.

Controlled Release System

If the system is successful at maintaining constant drug level in the blood or target tissues, it is considered as a controlled release system.

Prolonged Release System

If without maintaining constant level, the duration of action is extended over that achieved by conventional delivery; it is considered as a prolonged release system. This is illustrated in Figure.2.

3. Site-Specific and Receptor Release

It refers to targeting of a drug directly to a certain biological location. In the case of site-specific release, the target is a certain organ or tissue, while for receptor release; the target is the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspects of drug delivery.

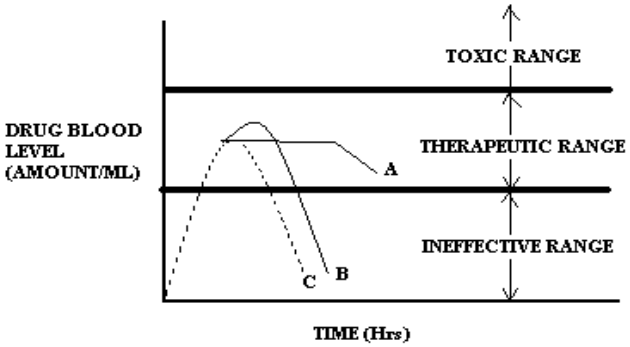
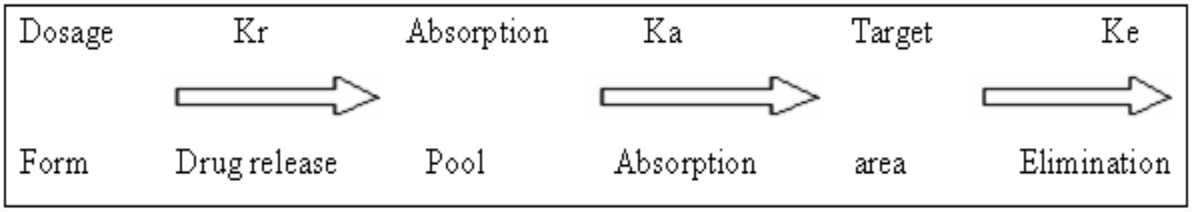


Figure 2: Drug blood level time profile showing the relationship between controlled release-(a), prolonged release-(b), and conventional release-(c)

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 kinetic 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. 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. 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. It means that the drug release from the dosage form should follows zero-order kinetics, as shown by the following equation:

Kr° = Rate In = Rate Out = Ke Cd Vd

Where, Kr°: Zero-order rate constant for drug release-Amount/time
Ke: First-order rate constant for overall drug elimination-time-1
Cd: Desired drug level in the body – Amount/volume, and
Vd: Volume space in which the drug is distributed-Liters

Classification of Sustained/Controlled Release Systems [11]

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 semi permeable 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 present on resins.
Regulated system Magnetic, Ultrasound	External application of magnetic field or ultrasound to device

The value of Ke, Cd and Vd are obtained from appropriately designed single dose pharmacokinetic study. The equation can be used to calculate the zero order release rate constant. For many drugs, however, more complex elimination kinetics and other factors affecting their disposition are involved. This in turn affects the nature of the release kinetics necessary to maintain a constant drug blood level.

It is important to recognize that while zero-order release may be desirable theoretically, non zero-order release may be equivalent clinically to constant release in many cases. Sustained-release systems include any drug-delivery system that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this is of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered a controlled-release system.

Sustained Release Preparations

These preparations provide an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific extended period of time. The major advantage of this category is that, in addition to the convenience of reduced frequency of administration, it provides blood levels that are devoid of the peak-and-valley effect which are characteristic of the conventional intermittent dosage regimen [4]. Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action [11].

Advantages of Sustained Release Products:

An ideal oral controlled drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled release delivery systems provide a uniform concentration of the drug at the absorption site and thus, after absorption, allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration. These formulations release active drug compounds into the body gradually and predictably over a 12 to 24 hour period.
As sustained release dosage forms are often more expensive than conventional formulations, these cannot be justified unless they offer some clinical or practical advantages. Some of the advantages offered by oral sustained release and controlled release drug delivery systems are as follows [12].

