



## ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEM: AN OVERVIEW

Chugh Isha<sup>1\*</sup>, Seth Nimrata<sup>1</sup>, Rana A.C.<sup>2</sup>, Gupta Surbhi<sup>1</sup>

<sup>1</sup>Rayat Institute of Pharmacy, Department of Pharmaceutics, Ropar, S.B.S Nagar-144533 (Punjab) India

<sup>2</sup>Rayat Institute of Pharmacy, Department of Pharmacology, Ropar, S.B.S Nagar- 144533 (Punjab) India

Article Received on: 19/04/12 Revised on: 30/04/12 Approved for publication: 20/05/12

\*E mail: ishachugh87@gmail.com

### ABSTRACT

In the recent years, focus on the development of oral controlled release drug delivery systems has increased. Oral ingestion has 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. Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. Sustained release of drugs in gastrointestinal tract following oral administration is not affected by the absorption process. Here this article concentrates on preparations, factors influencing, design, formulation, and the evaluation of oral sustained release preparations. The principal goal of sustained release dosage forms is the improvement of drug therapy assessed by the relationship between advantages and disadvantages of the use of sustained release systems.

**Key words:** Controlled drug delivery system, Sustained release preparations, Factors influencing, Oral route of administration, Pre-determined rate

### INTRODUCTION

If one were to imagine the ideal drug delivery system, two prerequisites would be required. First, it would be a single dose for the duration of treatment, whether it be for days or weeks, as with infection, or for the lifetime of the patient, as in hypertension or diabetes. Second, it should deliver the active entity directly to the site of action, thereby minimizing or eliminating side effects. This may necessitate delivery to specific receptors, or to localization to cells or to specific areas of the body. In the past decade great interest got generated on replacing conventional administration of drugs by novel delivery systems which would release effective quantities from a protected supply at a controlled rate over a long period of time. Ideally a drug to provide desired therapeutic action should arrive rapidly at the site of action (receptor) in optimum concentration, remain there for desired time, spare other sites and get removed from the site. One of the interesting results of pharmaceutical research is the fact that absorption rate of a drug can be decreased by reducing its rate of release from the dosage form. The products so formulated are designated as sustained action, sustained release, delayed action, prolonged action, depot, repository, retarded release and timed release medication<sup>1,2</sup>.

### ORAL ROUTE AS THE MOST CONVENIENT ROUTE<sup>3,4,5</sup>

Oral ingestion has 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. The reason 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 well absorbed as the food stuffs that are ingested daily. In fact, the development of pharmaceutical product for oral delivery, irrespective of its physical form involves varying extent of optimization of dosage form characteristics within the inherent constraints of GI physiology. Therefore the fundamental understanding of

various disciplines, including GI physiology, pharmacokinetics, pharmacodynamics 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:

1. Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug.
2. The anatomic and the physiologic characteristics of the GIT.
3. Physicochemical characteristics and drug delivery mode of the dosage form to be designed.

### The goal in designing sustained or controlled delivery system is to<sup>4,5</sup>

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of novel drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery system. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exists. The effectiveness of these drugs however is often limited by side effects or the necessity to administer the compound in a clinical setting. The major goal set in designing sustained or controlled delivery is to:

- Reduce the frequency of dosing.
- Increase effectiveness of the drug by localization at the site of action.
- Reducing the dose required.
- Providing the uniform drug delivery.

In the past, many of the terms used to refer therapeutic systems of controlled and sustained release have been used in an inconsistent and confusing manner. Sustained release, sustained action, prolonged action, controlled release (drug release with zero order kinetics) and repository dosage forms

are terms used to identify drug delivery systems that are designed to achieve prolonged therapeutic effects by continuously releasing medication over an extended period of time after administration of a single dose.

#### **MODIFIED-RELEASE DELIVERY SYSTEMS MAY BE DIVIDED CONVENIENTLY IN TO FOUR CATAGORIES<sup>6</sup>**

- Delayed release.
- Sustained release.
- Site-specific targeting.
- Receptor targeting.

