Chapter

1

Controlled Drug Delivery Systems and Polymers

CONTROLLED DRUG DELIVERY SYSTEMS

Introduction

The term, controlled drug delivery (CDD), is used to obtain specific release rates or locally targeting of active ingredients. CDD system is the one which delivers the drug at a predetermined rate, locally or systematically for a specified period of time. Drug delivery system can be a controlled release drug delivery system where there is predictive control over the release pattern, and subsequent tissue or blood levels may be achieved. Administration of drug in conventional dosage form needs large dose, frequent administration and lacks extended duration, with chances of toxicity. CDD system has been introduced to overcome the drawback of fluctuating drug levels associated with conventional dosage forms. While in CDD devices, there is efficient consumption of drug, desired extended duration with very low chances of toxicity, facilitating enhanced complication of patient, leading to better management of therapeutics. The efficacious use of drug influences cost factor, economy of therapy and adverse effect. Thus, control release formulation (CRF) involves a minimization of the amount of drug that is needed and a reduction of possible side effects. Generally concerning oral CRF, the gastrointestinal (GI) tract is of great importance to consider since it is the location of the drug release and from which the drug will be further transported to the target location. The pH value varies throughout the GIT and does also vary depending on fasting or fed condition. The pH value varies between 1 and 5.5 in the upper part while it is between 5.5 and 7 in the lower part. The different pH values of the different parts need to be considered when selecting the soft material to be designed to dissolve in the upper GI tract.

For the preparation of CRF, both natural and synthetic polymers are used. Natural polymers are various types of modified cellulose and cellulose derivatives. They are commonly used due to their susceptibility to chemical modification offering possibilities for material design. Although two cellulose derivatives have the same backbone, substitution groups can be added, resulting in one cellulose derivative becoming hydrophobic while another can become hydrophilic. To manufacture such type of the formulations is to raise the pharmaceutical efficiency for the patient, all involved materials require to fulfill the requirements for being human-body friendly. Hence, free from toxicity and not being harmful either before or after degradation.

Many different types of CDD system exist for the treatment of different pathological conditions. In these systems, *in vivo* performance is usually affected by the composition of the formulation along with manufacturing procedures. Apart from drug, such systems are usually manufactured by using polymer alone or combinations of polymers, waxy materials, and supplementary functional excipients. For the achievement of controlled drug release system, many approaches and technologies are available. Thus, it seems that the controlled delivery should be the goal for all products.

Terminology

Controlled release formulation: CDD or modified release delivery systems may be defined as the delivery of a regular supply of the active ingredient by continuously releasing for a certain period of time. An ideal CCD system is the one which delivers the active ingredient at a predetermined rate, locally or systematically, for a specific period of time.

Repeat action preparation (RAP): A dose of the drug (bioactive moiety) initially is released instantly after administration, which is generally equivalent to a single dose of the conventional drug formulation. After a definite period of time, a second single dose is released. In some preparation, one-third single dose is released after a definite time has elapsed, following the second dose. It provides the convenience supplying of additional dose or doses without the need of re-administration.

Extended release formulation (ERF): ERF is usually designed to reduce dose frequency and maintain relatively constant blood plasma drug concentration. This helps avoid the adverse effects associated with high concentration.

Delayed release preparation (DRP): The drug is released at a delay time after administration. The delayed action is obtained by the incorporation of a special coat, such as enteric coating. The purposes of such preparations are to reduce side effects related to the drug presence in the stomach, protect the active ingredient from degradation in the highly acidic pH of the gastric fluid.

Site-specific targeting: These systems refer to targeting of a bioactive molecule directly to a certain biological site. In such condition, the target is adjacent to or in the diseased organ or tissue.

Receptor targeting: These systems refer to targeting of a drug not indirectly to a certain biological location. In such condition, the target is the particular receptor for a drug within organ or tissue. Site-specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be CDD systems.

Rationale of CDD System

The main objective for CDD is to modify the pharmacokinetics and pharmacodynamics of bioactive moiety by using novel drug delivery systems or by altering the molecular structure or physiological parameters inherent in a selected route of administration. Thus, optimal design of controlled release systems requires a thorough understanding of the pharmacokinetics and pharmacodynamics of drugs. However, when doses are not administered properly, the resulting drug action is less than optimum drug therapy. For example, if doses are given too frequently, minimum toxic concentration (MTC) of bioactive moiety may be reached with toxic side effects resulting. Extended release tablets and capsules are normally taken only once or twice daily compared with

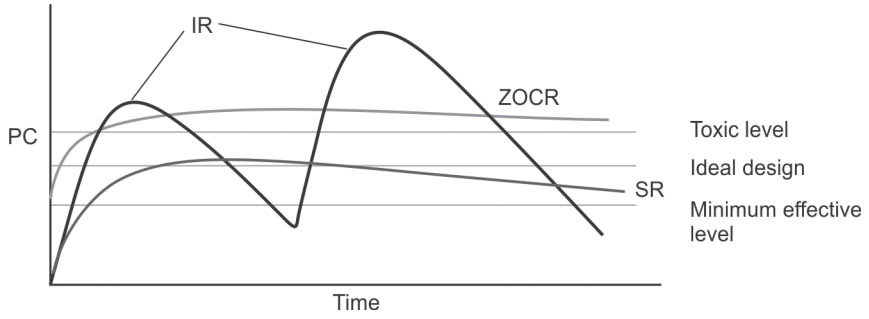

Fig. 1.1: Characteristic representation of plasma concentrations (PC) of a conventional immediate release (IR) dosage form, a sustained release (SR) dosage form and an idealized zero-order controlled release (ZOCR) dosage form (in combination with a start-up dose)

counterpart conventional forms that may need to be taken three to four times daily to achieve the same therapeutic effect. Typically, ERF gives an instant release of drug which then is followed by the gradual and continual release of additional amounts of drug to maintain this effect over a predetermined period of time (Fig. 1.1).

Advantages of Controlled Drug Therapy

- This delivery system improves the patient fulfillment especially with long-term treatments for chronic diseases.
- Conventional dosage form produces fluctuation in bioavailability. These fluctuations depend on the pharmacokinetics within the body like absorption, distribution, metabolism and excretion. Controlled release eliminates this type of fluctuation in bioavailability.
- Lessening in dose and dosing frequencies.
- Maintenance of required drug concentration in plasma thus eliminates the failure of drug therapy and improves the efficacy of treatments.
- An appropriate delivery system for drugs which is having a short biological half-life (3–4 hours) and drug rapidly eradicates from the body.

