1

Controlled Release Products

A.V. Jithan, B. Chandrasekhar Reddy and Y. Shravan Kumar
Vaagdevi College of Pharmacy, Warangal, India

1.1   Introduction

Controlled Release (CR) products are designed to maintain constant therapeutic plasma concentration of the drug within the therapeutic range of the drug over prolonged periods and offer minimum side effects. This can be achieved using a variety of delivery systems and also includes liposomes and drug-polymer conjugates. These products are designed to reduce the frequency of dosing by modifying the rate of drug absorption. Generally CR products administered by any route are designed such that rate of drug absorption should be equal to rate of drug elimination. Literally, the amount that is eliminated should be input into the compartment of interest at the same amount at any given time. These products can be administered by various routes including oral (peroral, buccal, sublingual), parenteral (IM, IV, SC, IP, IT, etc.), transdermal, respiratory, nasal, etc. Other miscellaneous routes such as intravaginal, rectal, etc. can also be used for CR products. Drug eluting stents is a novel concept in CR products. Examples of controlled release drug-eluting stents include Cypher® (reservoir) and TAXUS Express® (monolithic). The concept behind CR products was proposed long time ago. Early modified release products were often intramuscular/ subcutaneous injection of suspensions of insoluble drug complexes, eg. Procaine penicillin, protamine zinc insulin, insulin zinc suspension or injections of the drug in oil, eg. Fluphenazine decanoate. Advance in technology have resulted in novel modified release dosage forms.

Drug products that provide extended release first appeared as a major new class of dosage form in the late 1940's and early 1950s. Over the years, many terms (and abbreviations), such as sustained release(SR), sustained action (SA), prolonged action (PA), controlled release (CR), extended release (ER), timed release (TR), and long acting (LA), have been used by manufactures to describe product types and features. Although these terms often have been used interchangeably, individual products bearing these descriptions may differ in design and performance and must be examined individually to ascertain their respective features. In case of sustained release (SR) dosage forms the release of the active agent, although, is lower than in the conventional formulations, however, it is still substantially affected by the external environments into which it is going to be released. Controlled release (CR) systems provide drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time, with the release profiles of predominantly controlled by the special technological construction and design of the system itself. The release of the active constituent is therefore, ideally independent of exterior factors. Extended release formulation is a controlled release formulation designed to produce even and consistent release of active ingredient. Extended release (ER) dosage forms are those which due to special technology of preparation provided, soon after a single dose administration, therapeutic drug levels maintained for 8-12 hours. Prolong or long action products are dosage forms containing chemically modified therapeutic substances in order to prolong biological half life. Although there are a variety of these dosage forms, the purpose of all such dosage forms is the same and the main aim is to achieve the controlled or sustained release of the drug. However, controlled release is the ideal release of the drug from delivery systems. In this case, the release is either a zero-order or first-order release. Timed-release, sustained release, prolonged release are less superior than controlled release. However, as of today, it is not practical to achieve controlled release with all the drugs and all the delivery systems. Most of the times the drug release is either sustained, prolonged or timed. However, all these types of releases can be called as CR release for its ideal nature and convenience. As a reason, in this book these formulations are called together as CR products. Plasma time profile of a drug following a CR form administration is shown in Figure 1.1.
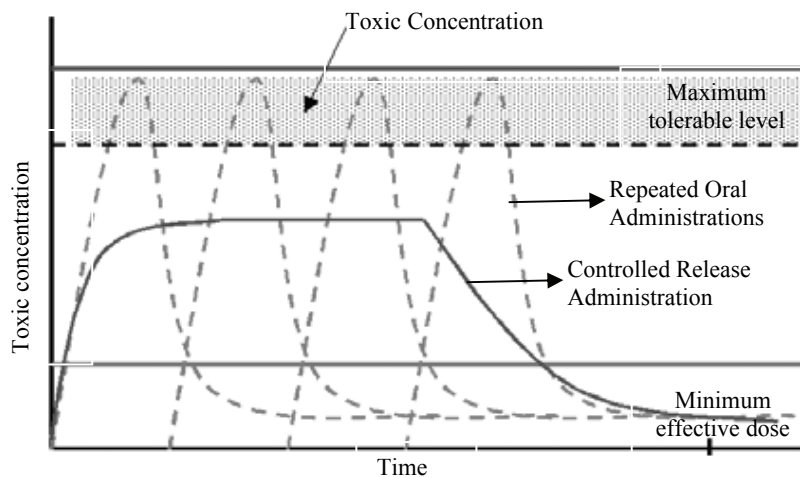
Figure 1.1 The plasma concentration time profile of a CR formulation.

The currently available CR products can be administered via various routes of administration. Based on this they could be classified into oral, parenteral, targeted, respiratory, vaginal and rectal. Parenteral CR products available in the market can release the drug upto five years. Some others release the drug for a period of two weeks to four weeks. On contrary, the currently available oral CR products or some products in clinical trials can release the drug, in case of short half-life for a period of 24 hours to seven days. Targeted CR products are generally administered at the site of the need and thereby release the drug for weeks. Several companies are now developing CR dosage forms to be administered by various routes other than the conventional routes mainly focusing on the respiratory tract. Recently, Acusphere, Inc. in the USA has conducted clinical trials on controlled release microsphere formulation of a leading asthma drug. This formulation releases the drug locally. Some of these formulations and the respiratory tract have been used in achieving the systemic sustained release of the drug. Similarly, vaginal and rectal route also have been investigated for CR products. The other CR formulations present in the market are transdermal dosage forms. Transdermal dosage forms are used either to achieve the drug levels in the skin tissue or the drug levels in the blood. These delivery systems sustain the release of the drug. They have been exhaustively investigated and ample information is available regarding these delivery systems. These CR delivery systems are dealt in a separate chapter in this book series.

1.2   Advantages and Benefits

All the conventional dosage forms excepting continuous IV infusion, release drugs largely according to first-order kinetics. Therefore immediately after administration and absorption, there is a higher plasma level which upon time will gradually reduce and the optimal therapeutic level is present for only a brief duration. On contrary, the CR systems release the drug at a constant rate (zero order) or at a predictably constant declining rate (first order) for a certain time period. This results in uniform concentration of drug in the plasma and tissue.

The high-peak blood concentration reached soon after administration of conventional formulations may result in adverse effects. For drugs with short biological half-life or with a clear relationship between concentration and response, it will be necessary to dose at regular, frequent intervals in order to maintain the concentration within the therapeutic range. Higher doses at less frequent intervals may result in higher peak concentrations with the possibility of toxicity. For drugs with wide margins of safety, this approach is satisifactory. Amoxycillin has a half-life of approximately one hour and a dosing frequency of eight hours. Therefore, there will be large fluctuations in the plasma levels with this drug in one dose. However, the drug has high therapeutic window and as a reason, such an administration is not a problem. On contrary, there are several examples available in the literature where such administration with low therapeutic window drugs is a problem. An example is hypotension in patients taking rapid-release nifedipine products. A CR nifedine product avoids the high initial blood concentration which causes the sudden hypotension and reflex tachycardia. Similarly, some times subtoxic levels can cause problems. Subtoxic levels due to conventional theophylline results in local irritation in the GIT. This happens whenever there is a consumption of conventional dosage form for this drug. Similarly, several examples can be seen in the market as well as literature. Gepirone, a psychoactive drug, is useful in the treatment of depressive and anxiety disorders. Pharmacologically, gepirone acts as a selective 5-HT$_{1A}$ receptor partial agonist. Gepirone was originally developed by Bristol-Myers Squibb, but was out-licensed to Fabre-Kramer in 1993. In 2001, Organon filed a new drug application for gepirone extended release (ER). The need for ER formulation has been realized because of its short half-life which necessitated frequent administration. High peak concentrations seen at higher doses were associated with an increased incidence of adverse effects. Initial placebo-controlled clinical trials demonstrated that gepirone Immediate Release (IR) product improved symptoms of

depression. The application for gepirone ER formulation is still pending with US Food and Drug Administration (FDA). On the other hand, the investigators concluded that gepirone ER appears safe and effective in short-term treatment of major depressive disorder and appears to be free of common side-effects.

CR products can significantly reduce the side effects associated with chronically administered drugs. Upon repeated administration of conventional products, the resulting pattern of drug concentration in plasma can vary widely and may cause inconsistent and undesired clinical effects. The saw tooth kinetic pattern that is noticed after repeated administration can result in the accumulation of the drug in tissues leading to undesirable side-effects especially after chronic administration. Several CR products for chronic drugs have been developed and the results clearly indicated a reduction in the side-effects. Also the subtherapeutic levels seen with every administration can result in times of ineffectiveness for this drug. This issue can be conveniently taken care using a CR dosage form. CR product of paroxetine delays the release of the active until the tablet has passed through the stomach; the drug is then released over four to five hours. Paroxetine CR was generally well-tolerated in clinical trials, as patients felt significantly less nausea than recipients of IR paroxetine. The effects of switching from IR carbamazepine formulations to an equal daily dose of carbamazepine ER capsules in epilepsy has shown significant benefits. Switching to ER formulation significantly improved patients adverse events and quality-of-life measures. It also improved seizure control. Risperidone is to date the only novel antipsychotic available as parenteral CR formulation (parenteral depot). Unlike the traditional esterification of conventional antipsychotics to achieve a long acting injectable formulation, long-acting risperidone is fabricated by a microsphere encapsulation process. This depot preparation significantly lowered several side-effects associated with the repeated oral administration of the drug. It also lowered the rate of reversible motor side effects when compared with oral therapy by constraining the peak levels below the moderate-to-severe threshold of reversible motor side-effects. In a study comparing regular alprazolam tablet, given four times a day and extended release alprazolam (XR) given once in the morning, drowsiness occurred more frequently with conventional alprazolam (86% of patients) than with the XR preparation (79%) or placebo (49%).

Several studies indicated that patient compliance also improves with CR products. Drugs with short half-life often need to be given at frequent intervals to maintain blood concentrations within the therapeutic range. An inverse correlation between the frequency of dosing and the patient

compliance has been found. A reduction in the number of daily doses offered by CR products has the potential to improve patient compliance. In one study patient compliance in hypertensive outpatients between amlodipine (5 mg once daily) and slow release nifedipine (20 mg twice daily) were compared in an open, crossover. Four methods of assessment for patient compliance (pill count, taking compliance, days with correct dosing, timing compliance) were used. The results indicated that the compliance of the 320 hypertensive patients with once-daily amlodipine was markedly superior to twice-daily slow release nifedipine. Therapeutic coverage was also significantly better for amlodipine in the hypertensive patients. Amlodipine was better tolerated than nifedipine slow release. Patient compliance and therapeutic coverage with the calcium antagonist amlodipine given once daily was superior to slow release nifedipine bid in hypertensive outpatients recruited in general practice. Ideally, CR products are not significantly affected by the external environment, so that patient-to-patient variability is greatly reduced.

There is also a reduction in health care costs with CR products. The total cost of therapy of the controlled release product could be comparable or lower than the immediate-release product. With reduction in side effects, the overall expense in disease management also would be reduced.

1.3 Disadvantages and Problems

More complicated CR formulations may be more erratic in result. A sustained release product may contain a larger dose, i.e. the dose for two or three (or more) 'normal' dosing intervals. A failure of the controlled release mechanism may result in release of a large toxic dose. CR technology is more expensive. A growing number of new CR products have been submitted for regulatory approval. As mentioned previously, CR products have many advantages in safety and efficacy over immediate release drug products in that the frequency of dosing can be reduced, drug efficacy can be prolonged and the incidence and/or intensity of adverse effects can be decreased. However, some CR products developed have less clear rationale or are developed for active ingredients which are not appropriate for prolonged release dosage forms. In other cases, CR products are designed without full consideration of the basic properties of the drugs. Additionally, there is a big problem with in vitro-in vivo correlation. As a result, it is often difficult to evaluate whether a CR form is acceptable or not. Incomplete or undesirable prolonged release drugs may merely cause therapeutic confusion and, in addition may interfere with development and spread of good quality drugs.

1.4 Classification of CR Systems Based on Fabrication Techniques

Either modulation of dissolution of the active drug component or diffusion of the dissolved or solubilized species is the basic mechanisms for controlling drug release. Erosion of the polymer followed by drug reaching the dissolution medium also is one of the mechanisms. Some times all the four mechanisms may be involved in the release of the drug from the CR formulations. They may operate independently, together or consecutively. Several other mechanisms are also reported to play a role. These mechanisms apply to all the CR delivery systems administered by different routes of administration. Specific examples of drug release and mechanisms can be found in the literature regarding a particular marketed product, whether administered by oral route, parenteral route, local delivery or by any other route.

Purely diffusion, dissolution, erosion, osmotic pump type of mechanism, ion-exchange based drug release, smart materials etc. are known to be the main mechanisms utilized in the fabrication and drug release investigations. Based on these mechanisms CR products that exist include: 1. Diffusion controlled systems 2. Dissolution controlled systems 3. Dissolution and diffusion controlled release systems 4. Erosion products 5. Water penetration controlled systems 6. Drug covalently linked to polymer 7. Ion - exchange resin controlled release systems 8. Responsive Drug Delivery Systems.

1.4.1 Diffusion Controlled Products

There are two types of diffusion controlled systems: matrix controlled systems and reservoir controlled systems.

1.4.1.1   Matrix controlled systems

Matrix systems are also called as monoliths since the drug is homogeneously dispersed throughout a rate controlling medium. There are two types of matrix devices. 1. Insoluble matrix of rigid non-swellable hydrophobic materials. 2. Soluble swellable hydrophilic substances. In these systems the therapeutic agent is dispersed in either of the two above matrices. Materials used for case 1 (rigid matrix) are insoluble plastics such as polyvinyl chloride and fatty materials like stearic acid, bees wax, etc. Swellable matrix systems are generally composed of hydrophilic gums of natural (guar gum, tragacanth, karaya gum), semisynthetic (hydroxypropylmethylcellulose, carboxy methyl cellulose, xanthan gum) and synthetic (polyacrylamides) origin. The drug and matrix materials are granulated together and compressed into CR

products. Examples include Plendil ER (Felodipine), Agon SR (Felodipine), Kapanol (Morphine sulphate) and Slow-K (Potassium chloride). TIMERx is a CR product based on agglomerated hydrophilic matrix consisting of xanthum gum and locust bean gum. Slofedipine XL (nifedipine) and Cystrin CR (oxybutynin) are other products developed using this technology. Drug release from insoluble nonswellable matrices involves penetration of fluid, followed by dissolution of the drug particles and diffusion through fluid filled pores. With case 2 matrices, the drug becomes available as the matrix swells or dissolves and the dissolved matrix then undergoes surface erosion with little or no bulk erosion. The surface area of the matrix decreases with time with a concomitant decrease in drug release. The diffusion depends on the solubility of the drug in the polymer. The drug may be either present below its solubility limit and dissolved in the polymer or present well above its solubility limit and dispersed in the polymer. The development of both matrices and reservoirs, which is discussed later, is a common place in pharmaceutical industries, as the technology is easy or enough experience has been gained. However, matrices have particular advantage over reservoirs in some cases and vice-versa is also true. For instance, Barochez et al., compared a monolithic matrix form with a reservoir device for a 80 mg highly soluble drug (1). At first, matrices were prepared containing 37.3 percent of a water soluble polymer: HPMC (Methocel or Metolose) and HEC (Natrosol). With such swelling agents, it was quite difficult to reach a zero order release. But industrial scale-up was easy, because the process uses only classical machines. With matrix formulations, variations between batches have been found very small and stability is good. Matrix formulations were also prepared using lipophilic matrix. Hard gelatin capsules were filled with a drug dispersion in Gelucire of different grades. The fabrication process is quite easy but at this time, information on stability is scanty. A third convenient way was a reservoir device, a tablet coated with an insoluble polymer film (Aquacoat ECD 30). A zero order release was obtained until 80 percent of drug released after 12 hours. But the coating was a very critical phase of the process. Slight disturbances in coating affected the drug dissolution rate. Additionally, there is a problem with the patients. The film may also be altered by the patient, who can break or crunch the tablet. In this case, all the drug is dissolved quasi instantaneously. It was suggested in this study that for all these reasons, the hydrophilic matrix was preferred, especially if a zero order is obtained. However, obtaining a zero-order drug release is not easy.

For instance, Mockel and Lippold, investigated the order of release of a drug from hydrocolloids (2). Matrices were manufactured by direct compression of a powder mixture of a polymer, e.g., methylhydroxypropyl cellulose (MHPC) or polyvinylalcohol (PVA), and a drug. The following factors that can influence the drug release mode were investigated at constant surface: (i) polymer solution viscosity, glass transition temperature, and swelling; (ii) drug concentration in the matrix and solubility; and (iii) conditions of release experiment (hydrodynamics). Only hydrocolloids with low viscosities yielded a zero-order release profile. In this case only the dissolution of the polymer appeared to control the drug release rate. Factors accelerating polymer dissolution resulted in higher release rates. Comparison of swollen and dry hydrocolloid matrices shows that the duration and kinetics of drug release were not controlled by the swelling front moving into the dry polymer, and water penetration and relaxation were not rate controlling. Therefore, the glass transition temperature had no effect on drug release from these hydrocolloids. The higher the hydrodynamic stress exerted on the eroding hydrocolloid, the faster the resulting drug release as a result of accelerated polymer dissolution. With hydrocolloids of very high viscosity the polymer dissolution is slow, and drug release from the swollen gel appears to be controlled by diffusion according to kinetics of the Higuchi type. Thus, different types of drug release can be obtained with different types of polymers. Additionally, the properties of the drug may also affect the release. Although a zero-order drug release is preferred, in the case of matrices very judicious selection of the polymers may be essential. On the other hand, zero-order drug release can be conveniently obtained from reservoir devices.

1.4.1.2   Reservoir controlled systems

A core of drug is coated with the water insoluble polymer. The polymer can be applied by coating or microencapsulation techniques. The drug release mechanism across the membrane involves diffusion of water through the membrane to the inside of the core, dissolution of the drug and then diffusion of the drug into the surrounding fluid. Materials used in such devices are hydroxypropyl cellulose, ethyl cellulose and polyvinyl acetate. The reservoir diffusion products are Plateau CAPS capsules (nicotinic acid), nio-bid (nitroglycerine), Nitrospan capsules (nitroglycerine), Brankadyl SR cap (theophylline). Some other examples of diffusion-controlled devices include drug-eluting stents such as Cypher® (reservoir) and TAXUS Express® (monolithic), intra-uterine

contraceptives such as Progestasert® and Norplant ®, and various transdermal patches such as Nicoderm® and Transderm Nitro®

1.4.2 Dissolution-controlled Products

There are two types of products: A. Matrix dissolution controlled products and B. Reservoir dissolution-controlled systems.