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 Preparation<sup>7</sup>**

These preparations may 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 usually 8-12 hrs. 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 characteristics of the conventional intermittent dosage regimen. 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.

#### **Controlled Release Preparations<sup>8</sup>**

Although this term has been interchanged widely with sustained release preparation in the past, recently it has become customary to restrict the latter term to formulations where the mechanism of prolonged action is dependent on one or more of the environmental factors in the GI tract such as pH, enzymes concentration, gastric motility etc. On the other hand, the term controlled release dosage form usually applies to preparations that are designed for all routes of administration and where the mechanism of prolonged action is inherent and determined totally by the delivery system itself. Consequently, this category offers the current state of the art products where the drug release profile is controlled accurately, following zero order kinetics and often can be targeted to a special body site or a particular organ.

#### **Advantages of Sustained Release Products<sup>8</sup>**

1. Decreased local and systemic side effects:
  - Reduced gastrointestinal irritation.
2. Better drug utilization:
  - Minimum drug accumulation on chronic dosing.
3. Improved efficiency in the treatment:
  - More uniform blood concentration.
  - Reduction in fluctuation in drug level and hence more uniform pharmacological response.
4. Improved patient compliance:
  - Less frequent dosing.
  - Reduced night-time dosing.
5. Economy
  - Although the initial unit cost of sustained release products is usually greater than that of the conventional dosage form because of the special nature of these products, the average cost of treatment over an extended time period may be less.

#### **Disadvantages<sup>8</sup>**

1. Dose dumping:
  - Dose dumping may occur with faulty formulations.
2. Need for additional patient education:
  - Patients may need substantial additional information as to the proper use of sustained release products e.g. "Do not crush or chew the dosage unit. Tablet residue may appear in the stools". In some instances, patients must be started on an immediate release product and then switched over to the sustained release products.
3. Possible reduction in systemic availability:
  - Reduced systemic availability has been shown for some sustained release formulations of Theophylline, Procainamide and Vitamin combinations.

#### **BIOLOGICAL FACTORS INFLUENCING ORAL SUSTAINED-RELEASE DOSAGE FORM DESIGN<sup>1</sup>**

##### **1. Biological Half-life**

Drug molecules with short half-life are excellent candidate for sustained-release formulation, since this can reduce dosing frequency. However, this is limited, in that drugs with very short half-lives may require excessive large amounts of drug in each dosage unit to maintain sustained effects, forcing the dosage form itself to become limitingly large. In general drugs with half-lives shorter than 2 hr such as furosemide or levodopa are poor candidates for sustained-release preparations.

##### **2. 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. Compounds that demonstrate the absorption rate constant will probably be poor candidates for sustaining systems. If a drug is absorbed by active transport, or transport is limited to a specific region of intestine, sustained-release preparations may be disadvantageous to absorption.

##### **3. 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.

#### **PHYSIOLOGICAL FACTORS INFLUENCING ORAL SUSTAINED-RELEASE DOSAGE FORMS<sup>1,2</sup>**

##### **1. Dosage Size**

In general, single dose of 500-1000 mg 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.

##### **2. 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 release system has been reported to be 0.1mg/ml.

### 3. Partition Co-efficient

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

### 4. 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 intestine may demonstrate decreased bioavailability when administered from a sustained dosage form.

## DESIGN AND FORMULATION OF ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEM<sup>10,11,12</sup>

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take into consideration, the various pH that the dosage form would encounter during its transit, the gastrointestinal motility, the enzyme system and its influence on the drug and the dosage form. The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood level time profile similar to that after intravenous constant rate infusion (as shown in figure 1, 2 and 3).

### Sustained (zero-order) drug release has been attempted to be achieved with various classes of sustained drug delivery system

1. Diffusion sustained system.

i) Reservoir type.

ii) Matrix type

2. Dissolution sustained system.

i) Reservoir type.

ii) Matrix type

3. Methods using Ion-exchange.

4. Methods using osmotic pressure.

5. pH independent formulations.