Disadvantages of Controlled Drug Therapy

- Dumping is a major disadvantage of control release DDS, which refers to the rapid release of a relatively large quantity of drug from controlled release formulations. This phenomenon becomes hazardous with potent drugs.
- Poor *in vivo* and *in vitro* correlation.
- Not easy to optimize the accurate dose and dosing interval.
- Patient variability affects the release rate like GI emptying rate, residential time, fasting or non-fasting conditions, etc.

Properties of Drug Candidate for Controlled Drug Delivery System

Physiological Properties

1. **Aqueous solubility:** Most of the active pharmaceutical ingredients (API) are weakly acidic or basic in nature that affect the H_2O solubility of API. Weak water-soluble drugs are difficult to design the CRF. High aqueous solubility drugs show burst

release followed by a rapid increment in blood plasma drug concentration. Such types of drugs are a good candidate for CRDDS. The pH depends on solubility also creates a problem in formulating CRDDS.

2. **Partition coefficient (P-value):** P-value denotes the fraction of the bioactive moiety into oil and aqueous phase that is a significant factor that affects the passive diffusion of the bioactive moiety across the biological membrane. The bioactive moiety is having high or low P-value not suitable for control release (CR), it should be appropriate to dissolve in both phases.
3. **Drug pKa:** pKa is the factor that determined the ionization of bioactive moiety at physiological pH in GIT. Generally, the high ionized bioactive moiety is poor candidate for CRDDS. The absorption of the unionized drug occurs rapidly as compared to ionized drugs from the biological membranes. The pKa ranges for acidic drug, pH is 3 to 5 and for a basic drug, pH is 7 to 11.
4. **Drug stability:** Bioactive moieties that are stable in acid/base, enzymatic degradation, and other gastric fluids are good candidates for CRDDS. If drug degraded in the stomach and small intestine, it is not suitable for CRF because it will decrease bioavailability of concerned drug.
5. **Molecular weight and molecular size:** The molecular weight and molecular size are two most significant factors which affect the molecular diffusibility across a biological membrane. The molecular size less than 400D is easily diffusible but greater than 400D generates problem in drug diffusion.
6. **Protein binding:** The drug–protein complex acts as a reservoir in plasma for the bioactive moiety. Bioactive moieties showing high plasma protein binding are not a good candidate for CRDDS because the protein binding increases the biological half-life. So, there is no need to sustain the drug release.

Biological Factors

1. **Absorption:** Uniformity in rate and extent of absorption is a significant factor in formulating the CRDDS. However, the rate-limiting step is drug released from the dosage form. The absorption rate should be faster than release rate to prevent the dose dumping. The various factors like aqueous solubility, acid hydrolysis affect the absorption of drugs.
2. **Biological half-life (t½):** Normally, the drug is having short half-life needed frequent dosing and suitable candidate for controlled release system. A drug with long half-life needed dosing after a long-time interval. Ideally, the drugs having half-life 2–3 hours are a suitable candidate for CRDDS. Drugs have half-life more than 7–8 hours are not used for CR system.
3. **Dose size:** The CRDDS formulated to eliminate the repetitive dosing, so it should contain the large dose than conventional dosage form. But the dose used in conventional dosage form provides an indication of the dose to be used in CRDDS. The volume of sustained dose must be as large as it comes under acceptance criteria.
4. **Therapeutic window:** The drugs with narrow therapeutic index are not good for CRDDS. If the delivery system failed to CR, it would cause dose dumping and ultimate toxicity.
5. **Absorption window:** The bioactive moieties which show absorption from the specific segment in GI tract are not a good candidate for CRDDS. Drugs which absorbed throughout the GIT are suitable candidates for CR.

6. **Patient physiology:** The physiological conditions of the patient like gastric emptying rate, residential time, and GI diseases influence the release of the drug from the dosage form directly or indirectly.

Approaches to Design CR Formulations

Based on the release mechanism, these are classified as follows:

1. Diffusion-controlled products
2. Dissolution-controlled products
3. Erosion products
4. Osmotic pump systems
5. Ion exchange resins

Diffusion-Controlled Products

In such a system, there is water-insoluble polymer which controls the flow of water and the subsequent release of dissolved bioactive moiety from the dosage form. Diffusion occurs when a drug passes through the polymer that forms the CR device. The diffusion may occur through pores in the polymer matrix or by passing between polymer chains (Fig. 1.2). These are broadly divided into two groups:

a. Reservoir devices
b. Matrix devices

The basic mechanisms of drug release from these two systems are basically different.

a. **Reservoir devices:** In such system, a water insoluble polymeric material encases a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particles or tablet. The bioactive agent is released to the surrounding environment by diffusion process through the rate limiting membrane. In these reservoir systems, the drug (bioactive moiety) delivery rate remains fairly constant.

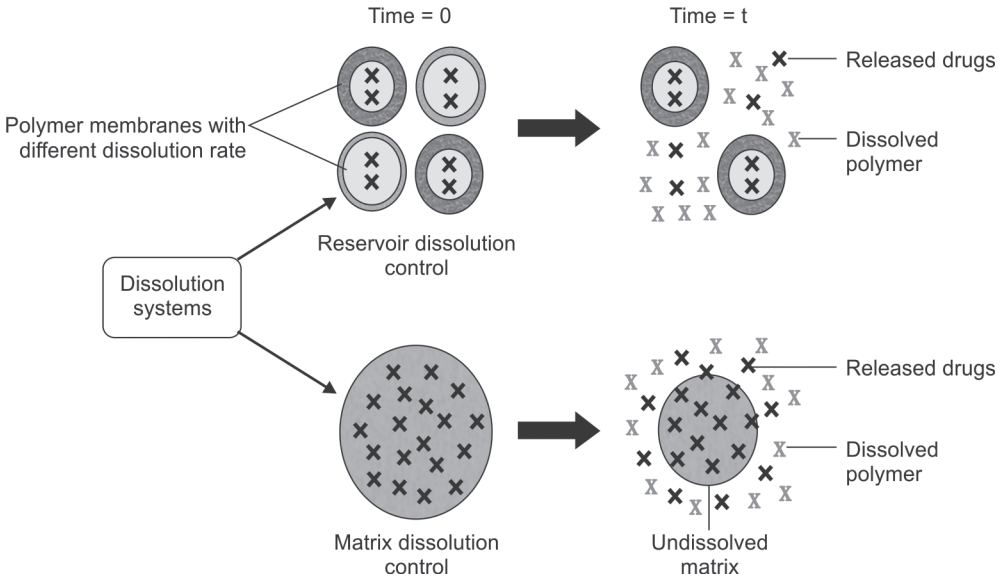

Fig. 1.2: Diffusion-controlled system

b. **Matrix devices:** In such matrix devices, the drug or bioactive molecule is dispersed in polymer matrix to form a homogeneous system known as a matrix system. Diffusion occurs when the bioactive molecule passes from the polymer matrix into the external environment. As the release continues, its rate normally decreases with such type of system, since the bioactive molecule has a progressively longer distance to travel and, therefore, needs a longer diffusion time to release.