- Decrease incidence and/or intensity of adverse effects and toxicity.
- Predictable and reproducible release rates for extended duration.
- Maintenance of optimum therapeutic drug concentration in the blood with minimum fluctuations.
- Delivery of drug in the vicinity of site of action.
- More efficient utilization of active agent.
- Improved patient compliance.
- Elimination of frequent dosing and wastage of drug, inconvenience of nighttime administration of drug.
- A greater selectivity of pharmacological activity.
- Reduction in GI irritation and other dose- related side effects.
- Enhanced bioavailability.
- Reduction of the incidences and degree of toxic and side effects and irritation of gastro intestinal tract caused by some orally administrated drugs.
- Greater effectiveness in treatment of chronic conditions.
- Enhanced duration of activity for short half-life drugs.

Disadvantages of Sustained Release Products:

Ordinarily, oral sustained release drug release dosage forms should not be developed unless the recommended dosage interval for the sustained release dosage form is longer than that for immediate release dosage form or unless significant clinical advantages of the sustained release dosage form can be justified like the decreased side effects resulting from a lower Cmax with the sustained release form as compared to the immediate release of conventional dosage form [13].
Some of the disadvantages of oral sustained release dosage forms are as follows,

- Toxicity due to dose dumping.
- Increased cost.
- Unpredictable and often poor *in vitro- in vivo* correlation.
- Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).

- Local irritation or damage of epithelial lining (lodging of dosage forms). Need for additional patient education and counseling.
- Increased potential for first- pass clearance.

Fabrication of Oral Sustained Release Products: [14]

1. Increasing particle size of the drug in dosage form:

To increase the particle size the surface to volume ratio is decreased as per the following equation:

$$R = \frac{(C_{1\ 2/3}\ \pi^{1/3})\ (D\ C_1)\ W^{2/3})}{P^{2/3}\ d}$$

Where,
R = rate of drug release.
C = Concentration driving the diffusion process.
D = Specific constant concerned with the ability and speed with which the drug move to be considered free of the dosage form.
π = Density of the drug pellet.
W = Weight of the drug pellet.
d = Distance through which drug moves from dosage form to the depot.

1. Embedding the drug in a matrix:

The matrix is a uniform dispersion of a drug in a solid which is less soluble than the drug in the depot fluid. The external phase in a matrix is usually a hydrophobic material embedding the drug. Matrices are of two types:

A. Slowly eroding matrix:

In this matrix system the active ingredients are either dissolved or suspended in a mixture of melted fats and waxes such as bees wax, carnauba wax, hydrated fats, synthetic waxes, butyl stearate, stearic acid, castor oil etc. The melt is either dispersed by spray congealing or the solidified drug vehicle mass is milled. These granules/ particles can be formulated into sustained release capsules, multilayer tablets, core coated tablets etc.

B. Embedment in plastic matrix:

The skeleton types of preparations are made by granulating active ingredients with inert plastic materials such as polymers. The liberation of the active ingredient from the dosage form is by leaching of the drug from the inert plastic skeleton or matrix.