6. Altered density formulations.

#### 1. Diffusion Sustained System

Basically diffusion process shows the movement of drug molecules from a region of a higher concentration to one 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.

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

D = diffusion coefficient in area/ time

$\frac{dc}{dx}$  = change of concentration 'c' with distance 'x'

In common form, when a water insoluble membrane encloses a core of drug, it must diffuse through the membrane.

#### The drug release rate $\frac{dm}{dt}$ is given by

$$\frac{dm}{dt} = ADK \frac{C}{L}$$

Where;

A = Area.

K = Partition coefficient of drug between the membrane and drug core.

L = Diffusion path length (i.e. thickness of coat).

$\Delta C$  = Concentration difference across the membrane.

#### i) Reservoir Type

In the system, a water insoluble polymeric material encases a core of drug (Figure 4.). Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media.

#### Characterization

**Description:** Drug core surrounded by polymer membrane which controls release rate.

**Advantages:** Zero order delivery is possible, release rates variable with polymer type.

**Disadvantages:** System must be physically removed from implant sites. Difficult to deliver high molecular weight compound, generally increased cost per dosage unit, potential toxicity if system fails.

#### ii) Matrix Type

A solid drug is dispersed in an insoluble matrix (Figure 5.) and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution.

Higuchi has derived the appropriate equation for drug release for this system:

$$Q = D\epsilon / T [2A - \epsilon Cs] Cst^{1/2}$$

Where;

Q = Weight in gms of drug released per unit area of surface at time t.

D = Diffusion coefficient of drug in the release medium.

$\epsilon$  = Porosity of the matrix.

Cs = Solubility of drug in release medium.

T = Tortuosity of the matrix.

A = Concentration of drug in the tablet, as gm/ ml.

#### Characterization

**Description:** Homogenous dispersion of solid drug in a polymer mixture.

**Advantages:** Easier to produce than reservoir or encapsulated devices, can deliver high molecular weight compounds.

**Disadvantages:** Cannot provide zero order release, removal of remaining matrix is necessary for implanted system.

A third possible diffusional mechanism is the system where a partially soluble membrane encloses a drug core. Dissolution of part of membrane allows for diffusion of the constrained drug through pores in the polymer coat.

#### The release rate can be given by following equation

$$\text{Release rate} = AD / L = [C_1 - C_2]$$

Where;

A = Area.

D = Diffusion coefficient.

C<sub>1</sub> = Drug concentration in the core.

C<sub>2</sub> = Drug concentration in the surrounding medium.

L = Diffusional path length.

Thus diffusion sustained products are based on two approaches the first approach entails placement of the drug in an insoluble matrix of some sort. The eluting medium penetrates the matrix and drug diffuses out of the matrix to the surrounding pool for ultimate absorption. The second approach involves enclosing the drug particle with a polymer coat. In this case the portion of the drug which has dissolved in the polymer coat diffuses through an unstirred film of liquid into the surrounding fluid.

#### 2. Dissolution Sustained Systems

A drug with a slow dissolution rate is inherently sustained and for those drugs with high water solubility, one can decrease dissolution through appropriate salt or derivative formation. These systems are most commonly employed in

the production of enteric coated dosage forms. To protect the stomach from the effects of drugs such as Aspirin, a coating that dissolves in natural or alkaline media is used. This inhibits release of drug from the device until it reaches the higher pH of the intestine. In most cases, enteric coated dosage forms are not truly sustaining in nature, but serve as a useful function in directing release of the drug to a special site. The same approach can be employed for compounds that are degraded by the harsh conditions found in the gastric region.