1.4.2.1   Matrix dissolution products

In these systems, the drug is homogenously dispersed through out a rate controlling membrane. The drugs, which are highly water-soluble can also be formulated as CR products by controlling their dissolution rate. Slowly soluble polymers control the rate of dissolution of the drug. Waxes such as beeswax, carnauba wax and hydrogenated castor oil have been used. The wax embedded drug is generally prepared by dispersing the drug in the molten wax and congealing and granulating them.

1.4.2.2   Reservoir dissolution-controlled systems

In reservoir dissolution control system the drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose derivatives, polyethylene glycols, polymethacrylates, waxes etc. The resulting reservoirs (coated beads, multi-particulate systems, pellets) may be filled as such in hard gelatin capsules (spansules) or compressed into tablets. The common multi-particulate systems are microparticles (microspheres or microcapsules), nanoparticles (nanospheres or nanocapsules), liposomes, etc. The dissolution rate of the drug depends upon the solubility and the thickness of the coating. By varying the thicknesses of the coat and its composition, the rate of drug release can be controlled. These products should not be chewed as the coating may be damaged. One of the advantages of encapsulated reservoir products is that the onset of absorption is less sensitive to stomach emptying. The entrance of the reservoir into the small intestine is usually more uniform than with non-disintegrating CR tablet formulations. An example of this type of product is fefol (Ferrous sulfate and folic acid).

1.4.3 Dissolution and diffusion controlled products (pore forming method)

In these system, the drug core is coated with a partially soluble membrane. Pores are thus formed due to dissolution of parts of the membrane, which permit entry of aqueous medium into the core and

release of dissolved drug by diffusion. Using a mixture of ethylcellulose with polyvinylpyrrolidone or methyl cellulose, the latter material dissolves in water and forms pores in the insoluble ethylcellulose membrane. Based on the above preparation techniques, CR transdermal formulations, buccal drug delivery systems, nasal drug delivery systems (inhalers), oral gastroretentive systems and ocular inserts etc. can also be formulated.

1.4.4   Erosion Products

The release of a drug from these products is controlled by the rate of erosion of a carrier (polymer) matrix. Erosion of the polymer can be by dissolution or can be by a chemical means such as degradation of the polymer. The rate of release (amount of drug released from the dosage form per unit of time as defined by in vitro or in vivo testing) is determined by the rate of erosion. An example of such a formulation is Sinemet CR (carbidopa/levodopa). Several parenteral dosage forms also undergo this type of release mechanism. An implantable therapeutic system is fabricated by dispersing a loading dose of solid drug, in micronized form, homogenously throughout a polymer matrix made from bioerodible or biodegradable polymer, which is then molded into a pellet or bead-shaped implant. The controlled release of the embedded drug particles is made possible by the combination of polymer erosion through hydrolysis and diffusion through polymer matrix. The rate of drug release is determined by the rate of biodegradation, polymer composition and molecular weight, drug loading, and drug/polymer interaction. The rate of drug release from this type of drug delivery system is not constant and is highly dependent upon the rate process of polymer matrix erosion. It is exemplified by the development of biodegradable naltrexone pellets fabricated from poly(lactide/glycolide) copolymer for the antinarcotic treatment of opioid-dependent addicts. In addition to poly(lactide/glycolide) copolymer, several other biodegradable or bioerodible polymers, such as polysaccharide, polypeptide and homopolymer of polylactide or polyglycolide, can also be used to prepare biodegradable, implantable therapeutic systems. A biodegradable polymer, poly(ortho esters) possess an interesting example. This polymer contains linkages in the polymer backbone that are relatively stable at the physiological pH of 7.4, but become progressively unstable as the pH is lowered. The erosion rate of such polymers is controlled by the use of buffering agent, e.g., calcium lactate, which is physically incorporated into the polymer, and when in contact with water, produces a pH that activates the polymer to hydrolyze at a desired rate. If the polymer is

maintained at a rather high hydrophobicity, then only the buffering agent in the surface layers is exposed to water and polymer hydrolysis will occur only in the surface layers. So, a constant (zero-order) rate of drug release is obtained.

1.4.5 Water penetration controlled systems

Some devices are designed using water as the main agent controlling the release of the drug. In these devices, the drug molecules cannot physically diffuse out of the device without water molecules diffusing in. There are generally two types of water penetration-controlled systems: 1. Swelling controlled systems. 2. Osmotic controlled systems.

1.4.5.1   Swelling controlled systems

These systems usually incorporate drugs in a hydrophilic polymer that is stiff or glassy when dry, but swells when placed in an aqueous environment. A typical oral capsule or pill is usually a swelling-controlled device. Although these devices are easy to manufacture, the release rates are often not steady. Swelling-controlled release systems are relatively new devices of the controlled release family of delivery devices for applications in pharmaceutical technology. To date, emphasis has been placed on swelling-controlled systems for release of a drug at a constant rate over a period of time (zero-order systems). Morita et al., investigated a swelling controlled system for a model drug (3). A novel controlled release system, the PVA swelling controlled release system, was evaluated in vitro and in vivo using emedastine difumarate. In the in vitro drug release study, the release profile of this system had almost zero-order kinetics. The effect of dissolution test conditions, which were paddle rotation speed, mechanical stress, and pH of the dissolution medium, on the release rate was very small. In an in vivo human bioavailability study of two formulations with a different release rate, the absorption rate was dependent on the release rate, and both formulations showed constant plasma levels of the drug for long periods. The variations of plasma concentration on the simulation of repetitive administration of the formulations at 24-h intervals were almost equal to the experimental value for the twice daily controlled release capsule currently on the market. It is concluded that the PVA swelling controlled release system is feasible for a long-acting preparation as a once-daily treatment.

1.4.5.2 Osmotic controlled systems

Reservoir systems have a drug core surrounded\coated by the rate controlling membrane. However factor like pH, presence of food and

other physiological factor may affect drug release from conventional controlled release systems. Drug delivery systems utilizing the principles of osmosis have been very successful at addressing a wide variety of disease conditions. With principles first described in 1975, oral osmotic systems now address areas as diverse as cardiovascular disease to attention deficit disorder, with more than a dozen products marketed worldwide. Osmotic systems utilize the principle of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameter to a large extent and it is possible to modulate the release characteristic by optimizing the properties of drug and system. The oral osmotic pumps are now in advanced stage and the available products on this technology and number of patents granted in the last few years indicates its market success. Alza corporation of the USA was first to develop an oral osmotic pump and today also they are the leaders in this field with a technology by name OROS. The rate of release of drug in these products is determined by the constant inflow of water across a semi-permeable membrane into a reservoir, which contains an osmotic agent. The drug is either mixed with the agent or is located in a reservoir. The dosage form contains a small hole from which the dissolved drug moves out at a rate determined by the rate of entrance of water due to osmotic pressure. The rate of release is constant and can be controlled within tight limits yielding relatively constant blood concentrations. The rate of release can be modified by altering the osmotic agent and the size of the hole. An example of this type of product is Adalat Oros (Nifedipine).

For the first time in 1955 an Australian pharmacologist Rose and Nelson developed an implantable osmotic pump. Next quantum leap in osmotic dosage form came in1972 when Theuwes invented elementary osmotic pump. After that many have been invented which enable controlled delivery of almost all drugs. These devices can be now classified into implantable, oral osmotic pump, and other specific types. Different types of implantable osmotic pumps include: the Rose and Nelson pump, Higuchi Leeper pump, Higuchi Theuwes pump and implantable Miniosmotic pump. Different types of oral osmotic pumps include: single chamber osmotic pump (elementary osmotic pump), multichamber osmotic pump (push pull osmotic pump, osmotic pump with non expanding second chamber). Specific type osmotic pumps include: controlled porosity osmotic pump, bursting osmotic pump, Liquid OROS, delayed delivery Osmotic device, telescopic capsule, oros ct (colon targeting), sandwiched oral therapeutic system, osmotic pump for insoluble drugs, monolithic osmotic systems and OSMAT. The basic

components of an osmotic pump include the drug, osmotic agent and semipermeable membrane. Drug generally incorporated has short biological half-life (2-6 hr), highly potent, and requires prolonged treatment. Examples of the drugs include nifedipine, glipizide and verapamil. Osmogents used for fabrication of osmotic dispensing device are inorganic or organic in nature a water soluble drug by it self can serve the purpose of an osmogent. Inorganic water-soluble osmogents include: magnesium sulphate, sodium chloride, sodium sulphate, potassium chloride, sodium bicarbonate. Organic polymer osmogents include: sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethylmethylcellulose, methylcellulose, polyethylene oxide, polyvinyl pyrollidine. The semi permeable membrane should be stable both to the outer/inner environment of the device. The membrane must be sufficiently rigid so as to retain its dimensional integrity during the operational lifetime of the device. The membrane should also be relatively impermeable to the contents of dispenser so that osmogent is not lost by diffusion across the membrane finally, the membrane must be biocompatible. Ideal properties of semi permeable membrane include: 1. The material must posses sufficient wet strength (-10^5) and wet modulus so as to retain its dimensional integrity during the operational lifetime of the device. 2. The membrane exhibit sufficient water permeability so as to retain water flux rate in the desired range. The water vapor transmission rates can be used to estimate water flux rates. 3. The reflection coefficient and leakiness of the osmotic agent should approach the limiting value of unity. Unfortunately, polymer membranes that are more permeable to water are also, in general more permeable to the osmotic agent. 4. The membrane should also be biocompatible. The substance forming a large part of the outer surface of the novel device of this invention is semipermeable, for example a material that is permeable to an external fluid such as water and the like while essentially impermeable to a selected product or other compounds in the device. This material can be non-erodible or bioerodible after a predetermined period of time and in each instance it is semi-permeable to solvent but not to solute and is suitable for construction of the outer layer of the device. Some materials which form semi-permeable membranes include cellulose acetate, cellulose nitrate, cellulose diacetate, cellulose triacetate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, cellulose acetate, cellulose acetate phthalate, polyurethanes, polyglycolic or polylactic acid and derivatives.

The following are the advantages of the osmotic pumps whether used for oral route or parenteral route. 1. They typically give a zero order

release profile after an initial lag. 2. Deliveries may be delayed or pulsed if desired. 3. Drug release is independent of gastric pH and hydrodynamic condition. 4. They are well characterized and understood. 5. The release mechanisms are not dependent on drug. 6. A high degree of in-vitro and in vivo correlation is achieved. The following are the disadvantages: 1 Costly. 2. If the coating process is not well controlled there is a risk of film defects, which results in dose dumping 3. Size of the hole is critical.

Another example regarding the osmotic pumps, worth mentioning is Duros technology platform. This technology platform can be conveniently applied to any drug. This technological platform is mainly applied for controlled release parenteral delivery of the drugs. The ALZET® osmotic pump for animal research studies has been the basis for almost 7000 research studies. More recently, osmotic principles have been applied to human parenteral therapy, resulting in the development of the DUROS® technology. The potential of the DUROS technology as a platform for providing drug therapy was demonstrated by the Food and Drug Administration's approval in March 2000 of ALZA's Viadur product (leuprolide acetate implant), the first approved product to incorporate the DUROS implant technology. The Viadur implant delivers the GnRH analog leuprolide for 365 days for the palliative treatment of prostate cancer and has achieved good patient acceptance. The research studies performed with the ALZET osmotic pump demonstrated the breadth of applicability of parenteral delivery based on the principles of osmosis and that parenteral osmotic systems could be designed for effective site-directed delivery. DURECT Corporation was founded in 1998 to further develop the DUROS technology for advanced applications licensed from ALZA Corporation for selected fields in pain management and site-directed delivery. The DUROS technology is a miniature drug-dispensing system that operates like a miniature syringe and releases minute quantities of concentrated drug formulations in a continuous, consistent flow over months or years. The system is implanted under the skin and can be as small as 4 mm OD X 44 mm L or smaller. The system consists of an outer cylindrical titanium alloy reservoir. This reservoir has a high-impact strength and protects the drug molecules from enzymes, body moisture, and cellular components that might deactivate the drug prior to delivery. At one end of the reservoir is positioned the membrane, constructed from a specially designed polyurethane polymer. The membrane is permeable to water but substantially impermeable to ions. Positioned next to the membrane is the osmotic engine. The engine contains primarily NaCl, which is combined with other pharmaceutical excipients in tablet form. Next to the engine is

the piston. The piston is made from elastomeric materials and serves to separate the osmotic engine from the drug formulation in the drug reservoir compartment. At the distal end of the titanium cylinder is the exit port. Exit ports can range from simple, straight channels to more complicated design configurations. The exit port design must be coupled to the rheological properties of the drug formulation. The drug formulation is contained in the drug reservoir compartment. The drug formulation may be either a solution or suspension. DUROS drug solutions can be both aqueous and non-aqueous in nature. DUROS drug formulations must exhibit stability at body temperature (37°C) for extended periods of time, usually ranging from 3 months to 1 year. Stable formulations have been developed for a number of drugs. It is possible to develop stable formulations of peptides and proteins, especially if suspension formulations are pursued. By formulating a non-aqueous suspension, the stability advantages of solids are exploited, and the absence of water greatly diminishes losses from hydrolytic degradation reactions. For many applications, the preferred site of implantation is subcutaneous placement in the inside of the upper arm. When implanted, a large, constant osmotic gradient is established between the tissue water and the osmotic engine. Osmosis is the movement of a solvent through a semi-permeable membrane from a region of low-solute concentration to a region of high-solute concentration; the osmotic engine provides a region of high NaCl concentration. The engine is specifically formulated with an excess of NaCl, such that solid NaCl is present throughout the delivery period. This results in a constant osmotic gradient throughout the delivery period. In response to the osmotic gradient, water is drawn across the membrane into the osmotic engine. The rate of water permeation is constant because of the constant osmotic gradient. Further, *in vivo* studies have shown that the rate is constant *in vivo*, confirming that the membrane is not fouled *in vivo*. The water imbibed into the osmotic engine expands its volume at a constant rate, thereby displacing the piston down the bore of the system at a controlled, steady rate. This displacement pumps drug formulation from the drug reservoir through the exit port and into the patient.

1.4.6 Drug Covalently Linked to the Polymer

Drug covalently linked to the polymer is now decisive in the design and preparation of control drug release formulations. There is an advantage with these systems compared when compared to other CR products. Ideally CR products should deliver a drug to specific site in a specific time and release pattern. Initially, constant or sustained drug release were

the kinetics pursued by most of the CR products in order to avoid problems associated with conventional administration in chronic treatments. This concept has now evolved to the trend of developing CR systems that fits to the circadian rhythm by using the so-called stimuli responsive polymers or "intelligent" polymers. In this sense, the main advantages of polymers are their great versatility from the structural point of view, the possibilities to combine hydrophobic and hydrophilic components, as well as the interactions polymer-polymer, polymer-drug, polymer-solvent that offer many possibilities to design and prepare formulations with specific properties and functions. Other aspects that DDS covers are: the slow release of water soluble drugs, the improvement of the bioavailability of low soluble drugs, the delivery of two or more drugs from the same formulation, the possibility of having readily clearable polymer carriers, the control of the release of highly toxic drugs, and the improvement of the targeting to tissues or cells. Covalent polymer-drug conjugates are a special type of CR products where the drug or bioactive compound (peptides, proteins, growth factors, hormones, enzymes, etc.) is covalently linked to the macromolecular backbone through a physiologically labile bond. The possibility of linking any bioactive molecule to a macromolecular chain make polymeric conjugated systems very useful for applications not only related to medication, but also in fields as tissue engineering, biosensors, affinity separations, enzymatic processes, cell culture, etc.

1.4.7 Ion Exchange Resins

Drug release characteristics depend on the ionic state of the environment when a drug is contained in a resin. Thus, in the case of oral administration the drug release is determined by the ionic environment of the GIT. This principle can be conveniently applied to sustain the release of the drug. Thus, CR products can be developed using ion exchange resins. Because this approach of sustained release requires the presence of ions in solution, it would not be applicable to the skin, the external ear canal, or other areas with limited quantities of eluting ions. The subcutaneous and intramuscular routes, where the pool of available ions is more controlled, would appear better suited for this approach. With the GI tract appears to possess a rather constant ionic content, the variability in diet, water intake, and GI content composition make this constant ionic content unlikely. Nevertheless, oral product employing this principle are available in the market, especially for the prolonged release of the drug. Resins are water-insoluble materials containing anionic or cationic groups in repeating positions on the resin chain. The drug-charged resin

is prepared by mixing the resin with drug solution either by repeated exposure of the resin to the drug in a chromatographic column or by keeping the resin in contact with drug solution for extended periods of time. The drug-resin is then washed to remove contaminant ions and dried to form particles or beads. When a high concentration of an appropriately charged ion is in contact with the ion-exchange group, the drug molecule is exchanged and diffuses out of the resin to the bulk solution. As is true with all CR products which involve diffusion processes, the area of diffusion and diffusional pathlength are important to the rate of diffusion. In addition, the amount of solvent in the matrix of the resin, as well as the structural rigidity of the resin also infuences the drug diffusion rate. For this reason, the porosity of the resin and the size of the bead or particle must be carefully controlled during the formulation process. The release rate can be further controlled by coating the drug-resin complex using one of the microencapsulation processes. Coated and uncoated drug-resin complexes may be mixed in certain ratios and filled into capsules with excipients or suspended in a palatable flavored vehicle containing suitable suspending agents. This has been shown to be a reliable technique to obtain desired release profiles. The release of drug from uncoated resin beads is expected to begin immediately while release from the coated form would be delayed depending on the type and thickness of the coat. Examples of ion-exchange resin type of product are Duromine containing the basic drug phentermine complexed onto an anionic resin and MS contin (Morphine sulfate) suspension which uses a polystyrene sulphonate resin.

1.4.8 Responsive Drug Delivery Systems

These devices are capable of releasing therapeutic agents by well-defined kinetics and have significant improvement over conventional CR systems. In these devices, the drug output is adjusted in reponse to physiological end. Responsive drug delivery systems can be classified as open- or closed-loop systems. Open-loop systems are also called pulse or externally regulated systems; the amount of drug released is not dependent on the environmental conditions the device is in. Among the most advanced externally-regulated devices are *mechanical pumps*, which dispense drugs from a reservoir outside the body via a catheter. Insulin-delivering pumps are commercially available with sophisticated control mechanisms and computers that can allow a programmed insulin delivery. Although these devices are not primarily made of polymers, the device-tissue interface can be expected to be polymeric. The rate of drug released can also be controlled and enhanced using external stimulants,

like magnetism and ultrasound. In *magnetically-controlled drug delivery devices*, small magnetic spheres are embedded in a drug-containing polymer, which release a significant amount of drug when exposed to an oscillating field. Similarly, the release rate also increases when analogous drug-containing polymers are exposed to *ultrasound*. Ultrasound was found to enhance erosion and degradation of some biodegradable polymers, and it can also act as an on-off switch as in certain drug delivery systems.