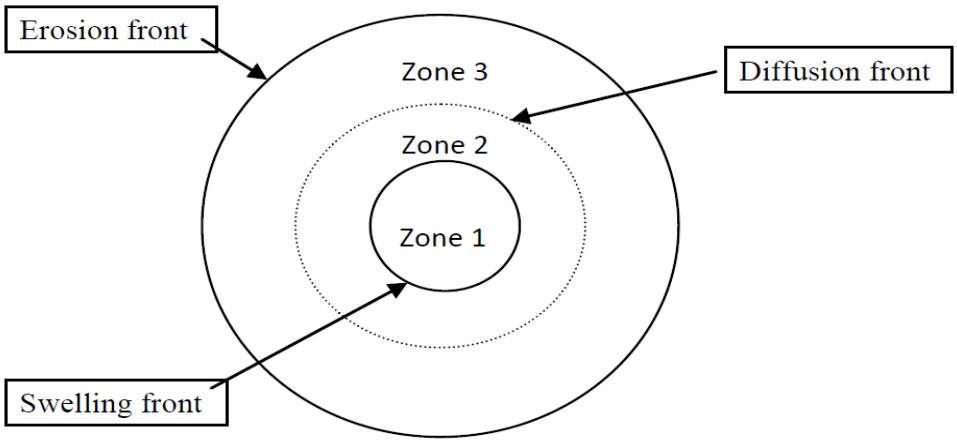


Figure 3: Matrix diffusion controlled drug delivery system

Zone 1: Undissolved drug, glassy polymer layer.
Zone 2: Undissolved drug, gel layer.
Gel layer thickness = Difference between erosion and swelling front position.

Introduction to Matrix Dosage Form [15-17]

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

Introduction to Hydrophilic Matrix Tablet

A matrix tablet is a compressed dosage form containing an active ingredient, matrix agent plus fillers, lubricants and excipients. Matrix systems are highly resistant to release inconsistencies and drug "dumping". A hydrophilic matrix controlled release system is relatively easy to formulate and equally important, easy to produce. At the same time, other soluble excipients or drugs will also wet, dissolve, and diffuse out of the matrix while insoluble materials will be held in place until the surrounding polymer/excipient/drug complex erodes or dissolves away. The mechanisms by which drug release is controlled in matrix tablets are dependent on many variables. The main principle is that the water-soluble polymer, present throughout the tablet, hydrates on the outer tablet surface to form a gel layer **(**Fig. 4**)**.