Dissolution-Controlled Products

In such products, the rate of dissolution of the drug or bioactive molecule is controlled by slowly soluble polymers or by microencapsulation. Once the coating is dissolved, the bioactive molecule becomes available for dissolution. By varying the thicknesses of the coat and its composition, the rate of bioactive molecule release may be controlled. Some formulations contain a fraction of the total dose as an immediate release component to give a pulse dose soon after administration. The pellet dosage forms of diffusion- or dissolution-controlled products may be encapsulated or prepared as a tablet. Dissolution-controlled products can be subdivided into two groups:

a. Encapsulation dissolution control
b. Matrix dissolution control

a. **Encapsulation dissolution control:** These systems involve coating of individual particles or granules of drug or bioactive molecule with a slow dissolving material. The coated particles may be compressed directly into tablets or placed in capsules. The rate of dissolution of the drug or bioactive moiety (and thereby availability for absorption) is controlled by microencapsulation. Once the coating is dissolved, the bioactive molecule becomes available for dissolution. By changing the thicknesses of the coat and its composition, the rate of drug release may be controlled. Such type of products should not be chewed as the coating may be damaged. One of the major advantages of encapsulated pelleted products is that the onset of absorption is less sensitive to stomach emptying. The entrance of the pellets into the small intestine (where the majority of drug absorption occurs) is generally more uniform than with non-disintegrating sustained-release tablet preparations (Fig. 1.3).
b. **Matrix dissolution control:** In such system, an alternative approach is to compress the drug with a slow dissolving carrier. In this system, the rate of drug or bioactive molecule release is controlled by the rate of penetration of the dissolution fluid into the matrix, porosity, presence of hydrophobic additives and the wet capability of system and surface of particle (Fig. 1.4).

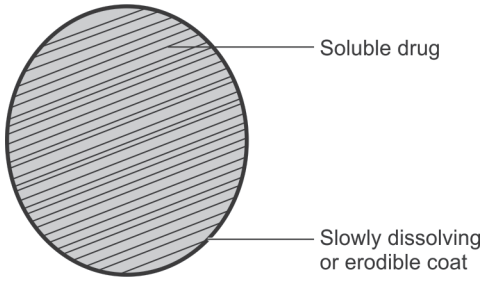

Fig. 1.3: Encapsulation dissolution control

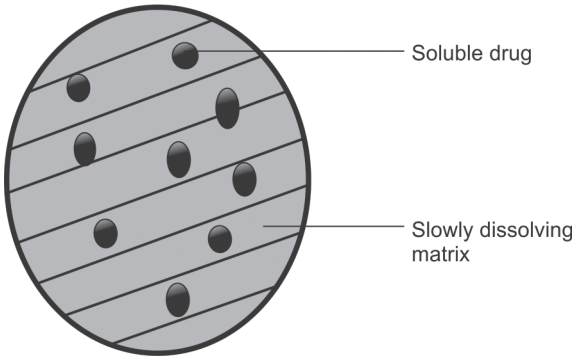

Fig. 1.4: Matrix dissolution control

Erosion Products

In such type of system, drugs or bioactive agents are mixed with biodegradable polymers. Such materials degrade within the body as a result of natural biological processes and drug release occurs at fixed rate. Many biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains into biologically acceptable and progressively smaller compounds. The release of drug from such products is controlled by the erosion rate of a carrier matrix. The rate of release is determined by the rate of erosion.

Osmotic Pump Systems

The osmotic pump is like a reservoir device but contains an osmotic agent (e.g. the active agent in salt form) which acts to imbibe water from the surrounding medium via a semipermeable membrane. A pressure is generated within the device which forces the active agent out of the device via an orifice (of a size designed to minimize solute diffusion, whilst preventing the build-up of a hydrostatic pressure head which has the effect of decreasing the osmotic pressure and altering the dimensions {volume} of the device). The advantage of such type of product is that the fixed release is unchanged by the environment of the gastrointestinal tract and relies simply on the passage of water into the dosage form. The rate of release may be modified by changing the osmotic agent and the size of the hole.

Ion Exchange Resins

A drug–resin complex for extended release is known and is successfully used commercially. The drug is bound to the resin and released by exchanging with suitable charged ions in contact with the ion exchange groups. Such a technique is applicable to certain drugs which have particular characteristics in terms of their relative affinity for the polymers being used.

Types of CR Preparation

On the basis of technical sophistication, controlled drug delivery system may be grouped into three major classes.

1. Rate-Programmed Drug Delivery System

This drug delivery system is that from which the drug release has been programmed at specific rate profiles. They are further subdivided into following subclasses.

a. Dissolution drug delivery system
- Slow dissolution rate of the drug
- Slow dissolution rate of the reservoir membrane or matrix

b. Diffusion drug delivery system
- Porous matrix-controlled system
- Porous membrane-controlled system

c. Erosion drug delivery system
- Surface erosion
- Bulk erosion

d. Dissolution, diffusion and/or erosion drug delivery system
- Reservoir system (membrane rectal drug delivery system)
- Matrix system (monolithic drug delivery system)
- Hybrid system (membrane cum matrix drug delivery system)

2. Stimuli-Activated Drug Delivery System

a. Activation by physical process
b. Activation by chemical process
c. Activation by biological system

3. Site-Targeted Drug Delivery System

a. Polymeric carriers for drug targeting
b. Albumin as carrier for drug targeting
c. Lipoprotein as carrier for drug targeting
d. Liposomes as carrier for drug targeting