In closed-loop systems, or self-regulated systems, the release is in direct response to the conditions detected, be it temperature, type of solvent, pH, or concentration, to name a few. Poly(N-isopropylacrylamide) is a well-known example of a *thermo-responsive polymer*: At its transition of 32ºC, the polymer is soluble in water; but, as temperature is increased, the polymer precipitates and phase separates. Poly(ethylene glycol) and poly(propylene glycol) copolymers and poly(lactic acid) and poly(glycolic acid) copolymers also exhibit thermo-responsiveness. These polymers are useful in developing thermogelling systems (Atridox®); the drug is dissolved in the liquid form of the polymer at room temperature. When this mixture is injected in the body, the polymer turns into a gel, which eventually degrades and releases the drug molecules. Self-regulating insulin-delivery devices depend on the concentration of glucose in the blood to control the release of insulin. One system proposed immobilizing glucose oxidase (an enzyme) to a pH-responsive polymeric hydrogel, which encloses a saturated insulin solution. At high glucose levels, glucose is catalyzed by glucose oxidase and converts it to gluconic acid, thus lowering the pH. This decrease in pH causes the membrane to swell, forcing the insulin out of the device.

1.5   Design of Sustained Release Dosage Forms

The development of CR delivery systems stemmed from the need to reduce the dosing burden by releasing active substance at a passively controlled rate over an extended period of time. The advantages include reductions in fluctuations in drug concentration and adverse side effects, an increase in patient comfort and compliance, and, potentially, reduced healthcare costs. Since the early 1970s, CR delivery systems exploded in popularity. This led to the use of drug delivery technologies as a life cycle management tool and repatentability strategy employed by many pharmaceutical manufacturers for their leading brands. The rapid and continuous innovation behind CR technologies is impressive as

evidenced by the creation of specialty drug delivery companies. CR dosage forms have been developed over three decades. They have increasingly gained popularity over other dosage forms in treating diseases. One of the first controlled release dosage form is the spansule introduced in 1950s. Spansule capsules were manufactured by coating a drug onto nonpareil particles and further coating with glyceryl stearate and wax. Subsequently, several formulations with different mechanisms of release have been introduced. Thus, the pharmaceutical companies have provided a variety of dosage forms and dosage levels of particular drugs, thus enabling the physician to control the onset and duration of drug therapy by selecting a suitable dosage form available.

Formulator should have knowledge of several important aspects before initiating the program of design of sustained release dosage form for a certain drug. To establish a procedure for designing sustained release dosage forms, it is useful to examine the properties of drug blood-level time profiles characteristics of multiple dosing therapy of immediate release forms. In general for drug therapy, selection of proper dose and dosage interval is a prerequisite to obtain a drug level pattern that will remain in therapeutic range. The minimum effective and maximum safe doses should be known. With sustained release dosage forms, the dosage interval is more compared to the conventional dosage forms. In general with oral CR dosage forms, the objective is to able to provide a sustained release plasma profile for upto 12 hours. With parenteral dosage forms, it depends on the need of the duration. Physicians and pharmacists were aware of plasma pattern of drug concentration versus time before even the CR formulations entered the market. Elimination of drug level oscillations can be achieved by administration of drug through constant-rate intravenous infusion. To design an efficacious sustained release dosage form, one must have a thorough knowledge of the pharmacokinetics of the drug chosen for this formulation. Either for conventional dosage form or for CR dosage form it is always assumed that drug blood levels are assumed to correlate with therapeutic effect and drug kinetics are assumed to be adequately approximated by a one-compartment model. In this case, the drug distribution is sufficiently rapid so that a steady state is immediately attained between the central and peripheral compartments, i.e., the blood-tissue transfer rate constants, k_{12} and k_{21} are large. Under the foregoing circumstances, the drug kinetics can be characterized by three parameters: the elimination rate constant (k_e) or biological half-life, the absorption rate constant (k_a) and volume of distribution (Vd). In case of the drug following a two compartment model Vc is the volume of the central compartment. In case of CR products,

several parameters such as the loading dose, maintenance dose, rate of release of the maintenance dose should be calculated. To obtain a constant drug level, the rate of drug absorption must be made equal to its rate of elimination. Consequently, drug must be provided by the dosage form at a rate such that the drug concentration becomes constant at the absorption site. Detailed theoretic treatments of a number of sustained release dosage for designs have been reported. These systems include:

1. No loading dose with zero-order drug release.
2. No loading dose with first-order drug release.
3. Loading dose with zero-order drug release.
4. Loading dose with first-order drug release.

When loading dose is included, designs based on both immediate and delayed release of maintenance dose have been described. Any of the above designs is simple. For instance, Meka et al., (2008) developed a biphasic gastroretentive floating drug delivery system with multiple-unit mini-tablets based on gas formation technique to maintain constant plasma level of a drug concentration within the therapeutic window (4). The system consists of loading dose as uncoated core units, and prolonged-release core units are prepared by direct compression process; the latter were coated with three successive layers, one of which is seal coat, an effervescent (sodium bicarbonate) layer, and an outer polymeric layer of polymethacrylates. Another type of these formulations can be prepared using HPMC. HPMC matrix / mini-matrix systems have been formulated to achieve such "fast/slow" drug release patterns. These matrices are reported to contain the drug fraction for the extended release phase, while the drug fraction for immediate release was integrated into the matrix / minimatrix via an immediate releasing layer in a double-layer tablet system, incorporated into a release controlling coating over the matrices or incorporated into the voids between compressed mini-matrices. The equations useful in the calculations of the loading dose and maintenance dose were clearly described by Nicholas Lordi in the Theory and Practice of Industrial Pharmacy (Eds. Lachman, Liberman and Kanig, 3rd Edition) (5). Thus, when intended for acute or intermittent administration it is desirable to have an initial slug of drug rapidly absorbed followed by a slower maintenance component. For chronic administration, a zero order absorption rate is the theoretical goal, where the rate of systemic drug appearance, $R_{systemic}$, is given by (6):

$$R_{systemic} = F.R = CL.C$$

Where F is the drug bioavailability, R is the rate of drug administration, CL is total plasma clearance and C is the target steady-state plasma concentration. The amount of drug contained in each unit dosage form, D_{unit} is given by:

$$D_{unit} = CL. \; C. \; \tau/F$$

Where τ is a constant dosing interval. In practice, very few (if any) CR dosage forms result in zero-order systemic drug appearance. There is a fundamental dilemma encountered with any oral dosage form, but this is particularly true with CR forms. There are several factors that may affect the performance of the CR dosage form and this may contradict the zero-order systemic drug appearance. Zero-order systemic drug appearance is important on several occasions. One aspect of research about controlled-release delivery systems involves designing a system which produces steady-state plasma drug levels, which is also referred to as zero-order drug release kinetics. To meet this objective, numerous design variations have been attempted, and their major controlling mechanisms include diffusion/dissolution, chemical reactions, the use of osmotic pump devices, and multiple layer tablet designs, all of which incorporate numerous manufacturing steps and many associated drug release mechanisms. In general, drug release parameters (duration of drug release, release rate), expected steady state plasma drug concentrations and dosage form index are calculated and these are compared with theoretical controlled release parameters developed based on the pharmacokinetic characteristics of the drug (See reference 5). As mentioned before, the common CR approach is to combine a rapid-release dose fraction with a fraction having pseudo-first order release characteristics. When absorption is not rate limiting, the ideal approach to this situation is a zero-order drug delivery of the drug to the absorption site. Thus, when absorption is not the rate limiting step, the release of the drug from the dosage form becomes important. A zero-order drug release to the absorption site will result in steady-state plasma concentration. The fact that drug in a CR dosage form is not absorbed at a zero-order rate does not imply a faulty product. The goals of CR therapy can be achieved with first-order absorption. Gibaldi and Perrier have demonstrated that for many drugs, acceptable steady-state plasma level-time profiles may be obtained assuming absorption half-lives of about 3-4 hours (7). Their criterion of acceptability was a low $C_{av,max}/C_{av, min}$ quotient, where the plasma concentrations are the time averaged maximum and minimum steady state values, respectively. Theeuwes and Bayne have termed this ratio the "dosage form index" and used it successfully to compare

acetazolamide CR products (8). It is widely held that zero-order in vivo release is the intent, but this is incorrect – the ultimate goal is zero-order systemic drug appearance. Zero-order in vivo release will produce zero-order systemic absorption only if: (1) the gut behaves as a one compartment model, i.e., its various segments are homogenous with respect to absorption; and/or (2) drug release rate is rate limiting for absorption. This has to be always kept in the mind. Just developing an in vitro zero-order drug release system may not be the only criteria. Scientists have successfully predicted plasma concentration-time profiles for drugs in oral CR dosage form based on in vitro dissolution and in vivo oral solution absorption profiles. This is under the implication that one of both of the above assumptions are mathematically valid under certain situations.

1.6   CR Formulations Used in Different Routes of Administration and the Salient Features

The goal of every drug delivery system is to deliver the precise amount of a drug at a pre-programmed rate to the desired location in order to achieve the drug level necessary for the treatment. A number of design options are available to control or modulate the drug release from a dosage form. Majority of the CR dosage form fall in the category of matrix, reservoir or osmotic system. This is true for all the routes of administration. In matrix system, the drug is embedded in polymer matrix and the release takes place by partitioning of drug into the polymer matrix and the release medium. In contrast, reservoir systems have a drug core surrounded\coated by the rate controlling membrane. However factors like pH, presence of food and other physiological factors may affect drug release from conventional controlled release systems. Osmotic systems utilize the principle of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the properties of drug and system. Some of these issues are discussed in this section taking into consideration each route of administration.

1.6.1 Oral CR formulations

Over the last few years, consumers witnessed the wide spread and availability of a plethora of oral controlled release (CR) products in the marketplace. For example, by 1998, the U.S. Food and Drug Administration (FDA) approved 90 oral CR products for marketing.

From 1998 to 2003, in just five years, the FDA approved an additional 29 new drug applications that used CR technologies. Consequently, oral CR technologies are becoming more complex and encompassing multiple presentations. It is well recognized in the pharmaceutical industry that oral CR dosage forms can be defined based on release-profile characteristics or the underlying release- controlling mechanism.

The technologies behind oral drug delivery have emerged from the mainstream pharmaceutical industry and have become influential forces in their own right, as evidenced by the burgeoning "drug delivery companies" that are at the forefront of innovation and hold their own niche market. CR products evolved with simple matrix technology. Several research articles in the 1950s and 1960s reported simple matrix tablets or monolithic granules. For the first time in 1952, Smith Kline & French introduced the Spansule, a timed-release formulation that launched a widespread search for other applications in the design of dosage forms. The aim behind the development of these dosage forms was to achieve a constant release of the entrapped drug. As a reason products like Procardia XL were developed and became one of the blockbusters in the market for the past several years. On the basis of zero-order drug release concept, the zero-order osmotic delivery system used in Procardia XL was developed.

1.6.1.1   Currently marketed oral CR products

The development of technology in leaps and bounds and the availability of various polymers and the machinery available to prepare novel designs has currently resulted in the development of these oral CR products in a reproducible manner. The main oral drug-delivery approaches that are currently available include:

1. Coating technology using various polymers for coating tablets, nonpareil sugar beads, and granules.
2. Matrix systems made of swellable or nonswellable polymers.
3. Slowly eroding devices.
4. Osmotically controlled devices.

Two distinct drug release profiles, extended and delayed release, are achievable, and they can be used in various combinations to provide the desired release rate. Three delivery systems dominate today's market of oral CR products: matrix, reservoir, and osmotic systems. Release mechanisms from these dosage forms have been the subjects of extensive studies. Among them, diffusion plays a key role in both matrix and reservoir systems, whereas osmotic pressure is the predominant

mechanism of drug release from osmotic systems and could also play a role in a reservoir system. Owing to technology accessibility, manufacturing, cost, and other considerations, diffusion-based CR products are used more widely than osmotic systems. For example, of the 29 CR products approved by the FDA between 1998 and 2003, 12 were based on matrix systems and 10 based on reservoir technologies compared with 2 osmotic tablets. In the design of single-unit, matrix-type controlled release dosage forms, conventional tablets are still popular. The advancement of granulation technology and the array of polymers available with various physicochemical properties (such as modified cellulose or starch derivatives) have made the development of novel oral controlled release systems possible. Matrix devices made with cellulose or acrylic acid derivatives, which release the homogeneously dispersed drug based on the penetration of water through the matrix, have gained steady popularity because of their simplicity in design. The drawback of matrix-type delivery systems is their first-order drug delivery mechanism caused by changing surface area and drug diffusional path length with time. This drawback has been addressed by osmotic delivery systems, which maintain a zero-order drug release irrespective of the pH and hydrodynamics of the GI tract. Multiparticulate systems are gaining favor over single-unit dosage forms because of their desirable distribution characteristics, reproducible transit time, and reduced chance of gastric irritation owing to the localization of drug delivery. Although several technologies for the production of microparticulate systems have been designed, thus far the mainstream technologies are still based on spray-drying, spheronization, and film-coating technology. Reservoir type of devices are very often mentioned. However, there is a problem of manufacture reproducibility and lack of safety.

1.6.1.2   Special features in the design of oral CR products

The design of oral CR products is based on several factors. The properties of the drug to be incorporated are important. Drugs with long elimination half lives are generally undesirable for CR products. Exception is for the use of this technology to prevent toxic effects due to a peaking effect or to reduce the dose. Also the pharmacological effect for some drugs is inherently sustained. For these drugs CR formulations may be redundant. Ex. 1. The drug binds to tissues (tissue bound ACE inhibitors). For these drugs, less frequent dosing is needed even though the drug may have a short half-life. 2. The drug that has irreversible effects (the inhibition of platelet cyclo-oxygenase by aspirin). 3. The relationship between response and plasma/blood concentrations is relatively flat or if the dose given results in concentrations which are in the plateau region of the

dose-response relationship (thiazides in hypertension). 4. The drug is metabolized to pharmacologically active metabolite (s), which are more slowly cleared than the parent drug (quinapril, trandolapril and venlafaxine). Several pharmacokinetic parameters associated with the drug also have profound influence on the suitability of a drug for CR formulation. To avoid accumulation in the body, generally drugs with biological half-life between 2-6 hr is preferred. If a drug that undergoes extensive first-pass metabolism is incorporated in a CR product its bioavailability may be significantly impaired. If the absorption site is limited, absorption is likely to decrease and variable bioavailability will occur for CR dosage forms. Drugs which undergo non-linear elimination due to drug metabolism, saturation or other factors may not be good candidates for oral CR dosage forms. Drugs that undergo non-linear absorption are also not suitable candidates for oral CR dosage forms. Undesirable adverse reactions may develop by using CR dosage forms. Prior to its application to a suitable drug, the following factors should be clarified: 1. The clinical response should be correlated with blood-drug concentrations or tissue concentrations at the site of action. 2. There should be no induction or inhibition of the metabolizing enzymes by prolonged concentration of the drug in the blood; nor it should chance the casual change of pharmacological response or lead to possible tolerance or addiction for the drug. 3. There should be no interactions with other drugs due to protein binding. The major purpose for developing CR products of the drug is generally to maintain the blood concentration of the active ingredient at therapeutically effective levels. Therefore, it is desirable that average minimum effective concentration and optimal therapeutic concentrations be clarified for each drug by evaluating blood concentrations of the active ingredient or therapeutic moiety(s) including active metabolite(s) in relation to drug efficacy. The intra- and intersubject variations should be investigated for further confirmation of these levels. It is also desirable to investigate toxic blood drug concentrations. If the effective blood drug concentration is not known, estimates should be made from dose levels, blood concentrations, and clinical data based on the immediate release drug product. If effective blood drug concentration is unclear, the usefulness of the CR forms should be demonstrated by well-designed clinical studies.

   Biopharmaceutical properties of the active ingredient incorporated into CR dosage form should be well known in rational formulation design. The following factors should be thoroughly investigated and understood: 1. location of major absorption sites or specificity in the site of absorption, 2. absorption rate, 3. the elimination half life of the drug,

4. whether absorption is non-linear due to the saturated drug absorption, first pass effects, or other reasons, 5. whether elimination is non-linear due to drug, 6. The effect of food, drugs likely to be used concurrently and physiological factors such as renal or hepatic function on the absorption, distribution, metabolism and excretion of the drug be studied and evaluated. In addition, the study effects of age, sex and smoking on the pharmacokinetics of the drug may be useful. Also, chemical and physicochemical properties of drugs, especially, pH- solubility characteristics should be known in advance. There are certain properties of the drug, which must be taken into consideration for the design of oral CR dosage form. The aqueous solubility and intestinal permeability of drug compounds are of paramount importance. A drug which has high solubility at intestinal pH and absorbed by passive diffusion has an ideal characteristics for fabrication of oral CR dosage form. A drug with high solubility and high permeability is also a best case for CR. Low soluble and low permeable drugs pose a worst case for oral CR formulations. A $p < 0.5 \times 10^{-6}$ mms^{-1} is not at all suitable for oral CR formulations. This is because once the drug is dissolved in the GIT, its permeability across the membrane becomes important. More than 90% absorption in vivo may be expected for compounds with permeability coefficient $p > 4 \times 10^{-6}$ mms^{-1}, whereas less than 20% absorption is expected when $p < 0.5 \times 10^{-6}$ mms^{-1}. A drug with no site-specific absorption characteristics is preferred. A drug with low aqueous (< 1 mg/ml) may already possess inherent sustained release potential. Generally, a dose preferable between 125-325 mg is suitable for oral CR dosage forms. However, this is slowly changing. Now technology is veering towards high dose oral CR formulations.

Physiological factors that affect the absorption should be thoroughly considered. The release of active ingredient from a CR formulation and its absorption are very much influenced by the physiological factors in the GIT. CR dosage forms are more susceptible to these factors than immediate release dosage forms. Therefore, the possible effects of the physiological factors should be fully considered for the dosage form design. The physiological characteristics of the gastrointestinal tract (the volume, composition, pH, surface tension and viscosity of the gastrointestinal content, and gastrointestinal motility) vary greatly from site to site. CR dosage forms remain in the gastrointestinal tract longer than conventional preparations. Therefore, physiological conditions of the gastrointestinal tract can affect the release of active ingredients of these forms much more than release from conventional forms. Noteworthily, gastric pH varies from acidic to neutral, and these variations can affect

release of the active ingredient from the dosage form. These points should be considered when a formulation is being designed and assessed. If the drug is intended for use in a specific subpopulation, attentions should be paid to the specific physiology of the subpopulation.

The transit rate of a dosage form through the gastrointestinal tract is known to depend on the formulation properties such as size, form, specific gravity and adhesiveness of the preparation and physiological properties such as the length, size and motility of the gastrointestinal tract; and on the composition and volume of the gastrointestinal content. It is also affected by food, diseases, posture, and stress. The bioavailability of drugs often depends on the gastrointestinal transit rate of the dosage form. Therefore, the traveling characteristics of the dosage form through the gastrointestinal tract should be fully considered in designing advantageous dosage forms.