#### i) Reservoir Type

Drug is coated with a given thickness coating, which is slowly dissolved in the contents of gastrointestinal tract. By alternating layers of drug with the rate controlling coats as shown in figure, a pulsed delivery can be achieved. If the outer layer is quickly releasing bolus dose of the drug, initial levels of the drug in the body can be quickly established with pulsed intervals. Although this is not a true sustained release system, the biological effects can be similar. An alternative method is to administer the drug as group of beads that have coating of different thickness. This is shown in figure. Since the beads have different coating thickness, their release occurs in a progressive manner. Those with the thinnest layers will provide the initial dose. The maintenance of drug levels at late times will be achieved from those with thicker coating. This is the principle of the spansule capsule. Cellulose nitrate phthalate was synthesized and used as an enteric coating agent for acetyl salicylic acid tablets.

#### ii) Matrix Type

The more common type of dissolution sustained dosage form as shown in figure 5. It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion.

#### Two types of dissolution sustained pulsed delivery systems

- Single bead type device with alternating drug and rate-controlling layer.
- Beads containing drug with differing thickness of dissolving coats.

Amongst sustained release formulations, hydrophilic matrix technology is the most widely used drug delivery system due to following advantages:

- Provide desired release profiles for a wide therapeutic drug category, dose and solubility.
- Simple and cost effective manufacturing using existing tableting unit operation equipment.
- Robust formulation.
- Broad regulatory and patient acceptance.
- Ease of drug release modulation through level and choice of polymeric systems and function coatings.

A hydrophilic matrix tablet consists of mixture of drug, polymer and excipients (filler/diluent as well as other excipients) prepared by common tableting equipment. Drug release is controlled by hydrophilic (water swellable) polymer in the matrix. Formulators often choose from a range of hydrophilic polymers, as stand alone or in combination with different polymers for release rate control. Majority of commercially successful hydrophilic matrix tablets are based on HPMC (hydroxy propyl methyl cellulose) due to wide range of chemistries and viscosity ranges to modulate release profiles of different dose / solubility characteristics of active pharmaceutical ingredient.

### 3. Methods Using Ion Exchange

It is based on the formation of drug resin complex formed when a ionic solution is kept in contact with ionic resins. The drug from these complex gets exchanged in gastrointestinal tract and released with excess of  $\text{Na}^+$  and  $\text{Cl}^-$  present in gastrointestinal tract.

- **Anion Exchangers:**  $\text{Resin}^+ - \text{Drug}^- + \text{Cl}^-$  goes to  $\text{Resin}^+ - \text{Cl}^- + \text{Drug}^-$
- **Cation Exchangers:**  $\text{Resin}^- - \text{Drug}^+ + \text{Na}^+$  goes to  $\text{Resin}^- - \text{Na}^+ + \text{Drug}^+$

These systems generally utilize resin compounds of water insoluble cross linked polymer. They contain salt forming functional group in repeating positions on the polymer chain. The rate of drug diffusion out of the resin is sustained by the area of diffusion, diffusional path length and rigidity of the resin which is function of the amount of cross linking agent used to prepare resins. The release rate can be further sustained by coating the drug resin complex by microencapsulation process.

### 4. Methods Using Osmotic Pressure

A semi permeable membrane is placed around a tablet, particle or drug solution that allows transport of water into the tablet with eventual pumping of drug solution out of the tablet through a small delivery aperture in tablet coating.

#### Two types of osmotically sustained systems are

- Type A contains an osmotic core with drug.
- Type B contains the drug in flexible bag with osmotic core surrounding.

### 5. pH- Independent Formulations

The gastrointestinal tract present some unusual features for the oral route of drug administration with relatively brief transit time through the gastrointestinal tract, which constraint the length of prolongation, further the chemical environment throughout the length of gastrointestinal tract is constraint on dosage form design. Since most drugs are either weak acids or weak bases, the release from sustained release formulations is pH dependent. However, buffers such as salts of amino acids, citric acid, phthalic acid phosphoric acid or tartaric acid can be added to the formulation, to help to maintain a constant pH thereby rendering pH independent drug release. A buffered sustained release formulation is prepared by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH thereby rendering a constant rate of drug release e.g. propoxyphene in a buffered sustained release formulation, which significantly increase reproducibility.