Liquid-Sustained Release Systems

The development of liquid oral-sustained release formulations is gained much interest currently. Such preparations eradicate the problems associated with the solid dosage forms while maintaining the advantages and convenience of sustained release drug delivery. Alternative strategies are adopted to develop such systems. One of the techniques examined the use of suspended microspheres which are incorporated as a dispersed phase in a suspension. Another strategy studied the use of ion exchange resins or employing sparingly soluble salts to prepare oral sustained release suspensions. The use of *in situ* gelling systems gives other promising alternative with most of the reported investigations employing the sol to gel phase transition of alginate solution after addition of polyvalent cations as calcium. A suspension is reported to form a gel when comes in contact with simulated gastric fluid. In recent study, a liquid-sustained release formulation for eradication of *Helicobacter pylori* is developed in presence of alginate solution. In such study, the *in situ* gelation is obtained by separate oral administration of calcium solution which is taken immediately after administration of sodium alginate solution. Shortly after this, it is attempted to prepare systems containing sodium alginate combined with calcium. Such systems retained the fluidity in the bottle but undergo immediate gelation on coming into contact with gastric or simulated gastric acidity. To inhibit the interaction of calcium with alginate in the

bottle, calcium ions are sequestered with sodium citrate. This complex breaks immediately in strong acidity librating free calcium which can interact with alginate lead to spontaneous gelation. The optimal quantities of calcium chloride and sodium citrate that maintain fluidity of the preparation before administration but gel spontaneously after contact with simulated gastric fluid (pH 1.2) are determined. It should be noted that such type of gel is pH sensitive and breaks in presence of intestinal pH. Accordingly, the release pattern will depend on the gastric emptying rate which is highly changeable. Such a problem draws the attention to new *in situ* gelling system with a stronger gel structure that can keep up the sustained release pattern after gastric emptying. The gel structure of alginate-based systems is enhanced by combination with chitosan. This combination is employed in development of controlled release particulate and other solid drug delivery systems. The synergism between chitosan and alginate is due to the electrostatic interactions between carboxyl groups of alginate and amino groups ($-NH_2$) of chitosan and existence of interactive Coulomb forces. Such effects increase the gel strength. This drug is selected as it has high water solubility and short half-life.

Preparation of In Situ Gelling Systems

In situ gelling liquid formulations consisting of increasing concentrations of sodium alginate is prepared in absence and presence of chitosan. Sodium alginate is added to ultrapure water containing 0.45% w/v sodium citrate and 0.15% w/v calcium chloride and 0.6% w/v dextromethorphan hydrobromide. Such mixtures are heated to 60°C while stirring. Stirring is continued at ambient temperature until cooling to less than 40°C. For chitosan-containing systems, amount of chitosan is levigated gradually with the lead to alginate solution under continuous stirring using a mortar and pestle to produce homogenous dispersion.

Evaluation

This type of study is conducted to assess the gel forming property of the tested formulation. The formulation (10 ml) is packed into cellulose bag. This is immersed in 0.1 N HCl (100 ml) and maintained at 37°C for 24 hours. The fluid content of the cellulose bag is separated from the gel by sieving through a 355 μm sieve for 30 seconds. The weight of the gel remaining on the sieve is determined.

Determination of *In Vitro* Drug Release

The method of assessment of drug release from enteric-coated systems is adopted (USP 24). In addition, the study is further extended to monitor drug release at pH 7.4. The release experiments employed a USP dissolution apparatus (Model: UDT-804, LOGAN Inst. USA) with a paddle stirrer being maintained at 50 rpm. The release medium is 500 ml of simulated gastric fluid without enzymes (0.1 N HCl, pH 1.2) and the temperature is maintained at 37 ± 0.2°C. The test preparation (10 ml) is loaded into a petri dish (2.7 cm, internal diameter) before immersion into the dissolution vessel containing release medium without much disturbance. Samples (5 ml) are collected at predetermined time intervals (5, 15, 30, 60, 90 and 120 minutes, respectively). Fresh release medium is added to replenish for each sample. The samples are filtered through 0.45 μm filter, immediately after collection and the filtrate is analyzed for drug content using the HPLC method. After the last sample (2 hours), the pH of the release medium

is adjusted to 6.8 to simulate the intestinal pH (USP 24). This is achieved by addition of 200 ml of 0.3 M dibasic sodium phosphate and 25 ml of 1 N sodium hydroxide. Sampling is then continued for another 4 hours at the end of which the medium is adjusted to 7.4 using 1N NaOH and sampling is continued for another 2 hours. These samples are treated as before. The cumulative amounts of the drug released (expressed as % of the total drug added) are plotted as a function of time to produce the drug release profiles. The release efficiency is calculated from the area under the release curve at time t (determined using the non-linear trapezoidal rule) and expressed as a % of the area of the rectangle describe by 100% release in the same time. The results are compared to the release data of the marketed formulation (Delsym® suspension). In addition, the release data for each phase are fitted to different kinetic models to determine the release kinetics. This includes fitting the data to zero order, first order and Higuchi diffusion system. Each study is conducted in triplicate.

Pharmacokinetic Design for DDS

The objective of drug therapy is to maximize the desired pharmacological response while minimizing drug toxicity. The goal of CR or SR formulations is to minimize the ratio of maximum to minimum plasma drug concentrations (C_{max}/C_{min}) at steady-state; this depends on the dosing interval and the terminal half-life (t½) of the drug. However, this is true for drugs that decline monoexponentially in plasma or for drugs that do not distribute extensively in tissues. For drugs with a distinct distribution phase (drugs that distribute extensively in tissues), plasma concentrations during the terminal phase would be very much lower than those during the early distribution phase. The use of the terminal t½ of these drugs (those with distinct distribution phase) as a guide for multiple dosing could result in large C_{max}/C_{min} ratios and in unsuccessful drug therapy, if the C_{max}/C_{min} ratio exceeds the therapeutic index (TI), which is defined as the ratio of effective and safe plasma concentrations to concentrations eliciting unwanted toxic effects. For drugs with narrow TI values and those that decline multi-exponentially in plasma, it is necessary to identify the t½ of a particular phase of the log concentration-time profile as a guide for multiple-dosing calculations. The t½ value that is used as the guide for multiple-dosing therapy should be the multiple-dosing t½ (t½, md). This t½ value is the one that most significantly affects drug concentrations after multiple dosing. In general, the terminal or distribution t½ should be used as the t½, md for drugs with shallow or steep distribution phases, respectively. However, it should be emphasized that the use of the distribution t½ as the t½, md would result in extensive accumulation of drug in the body. The t½, md should also be chosen based on the site(s) of action related to the pharmacologic and toxic effects of the drug. For example, if the site of action is located in deep tissue compartments of the body, the terminal t½ used should be the t½, md. To minimize the C_{max}/C_{min} ratio, the, md has to be longer than τ. For drugs with $t_{1/2}$, md values less than *r*, *a* smaller C_{max}/C_{min} ratio can be achieved by controlling the rate of drug release (and absorption) from the formulation. If a formulation can be developed with a release rate much slower than the quotient of t½, md, the t½ of a drug after administration of the SR or CR formulation will reflect the rate of release of drug from the formulation (flip-flop) and a smaller C_{max}/C_{min} ratio can, therefore, be achieved. The first step in the development of CR or SR formulations, therefore, is to determine, if a CR or SR formulation is even necessary. This can be determined by comparing the C_{max}/C_{min} ratio to the therapeutic index of the drug. However, this criterion requires that a