Desirable criteria of performance for CR dosage forms are: 1. duration of appropriate blood drug concentration for a sufficient time with minimal influence of food and physiological conditions of the gastrointestinal tract. 2. minimal contribution to intra- and intersubject variation. To select the best possible dosage form, all candidate forms should be fully tested for release characteristics. Moreover the pharmacokinetic profile should be evaluated in an appropriate species of animal or volunteer.

The release of the active ingredient from the preparation in the gastrointestinal tract is affected by many physiological factors including the mechanical force exerted by the digestive tract in relation to its movement, and the volume, composition, pH, surface tension, and viscosity of the gastrointestinal fluid. Therefore, the in vitro release behaviors should be investigated under as many conditions as possible to understand possible effects of gastrointestinal variables on in vivo release. To achieve stable blood concentrations, it is generally desirable to prepare prolonged release dosage forms whose release rates are minimally pH dependent. Therefore, release of the active ingredient should be evaluated at multiple levels of pH, such as 1.2, 4.0 and 6.8, representing typical gastrointestinal pH variation. Considering the variation in gastrointestinal motility; agitation rates should also vary more than 2 levels among 50, 100 and 200 rpm, when the paddle method is used, at an appropriate pH. If it is anticipated that the release rate is influenced by the wettability, ionic strength and composition of the test medium, their effects should also be investigated. It is also desirable to perform release tests using different kind of apparatus. On the other hand, taking into consideration the variation of mechanical stress in the

gastrointestinal tract, the drug release from CR dosage forms containing an active ingredient with a narrow therapeutic window should be tested by the methods having a high mechanical stress, such as JP disintegration test method, the rotating flask method using beads and solubility simulator.

The specifications for drug releases should be established for quality control of CR dosage forms. Basically, it is desirable to employ the release tests which can predict the blood level profile of the drug as precisely as possible. It is also desirable to set the specification including sampling time and amount of drug to be released so as to show the release profile as accurately as possible. The tolerable range of the drug release change depending on the effect of the release rate on absorption or a related pharmacodynamic property (therapeutic window, toxicity or adverse reactions). Therefore, based on the relation between release rate and blood concentration or pharmacological effects, the tolerable range should be set within limits which do not allow great changes in blood concentrations or in clinical efficacy. The narrow tolerance limits should be set as much as possible to decrease the variation in drug release which will provide stable clinical effects. If the relation between the release rate and blood concentration is not clear, or if sufficient data are not available to prove the correlation, it is difficult to set rational specification. In such a case it is desirable to set specifications using the second method (paddle method) in the Japanese Pharmacopoeia at sampling time points of 20-40%, 40-60%, and more than 70% of the labeled amount of the active ingredient is released. If 100 rpm and 900 ml of test fluid was used for the paddle method, the tolerance ranges at 1st, 2nd and 3rd points should be set within 15%, 15% and 10% of the average release, respectively. At the 3rd sample point, only lower limit is acceptable instead of the tolerance range. The acceptance criteria of the drug release follow the criteria of dissolution or release tests of JP XI or USP XXI. Specimens for long term stability tests should be subject to dissolution testing and comply with the standards of the specifications.

As far as possible, the pharmacokinetics of the prolonged release dosage form should be compared with the immediate release product in healthy volunteers. Pharmacokinetic evaluation should be made, based on blood concentration data, except for the case that the concentrations of the active ingredient can be determined at the site of action whose effective concentrations are known. Data on drug concentration in the urine, saliva, or other body fluids will be accepted only when the concentrations of the active ingredient in the blood or at the site of action are correlated with that in these fluids. Unless the drug shows linear

pharmacokinetics within the clinical dose range, the investigation should be made at two dose levels, high and low.

(i)   *Single dose study:* The usefulness of the new CR dosage form given according to the dosage regimen should be evaluated by comparing the blood concentration with that of the immediate release dosage form or alternative forms such as solution or a powder; or with a prolonged release product which has already been approved, when better prolonged release characteristics are claimed. The parameters to be compared are AUC (zero to the final sampling time), AUC (0-∞), Cmax, the duration of the minimum effective concentration, or optimal effective concentrations of the active ingredient if these concentrations are known or can be estimated. It is desirable to determine the time to reach the minimum effective concentration or the optimal effective concentration, Tmax, absorption rate constant, elimination rate constant, clearance, extent of absorption and MRT and VRT by the moment analysis method.

(ii) *Multiple dose study:* Prior to a multiple dose study, a blood concentration profile at steady state for multiple dosing of both standard and test dosage forms should be simulated from the single dose pharmacokinetic trials. In the multiple dose studies, it should be ascertained that Cmax and Cmin at steady state are within the estimated ranges, and the usefulness of the prolonged release dosage form should be evaluated by comparing it with the reference product in 1) Cmax, 2) Cmin, 3) the difference between Cmax and Cmin or the ratio (dosage form index, Cmax/Cmin), and the duration of the minimum effective concentration or that of optimal effective concentration. For drugs with non-linear absorption or elimination, those with a narrow therapeutic window, or those which may cause severe adverse reactions, the blood concentration profile at steady state should be characterized by multiple dose studies. When multiple dose studies in healthy volunteers are not done, the usefulness of the prolonged release dosage form should be shown using the simulated parameters, where it is necessary to confirm that Cmax and Cmin are within the predicted range, by monitoring blood concentrations in clinical studies.

Factors which might affect the pharmacokinetics of a CR dosage form should be studied in which food is particularly an important factor because it is know to affect transit of dosage forms in gastrointestinal tracts, disintegration, and release of the drug. Therefore, the blood

concentration profiles of the prolonged release dosage form should be compared between fasting and fed conditions. If a significant effects of food was observed, a special caution should be included in the dosage regimen (i.e. indication of drug administration only after meals), and it should be clarified whether the food effect was related to the drug itself or dosage forms by performing similar food studies using the drug solution or the immediate release product, although the studies are not needed when there is published evidence. In addition, as far as possible, it is desirable to clarify other factors of food (e.g., the volume and composition of meal, and intervals between food and drug administration) affecting the in vivo release and absorption. It is also desirable to investigate diurnal variations of pharmacokinetic parameters.

The clinical usefulness of the prolonged release dosage form should be shown comparing it with its already approved immediate release product or its already approved CR product (if a better CR dosage form is claimed). If the relation between the pharmacological effectiveness and blood concentration is unclear, the usefulness should be proved by the well-controlled clinical studies where the effective and toxic concentrations should be investigated by monitoring blood concentrations of the drug. The appropriate dosing regimen should be established during Phase I and II clinical studies in which it is recommended that the blood concentrations are monitored during Phase II clinical trials to establish a better dosing regimen. Factors that are to be considered in establishing dosing regimen include: 1. Overdose or dose dumping: Sustained release dosage forms might be more likely to produce significant adverse and toxic effects than immediate release dosage forms in case of overdose or dose dumping because of the higher doses of active ingredients which are absorbed over a prolonged time. Dose dumping, e.g. resulting from crushing by the teeth, may be another problem with prolonged release dosage forms. This is of particular concern for drugs with a narrow therapeutic window, and so studies are desired to establish preventive measures and actions to be taken in such cases. 2. Disease state: The physiological changes in gastrointestinal tract, liver, kidneys, or heart due to diseases often affect absorption, distribution and elimination of drugs and there is a possibility that CR dosage forms are particularly susceptible to the changes. In such cases, the dosing regimen should be studied and established as to reflect the pathological changes. 3. Combination therapy: If any other drug is used concurrently, it may affect the absorption, distribution, and elimination of the drug contained in the CR dosage form. As a result, blood concentrations of the drug may be changed, and this may affect the efficacy. The possible effect of drugs

which might be used together in practice should be studied, and suitable indications and special warnings for the concurrent use of other drugs should be established. Dosing guidelines have to be set very well in advance. Recommendations for dosing conditions, frequency of dosing per day, and dose levels (initial dose, maintenance dose, dose adjustment for insufficient response, and the maximum tolerable dose) should be established, based on the available pharmacokinetic data during Phase II clinical studies. The action to be taken if toxic signs or adverse effects develop should also be specified in these guidelines. Detailed dosing guidelines including information about dose adjustment based on blood concentration monitoring or changes in renal clearance of each patient may be useful to maximize the therapeutic efficacy by making the utmost use of the advantages of the CR dosage form. It is desirable to set up corresponding detailed guidelines particularly for CR products containing A) drugs, blood concentrations of which may change strikingly by minimal changes in dose (drugs with non-linear absorption or elimination), B) drugs, the clearance and blood concentrations of which are susceptible to physiological conditions, age and so forth, C) drugs with a narrow therapeutic window, and D) drugs which might cause tolerance and/or severe adverse effects

1.6.1.3   Techniques of preparation and manufacture

Oral drug delivery is the largest and the oldest segment of the total drug delivery market. It is the fastest growing and most preferred route for drug administration. The fabrication of existing forms of orally administered pharmaceutical product is a relatively inexpensive and straightforward process. For example the process may involve insertion of the beneficial substance into a gelatin shell to form a capsule, or it may involve forming a drug and filler into a tablet. In general, lactose is the most common excipient in the tablet compression process. However, dose dumping may occur with hydrophilic drugs when incorporated as lactose tablets. One of the effective ways of prevention of dose dumping is to formulate into CR products. Materials currently used in known orally administered pharmaceuticals are relatively difficult to engineer in relation to control of rate and location of drug release. Variations, in gastrointestinal conditions, from human patient to human patient are not easily accommodated by existing orally administered products. The same methods with some modifications can be used to fabricate oral CR products. Along with the conventional techniques of preparation, there are several other improvements in the techniques and currently there are several other patented technologies.

As of today, tableting is the simplest, most common, and most economical method of processing an active agent into a drug-delivery product. Most of the times tablets are mainly intended for oral delivery of the active ingradient. However, some parenteral depot formulations such as tableted or compressed wafers are available. Examples of such tablet forms of controlled release implant depots intended for parenteral or local delivery is Gliadel Wafer. The tableting process involves feeding a metered amount (usually from 0.5 to 5 g) of a "granulation" (large particle blend) of an active agent to the dies of a tableting press where the granules are compressed into a tablet of the desired shape. Some manufacturers use intricate shapes for product identification. The premixed granulation contains the active and various excipients to modify the flow, compaction, die release, and dissolution characteristics of the tablet. Granulation is accomplished wet (using solvent) or dry (using no solvent) by high intensity mixers or fluidized-bed granulators. Although single-cavity presses can be used for specialized applications and testing, high-speed rotary presses capable of producing thousands of tablets per minute are typical. The pressures used in tablet compression are quite high, ranging from 50 to 500 mPa; therefore, the dies used in tableting are typically made with high-strength, surface hardened alloys. The same principles of tablet preparation and manufacture can be applied to controlled release oral tablets. These are much more sophisticated as the demand for controlled release has increased. Recently technology can produce bilayer tablets providing two different release rates for a drug. The technologies use different polymeric excipients in the tablet providing both immediate and sustained release. Various over-the-counter analgesics use this technology. Tablets composed of compacted microencapsulated beads have also been developed to provide both sustained release and protection from the irritating effects of certain drugs such as non-steroidal anti-inflammatory drugs. The drug is microencapsulated in a separate process, such as the fluidized-bed process, and then incorporated into the tableting formulation. Effervescent tablets are also produced to provide chewable and fast-dissolving tablets for patients who have difficulty swallowing. The drug is again typically incorporated into the effervescent tablet formulation as microencapsulated beads. Many tableted products are also subsequently coated to provide controlled release products. Coating usually takes place in a pan coater, which is a rotating drum, similar to a clothes drier, which tumbles the tablets in front of a spray nozzle for application of the coating. The coating is dried by a continuous flow of process air. The process air is often heated and solvent reclamation is used for organic-

solvent based coatings. The batch sizes for pan coating can vary between 100 and 2,000 kg. Small laboratory models are also available. Various wax and enteric coatings are applied in this manner. For very small tablets, fluidized-bed coating may also be used.

The other types of oral SR dosage forms are available in the forms of capsules. By far the most versatile of all dosage forms is the gelatin capsule. Gelatin capsules can be filled with powders, small pellets or small tablets, liquids, or semisolids, as well as some combinations of these forms. The capsule also provides efficient taste-masking. The drug product is released by dissolution of the gelatin in the stomach. Gelatin capsules can be prepared from hard or soft gelatin; however, hard-gelatin capsules are more versatile for controlled drug delivery. Hard-gelatin capsules are available in several different sizes, and high-speed filling machinery, capable of filling 1,500 capsules per minute, is available. The machines typically consist of a drug hopper, a capsule hopper, a dose metering device, a dose chamber, a filling or tamping pin, a capsule tray, and a finished-capsule collection bin. The capsules are automatically opened, filled, and closed during the manufacturing process. Technologies have been developed whereby controlled release beads and mini-tablets are used to fill a gelatin capsule for convenient administration of an oral, controlled release dosage form. Examples of such products are the sustained release cold medications, where sustained release antihistamines, antitussives, and analgesics are first preformulated into extended release microcapsules or microspheres and then placed inside a gelatin capsule. Another example is enteric-coated lipase minitablets that are placed in a gelatin capsule for more effective protection and dosing of these enzymes.

Several factors are needed to be considered for the development of the oral SR dosage forms. Apart from those developments mentioned previously, several other techniques with different principles are also worthy to know. For instance, use of hydrophilic matrices for oral extended release of drugs is a common practice in the pharmaceutical industry. Hydrophilic matrices of high gelling capacity are of particular interest in the field of controlled release. Other matrix types of tablets with modifications and different other polymers also are in use. In the tablet matrix system, the tablet is in the form of compressed compact containing an active ingredient and tablet excipients such as filler, antiadherent and lubricant. The matrix may be compressed by direct compression of dried powder mixtures or granules. Unlike reservoir and osmotic systems, products based on matrix design can be manufactured using conventional processing and equipment. Second, development time

and cost associated with a matrix system generally are viewed as favorable, and no additional capital investment is required. Lastly, a matrix system is capable of accommodating both low and high drug load and active ingredients with a wide range of physical and chemical properties. As with any technology, matrix systems come with certain limitations. First, matrix systems lack flexibility in adjusting to constantly changing dosage levels, as required by clinical study outcome. When a new dosage strength is deemed necessary, more often than not a new formulation and thus additional resources are expected. Furthermore, for some products that require unique release profiles (e.g., dual release or delayed plus extended release), more complex matrix-based technologies such as layered tablets (e.g., Allegra D) will be required. Nevertheless, we expect continued popularity of matrix systems because they have demonstrated success across a wide range of product profiles. With the growing need for optimization of therapy, matrix systems providing programmable rates of delivery become more important. Constant rate delivery always has been one of the primary targets of controlled release systems, especially for drugs with a narrow therapeutic index. Over the past 40 years, considerable effort has been and continues to be expended in the development of new delivery concepts in order to achieve zero-order or near-zero-order release. Examples of altering the kinetics of drug release from the inherent nonlinear behavior include the use of geometrical factors (cone shape, biconcave, donut shape, hemisphere with cavity, core in cup, etc.), erosion/dissolution control and swelling control mechanisms, nonuniform drug loading, and matrix-membrane combinations. Some of the systems are difficult or impractical to manufacture.

A typical reservoir system consists of a core (the reservoir) and a coating membrane (the diffusion barrier). The core contains the active ingredients and excipients, whereas the membrane is made primarily of rate-controlling polymer(s). A reservoir system normally contains many coated units (particulates) such as beads, pellets, and minitablets. Unlike single-unit tablets, the number of particulates in a reservoir system often is sufficient to minimize or eliminate the impact of any coating defect associated with a limited number of units. Another attractive feature of reservoir systems is that tailored drug release can be obtained readily by combining particulates of different release rates. An increasing number of products (e.g., Metadate CD and Ritaline LA) have been introduced using such a concept. Lastly, reservoir systems offer the flexibility of adjusting to varying dosage strengths without the need of new formulations. This is highly desirable during clinical development programs, where dose levels

frequently are revised based on study outcome. Typically, special coating equipment such as the Wurster coater is required to apply the coating material uniformly. Scale-up of such processing can be challenging and may require changes in formulations between scales in order to maintain similar release characteristics. In addition, it has been recognized that dissolution of certain reservoir system–based products may change on storage. One way to minimize this problem is adding a curing step at the end of the coating process.

Dispensing systems for the delivery of compositions of matter are well known to the prior art. These systems generally delivery their composition by diffusion, for example, from an enclosed capsule or by diffusion from a multi-structured device having a wall formed of a known polymer permeable to the composition into a selected environment. However, there is a large category of compositions that cannot be delivered by the prior art delivery systems because of at least one feature inherent in these devices which adversely affects their rate of release from the system or substantially prevents the release of the composition from the system. For example, many compositions cannot be delivered from a diffusion controlled delivery system because their permeation rate through the rate controlling material comprising the system is too small to produce a useful effect, or in many instances the composition molecules are too big and will not diffuse through the rate controlling material forming the device. Also, there is an additional class of useful products that cannot be satisfactorily delivered by diffusion devices because of a particular chemical characteristic of the product. This additional class includes salts that because of their ionic character will not diffuse through most polymers and polymeric like materials and unstable polar compounds that cannot be formulated into a satisfactory composition suitable for storage and delivery from a prior art device. In all these situations, use of an osomotic pump for oral CR delivery is a solution. An osmotic drug (or other beneficial substance) delivery system comprises a multi-chamber compartment formed by an external shell and one or more chamber-dividing walls each with a small orifice, of a microporous material and overlayers of semipermeable membranes completely covering the outer shell of all but one chamber and substantially covering the outer shell of the remaining chamber. Osmotic agents, adjuvants, enzymes, drugs, pro-drugs, pesticides and the like are incorporated in the chambers covered by the semipermeable membrane, and external fluids that diffuse into those chambers form solutions and by osmotic pressure are forced through the orifice to the drug chamber to

form a solution thereof and then through the exposed microporous shell to the exterior of the device at a rate controlled by the permeability of the semipermeable overlay and the osmotic pressure gradient across the shell.

Osmotic devices can be manufactured using a variety of methods. In the first method, manufacturing the device with an agent compartment and an osmogent compartment separated by a film, which film is movable from a rested to an expanded state is present. The device delivers agent by fluid being imbibed through the wall into the osmogent compartment producing a solution that causes the compartment to increase in volume and act as a driving force that is applied against the film. This force urges the film to expand against the agent compartment and correspondingly diminish the volume of this compartment, whereby agent is dispensed through the passageway from the device. While this device operates successfully for its intended use, and while it can deliver numerous difficult to deliver agents, its use is somewhat limited because of the manufacturing steps needed for fabricating and placing the movable film in the device. The osmotic device in an another method of manufacture comprises a semipermeable wall surrounding a compartment containing a beneficial agent that is insoluble to very soluble in an aqueous biological fluid and an expandable hydrogel. In operation, the hydrogel expands in the presence of external fluid that is imbibed into the device and in some operations mixes with the beneficial agents, thereby forming a dispensable formulation that is dispensed through the passageway from the device. This device operates successfully for its intended use, and it delivers many difficult to deliver beneficial agents for their intended purpose. Similarly, several techniques can be used in the manufacture of oral osmotic pumps. Based on the availability the following comprehensive information regarding osmotic pumps can be provided. There are two broad categories of osmotic pumps: elementary osmotic pumps and osmotic pumps having an expandable push layer or material. Elementary osmotic pumps are typically formed by compressing a tablet of an osmotically active drug (or an osmotically inactive drug in combination with an osmotically active agent or osmagent) and then coating the tablet with a semipermable membrane which is permeable to an exterior aqueous-based fluid but impermeable to the passage of drug and/or osmagent. One or more delivery orifices may be drilled through the semipermeable membrane wall. Alternatively, orifice(s) through the wall may be formed in situ by incorporating leachable pore forming materials in the wall. In operation, the exterior aqueous based fluid is imbibed through the semipermeable membrane wall and contacts the drug

and/or salt to form a solution or suspension of the drug. The drug solution or suspension is then pumped out through the orifice as fresh fluid is imbibed through the semipermeable membrane.