### 6. Altered Density Formulations

It is reasonable to expect that unless a delivery system remains in the vicinity of the absorption site until most, if not all of it it would have limited utility. To this end, several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract.

#### High Density Approach

In this approach the density of the pellets must exceed that of normal stomach content and should therefore be at least  $1-4\text{gm/cm}^3$ .

#### Low Density Approach

Globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug for sustained release purpose.

**Evaluation of sustained release formulation<sup>9</sup>**

**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**

Development of oral sustained release oral dosage form which will prolong the drug release leading to minimize the peak and valley effect in plasma and provide patient convenience. The advantages of sustained-release tablets or capsules are that they can often be taken less frequently than instant formulations of the same drug, and that they keep steadier levels of the drug in the bloodstream. By several approaches the residence time of drug delivery system in the gastrointestinal tract can be prolonged. Difference between controlled release and sustain release or sustained release is

that controlled release is perfectly zero order release that is, the drug releases with time irrespective of concentration. On the other hand, sustain release or sustained release implies slow release of the drug over a time period. It may or may not be controlled release.

**REFERENCES**

1. Jantez GM, Robinson JR. Sustained- and Controlled- release drug delivery systems. In: Banker GS, Rhodes CT, editors. Modern pharmaceuticals. 3<sup>rd</sup> ed. New York: Marcel Dekker Inc; 1996.
2. Popli H, Sharma SN. Trends in oral sustained-release formulations-I The Eastern Pharmacist 1989; 32: p.99-103.
3. Hui HW, Robinson JR, Lee VHL. Design and fabrication of oral controlled release drug delivery systems. In: Robinson JR, Lee V, editors. Controlled drug delivery fundamentals and applications. 2<sup>nd</sup> ed. New York: Marcel Dekker Inc; 1987.
4. Chien YW. Novel drug delivery systems. 2<sup>nd</sup> ed. New York: Marcel Dekker Inc; 1992.
5. Lachman L, Lieberman HA, Kanig JL, editors. The theory and practice of industrial pharmacy. 3<sup>rd</sup> ed. Bombay: Varghese Publishing House; 1987.
6. Lee TWY, Robinson JR. Controlled-release drug-delivery systems. In: Gennaro AR, editor. Remington: the science and practice of pharmacy. 20<sup>th</sup> ed. Easton, Pennsylvania: Mac Publishing Company; 2001.
7. Pandey VP, Manawalan R, Rajan TS, Ganesh KS. Formulation and release characteristics of sustained release Diltiazem hydrochloride tablets. Ind. J. pharm. Sci. 2003; 65(1): p. 44-48.
8. Gudsoorkar VR, Rambhau D. sustained release of drugs. The Eastern Pharmacist 1993; 36 (429): p. 17-22.
9. Gudsoorkar VR, Rambhau D. sustained release of drugs. The Eastern Pharmacist 1994; 37(433): p. 87-90.
10. D. M. Brahmanekar & Sunil B. Jaishwal, "Controlled release medication" chapter 15th in "Biopharmaceutics and Pharmacokinetics – A Treatise, 1st edition, Vallabh Prakashan: 347-353pp.
11. Rane Manish, Parmar Jayesh, Siahboomi Ali Rajabi. Hydrophilic Matrices for Oral Extended Release: Influence of Fillers on Drug Release from HPMC Matrices. Pharma Times - Vol 42 - No. 04 - April 2010.
12. Kumar K. P. Sampath, Bhowmik Debjit, Tripath K. K. Innovations in Sustained Release Drug Delivery System and Its Market Opportunities. Journal of Chemical and Pharmaceutical Research, J. Chem. Pharm. Res., 2010, 2(1): 349-360.