relationship be known between the effect of the drug (pharmacologic and toxic) and plasma concentrations. If there is no such relationship, other considerations can be reviewed. For example, one can consider whether the pharmacologic or toxic effects of the drug are a function of drug input rate or a function of the maximum plasma concentrations attained.

In the simplest release pattern called zero-order release (Fig. 1.5). In zero-order release, the delivery rate remains constant. The release rate from these devices is given as,

$$dMt/dt = k$$

where, k is constant, t is time and Mt representing the mass of active agent released.

The release rate is directly proportional to the amount of active ingredient loaded in device (Fig. 1.6). Mathematically, this may be represented as:

$$dMt/dt = k\ (Mo–Mt)$$

where, Mo = mass of active moiety in the device

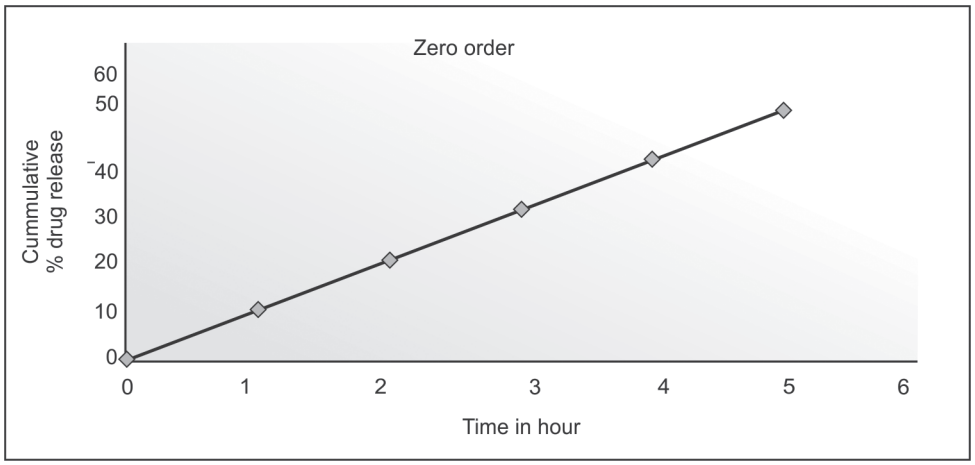

Fig. 1.5: Zero-order release of a drug from CR formulation

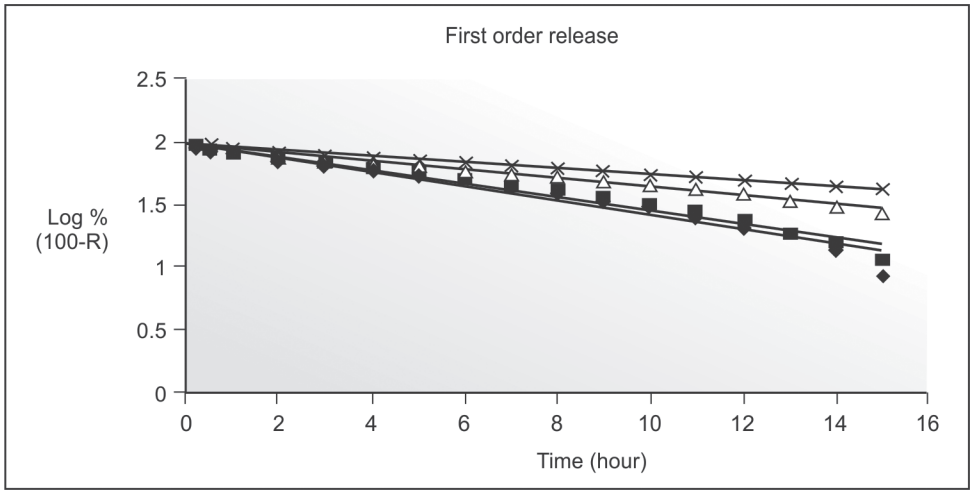

Fig. 1.6: First-order release of a drug from CR formulation

This indicates that the release rates decline exponentially with time and with depletion of active ingredient the release rate approaches zero.

POLYMERS

Introduction

Polymer is long chain organic molecule assembled from several smaller molecules called monomers. Natural-based and synthetic polymers have found their way into the pharmaceutical and biomedical industries and their applications are growing at a fast pace. Polymers may be applied in drug delivery systems, as scaffolds for tissue engineering and repair, and as novel biomaterials. Polymer is becoming increasingly significant in the field of drug delivery. The pharmaceutical utilization of polymers varies from their use as binders in tablets to viscosity and flow controlling agents in liquids, suspensions and emulsions. Polymers may be used as film coatings to mask the unpleasant taste of a drug or bioactive molecule, to enhance drug stability, and to modify drug release characteristics. In pharmaceutical preparations also, they have several applications in manufacturing of bottles, syringes, vials, catheters, and also in drug formulations.

Classification of Polymers

Since polymers are numerous in number with different behaviours and can be naturally found or synthetically created, they can be classified in various ways. The following are some fundamental ways in which we can classify polymers.