1.6.2 Parenteral CR Formulations

The parenteral administration route is still the most effective and common form of delivery for macromolecules (such as peptides and proteins), for active drug substances with metabolic liabilities (i.e. drugs for which the bioavailability is limited by high first pass metabolism effect or other physico-chemical limitations) and for drugs with a narrow therapeutic index (i.e. several anticancer drugs - where slow infusion is the best way to control the exact pharmacokinetic into the blood). Moreover, at the same time, this administration route is the least preferred by patients because of the discomfort and inconvenience that it causes. For this reason, whatever drug delivery technology that can reduce the total number of injections throughout the drug therapy period is truly advantageous not only in terms of compliance, but also for the potential to improve the quality of the therapy. Such reduction in frequency of drug dosing is achieved, in practice, by the use of specific formulation technologies that guarantee that the release of the active drug substance happens in a slow and predictable manner. For several drugs, depending on the dose, it may be possible to reduce the injection frequency from daily to once or twice monthly or even less frequently. In addition to improving patient comfort, less frequent injections of drugs in the form of depot formulations smoothes out the plasma concentration-time profiles by eliminating the hills and valleys. Such smoothing out of the plasma profiles has the potential to not only boost the therapeutic benefit, but also to reduce unwanted events and side effects. Continuous release profiles are suitable to generate on 'infusion like' plasma level time profile in the systemic circulation without the necessity of hospitalization. This can be achieved by IV infusions which need hospitalization. However, recently several novel delivery systems for parenteral delivery of drugs have been developed.

Drug delivery systems that can precisely control drug release rates or target drugs to a specific body site, although a relatively recent technology have had an enormous medical and economic impact. New drug delivery systems impact nearly every branch of medicine and annual sales of these systems are far in excess of 10 billion dollars. However, to

intelligently create new delivery systems or to understand how to evaluate existing ones, much knowledge is needed. New approaches in treating diseases such as alcoholism, cancer, heart disease, and infectious diseases using parenteral sustained release systems are needed to be examined. Delivery of vaccines, contraceptive agents, anticalcification agents, orthopedic agents, and veterinary agents is the need of the hour. Novel polymeric materials including polyanhydrides, chitosan polyesters, polyphosphates, polyphosphazenes, hydrogels, bioadhesive materials, and poly(ortho esters) are being evaluated for their utilization in parenteral sustained release dosage forms. Extensive characterization approaches including differential scanning calorimetry, gel permeation chromatography, spectroscopy, X-ray photoelectron spectroscopy, X-ray powder diffraction, and surface characterization are being explored. New areas related to drug delivery such as gene therapy, blood substitutes, food ingredients, and tissue engineering come into the perview of parenteral sustained release dosage forms. An analysis of various routes of administration for parenteral delivery should be investigated. Different controlled release designs such as osmotic pumps, pendent-chain systems, membrane systems, nanoparticles, and liposomes needs examination. Further, patents, regulatory issues, manufacturing approaches, economics, in vitro-in vivo correlations, pharmacokinetics, release kinetics, assays, diagnostics, and related issues are considered for investigations.

Controlled and sustained release parenteral drug delivery systems include liposomes, microspheres, suspensions, gels, emulsions, and implants. They are generally used to improve the therapeutic response by providing appropriate dosing strategies (this may be constant or pulsatile release). Such systems can be considered safer than conventional parenteral dosage forms since less drug is required and since the drug may be targeted to the in vivo site, avoiding high systemic levels. Due to the lower dosing frequency and simpler dosage regimes, patient compliance can be improved with these dosage forms. For example, microspheres and larger implantable devices can be used to modify release over periods of months to years. Liposomes may achieve targeted delivery both by passive and active means following intravenous administration and are utilized to target toxic drugs, such as anti-cancer agents, to avoid systemic side effects. Perhaps the most complex of the controlled drug delivery systems are the human parenteral systems.

Biodegradable microsphere and implantable-rod systems which deliver peptides for treatment of prostate cancer have been developed and approved in several countries. Implantable osmotic pumps are used in laboratory animals to conveniently evaluate the controlled delivery of active agents under a variety of conditions. Implantable silicone rods have also been developed and marketed for delivery of steroidal hormones. Prior to the development of these dosage forms, parenteral sustained release dosage forms in the forms of drug suspensions were known to the pharmaceutical industry. These are the first controlled release parenteral dosage forms. While for a series of sparingly soluble active drug substances, such as steroids, sterile aqueous, oleaginous suspensions or oily solutions are formulation approaches that allow an extended duration of action (in these cases the release of the active from the injected formulations is governed quite exclusively by the dissolution kinetic of the active drug substance, which can last up to several months according to the administered dose and the physico-chemical properties of the drug). However, for the majority of the drug substances, such as peptides and macromolecules, it is mandatory to utilize specific drug delivery technologies that can tailor and govern the release profile of the active drug substance from the formulation itself. As the reason various parenteral sustained release dosage forms other than those utilizing drug suspensions was developed. Now, we see this area is attractive research area for a pharmaceutical scientist as well as several such CR products are now available in the market.

A controlled release parenteral dosage form is usually selected when there are problems associated with oral delivery (eg, gastric irritation, first pass effects or poor absorption) and a need for extended release and/or targeted delivery (eg, rapid clearance, toxic side effects). The CR dosage form selected may be dependent on the desired effect (eg, long term localized release) as well as compatibility of the drug with the manufacturing process. Examples of applications for CR parenteral delivery include: fertility treatment, hormone therapy, protein therapy, infection treatments (antibiotics and antifungals), cancer therapy, orthopedic surgery and post-operative pain treatment, chronic pain treatment, vaccination/immunization, treatment of CNS disorders, and immunosupression.   Approved CR parenteral products are listed in Table 1.1.

Table 1.1 Approved Parenteral CR Products.

Trade Name	Active Ingredient	Approval Date*
Suspension Products:		
Depo-Medrol	Methylprednisolone	pre-1982
Depo-Provels	Medoxyprogesterone	pre-1982
Celestone Soluspan	Betamethasone	pre-1982
Insulin	Lente Unltralente NPH	pre-1962
Plenaxis	Abarelix	2003
Microsphere Products:		
Lupron Depot	Leuprolide	1989
Sandostatin LAR	Octreotide	1998
Nutropin Depot	Somatropin	1999
Trelstar Depot	Triptorelin	2000
Plenaxis	Abarelix	2003
Suspension Products:		
Depo-Medrol	Methylprednisolone	pre-1982
Depo-Provels	Medoxyprogesterone	pre-1982
Celestone Soluspan	Betamethasone	pre-1982
Insulin	Lente Unltralente NPH	pre-1962
Plenaxis	Abarelix	2003
Liposome Products:		
Doxil	Doxorubicin	1995
Daunoxome	Daunorubicin	1996
Ambisome	Amphotericin B	1997
Depocyt	Cytarabine	1999
Lipid Complex Products:		
Ambelcet	Amphotericin B	1995
Amphotec	Amphotericin B	1997
Implant Products:		
Norplant	Levonorgestrel	1990
Gliadel	Carmustine	1996
Zoladex	Goserelin	1989
Viadur	Leuprolide	2000

*Approval dates refer to the date of approval by US FDA.

Although apart from polymeric devices, several dosage forms that can sustain the drug levels in the systemic circulation which include osmotic

pumps, silicone devices, so far, only drug delivery devices based on polymers and copolymers deriving from lactic acid (LA) enantiomers, glycolic acid, and e-caprolactone (abbreviated as PLA, PGA, and PCL, respectively) have been commercialized. The prospective applications include devices to treat cancer, drug addiction, and infection, as well as drugs for contraception, vaccination, and tissue regeneration. A number of products are commercially available such as Decapeptyl'", Lupro Depots, Zoladexv, Adriamycinv, and Capronorv. Different types of implants are now available or are under active research investigations. Large-size implants require surgery, whereas needle-like implants can be injected subcutaneously (s.c.) or intramuscularly (i.m.) using a trochar. Microparticles can also be injected s.c. and i.m. and behave as tiny implants. Intravenous (i.v.) injection is possible with microparticles, the size of which must be below 7 *um* to avoid lung capillary embolization. However, microparticles can be taken up very rapidly by the macrophages of the reticuloendothelial system to finally end up in Kupffer cells in the liver. Although nanoparticles have been proposed to overcome the size limitation imposed by capillary beds; they can also be taken up by macrophages. Stealth nanoparticles with a surface covered by a brush of poly(ethylene oxide) (PEO) have been proposed to avoid macrophage uptake (9). In any event, nanoparticles, as well as microparticles, can hardly leave the vascular compartment. Recently, colloidal particles have been considered in the form of macromolecular micelles of amphiphilic biblock copolymers (10) or of aggregates of hydrophilic polymers bearing hydrophobic side chains (11). These systems can serve as a drug carrier via physical entrapment of a lipophilic drug within the hydrophobic microdomains formed by the core of micelles or aggregates. Macromolecular prodrugs, where a drug molecule is temporarily attached to a polymeric carrier, have also been proposed (12). Last but not least, the next century might see the development of polymeric drugs, because any synthetic polymer can advantageously interact with elements of living systems, such as molecules, cell membranes, viruses, and tissues (13). Liposomal formulations also are helpful as sustained release parenteral dosage forms. Liposomes, lipid based drug carrier vesicles have recently emerged as a new technology in pharmaceutical sciences. Liposomes are composed of nontoxic, biodegradable lipids, in particular of phospholipids. Attempts have been made to prepare liposomes from nonphospholipid components which have the potential to form lipid bilayers that are more durable than

conventional liposomes. Currently, both conventional and non-phospholipid liposomes are rapidly becoming accepted as pharmaceutical agents which improve the therapeutic value of a wide variety of compounds. Liposome drug delivery systems are reviewed in detail in another chapter of this book series and as a reason it is not discussed in detail here. In general, liposomes are advantageous in that they can provide controlled release of an entrapped drug, reduce side effects by limiting the concentration of free drug in the bloodstream, alter the tissue distribution and uptake of drugs in a therapeutically favorable way, and make therapy safer and more convenient by reducing the dose or frequency of drug administration. Liposomes generally have been known to improve formulation feasibility for drugs, to provide prolonged sustained release, to reduce toxicity and to improve the therapeutic ratio, to prolong the therapeutic effect after each administration, to reduce the need for frequent administration, and to reduce the amount of drug needed and/or absorbed by the mucosal or other tissue. Advantages such as decreased toxicity and degradation, use of smaller doses, the possibility of targeting the liposome towards a specific site, and reducing side effects of a liposome-bound drugs over the use of a free or polymer-bound drugs is well documented. These dosage forms are not only popular for human use but several of these dosage forms are currently used or being developed for veterinary purposes.

The majority of implants used in veterinary medicine are compressed tablets or dispersed matrix systems in which the drug is uniformly dispersed within a nondegradable polymer. Drug release from dispersed matrix systems involves dissolution of the drug into the polymer, followed by diffusion of the drug through the polymer, and partitioning from the surface of the polymer into the surrounding aqueous environment. Implants are available to increase weight gain and feed conversion efficiency in food-producing animals. These implants are typically prepared in a manner similar to tablets. One controlled-release implant consists of a cylindrical core of silicone, surrounded by an outer layer of estradiol-loaded silicone. A range of implants is available to enhance reproductive performance in breeding animals. These include ear implants containing norgestomet dispersed in polyethylene methacrylate or silicone, a biocompatible tablet implant containing deslorelin (a GnRH agonist) for use in mares that does not require removal, and a sustained-release pellet of melatonin, which is implanted in the ear of ewes to

enhance breeding performance. Testosterone pellets are available for implanting in the ears of wethers at doses of 70-100 mg every 3 mo for the prevention of ulcerative posthitis. It is worth mentioning briefly about development of the various biodegradable and other polymers that are used in the development of these parenteral sustained release dosage forms.

During the past 50 years, synthetic polymers have changed the everyday life of humans due to the possibility of covering a wide range of properties by modification of macromolecular structures and introduction of additives (fillers, plasticizers, etc.). In the meantime, surgeons and pharmacists tried to use these materials as biomaterials. About 30 years ago, distinction was made between permanent and temporary therapeutic uses. The former requires biostable polymeric materials, and the main problem is resistance to degradation in the body. In contrast, the latter needs a material only for a limited healing time. In this regard, degradable polymers became of great interest in surgery as well as in pharmacology. The first degradable synthetic polymer was poly(glycolic acid) (PGA), which appeared in 1954. This polymer was first discarded because of its poor thermal and hydrolytic stabilities, which precluded any permanent application. Later on, people realized that one could take advantage of the hydrolytic sensitivity of PGA to make polymeric devices that can degrade in a humid environment and, thus, in a human body. This led to the first bioabsorbable suture material made of a synthetic polymer. It is worth noting that terminology is one of the sources of confusion in the field. Nowadays, people tend to use the word *degradable* as a general term and reserve *biodegradable* for polymers that are biogically degraded by enzymes introduced in vitro or generated by surrounding living cells. The possibility for a polymer to degrade and to have its degradation by-products assimilated or excreted by a living system is thus designated as *bioresorbable*. Most of the degradable and biodegradable polymers identified during the past 20 years have hydrolyzable linkages, namely ester, orthoester, anhydride, carbonate, amide, urea, and urethane in their backbone. The ester bond-containing aliphatic polyesters are the most attractive because of their outstanding biocompatibility and versatility regarding physical, chemical, and biological properties. The main members of the aliphatic polyester family are numerous. Only a few have reached the stage of clinical experimentations as bioresorbable devices in drug delivery. This is

primarily due to the fact that being degradable or biodegradable is not sufficient. Many other prerequisites must be fulfilled for clinical use and commercialization.

Many classes of cross-linked polymer gels display phase transition characteristics i.e. abrupt change in swollen volume in response to small environmental changes like pH, light, temperature, intensity, electric field, ionic strength, and even specific stimuli like glucose concentration. Drugs containing charged hydrogel networks have been recognized as useful matrices for delivering drugs because their volume, consequently, deliver drug solution in response to external pH variation. Such hydrogels have been applied in glucose sensitive insulin releasing devices, an osmotic insulin pump and site specific delivery in the gastrointestinal tract .The polymeric devices are generally classified into the following categories: 1. Diffusion controlled devices: Monolithic devices and Reservoir devices 2. Solvent controlled devices: Osmotically controled devices and Swelling controlled devices 3. Chemically controlled devices: Bioerodible system and Drug polymer conjugates. Biodegradable polymer may be classified based on the mechanism of release of the drug entrapped in it:

Natural: albumin, starch, dextran, gelatin, fibrinogen, hemoglobin.

Synthetic: Poly ethyl-poly (alkyl cynoacrylates), poly amides, Nylon, 6-10 nylon-cynoacrylates, poly butyl - 6-6, poly acryl amides, poly amino acid, poly urethane. Aliphatic poly esters are poly (lactic acid) poly (lactide – co glycolide), poly (glycolic acid), poly caprolactone, polydihydroxy butyrate, poly hydroxy butyrate co-valently cross linked protein, hydrogel. Biodegradable polymers investigated for controlled drug delivery are 1. Poly lactide / poly glycolide polymers. 2. Poly anhydrides. 3. Poly caprolactone 4. Poly orthoesters 5. Psuedo polyamino acid 6. Poly phosphazenes 7. Natural polymers.

Interest in poly lactide material has been generated due to its considerable chemical, biological and mechanical characteristic. Most of polylactide materials developed so far are designed to deliver drugs to the systemic compartment. Also local drug delivery is a possibility in this case one attempts to achieve high drug concentration at the site of implantation without exposing non affected tissue to the drug. Implants are used as depot formulations either to limit high drug concentrations to the immediate area surrounding the pathology or to provide sustained

drug release for systemic therapy. Clinically, implant systems have been used in situations where chronic therapy is indicated, such as hormone replacement therapy and chemical castration in the treatment of prostate cancer. Biodegradable materials, such as polylactic acid co-glycolic acid, are of course preferred as this removes the need for surgical removal of the implant after treatment has ended. However, non-biodegradable materials do provide therapeutic levels of drug for up to one year in vivo. One of the reasons for the popularity of the lactide/ glycolide material in drug delivery system is their relative ease of fabrication into various types of delivery systems: Micro particles (Microspheres and microcapsules), implants and fibers. Aliphatic poly esters undergo biodegradation by bulk erosion the lactide/glycolide polymer chains are cleaved by hydrolysis to the monomeric acids and are eliminated from body through Krebs cycle, Primarily as carbon dioxide and in urine. Very little difference in observed in the rate of degradation at different body sites as the hydrolysis rate is dependent only on significant changes in temperature and pH or presence of catalysts. The role of enzyme in the biodegradation of the polymers has been still unclear. Lactide glycolide polymers show wide range of hydrophilicity which makes them versatile in designing controlled release system. The use of different PLGA polymers for the development of parenteral SR dosage forms for desired period is given in Table 1.2.

Table 1.2 Biodegradation of lactide/glycolide polymers.