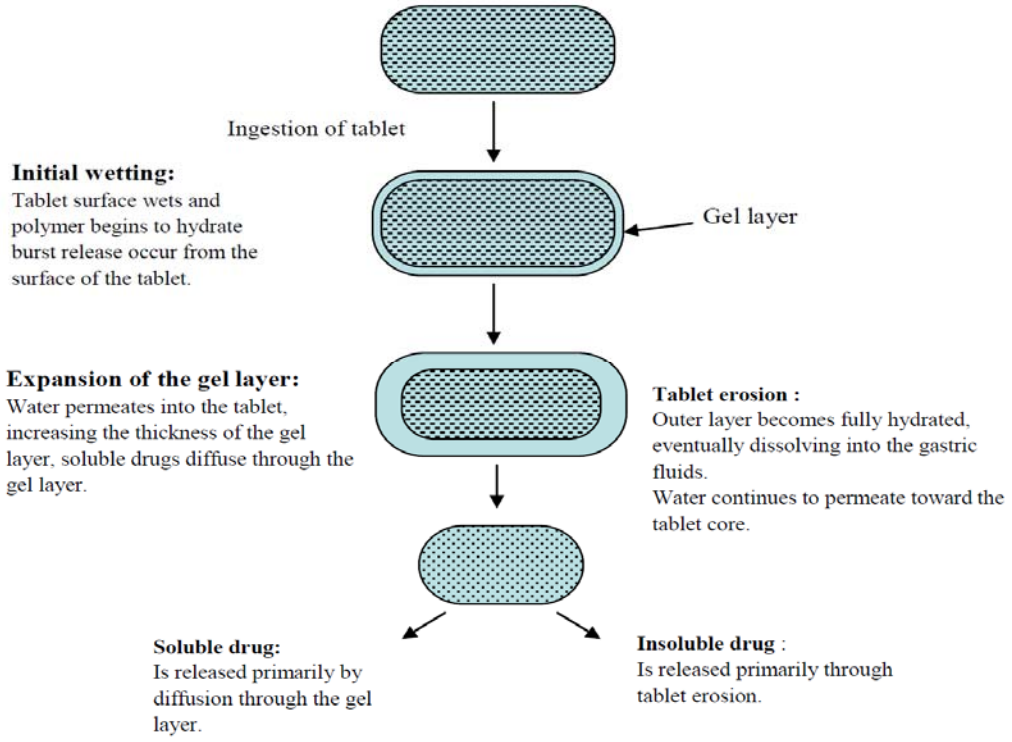


Figure 4: Drug release from hydrophilic matrix tablet

Throughout the life of the ingested tablet, the rate of drug release is determined by diffusion (if soluble) through the gel and by the rate of tablet erosion. With soluble drugs, the primary release mechanism is by diffusion through the gel layer. With insoluble drugs, the primary mechanism is by the tablet surface erosion.

As increasing viscosity of the polymer yields slower drug release as a stronger more viscous gel layer is formed, providing a greater barrier to diffusion and slower attrition of the tablet, with insoluble drugs. The fine tuning of modified release systems may be achieved by blending of different viscosity grades of polymer where the desired dissolution rate is not obtained with a single polymer.

A fast rate of hydration followed by quick gelation and polymer/polymer coalescing is necessary for a rate-controlling polymer to form a protective gelatinous layer around the matrix. This prevents the tablet from immediately disintegrating, resulting in premature drug release. Fast polymer hydration and gel layer formation are particularly critical when formulating with water-soluble drugs and water-soluble excipients. Hydrophilic matrix tablet using HPMC were prepared and evaluated by Sunada et al. They found that the type and amount of HPMC could affect the release rates as well as kinetics from the swellable matrices. Several investigators investigated the drug release rates and release kinetics from carbomer matrix tablets. Tablets exhibiting zero-order release mechanisms could be obtained at several different levels of concentration of different carbomers, such as Carbopol 934P, 971P and 974P. The results indicated that drug release from the carbomer matrix tablets could occur, both by diffusion through low microviscosity pores and by a swelling-controlled mechanism. As the amount of the carbomers in their respective formulations increased, drug release rate decreased and the release mechanism gradually changed from anomalous type of release to the Case II transport mechanism. Other factors responsible for the reduction in the number and/or size of low microviscosity pores, such as higher pH that increased polymer swelling and decreased drug release, tended to shift the release profiles towards the swelling controlled, Case II type release mechanism.

Advantages of Hydrophilic Matrix Tablets

With proper control of manufacturing process, reproducible release profiles are possible. They variability associated with them is slightly less than that characterizing coated release forms. Their capacity to incorporate active principles is large, which suits them to delivery of large doses.

Disadvantages of Hydrophilic Matrix Tablet

For a hydrophilic sustained release matrix tablet, in which the release is mainly controlled by erosion of the swollen polymer gel barrier at the tablet surface, the presence of food may block the pores of the matrix and inhibit the drug release rate. 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.

Evaluation of Sustained Release Formulation: [18]

In-vitro Data:

The data is generated in a well-designed reproducible *in-vitro* test such as dissolution test. The method should be sensitive enough for discriminating any change in formulation parameters. The key elements for dissolution are-

- Reproducibility of the method.
- Proper choice of media.
- Maintenance of sink condition.
- Control of solution hydrodynamics.
- Selection of the most discriminating variables (media, pH, rotation speed etc.) as the basis for dissolution test and specification.

In-vivo Data:

This data consists of the following:

- Pharmacokinetic profile of the test product and reference product.
- Bioavailability data-either comparable to the reference dosage form with same labeling indications and same effects or non-equivalent to the reference dosage form with demonstration of safety and efficacy and different labeling.
- Evidence of reproducible *in-vivo* performance.

CONCLUSION

From this above discussion, it can be easily conclude that development of sustained release dosage form which will prolong the drug release leading to minimize the peak and valley effect in plasma and provide patients compliance. More over all these comes with reasonable cost. The drug releases with time irrespective of concentration. On the other hand, sustained release implies slow release of the drug over time period. It may or may not be controlled release. The dosage form is easy to optimize and very helpful in case of the antibiotics in which irrational use of the same may result in resistance.

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