Classification Based on Source of Origin

1. **Natural polymers:** The simplest way to classify polymers is their source of origin. Natural polymers are polymers which occur in nature and are existing in natural sources like plants and animals. Some common examples are proteins (which are found in humans and animals alike), cellulose and starch (which are found in plants) or rubber (which we harvest from the latex of a tropical plant).
2. **Synthetic polymers:** Synthetic polymers are polymers which humans can artificially create/synthesize in a lab. These are commercially produced by industries for human necessities. Several commonly produced polymers which we utilize day-to-day are polyethylene (a mass-produced plastic which we use in packaging) or nylon fibres (commonly used in our clothes, fishing nets, etc.)
3. **Semisynthetic polymers:** Semisynthetic polymers are polymers achieved by making changing in natural polymers artificially in a laboratory. These polymers synthesize by chemical reaction (in a controlled environment) and are of commercial importance. Example: Vulcanized rubber (sulphur is used in cross-bonding the polymer chains found in natural rubber), cellulose acetate (rayon), etc.

Classification Based on Structure of Polymers

Classification of polymers based on their structure may be of three types:

1. **Linear polymers:** Such types of polymers are similar in structure to a long straight chain with identical links connected to each other. The monomers in these types are linked together to form a long chain. Such polymers have high melting points and are of higher density. A common example of this polymer is PVC (polyvinyl chloride). This type of polymer is largely used for making electric cables and pipes.

2. **Branch chain polymers:** The structure of such polymers is like branches originating at random points from a single linear chain. Monomers unite together to form a long straight chain with some branched chains of different lengths. As a result of such branches, the polymers are not closely packed together. They are of low density having low MP. Low-density polyethene (LDPE) used in plastic bags and general-purpose container is a very common example.
3. **Cross-linked or network polymers:** In such type of polymers, monomers are joined together to form a three-dimensional network. The monomers having strong covalent bonds as they are composed of bifunctional and trifunctional in nature. Such polymers are hard and brittle, e.g. melamine, bakelite (used in electrical insulators), etc.

Classification Based on Mode of Polymerization

Polymerization is a process by which monomer molecules are reacted each other in a chemical reaction to form a polymer chain, which is a three-dimensional network. On the basis of type of polymerization, polymers may be classified as:

1. **Addition polymers:** Such types of polymers are generally formed by the repeated addition of monomer molecules. The polymer is formed by polymerization of monomers with double or triple bonds such as unsaturated hydrocarbon compounds. Note, in such process, there is no removal of small molecules like H_2O or alcohol (–OH), etc. (no byproduct of the process). They always have their empirical formulas same as their monomers, e.g. ethene ($CH_2 = CH_2$) to polyethene $– (CH_2 – CH_2)\ n^–$.
2. **Condensation polymers:** Such polymers are formed by the combination of monomers, with the removal of small molecules like H_2O or alcohol (–OH), etc. The monomers in such types of condensation reactions are bifunctional or trifunctional in nature. A very common example is the polymerization of hexamethylenediamine and adipic acid to give nylon-66, where molecules of water are removed in the process.

Classification Based on Molecular Forces

Intramolecular forces are those forces that join atoms together within a molecule. In polymers, strong covalent bonds link atoms to each other in individual polymer molecules. Intermolecular forces (between the molecules) attract polymer molecules towards each other. The properties exhibited by solid materials like polymers depend largely on the strength of the forces between these molecules. Using this, polymers may be classified into four types:

1. **Elastomers:** These are rubber-like solid polymers, which are elastic in nature. Elastic basically mean that the polymer can be easily stretched by applying a little force. The very common example of this can be seen in rubber bands (or hair bands). Applying a few stresses elongates the band. The polymer chains are held by the weakest intermolecular forces, hence allowing the polymer to be stretched. But removing that stress results in the rubber band taking up its original form. This happens as cross-links between the polymer chain which help it in retracting to its original position, and taking its original form. Car tyres are made of vulcanized rubber. This is when introduce sulphur to cross-bond the polymer chains.
2. **Thermoplastics:** Thermoplastic polymers are those long-chain polymers in which intermolecule forces (van der Waals forces) unite the polymer chains together. Such

polymers become softened after heating (thick fluid like) and hardened when they are allowed to cool down, forming a hard mass. They do not have cross-bond and can easily be shaped by heating and using moulds. A very common example is polystyrene or PVC (which is used in making pipes).

3. **Thermosetting:** Thermosetting plastics are those polymers which are semi-fluid in nature with low molecular masses. When heated, they start cross-linking between polymer chains, hence becoming hard and infusible. They form a three-dimensional structure on the application of heat. This reaction is irreversible in nature. The most common example of a thermosetting polymer is that of Bakelite, which is used in preparing electrical insulation.
4. **Fibres:** These are a class of polymers which are thread-like in nature, and can easily be woven. They have strong intermolecular forces between the chains giving them less elasticity and high tensile strength. The intermolecular forces may be hydrogen bonds or dipole-dipole interaction. Fibres have sharp and high melting points (MP). A very common example is that of nylon-66, which is used in carpets and apparels.

Above are the very general ways to classify polymers. Another category of polymers is that of biopolymers. Biopolymers are those polymers which are obtained from living organisms. They are very biodegradable and have a very well-defined structure. Many biomolecules like carbohydrates and proteins are a part of the category.

Characteristics of an Ideal Polymer

- It should be inert and compatible with the environment.
- It should be non-toxic.
- It should be easily administered.
- It should be easy and inexpensive to fabricate.
- It should have good mechanical strength.
- Low density
- Poor temperature resistance
- It can be produced transparent or in different colours.
- Low coefficient of friction
- Good mould ability

Properties of Polymers

Physical Properties

- As chain length and cross-linking increases, the tensile strength of the polymer increases.
- Polymers do not melt; they change state from crystalline to semicrystalline.

Chemical Properties

- Compared to conventional molecules with different side molecules, the polymer is enabled with hydrogen bonding and ionic bonding resulting in better cross-linking strength.
- Dipole-dipole bonding side chains enable the polymer for high flexibility.
- Polymers with van der Waals forces linking chains are known to be weak, but give the polymer a low melting point.

Optical Properties

Due to their ability to change their refractive index with temperature as in the case of PMMA and HEMA: MMA, they are used in lasers for applications in spectroscopy and analytical applications.

Advantages of Polymers

- Cheap to make
- Many uses because of their different properties
- Provide jobs in firms which make the polymer and the product.
- Some polymers can be recycled, melted down and made into something else which saves valuable natural resources.
- If polymers are used instead of wood, fewer trees will have to be cut down.

Disadvantages of Polymers

- People do not like to live near polymer-producing industrial works.
- Some people think plastic products look cheap compared with natural materials.
- Made from oil, a non-renewable resource.
- Most plastics are not biodegradable, so there is a problem of how to get rid of them.
- Landfill sites are ugly.
- Give off toxic fumes when they burn.
- Sorting types of polymers for recycling can be expensive.