Polymer	Months
Polylactide	18-24 months
Poly dl-lactide	12-16 months
Poly glycolide	2-4 months
PLGA 50:50	2 months
PLGA 85:15	5 months
PLGA 90:10	2 months

Some pictures of microspheres under Scanning Electron Microscope are provided in Figure 1.2(a) and 1.2(b).
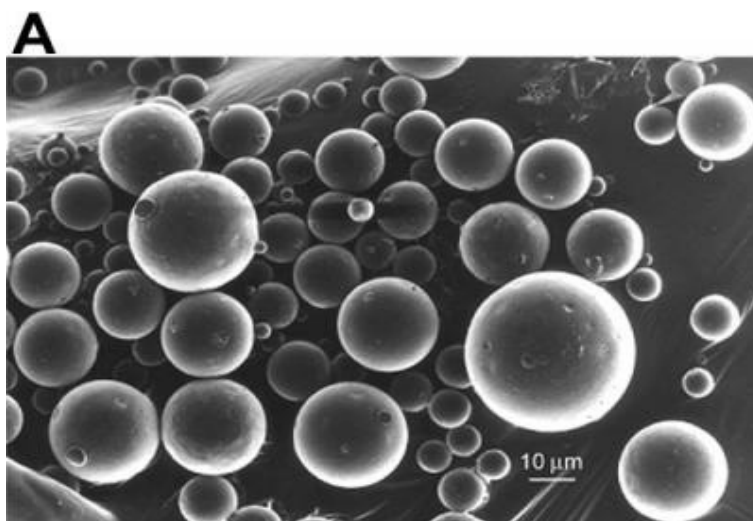
Figure 1.2(a) Characteristics of PLGA microspheresA: Picture of rhGDNF-loaded microspheres analyzed by scanning electron microscopy. Scale bar in A represents 10 µm.
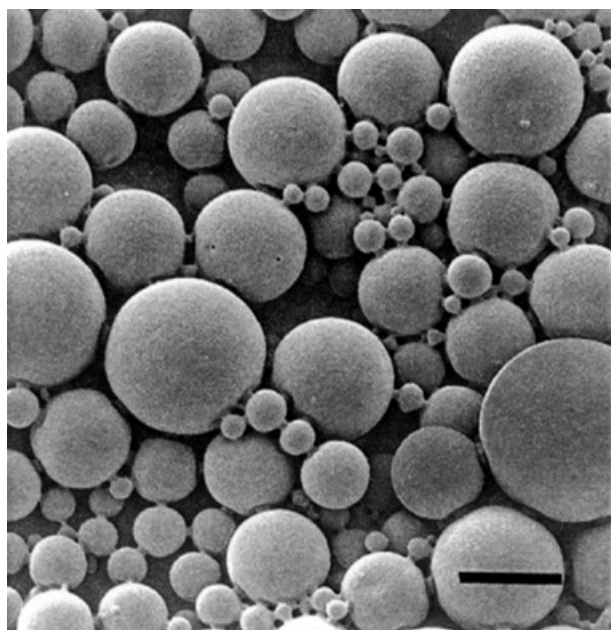

Figure 1.2(b) Scanning electronic photomicrograph of PLGA microspheres obtained by the multiple emulsion W/O/W method. Bar = 5 µm.

Examples of sustained release parenteral dosage forms and the drawbacks and need for different dosage forms is illustrated with the following drug. Buprenorphine is a semi-synthetic opioid analgesic with mixed agonist-antagonist properties (14). Besides being 20-40 times more potent than morphine, one of its main advantages is that the dose does not need to be increased during chronic administration. Buprenorphine can be in various forms such as sublingual tablets (0.2 mg) for the treatment of moderate, severe acute, and chronic pain, or as a pre-operative medication. Sublingual tablets containing 0.4, 2 and 8 mg of the drug are used for the treatment of opioid addiction. Alternatively, it is available as an injection (0.3 mg/mL) for IV, IM, intrathecal, and epidural administration as an analgesia in cases of severe acute pain and as a pre-medication. Recommended doses are 200-600 μg by IV or IM injection every six to eight hours, 30-45 μg intrathecally or 100-300 μg epidurally every six to twelve hours or 400 μg sublingually every six to eight hours. Different injectable SR dosage forms for this drug are available. For example, U.S. Pat. No. 6,495,155 discloses an injectable slow-release partial opioid agonist and/or opioid antagonist formulation in a poly (D, L-lactide) excipient with a small amount of residual ethyl acetate (15). The microparticles are under 125 μm in diameter and can be readily injected intramuscularly to provide at least about 0.5 ng/ml of drug over an extended period of time (28-60 days). The formulations are provided for use in the treatment of alcoholics and heroin addicts. Additionally, a subcutaneous depot product (Norvex®) exists wherein buprenorphine microcapsules consisting of buprenorphine base and biodegradable PLA-PGA polymer are disclosed. A study has found that buprenorphine propionate when prepared as a depot had a long-lasting analgesic effect, which was 7.5-fold longer than the traditional dosage form of buprenorphine in saline preparation, following IM injection in rats. The long lasting effect of IM depot of buprenorphine propionate is reported to be due to a slow release of buprenorphine propionate from its oil vehicle. They have subsequently synthesized and formulated other depots of buprenorphine esters, buprenorphine enanthate and decanoate. The buprenorphine decanoate in oil produced a 14-fold longer duration of action than buprenorphine HCl in saline. U.S. Pat. No. 6,335,035 discloses the preparation of a sustained release delivery system using a polymer matrix containing a drug for use in treating acute or chronic conditions (16). The drug is dispersed within a polymer matrix solubilized or suspended in a polymer matrix. The polymer matrix is composed of a highly negative charged polymer material such as

polysulfated glucosoglycans, glycosaminoglycans, mucopolysaccharides and mixtures thereof, and a nonionic polymer such as carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, and mixtures thereof.

Although the use of emulsions and suspensions for drug delivery is not uncommon and has been used in other analgesics, there are also problems associated with them. However, sustained release injectable buprenorphine formulations that exist in the prior art utilize more complicated systems such as microparticles or prodrugs in an oil vehicle. More particularly, the manufacturing of microparticles involves utilizing complex and costly processes with the use of organic solvents. Additionally, it can be difficult to achieve sterility of microparticles and other oil solutions because terminal sterilization is not always possible. In addition to these disadvantages, it is difficult to appropriately control the release of a drug such as buprenorphine in an injectable dosage form in order to achieve the desired onset and duration of analgesic effects in the target species. Accordingly, there continues to be a need for reasonably simpler and more practical formulations for sustained release of buprenorphine. To weed out the problems associated with the existing parenteral SR dosage forms, one embodiment, an oil-in-water buprenorphine formulation including buprenorphine and a surfactant that emulsifies the buprenorphine in oil, wherein the buprenorphine release is controlled by varying the oil concentration and/or pH of the emulsion has been disclosed.

1.6.2.1   Currently marketed parenteral CR products

The majority of sustained release technologies are designed for the use of biodegradable materials and a great number of them are specifically based on the use of polyesters, such as poly-lactides (PLAs) and poly-lactide-co-glycolide (PLGAs) copolymers. These polymers, once injected in the body, undergo random, non-enzymatic, hydrolytic cleavage of the ester linkages to form lactic acid and glycolic acid, which are normal metabolic compounds, eliminated via the tri-carboxylic acid cycle as carbon dioxide and water. The kinetic degradation of the polymers, and thus the release profile of the active drug substance incorporated into them, strongly depends on the selected polymer and on its physico-chemical properties. As an example, PLA/PLGAs bio-degradation kinetic is governed by a series of variables that interplay, among them the lactide-to glycolide ratio (the higher the glycolide content, the quicker the degradation rate), molecular weight of the polymer, end-caps of the

polymer (i.e. acidic or neutral), drug to polymer ratio, solubility and hydrophobicity of the incorporated active drug substance and the formulation manufacturing method. Active drug substances are released from these formulations via a combination of diffusions through the polymeric matrix and from holes that are created by the erosion of the matrix itself. As drug particles diffuse out of the matrix, the exposed polymer is hydrolyzed, solubilized and released as monomers. New drug/matrix surface is thus exposed, and the process of diffusion and erosion continues. Several manufacturing procedures can be applied to obtain such formulation systems. The manufacturing method that will be chosen and tailored to the specific drug substance needs to take into consideration the stringent requirements needed for parenteral-acceptable products, such as: citing only some key features; using approved excipients (in this case no further insights on the toxicological characterization of the excipients will be needed); needing to produce particle size distribution or a rod/implant that can be delivered via convenient needles (19 gauge and above); needing to have high encapsulation/loading efficiency and manufacturing yields (this is particularly valid for costly biotechnological products); limiting as much as possible the use of organic solvents into the manufacturing process and in the final product; being relatively easy to scale-up and reliable in terms of batch to batch consistency and reproducibility; and being sterilizable or manufacturable through an aseptic process.

These currently available delivery systems have the following salient features: 1. No surgical removal of depleted system is required as it is metabolized in non toxicological by product. 2. The drug release from this system can be controlled by following a. Diffusion of drug through the polymer, b. Erosion of the polymer surface with concomitant release of physically entrapped drug, c. Cleavage of covalent bond between the polymer bulks or at the surface followed by diffusional drug loss, d. Diffusion controlled release at the physically entrapped drug with bio adsorption of the polymer until drug depletion. Long acting parenteral drug formulation are designed, ideally to provide slow constant, sustained, prolonged action.

The other sustained release parenteral formulations include infusion pumps. Implantable infusion pumps were introduced for continuous drug delivery in 1969. Several implantable pumps have been approved by the FDA, and many more are being tested and used clinically around the world. The Infusaid Models 100, 100, and 550 (Pfizer Infusaid, Inc., Norwood, MA) were FDA approved starting in 1982 for the delivery of

various cancer therapeutics, including floxuridine (FUDR), fluorouracil (5-FU), methotrexate sodium (MTX), and cisplatin (CDDP). They have also been approved for the delivery of morphine sulfate for the treatment of pain resulting from incurable cancer. The Infusaid pumps consist of a flexible bellows containing the drug solution that is surrounded by a rigid chamber filled with a charging fluid (usually a volatile chlorofluorocarbon). Vapor pressure from the charging fluid expels the drug solution by compressing the internal drug reservoir. The release of the drug solution is regulated by a capillary flow restrictor or a valve/accumulator combination. The reservoir can be refilled by percutaneous puncture of a needle, which reexpands the reservoir and increases the pressure in the adjacent charging fluid chamber, causing the fluid to recondense. The pump is then ready for its next infusion cycle. Medtronic, Inc. (Minneapolis, MN) received FDA approval for its SychroMed Infusion System in 1988 for the delivery of CDDP, FUDR, doxorubicin hydrochloride (DOX), and MTX and received FDA approval in 1996 for the intrathecal delivery of morphine sulfate for the treatment of pain. The SynchroMed pump delivers a drug solution from a percutaneously refillable reservoir via a peristaltic pump mechanism that is driven by a lithium battery with a life of 1 to 3 years. The pump can be programmed with an external computer and a magnetic field telemetry link, allowing for more complex delivery regimens, including those based on circadian rhythms. The doctor has the option of tailoring the drug dosage, flow rate, and dosage schedule to best fit the needs of the patient, while the patient is able to receive treatments untethered.

1.6.2.2   Special Features in the Design of Parenteral CR Products

The development of parenteral sustained release dosage forms is achieved after taking several factors into consideration. The route of administration, the release rate both in vitro and in vivo, duration of action needed, all should be considered when a parenteral sustained release dosage form for a particular drug is designed. Route of administration is a very important aspect. Not all the types of dosage forms can be administered by all the routes of administration. The needed release of the drug can be achieved after using a particular polymer, particular dosage form and particular geometry. These are prepared using a variety of approaches. Implantable large devices such cylinders, pellets, slabs, discs, and films thicker than 0.1 mm are usually prepared by compression molding an intimate polymer-drug mixture. However, there is risk of thermal degradation. Tubings and needle-like implants can be obtained by extrusion. The temperature of compression molding or

extrusion depends on the morphological characteristics of the polymer. For crystalline polymers, the processing temperature has to be above the melting temperature $(Tm)'$.

In the case of amorphous polymers, temperatures above the glass transition (Tg) are usually sufficient. Prior to processing, the polymer should be thoroughly dried to prevent thermal and/or hydrolytic degradation. Thin films can be prepared by casting a polymer-drug solution. Hollow fibers of highly crystalline PLA100 can be prepared by using a "dry-wet" coagulation spinning process. The use of different spinning systems (i.e.,different solvent-nonsolvent pairs and with or without additive) leads to hollow fibers with varying asymmetric membrane structures. PCL fibers containing tetracycline hydrochloride, with an outer diameter of 0.5 mm, have been prepared by melt spinning at 161°C (17). When organic solvents are used, the elimination of residual solvents is of major importance because they can generate toxicity regardless of the polymer matrix. Implantable mesh sheets were also reported. Implantable systems provide various advantages such as prolonged release of drugs, reproducibility of drug release profiles, and ease of fabrication. However, implantation of such systems requires surgery with risk of infection. Some commercial examples of these types of preparation are illustrated here. Currently, two controlled-release systems have been approved by the FDA to treat cancer. Both act as depots for the sustained release of anticancer peptides. The first, Zoladex® (Zeneca Pharmaceuticals), contains goserelin acetate, a synthetic decapeptide analogue of luteinizing hormone-releasing hormone (LH-RH) dispersed in a poly(lactide-coglycolide) rod. Zoladex® is indicated for the palliative treatment of advanced prostate cancer and breast cancer. One formulation contains 3.6 mg of goserelin acetate and is designed to last 4 weeks; the second formulation contains 10.8 mg of the peptide and is designed as a 3-month implant. The 4-week rods are 1 mm in diameter, and the 3-month rods are slightly larger, with a diameter of 1.5 mm. The 3-month implant is indicated for prostate cancer patients only. The rods are supplied in a special syringe that is used to implant the delivery system subcutaneously in the upper abdominal wall. In a randomized, prospective clinical trial comparing radiation therapy alone to radiation therapy combined with Zoladex® implants, survival of patients with locally advanced prostate cancer was improved with the addition of Zoladex® to the treatment. Both groups of patients received 50 Gy of radiation to the pelvis over 5 weeks and an additional 20 Gy over the following two weeks. Patients in the combined

therapy group received the 4-week implants (Zoladex® 3.6 mg) starting on the first day of radiotherapy and again every 28 days for 3 years. In the combined therapy group, 85% of the patients were disease free at 5 years compared with only 48% of the radiotherapy-only group. Lupron Depot® (TAP Pharmaceuticals, Inc.) has also been FDA approved for the treatment of prostate cancer. The formulations are supplied as lyophilized microspheres that are resuspended in a diluent for intramuscular injections every 1, 3, or 4 months.

The amount of the drug incorporated into the delivery systems is also important. This is decided on the entire dose of the drug. The drug is slowly released from the injection site and is absorbed into the blood stream. Thus, in this case drug levels are absorption limited. This definitely depends on the polymer and the characteristics of the drug also. The design should be such that there should be a strict manufacturing control, less pharmacokinetic pitfalls, predictions of injection site residues should be easy, and safety of injection residues should be high. Ideal parenteral sustained release formulation should be administered once, give long term effects as desirable, be easy to manufacture and possess enough shelf-stable properties.

The physicochemical and biopharmaceutical properties of the drug can have a tremendous impact on its bioavailability and, hence, on its efficacy and toxicity profile. Thus, understanding these parameters is often tantamount to the selection and development of the optimum dosage form. Several physicochemical factors controlling the delivery of a bioactive agent to the host:

1. Size and Geometry of the delivery system.
2. Local pH of the host site.
3. Hydrophilic or hydrophobic nature of the active agent.
4. Solubility of the active in the local environment.
5. Solubility of the active in the delivery matrix.
6. Permeability of the delivery matrix to water.
7. Permeability of the delivery matrix to the active agent.
8. Biostability of the delivery matrix.
9. Concentration gradient across the delivery system.
10. Drug loading.
11. Polymer characteristics such as glass transition temperature and molecular weight etc.

12. Morphological characteristics such as porosity, tortuosity, surface area and shape of the system.

13. Chemical interaction between drug and the polymer.

14. External stimuli such as pH, ionic strength, thermal and enzymatic action.

The release of the drug can be modified using a variety of approaches (18). Microspheres of etoposide prepared by oil/oil suspension and solvent evaporation technique using polylactide (PLA) of molecular weight 50,000 Da were divided into size ranges of less than 75 μm, 75 to 180 μm, and 180 to 425 μm by passing through series of standard sieves, and their drug release was evaluated. Particles that are less than 75 μ showed faster release rates compared with larger size fractions. The difference in the rate of release is attributed to the difference in the surface area. Alterations in drug release rates therefore could be attained by simple mixing of different size fractions of microspheres. Drug loading is another important factor that effects the release of the drug from the delivery system. The release of the drug can be controlled by achieving suitable drug loading. The rate of diffusion will be higher for drugs with higher aqueous and polymer solubility, as well as for those not chemically interacting with the polymer. Higher drug loading will mean higher amounts of drug present on the surface or proximal to the surface that will lead to higher initial release. In addition, the rate of pore formation can be higher on drug depletion because the drug-polymer ratio is higher. An example illustrates the effect of leuprolide acetate loading on the physicochemical properties and in vitro drug release of PLGA microspheres. Formulations *A* and *B* with 11.9 and 16.3 percent of drug loads were prepared by a solvent-extraction-evaporation method. Higher drug incorporation resulted in a substantial increase in specific surface area and a decrease in bulk density. When observed under the scanning electron microscope, higher-drug-loaded microspheres showed a higher surface porosity. This resulted in higher initial release from microspheres with higher drug incorporation. Another important maneuver that can be performed to obtain the desired release is the selection of the polymer with desired molecular weight. To date, the largest body of literature exists on polyesters such as poly(DL-lactide) or poly(DL-lactidecoglycolide). These polyesters are available from a variety of vendors on a commercial scale with varied molecular weights and monomer ratios of lactide and glycolide. They are also available with acid end groups to impart higher hydrophilicity. Addition of low-

molecular-weight poly(DLlactide) (MW 2000 Da) increases drug release from a biodegradable poly(DL-lactide) (MW 120,000 Da) drug delivery system. Bodomeier et al. found that the duration of action could be varied over a range of several hours to months by varying the amount of low-molecular-weight poly(DL-lactic acid) (18). Degradation of these polymers occurs by hydrolysis of ester linkages causing random scission and mainly depends on the polymer concentration, ratio of comonomers, and hydrophilicity. Drug solubility is another important feature that can have a significant influence on the drug release. In case of macromolecular drugs, a major portion of drug is released by polymer degradation and erosion, and a small portion is released by the diffusion mechanism. Polypeptides usually have limited solubility in the polymer, which greatly prevents their diffusion. In addition, the aqueous channels present in the delivery system could be too narrow or tortuous for these macromolecules. Reports from the literature indicate that the drug release is multi-or triphasic, which is characterized by higher initial release (can be termed *burst* in some cases), a lag phase where minimal amount of drug is released, and finally, release of drug at a higher rate until depletion. Similarly, the influence of the other factors is profound and can be found from various literature sources.