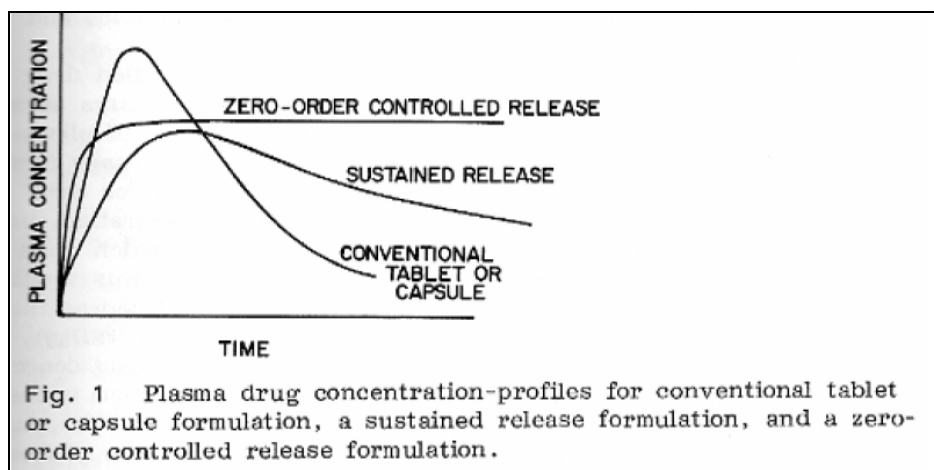


Figure 1. Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero order sustained release formulation.

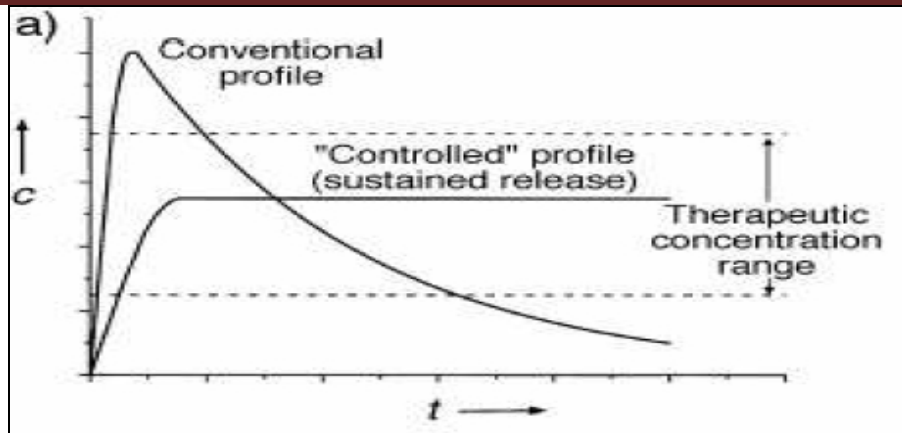


Figure 2. Comparison of Conventional and Controlled Release Profiles

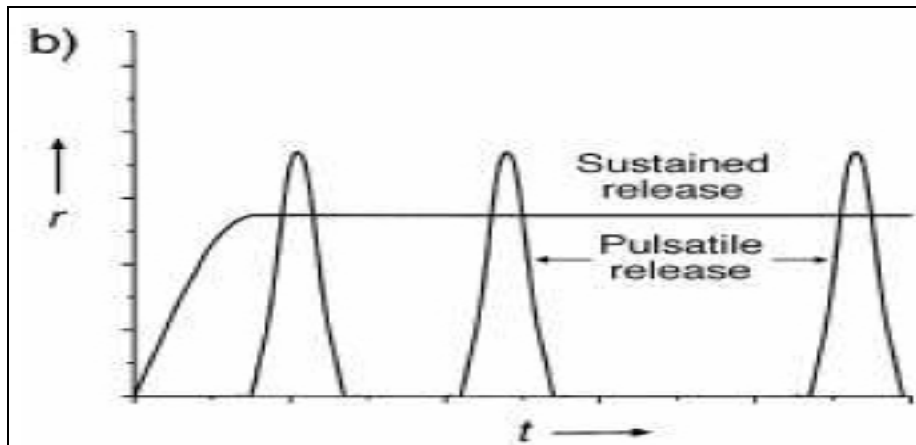


Figure 3. Dosage Regime for Conventional and Controlled Release Systems.