Applications of Polymers for Controlled Drug Delivery

Over the past four decades, an interest has developed in the design and formulation of dosage forms that control the subsequent release of drug from the dosage form into the surrounding biological fluids. This rate process effectively controls the therapeutic properties of the medicinal agent. Vital to the development of these systems is role of pharmaceutical polymers. In light of the current and continuing importance of this category of drug delivery system provides a concise range of designs of CRDDS and the contribution/significance of polymers to their function.

Reservoir Systems

In such type of systems, the drug having core is separated from the biological fluids by a water insoluble polymeric coat or layer, depending on the geometry of the drug delivery system. Examples of polymers that are commonly used as the polymeric coats/layers include ethyl cellulose, poly (ethylene-vinyl acetate), silicone and various acrylate copolymers. A diagrammatic representation of the design and operation of a reservoir system is presented in Figure 1.7.

Drug release from these systems occurs in a number of steps, initially involving the partitioning of the drug into the polymeric coat/layer.

The Ocusert System

The delivery of therapeutic agents to the eye for the treatment of disorders of the eye (e.g. glaucoma) using conventional drug delivery systems, e.g. drops, ointments, is an inefficient process. These are primarily due to the rapid clearance of drugs from the surface of the eye due to blinking and tear flow. One method by which the efficiency of ocular drug delivery may be improved is through the use of polymeric implants

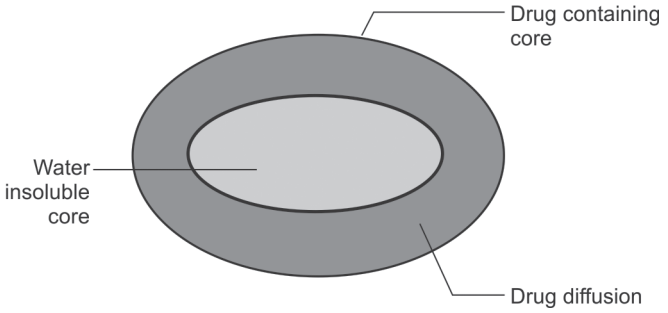

Fig. 1.7: Diagrammatic representation of the design and operation of a reservoir-controlled release system

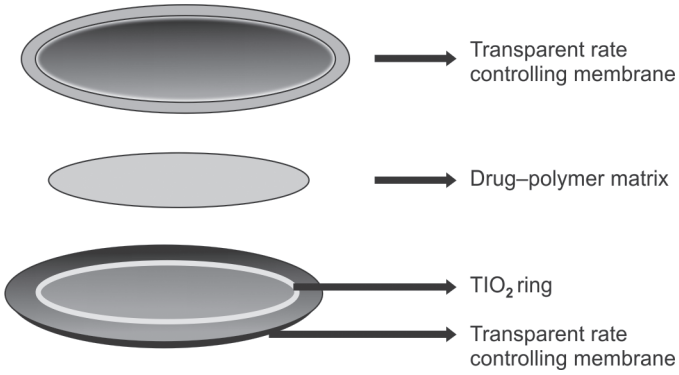

Fig. 1.8: Ellipsoidal shaped Ocusert

that are implanted under the lower cul-de-sac of the eye. The Ocusert represents one such example that has been designed to release either 20 μg h^{-1} or 40 μg h^{-1} of a therapeutic agent (pilocarpine) for a 7-day period following implantation. In design terms, the Ocusert is an ellipsoidal-shaped implant that is composed of several layers, diagrammatic representations of which are shown in Figure 1.8.

In this system, pilocarpine is dispersed within an alginic acid matrix which is sandwiched between two layers each composed of poly (ethylene-co-vinyl acetate). These layers act as the rate controlling membranes. The fourth layer is composed of an opaque, annular ring that is housed beneath the rate controlling layer and, as both the rate controlling membranes and the drug-containing matrix are transparent, the function of this ring is to offer visibility of the device following instillation. Drug release from this delivery system occurs by diffusion.

The Progestasert System

A second example of a reservoir CDDS is the Progestasert intrauterine device (IUD), a medicated implant that is used for contraceptive purposes. In the 1960s, IUDs emerged as an available method of contraception that prevented implantation of the ovum due to the mechanical effects of the device on the uterine endometrium. It is accepted that to achieve greater contraceptive efficiency, larger IUDs should be used, as these offer greater coverage of the endometrium. However, patients using these larger IUDs will be more prone to side effects including bleeding, cramps and possibly expulsion. One method by which the contraceptive efficacy of these devices may be improved whilst

lowering the incidence of side effects is to use the IUD to locally deliver contraceptive agents to the endometrium at a defined rate for a prolonged period. Local delivery of progesterone is advantageous for a number of reasons. Most noticeably, the drug is rapidly metabolized oral administration and, therefore, requires frequent oral administration of high doses of this drug.

Reservoir-Designed Transdermal Patches

One-third example of the use of reservoir systems for controlled drug delivery may be observed in the transdermal delivery of therapeutic agents. Transdermal drug delivery involves the diffusion of the drug through the skin and ultimately absorption into the systemic circulation. One of the anatomical purposes of the skin is to protect the body from the ingress of possibly dangerous chemicals and, therefore, it is little surprise that only a limited number of therapeutic agents possess the appropriate physicochemical properties to traverse this anatomical barrier. There are three main anatomical barriers that therapeutic agents must partition into and diffuse through prior to possible absorption into the systemic circulation, namely the stratum corneum (a keratinized layer at the outermost region of the skin), the viable epidermis and the dermis, into which the microcirculation may be found (Fig. 1.9).

Matrix Systems

In this matrix designed drug delivery systems, the drug or bioactive moiety is homogeneously dispersed, either at the molecular scale or as solid particles, within a polymeric medium. In comparison to reservoir systems, the manufacture of matrix designed drug delivery systems is more straight forward and may be performed using a number of different approaches. Examples of these include:

- Mixing of a polymer with the drug or bioactive particles followed by direct compression into tablets.
- Incorporation of a drug into a polymer by polymerization of a drug-monomer mixture or by hydrogel swelling within a drug solution.
- Dissolving the drug and polymer in an appropriate solvent followed by solvent removal.
- Curing the polymer in the presence of dissolved/dispersed drug.