In the design of parenteral CR products, the drug release studies and the in vivo absorption determination are one of the main criteria. Current uses of in vitro release testing include: 1) formulation development, to include assessment of dose-dumping and in vivo stability (e.g., Stealth-type liposomes, which should remain stable without significant drug release until uptake at the target site in vivo); 2) quality control to support batch release, 3) evaluation of the impact of manufacturing process changes on product performance, 4) substantiation of label claims; and 5) compendial testing. Although in vitro release testing of CR parenterals is primarily utilized for quality control purposes, in vitro release tests should be developed with regard to clinical outcomes (bio-relevance). The rationale for this understanding is that the ultimate purpose of quality control testing is to ensure the clinical performance, i.e., efficacy and safety of the product. In order to achieve in vivo relevance, physiological variables at the site need to be considered including: body temperature and metabolism (both can significantly affect blood flow), muscle pH, buffer capacity, vascularity, level of exercise, as well as volume and osmolarity of the products. Any tissue response, such as inflammation and/or fibrous encapsulation of the product may need to be considered. In

vitro release methods should be designed based on in vivo release mechanisms. With this understanding, the following general approaches for in vitro test method design are important: 1) identification of release media and conditions that result in reproducible release rates; 2) preparation of formulation variants that are expected to have different biological profiles; 3) testing of formulation variants in vitro as well as in vivo; and 4) modification of in vitro release methods to allow discrimination between formulation variants that have different in vivo release profiles. The relevance of sink conditions is also very relevant in in vitro test design for CR parenterals, considering that sink conditions may not exist at a particular in vivo site. General agreement was that sink conditions should be used for in vitro testing for quality control purposes provided that the study design allowed for discrimination between formulation variants with different in vivo release profiles. However, it can be argued that non-sink conditions may be necessary if the purpose of the in vitro test is to establish in vitro-in vivo correlation (IVIVC). Although IVIVC is not utilized at present for CR parenterals, with sufficient bio-relevance built into the in vitro tests to support an IVIVC it may allow subsequent waiver of in vivo studies

Although IVIVC may not be possible for all CR parenteral products, it is an important area for research. The principles used in IVIVC of oral extended-release products may be applied to parenterals with appropriate modification, justified on a scientific basis. IVIVC modeling and measurements may be different for different types of products (e.g. targeted release versus extended release products). Similarly, in vitro release methods and media are likely to vary depending on the product and should be developed based on in vivo relevance. For example, in vitro cellular tests may be acceptable as long as they are reproducible and can be validated. Similarly, in vivo measurements may vary and may include plasma concentrations, efficacy/safety data, surrogate endpoint data, as well as tissue concentrations. In vitro and in vivo measurements must be justified scientifically. In the case of some products, such as liposomes, it may be necessary to measure in vivo concentrations of both free and encapsulated drug. Models that represent multiple processes (e.g., physical and biological) should be considered, as appropriate. The use of animals was considered to be acceptable to prove that an in vitro release system is discriminating. However, the use of animal models was considered inappropriate to prove an IVIVC for regulatory purposes.

Instead, bio-relevance should be developed using clinical data. Nevertheless, IVIVC modeling using animal data would be suitable for "proof of principle" for initial research purposes. Research in this area should be encouraged, possibly coordinated through Product Quality Research Initiative (PQRI).

The issue of data variability with respect to IVIVC should consider the following salient features:

- Increase the number of dosage units or individuals.

- Variability may be acceptable as long as its source can be estimated and a valid IVIVC is obtained.

- If the source and importance of the variability can be determined, it may be possible to minimize it.

Fibrous encapsulation, may affect release in vivo and this needs to be considered in establishing an IVIVC. However, these types of tissue response may be difficult to simulate in vitro.

In the development of in vitro release methods, animal data may be used to obtain tissue distribution and pharmacokinetic information. Plasma levels may not be the best measure of in vivo behavior for CR parenteral products intended for local delivery or targeted release, and therefore, the use of animal models to investigate in vivo product performance should be more exhaustive. More extensive bio-data can be obtained using animal models, including tissue levels at the local site. Animal models were considered to be invaluable and serial tissue samples might be used to compare product performance before and after manufacturing changes for CR parenterals with tissue-specific delivery. Although data will be useful in initial development, ultimately human data must be used to establish an IVIVC. As this could be important issue, the use of just in vitro testing may eventually become the reality for product approval. A brief overview of in vitro release testing methodologies suitable for parenteral CR products is very relevant at this current juncture.

Current USP apparatus for in vitro release testing are designed for oral and transdermal products and may not be optimal for controlled release parenteral products. USP apparatus 1 (basket) and 2 (paddle) were designed for immediate- and modified-release oral formulations. USP apparatus 1 and 2 suffer from problems with sample containment and although this can be overcome by use of a sinker for monolithic depots and dialysis tubing to contain dispersed systems (such as, microspheres),

these solutions in themselves create additional problems. For example, microsphere aggregation due to confinement in the dialysis tubing, and un even dissolution from the sides of monolithic depots associated with the sinker device. Violation of sink conditions may also result from confinement within dialysis tubing. Another concern is the large volume required with apparatus 1 and 2, which may not be relevant for small volume parenterals injected subcutaneously and intramuscularly. USP apparatus 5 (paddle over disc), 6 (cylinder) and 7 (reciprocating holder) were designed for the transdermal route and do not offer any advantages for parenteral delivery systems. USP apparatus 3 (reciprocating cylinder) and 4 (flow through cell) were designed for extended release oral formulations. These latter two methods may be the most relevant to CR parenterals and may be suitable following appropriate modifications. Some researchers have noted evaporation problems with apparatus 3. Alternative apparatus, such as small sample vials and vessels, with and without agitation, are currently used for CR parenterals. However, problems are associated with these alternative apparatus, including lack of sink conditions and sample aggregation. USP apparatus 4 can be currently described as the most suitable USP apparatus for controlled and sustained release parenterals. This apparatus allows flexibility in volume, sample cell, flow rate and can be modified for specific product applications (such as avoidance of aggregation problems and of potential violation of sink conditions). There are some disadvantages with USP 4 apparatus. It is considered not robust under extreme conditions applied for accelerated testing. Examples of robustness problems were O-ring failure and filter blockage leading to variable flow rates, as well as polymer migration resulting in valve problems. These problems were product specific and they could be overcome by suitable method alteration (e.g. solvent change) and apparatus modification with parts that could with stand the desired operating conditions (such as high temperature).

1.6.2.3   Techniques of Preparation and Manufacture

Scale-up of a manufacturing process to prepare a polymer for controlled delivery applications is somewhat different than for most commodity applications. For most commodity applications, the specifications of the final polymer are far less stringent than for polymers used in controlled delivery with far fewer regulatory requirements. And often there are numerous final products that can be made from a particular grade of such a polymer. Thus, the market size for a particular type and grade of a polymer used to make commodity products is typically very large. Here,

cost is normally a key factor. On the other hand, final controlled delivery products are usually high value-add and their performance in the intended application usually requires very exacting specifications. Therefore, the specifications of all raw materials, including any polymers used to manufacture these products, are also very exacting. Also, the market for a controlled release product is typically a relatively small niche market requiring much smaller volumes of raw materials. Thus, for many controlled release applications the polymers used are custom made in relatively small size lots. A production lot of such polymers is therefore often very small by comparison and may range in size from < 1 kg to 25 kg, especially for biodegradable controlled drug delivery products for human use. Production quantities of such polymers are therefore usually prepared in small-scale stirred batch reactors ranging in size from 1 to 50 gallons in a clean-room environment with close adherence to applicable regulatory guidelines. There are, however, some polymers used for human drug delivery that are prepared in relatively large quantities. Examples are the cellulose ethers and esters that are prepared in large-scale batch reactors. Typical batch sizes are 1,000-2000 kg. These polymers are used in enteric-coated oral formulations and currently represent one of the largest volume polymeric raw materials used in human controlled drug delivery. Several techniques are available for the preparation of various parenteral SR dosage forms. These are discussed in detail here.

Techniques based on Extrusion and Compression

Extrusion: Extrusion is a process used for melting, blending, and forming a polymeric material into a desired finished product. Post forming operations such as orientation, pressing, or final molding may also be coupled with extrusion. Rod, tubing, film, channels, and filaments are examples of shapes that can be continuously extruded. Coatings and coextruded shapes (two different polymers extruded through a die and combined into the final product shape) of all of the above can also be produced. Extruders are also used for compounding and pelletizing materials to be later molded by various processes. An extruder consists of a heated barrel having one or more rotating extrusion screws through it. The single screw variety is the most common. The screw turns and the material moves forward through the extruder in a fashion similar to the action of a progressive-cavity pump. The barrel is often vented to remove volatiles (residual monomers, solvents, moisture, and entrapped air), thus preventing defects in the finished product. A screen pack and breaker plate (support for the screen) for filtering the material are located at the

barrel exit. The pressure is measured and controlled at the exit by a feedback control loop to the screw-rotation-speed controller. Heated dies are attached to the end of the extruder to form the polymeric material into the desired shape. A melt-metering pump usually precedes the forming die to provide precise flow control. Extruders are sized by barrel diameter and can be as small as one-half inch to as large as about 8 inches; although, for most controlled delivery applications the smaller size machines will most likely be used. The length of the flighted portion of the screw to the inside diameter of the barrel determines the available surface area of the barrel and the average residence time of the material. The barrel and screw are designed of materials suitable for the temperature, pressure, and chemical aggressiveness of the material being extruded. Typical process pressures are <35 mPa; however, pressures up to 70 mPa are not uncommon. The materials used are usually surface-hardened, high-strength alloys. They are sometimes chromeplated for added corrosion resistance. Barrel liners of highly corrosion-resistant materials are also available. Extruders are usually heated by external electrical heater bands controlled in various zones over the length of the barrel. Heating is controlled through a feedback controller loop which actuates an electrical contacter to activatethe heating elements. Because of the high shear forces involved in extrusion, heat can begin to build once the materials begin to be extruded, and it often becomes necessary to cool the extruder. Extruders are typically cooled by passing a heat transfer fluid through internal cores or jackets in the barrel, or cooling coils surrounding the barrel. Cooling is controlled through a feedback controller loop which actuates a valve to the circulating heat-transfer fluid system.

The geometry of the screw can vary considerably depending on the material and the final product desired. The screw can have a constant pitch or "lead" or variations in screw pitch or lead beginning larger at the feed throat (point of introduction of material) and getting progressively smaller as the material progresses through and exits the barrel. The later is usually used when an intense mixing action is desirable. However, each application typically has its own requirements. The major or outer diameter of the screw is as close as possible to the barrel diameter to prohibit material from passing over the screw flights. The minor or "root" diameter of the screw will typically vary in the first screw type already described, having a smaller minor or root diameter at the feed throat and getting progressively larger and becoming constant as the later portion of the barrel (metering section) is approached. This provides a deep

"channel" on material entry to accommodate incoming unmelted and uncompressed material and floods the entry zone with material to prevent starving of the extruder. Most screws are also bored, at least in the feed section, to provide entry of heat-transfer fluids for cooling. The screen pack is located at the exit of the barrel and consists of several screens of different mesh size to filter rough contaminants from the melt. The finest mesh screen is located in the middle of progressively coarser mesh screens. The ones preceding it are for progressively finer filtering of the melt, and the ones after it are for support. The breaker plate is a thick metal plate with numerous large (-1/8-inch diameter) holes located past the screen pack and before the melt-metering pump and the forming die; it serves to support the screen pack and equilibrate the melt pressure to the pump. The metering pump is a positive displacement pump, which is controlled separately from the extruder screw to provide precise flow to the forming die.

Injection molding: Injection molding is probably the most widespread molding technique for quickly and easily forming a polymer melt into a finished product. In this process, the mold is split to allow part removal. It is kept closed during injection by an appropriate clamping force. The mold is filled by forcing a precompounded (containing all additives), molten polymer formulation into the mold. The injection molding machine may be a simple piston (ram) injector design, or a more complex reciprocating-screw design. Either type consists of a feed hopper attached to a heated cylindrical barrel with an injection nozzle attached to the end of the barrel. The reciprocating screw or ram are typically capable of applying 70-140 mPa of pressure to the melt during the injection cycle. This is the operation sequence of the reciprocating-screw machine:

1. With the reciprocating screw forward, unmelted material is fed from the hopper.
2. The material is then plasticated and forced to the front of the barrel by the rotating screw, which simultaneously moves backward against a hydraulic cylinder (reciprocates) as the front of the barrel fills.
3. The mold clamp is released, the mold opens, and the part, formed on the previous cycle, is ejected.
4. The mold closes and the clamp pressure is reapplied.
5. The screw moves forward, as a ram, injecting the melt into the mold, and remains forward to begin the next cycle.

The mold temperature is kept warm but held at a suitable solidification temperature for the material being injected. Too cold a mold can lead to material freezing before the mold is filled. Materials used to construct injection molding equipment are similar to those used to build extruders. The molds must also be constructed of rugged materials to avoid both the erosive and corrosive forces of material flow. The major advantages to injection molding are speed and the ability to simultaneously form multiple complex geometric parts. These are the disadvantages: 1. The high temperature and shear require the polymers and actives to be very stable. 2. The process wastes materials in runners and sprues. 3. The mold and equipment costs are high. 4. Mold erosion occurs from material flow. 5. Runners and sprues are difficult to clean from the final products. 6. The directional flow patterns, inherent in the process, can leave residual internal stresses in the part. Some examples of controlled delivery products produced by extrusion and injection molding are antibiotic periodontal fibers and insecticidal collars and ear tags. Extrusion and injection molding processes are very efficient and available equipment is capable of producing several pounds to several hundred pounds of final product per hour.

Compression Molding: Compression molding is usually used to process thermosetting polymers and is a simple and economical process. However, it can also be used to process thermoplastic materials where it is advantageous in producing the product and provided that appropriate molding conditions are used. In compression molding, the material to be molded is placed in the preheated mold in the form of a loose powder or prill. An excess of several percent is usually added to the mold to ensure complete filling. The mold is closed and sufficient pressure (several mPa) is applied to force the material into the mold cavity. The pressure is dependent on the flow characteristics of the molding material and the complexity of the part being molded. Excess material is forced out of the mold as flash or through a vent. For thermosetting materials the pressure is maintained long enough for the part to cure. The molds are generally heated and cooled by passing a heat transfer fluid through internal cores; however, internal or external electrical heating elements can also be used if precautions are taken to avoid hot spots. The advantages of compression molding are several: 1. Waste is low because no runners or sprues are used. 2. The final parts are easier to clean because no runners or sprues are used. 3. Mold erosion from material flow is minimized. 4. Residual internal stresses are low because of the short, multidirectional flow patterns of the material. 5. The mold and equipment costs are low. 6.

Low process temperatures can be used. There are some disadvantages to compression molding: 1. It is not suitable for intricate parts because the flow is minimal. 2. Because of polymer viscoelasticity, thermoplastic parts are difficult to mold without distortion. 3. It is best suited for fairly thin products.

Solvent Processing of Polymeric Controlled Delivery Products

Solvent Casting of Films: Solvent casting has been an established process for the preparation of polymeric films for decades. The polymer and soluble or dispersable additives are first dissolved and dispersed in a suitable solvent. The solution is then cast onto a continuous, release-coated belt or web-supported film and passed through an oven to drive off the solvent. The solvent is usually reclaimed. The dried film is continuously removed from the belt and wound as it passes from the oven. Care must be taken in design of the process line to ensure that it is particularly suited to the product being manufactured. Consideration should be given to the flow characteristics of the casting solution, the evaporation rate of the solvent, and the changing flow characteristics of the polymer solution throughout the drying process to ensure a uniform film. The thermal stability of the polymer and any additives or active agents must also be considered. Solvent casting of films containing active agents for controlled delivery can be advantageous to melt processing if the active is thermodynamically unstable. However, because of the high initial process investment and the inherent difficulty in process control, solvent casting should only be considered for manufacturing controlled drug delivery devices when absolutely necessary. Solvent casting of films is often used as a part of the overall manufacturing process in manufacturing transdermal patch products.

In Situ-Forming Implant Depots: The first in situ forming implant depot formulation to be approved for delivery of a drug in humans is ATRIDOX. The product is designed for controlled delivery of an antibiotic for treatment of periodontal disease. It is supplied as an injectable liquid. When injected into the periodontal cavity, the formulation sets forming a drug-delivery depot that delivers the antibiotic doxycycline to the cavity. ATRIDOX is based on the ATRIGEL® drug-delivery technology developed by Atrix Laboratories, Inc. The technology consists of a biodegradable polymer, a bioactive agent, excipients, and additives dissolved in a water-soluble, bioabsorbable, and biocompatible solvent. The formulations may be liquids, pastes, or putties; however, the liquid injectable is the preferred form for most

applications. Products based on the ATRIGEL technology are typically made using a high-intensity mixer to dissolve the polymer and dissolve or disperse the active agent and any excipients. Another company, Matrix Pharmaceutical, Inc., has developed a proprietary biodegradable gel matrix consisting of purified bovine collagen for the targeted, intralesional delivery of chemotherapeutic agents. The system is prepared by dispersing chemotherapeutic agents in an aqueous solution of a protein such as purified bovine collagen. The chief advantage of this system is that the bovine collagen gel allows one to optimize the retention and release of the drug at a targeted injection site, thus minimizing systemic toxicity. The therapeutic effect of the delivery is further enhanced by the inclusion of a vasoconstrictor such as epinephrine. The tumor or other diseased tissues are exposed to high concentrations of the drugs for prolonged periods of time because of the site specific and sustained release of the drug. In one study, cisplatin either in a single solution (CDDP suspension) or within the Matrix gel (cisplatin/epinephrine gel) are injected into a mouse tumor (100 mm"). The free cisplatin was cleared from the site within 1 h, whereas the gel retained the drug between 24 to 72 h. One product based on this concept, AccuSite (fluorouracil/epinephrine) Injectible Gel for the treatment of recurrent genital warts has been approved in seven European countries and has completed Phase III studies in the United States. Here the gel matrix is a viscous, aqueous gel consisting of fluorouracil (30 mg/mL) and epinephrine (90.1 mg/mL) and other inactive buffering and osmotic excipients, within a purified bovine collagen matrix gel. This technology is covered by several U.S. and European patents. Another Matrix product, IntraDose Injectable Gel, has advanced into a second level of Phase II clinical trials in the U.S. for treatment of inoperable liver cancer. The product consists of a dispersion of cisplatin and epinephrine in a purified bovine collagen matrix. The protein gel matrix is a simple yet effective delivery system that permits direct delivery of chemotherapeutic agents to a tumor and provides a high local concentration of drug while minimizing systemic toxicity. The major disadvantage of the system is that it cannot provide long-term release of the drug (usually less than 1-3 days) because the drug can easily diffuse out of the gel matrix.

Encapsulation: Encapsulation, especially microencapsulation (particles ranging in size from a few to several hundred micrometers), is a process whereby particles of an active agent are surface coated to provide changes in the physicochemical properties of the active agent. There are many different processing techniques used depending on the desired

properties of the final product, the properties of the agent being coated, and the properties of the coating material. The term microsphere is often used synonymously with microcapsule; however, a distinction should be made between the two terms as they are used in controlled delivery, because the final products produced and their release characteristics are quite different. Microcapsules are essentially discontinuous microspheres where the active core material is completely covered with a nonactive surface coating. The coating thickness may be varied depending on the characteristics desired in the final product. The surface coating of a microcapsule sequesters the active and serves as a protectant and/or a sustained release, rate-controlling membrane. The release mechanism of the active agent is usually mediated by diffusion of the active agent through the coating. On the other hand, microspheres are micrometer-sized homogeneous, monolithic spheres containing the active agent dispersed in a nonactive matrix material. The matrix material is often biodegradable. And in this case, the release mechanism of the active agent is usually mediated by degradation of the matrix. Although the final products are quite different, some of the processes used to prepare microspheres and microcapsules are very similar. Some of the more common processes used to form microspheres and microcapsules are as follows:

1. Spray-drying.
2. Fluid-bed coating.
3. Phase separation.
4. Solvent evaporation.
5. Solvent extraction.
6. Cryogenic solvent extraction.