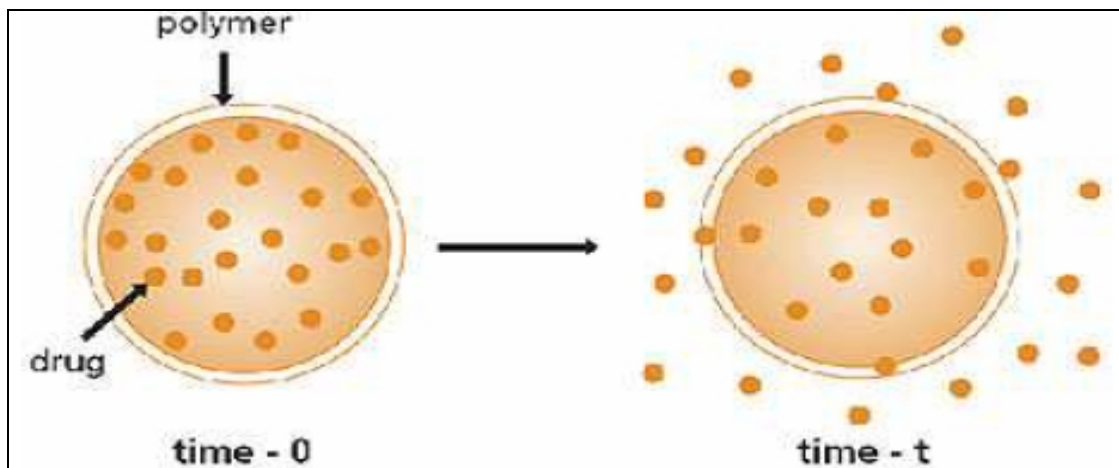


Figure 4. Schematic representation of diffusion sustained drug release: Reservoir system

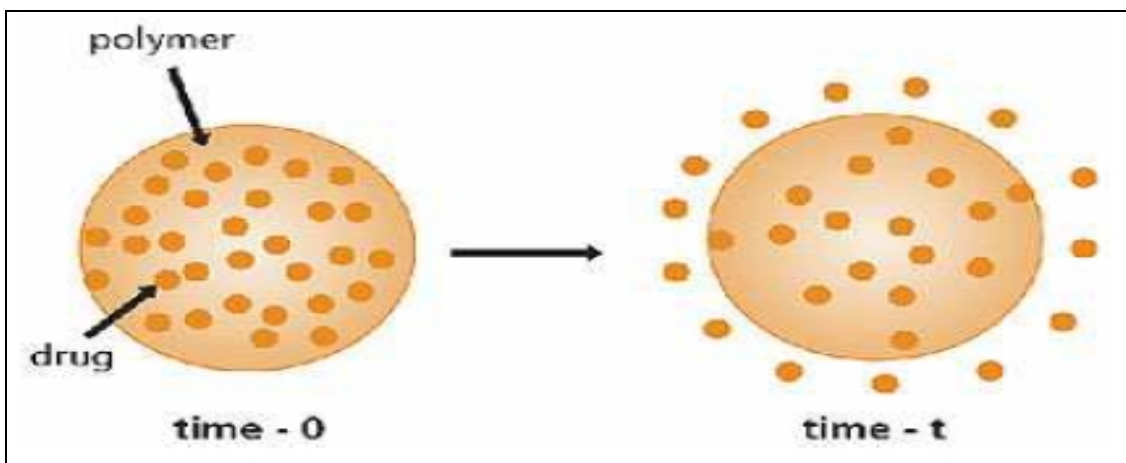


Figure 5. Schematic representation of diffusion sustained drug release: Matrix system