Swelling-Controlled Release Systems

In the previous sections, the release of therapeutic agents from reservoir and matrix designs was described. Whilst the designs of these systems differ, it is assumed that

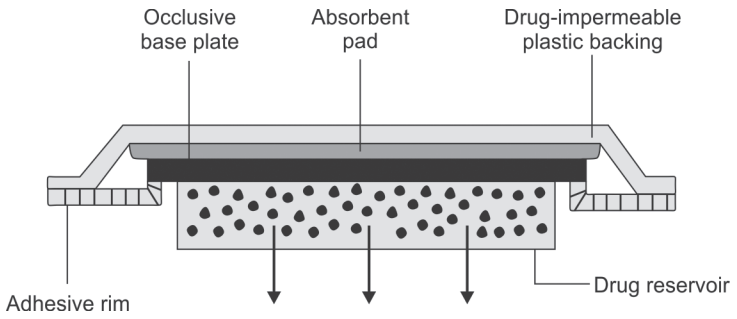

Fig. 1.9: Cross-section view of matrix diffusion controlled transdermal drug delivery system showing major structural components

the shape and dimensions of the devices do not change during the course of drug release. This is due to the hydrophobic nature of the polymers used in the formulation of these systems. Hence, in the reservoir systems, the thickness of the coating remains constant whereas in matrix systems there is a defined thickness of the device (e.g. slab, cylinder, sphere) over which diffusion occurs. As a result, in the equations that describe drug release, the thickness of the system/membrane is defined. However, in many drug delivery systems, the dimensions of the dosage form will change during the course of drug release due to swelling of the polymer matrix. Although the mechanism for drug release is diffusion.

Biodegradable Systems

Biodegradable systems are those in which a therapeutic agent has been incorporated into a matrix that is composed of a biodegradable polymer, i.e. a polymer that will undergo controlled degradation within a biological environment. As a result, following implantation, the molecular weight of the polymer matrix will be reduced due to hydrolysis of crosslinks or hydrolysis of the main polymer chain, and in doing so the previously insoluble polymer matrix will be rendered soluble in the biological fluids thereby facilitating elimination. There are several examples of biodegradable polymers that have been examined for controlled release applications. These include poly (lactic acid), poly (glycolic acid) and their copolymers, poly (ε-caprolactone), poly (ortho esters) and polyanhydrides.

Osmotically Controlled Drug Delivery Systems

In these systems, the difference between the osmotic pressure within a formulation and the surrounding biological fluids is used as the driving force for drug release. The first osmotic systems were developed by the Alza Corporation in the 1970s and since that time, both the number and types of designs of these systems have increased. The basic design of the OROS system, one of the original elementary osmotic pumps (Fig. 1.10).

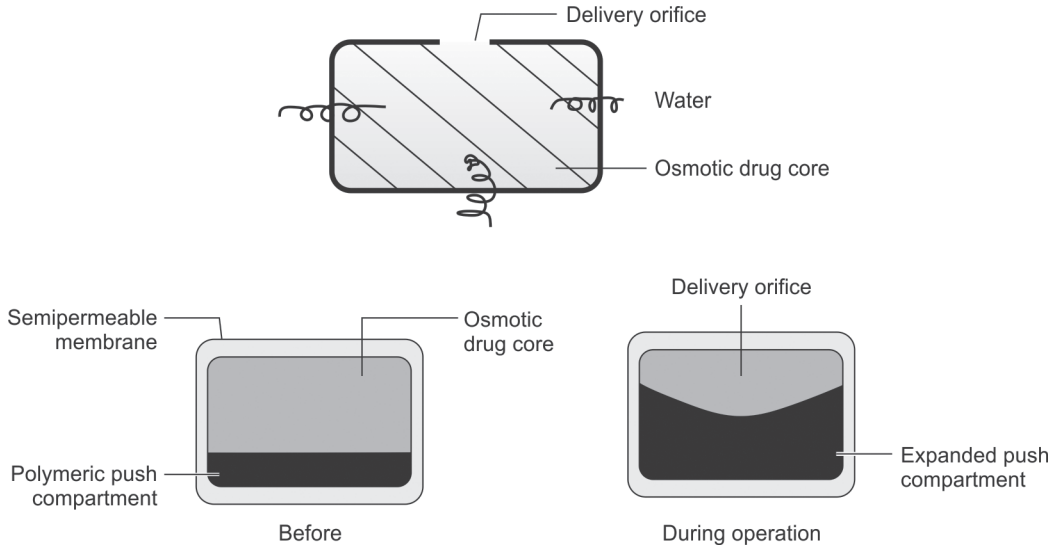

Fig. 1.10: The basic design of the OROS system

Stimulus Responsive Drug Release

Up to this section, the discussion of drug release is primarily concerned with systems from which drug release is facilitated by simple diffusion. Osmotically controlled systems and the use of biodegradable polymers offer possibilities for the enhancement of drug release through ancillary processes, namely osmotic pressure and polymer degradation. However, another aspect of great interest in drug delivery is the ability to engineer dosage forms to release the drug on demand following the application of an appropriate stimulus, e.g. drug release at a specific location within the gastrointestinal tract.

Polymer-Drug Conjugates

Polymer-drug conjugates offer an exciting strategy for the improved delivery of therapeutic agents, both in terms of the provision of controlled release but also for the improved targeting of the therapeutic agent to a particular site. As the title suggests, polymer-drug conjugates are composed of a drug that is covalently bound to a polymer, which may be either hydrophilic or hydrophobic.

QUESTIONS

A. Short Answer Type Questions

1. Describe properties of drug candidates for controlled drug delivery system.
2. Discuss about biological properties of drugs appropriate to controlled release formulations.
3. Write a short note on pharmacokinetic design for drug delivery system.
4. Mention the application of polymers.
5. Write about physicochemical properties of drugs related to controlled release formulations.
6. Write a short note on controlled release preparation and their formulations.
7. Define polymers and classify them.
8. What are the characteristics for ideal polymers?

B. Long Answer Type Questions

1. Write different approaches for design-controlled release formulation.
2. Mention advantages and disadvantages of polymers in detail.
3. Discuss on physicochemical and biological properties of drugs relevant to controlled release formulations.
4. Describe in detail about controlled drug delivery systems and their importance.
5. What are the advantages and disadvantages for controlled release drug formulation?
6. Define site specific and receptor targeting. Discuss about rationale for controlled release drug formulation.
7. Give the different properties and application of polymers comprehensively.