Several proprietary processes also exist.

Spray-Drying: Spray-drying is a process that transforms the feed material from a fluid state into a dried particulate form by spraying the feed into a hot drying medium. It is a one-step, continuous, particle-drying process. The feed material can be in the form of a solution, suspension, emulsion, or paste. The resulting product can be powdered, granular, or agglomerated particles, depending upon the physical and chemical properties of the feed material, the drier design, and its operation. Spray-drying is used in all major industries where particle drying is required, ranging from food and pharmaceutical manufacturing to chemical industries such as mineral ores and clays. Spray-drying involves

atomization of the feed into a drying medium, resulting in the evaporation of the solvent and the formation of dried particles. Atomization is a process that breaks up the bulk liquid into millions of individual spray droplets. The energy necessary for this process is supplied by centrifugal force (rotary atomizer), pressure (pressure nozzle), kinetic (two-fluid nozzle), or sonic vibration (ultrasonic nozzle). The selection of the atomizer type depends on the nature of the feed and the desired characteristics of the final product. For all atomizer types, increasing the amount of energy available for atomization results in smaller droplet sizes. If the atomization energy is held constant and the feed rate is increased, larger particles result. Atomization also depends upon the fluid properties of the feed material, where higher viscosity and surface tension result in larger droplet sizes at the same atomization energy. In most cases, air is used as the spray-drying medium; however, dry nitrogen can be used for moisture-sensitive compounds. Contact with the spray-drying medium causes evaporation of the solvent (water or organic solvent) from the droplet surfaces. The evaporation is rapid due to the vast surface area of the droplets in the spray. The manner in which the spray contacts the drying medium is an important design factor. It influences droplet behavior; and therefore, has a great effect on the properties of the dried product. Contact with the spray-drying medium is determined by the position of the atomizer in relation to the drying air inlet. Co-current flow (the product and air pass through the dryer in the same direction), counter-current flow (the spray and air enter the dryer at the opposite direction), and mixed flow driers are available. The selection of the appropriate design is based on the required particle size, the required dried particle form and the temperature to which the dried particle can be subjected. For example, if a fine-particle product (mean size 20-120 µm) is required, but a low product temperature must be maintained at all times during the drying operation, a co-current, rotary-atomizer spray-drier is selected. Product separation from the drying air follows completion of the drying stage. Primary separation of the dried product takes place at the base of the drying chamber. Small fractions can be recovered in separation equipment such as a cyclone. Spray-drying is a useful method for the processing of pharmaceuticals since it offers a means for obtaining powders with predetermined properties, such as particle size and shape. In addition a number of formulation processes can be accomplished in one step in a spray-drier; these include encapsulation, complex formation, and even polymerization. Spray-drying and spray-congealing processes can be used for preparing microparticles for controlled release

applications. In the spray-congealing process, no solvent is used. The feed, which consists of the coating and core materials, is fed to the atomizer in the molten state. Microparticles form when the droplets meet cool air in the drying chamber and congeal. Oil-soluble vitamins, such as A and D, have been microencapsulated by spray-drying an emulsion of the oil in a gum arabic or gelatin solution. Spray-drying has also been used in the preparation of polymer-coated microcapsules for the purposes of taste masking. Biodegradable microparticles have also been prepared by spray-drying. PLA and PLGA microspheres have been prepared from solutions or suspensions of a number of drugs dissolved or dispersed in methylene chloride. Microcapsules of progesterone and PLA were formed with diameters of less than 5 μm. Crystallization of the drug occurred in the aqueous phase when microspheres were prepared by a solvent evaporation method, but spray drying avoided this problem. The main difficulty encountered in preparing spray-dried microcapsules is the formation of polymer fibers as a result of inadequate forces to disperse the feed liquid into droplets; the successful atomization into droplets is dependent on both the type of polymer used and the viscosity of the spray solution.

Fluid-Bed Coating: Fluid-bed coating is a process whereby particulates are suspended in a column of heated air or inert gas while a solution or emulsion of a polymer or other film-forming coating material is applied to the particles through spray nozzles. High-quality microcapsule products are economically produced by this process. Typical products are taste-masked drugs, enteric-coated drugs, and sustained-release drugs. Fluid-bed coating is a complex process consisting of three major operations: fluidization, atomization, and drying. The coating chamber has a high volume of flow to suspend, agitate, and dry the coated particles. The spraying nozzles can be located at various positions in the coating chamber providing top, bottom, and side or tangential spraying of the particles. Bottom spraying, or Wurster coating as it is often called, is the most common technique used for encapsulation particles as small as 30-40 μm.

Phase Separation: The phase separation process, or coacervation process as it is sometimes called, involves: 1. Preparing an organic solution of a water-insoluble, matrix material (usually polymeric), 2. Addition of an aqueous solution of the active agent or dispersion of particulates of an active agent to the organic solution with vigorous agitation, 3. Introduction of a coacervating agent or event for the matrix material to

the matrix solution/active agent emulsion or dispersion 4. Depending on the means of coacervation, the coacervated matrix solution/active agent emulsion or dispersion is then added to an appropriate hardening agent to extract the excess matrix solvent, 5. collecting, washing, and drying of the final product Coacervation may be brought about by various means. It can be induced by:

- A change in the temperature of the system.
- A change in the pH of the system.
- A change in electrolyte balance.
- Addition of nonsolvents.
- Addition of other materials which are incompatible with the polymer solution.

Solvent Evaporation: It is the most widely used manufacturing technique for biodegradable microspheres. The microsphere formation process consists of three stages:

1. Droplet formation.
2. Droplet stabilization.
3. Microsphere hardening.

First, a dispersed phase containing the polymer is emulsified in an immiscible continuous phase containing a stabilizing agent. The second phase involves the diffusion of the solvent from the emulsion droplet into the continuous phase and its subsequent evaporation. Simultaneous inward diffusion of the nonsolvent into the droplet causes polymer precipitation, microsphere formation, and hardening. Depending on the nature of the two phases, the process may be termed oil-in-water (o/w) or water-in-oil (w/o) method. The solvent evaporation process requires the use of a surfactant to stabilize the dispersed-phase droplets formed during emulsification and inhibit coalescence. Surfactants are amphipathic in nature and therefore align themselves at the droplet surface, thereby promoting stability by lowering the free energy at the interface between the two phases. Furthermore, the creation of a charge or steric barrier at the droplet surface confers resistance to coalescencing and microsphere flocculation. Surfactants employed in the o/w process tend to be hydrophilic in nature and by far poly(vinyl alcohol) is the most widely used. The emulsification systems used for microparticle production have included both low- and high-speed mechanical stirring, sonication, and

microfluidization. The particle size and size distribution can be controlled by the emulsification speed and mixing vessel design. Following emulsification, the removal of remanent solvent and complete microsphere hardening is usually accomplished by gentle agitation of the suspension. After evaporation of the solvent, the final stage of the emulsification-solvent evaporation process is the isolation of microspheres from the dispersed phase containing surfactant. This has generally been achieved by centrifugation and filtration, and it is usually followed by a further cleaning process in which the particles are washed several times with distilled water. The microspheres are finally dried using lyophilization or fluid-bed drying. There are several other techniques of preparing microspheres. Information on these systems can be obtained from research literature.

The limiting factor with regard to melt process of implant preparation for drug delivery is of course the heat stability of the active agent. Most of the lactide/ glycolide are injection molded at temperatures between 140°C and 175° C, hence they are not suitable for thermo labile drugs. Monomers levels greater than 2-3% by weight often cause substantial degradation of lactide/ glycolide copolymer in injection molding operation. Drug loaded fibers of both monolithic and reservoir types using lactide/ glycolide polymers have been reported. Monolithic formulation can readily be produced with melt extrusion using the blend of the active agent and polymer extruded under pressure at the lowest possible temperature. Reservoir or coaxial fiber can be produced from the glycolide/ lactide polymers by two important methods. ·Melt spinning technique in which the drug was introduced during the spinning process as a suspension or solution in a suitable lumen fluid. Dry wet phase process for poly lactide fibers, in which the drug must be added to the hollow fiber after the fibers are produced.

1.7   Testing of CR Systems

For oral controlled release dosage forms, apart from various test parameters, in vitro dissolution testing and in vivo bioequivalence studies are mandatory for approval. Dissolution testing should be conducted on 12 individual dosage units of the test and products. The potential for pH dependence of drug release from an extended release product is well recognized. Dissolution profiles should therefore be generated in aqueous media of the following pH ranges: 1 - 1.5, 4 - 4.5, 6 - 6.5, and 7 - 7.5.

Early sampling times of 1, 2, and 4 hours should be included in the sampling schedule to provide assurance against premature release of the drug (dose dumping) from the formulation. The general dissolution conditions to be followed are shown below:

1. Apparatus USP XXII Apparatus 1 (rotating basket) for capsules USP XXII Apparatus 2 (paddle) for tablets.

2. Rotation Speed 100 rpm (basket) 50 and 75 rpm (paddle).

3. Temperature $37 + 0.5°C$.

4. Units To Be Tested 12.

5. Dissolution Medium 900 ml of aqueous media of various pH.

6. Sampling Schedule 1, 2, 4 hours, and every two hours thereafter, 12 until 80% of the drug is released.

7. Tolerances as established.

8. Content Uniformity testing of the test product lot should be performed as described in the USP XXII.

In vivo bioequivalence studies recommended for approval for extended release formulations are designed to document that: The drug product meets the extended release claim made for it. The drug product does not release the active drug substance at too rapid a rate (dose dump). Performance is equivalent to that claimed following single doses and dosing to steady state. The impact of food on the *in vivo* performance on the bioavailability has to be assessed. The above objectives are generally met by the following three *in vivo* studies: 1. A single dose, randomized, two-period, two-treatment, two-sequence crossover study under fasting conditions. 2. A single dose, randomized, three-treatment, three period, six sequence, crossover, limited food effects administered under fasting conditions with those of the test products administered immediately after a standard breakfast. And 3. A multiple dose, steady state, randomized, two treatment, two-period, two-sequence crossover study under fasting conditions for the test formulation. For safety reasons, this study may be performed in the non-fasting state.

The different tests employed with other CR products are different. The compendial and the modified flow-through cell have been used successfully for implants and microparticulate formulations. The compendial flow-through apparatus is modified with regard to the inner diameter to suit the special properties for testing parenterals—that is, a

low volume of fluid is used in the acceptor compartment. The flow rate of the medium has to be set very slow. Use of High Pressure Liquid Chromatography (HPLC) pumps may be considered to provide the necessary accuracy and precision at very low flow rates. In this case, the flow-through system may need to be redesigned with small internal diameter tubing. Intermittent flow might also be an option. Static or rotating bottles have also been used for in vitro release testing. As tests are often run over a long time period (eg, several weeks to months), measures have to be taken to compensate against evaporation. Suitable preservatives may be added to prevent microbial contamination. Standard preservatives, including cetylammonium bromide, benzalkonium chloride, parabens, phenol derivatives, and mercury salts, along with appropriate concentrations to be used, are listed in many pharmaceutical textbooks. The selection has to be based on criteria such as compatibility with the active pharmaceutical as well as other formulation ingredients and the pH of the test medium. Issues with these compounds include their ionization properties, physicochemical interactions, and analytical interferences. 0.1% sodium azide has also been used as preservative, but because of safety concerns, it cannot be generally recommended. The composition of the medium should take into consideration the osmolarity, pH, and buffer capacity of the fluids at the site of administration, which are usually assumed to resemble those of plasma (or muscle) but with lower buffer capacity. However, the main challenges with this type of dosage form are to determine the appropriate duration of the test and the times at which samples are to be drawn in order to characterize the release profile adequately. An in vitro release test for assessing the quality and for process control of liposome drug products is important, but the challenge remains to develop and identify a reliable method that can characterize drug release from the product.

These CR formulations can be characterized for various properties. To characterize the release from the dosage form adequately, one must generate a drug release profile in which release (dissolution) values are determined as a function of time. This multipoint characterization has been in place for modified release oral dosage forms for some time and is also recommended for slower dissolving immediate release products. Because many of the dosage forms discussed here are complex in composition and release mechanism, a multipoint drug release test will be required to characterize release from the drug product in general and to test for possible alterations in the release profile during storage.

Multipoint tests may also be needed for batch release testing in order to confirm acceptable batch-to-batch consistency. Typical cases where multipoint tests are likely to be needed include transdermal patches, semisolid preparations, chewing gums, implants, microparticulate formulations, solid solutions, solid dispersions, and liposomes. The experimental test conditions should be discriminating enough ("mild" conditions) to detect manufacturing variables that may affect biopharmaceutical product performance. Test conditions that may not be able to discriminate adequately among products/batches with different in vivo release profiles include those with very high agitation/flow rates, the use of strongly alkaline solutions to dissolve poorly soluble acids, and the use of very high surfactant concentrations to create sink conditions, to name but a few. As for solid oral dosage forms, development of in vitro dissolution/release tests and specifications for novel/special dosage forms should take into account relevant bioavailability or clinical data. However, expectations with respect to the quality and/or level of in vitro/in vivo correlation should not be set as high as for solid oral dosage forms, because of the higher level of complexity and data variability for novel/special dosage forms.

Ideally, physiological conditions at the site of administration should be taken into account when selecting the in vitro dissolution/release test conditions. The complexity of the release mechanism of some novel/special dosage forms and the lack of knowledge about the conditions under which release occurs in vivo make it difficult to design physiologically based tests in all cases, but it should be possible to conceive a test that can detect the influence of critical manufacturing variables, differentiate between degrees of product performance, and to some extent characterize the biopharmaceutical quality of the dosage form. As the release mechanism and site of application vary dramatically among the novel/special dosage forms, the experimental test conditions have to be tailored according to the conditions at the site of administration (eg, temperature of the test) and the release mechanism (eg, chewing gums will require different agitation rates than suspensions). Within a given category, it may be necessary to have product type-specific dissolution tests (eg, separate tests for lipophilic and hydrophilic suppositories), and in some cases for products containing the same drug and administered in the same type of novel/special dosage form but with a different release mechanism (analogous to the range of tests available in the USP for theophylline extended release dosage forms).

The quality control tests employed has a variety of applications. A specific value of in vitro dissolution/drug release testing is recognized in its application as a batch-to-batch quality control test and its value in evaluation and approval of SUPAC. SUPAC-SS defines the levels of changes with respect to component and composition, site of manufacturing, scale of manufacturing, and process and equipment changes. In vitro drug release is used to ensure product sameness for semisolid dosage forms under SUPAC-related changes. The same principles can easily be extended to other dosage forms where the product sameness can be ensured by profile comparison between prechange and postchange products using an appropriate in vitro test and profile comparison (eg, for transdermal patches). In addition to this, the dissolution/drug release test can also be used for providing biowaivers for lower strengths of a product from a given manufacturer, once the higher strength is approved based on the appropriate bioavailability/ bioequivalence test procedure. Even though less experience is available with novel/special dosage forms than is available with conventional dosage forms, in vitro/in vivo correlations have been established. In such cases it is legitimate to use in vitro dissolution as a surrogate for the in vivo performance of a drug product, as long as the rate-limiting step is the release of the drug from the formulation; regulations should also support this. Because of the typically higher variability of in vivo and in vitro data in the case of many novel/special dosage forms, expectations about the quality and level of in vitro/in vivo correlations might have to be adjusted in comparison to those for conventional dosage forms. It is worth noting that in general, an in vitro dissolution/release test is expected for each novel/special dosage form regardless of whether the intended effect is systemic or nonsystemic (eg, topical semisolid dosage forms), for formulation development, for investigations to support postapproval changes, and for batch-to-batch quality control. It has to be noted, however, that because of the specific formulation design, because of potential (physicochemical) interactions between the dosage form and the physiological environment at the site of administration, and because of the necessary design of in vitro dissolution equipment for novel/special dosage forms, dissolution/release data in vitro might be more strongly influenced by test or equipment parameters or less predictable for in vivo release than is usually experienced for conventional dosage forms. Therefore, a scientifically sound assessment

of the relevance and validity of an in vitro dissolution test should affect the final decision about the application of the test and the specifications set for batch-to-batch quality control.

1.8   Conclusions

Controlled release systems are in high demand as of today. This is simply because of the commercial aim of a pharmaceutical company. Pharma companies are now aiming to improve productivity and lower the risks associated with new drug candidates. Often simply developing a new generation of medicines, often proprietary, formulation and delivery technologies saves companies millions of dollars. These new technologies can modulate release profiles to achieve dosing that enhances patient outcome, compliance and safety. Growth in controlled release formulations is driven in part by the dramatic increase in generic drugs and generic drug companies. These off-patent APIs often suffer from sub-optimal pharmacokinetics and unpleasant side effects, issues which can be typically be addressed by controlled release platforms. As generic drug suppliers search for ways to increase the marketability and positioning of their products, the number of controlled release technology formulations entering the marketplace will accelerate. Understanding controlled release technology through a quantitative and mechanistic approach by examining the common principles shared by several dosage forms regardless of the shape of the dosage form or the route of administration is always helpful. Thus, designing controlled release products in a systematic and encyclopedic manner rather than using trial and error approach is the most beneficial approach. Some basic concepts of controlled release dosage forms have been comprehensively covered in this chapter.

References

1. Barochez B, Lapeyre F and Cuine A. Oral sustained release dosage forms comparison between matrices and reservoir devices. Drug Dev and Ind Pharm, 15(6-7):1001-1020 (1989).

2. Mockel JE and Lippold BC. Zero-order drug release from colloid matrices. Pharm Res, 10(7):1066-1070 (1993).

3. Morita R, Honda R and Takahashi Y. Development of oral controlled release preparations, a PVA swelling controlled release system (SCRS). II. In vitro and in vivo evaluation. J Control Rel, 68(1):115-120 (2000).

4. Meka L, Kesavan B, Kalamata VN, Eaga CM, Bandari S, Vobalaboina V, Yamsani MR. Design and evaluation of polymeric coated minitablets as multiple unit gastroretentive drug delivery systems for furosemide. J Pharm Sci, 98(6):2122-2132 (2008).

5. Lordi NG. Sustained release dosage forms in The Theory and Practice of Industrial Pharmacy, 3rd edition (Eds. Leon Lachman, Herbert A. Lieberman, Joseph L. Kanig), pp. 430-456 (1986).

6. Boxenbaum H. Pharmacokinetic determinants in the design and evaluation of sustained release dosage forms. Pharm Res, 1(2): 82-88 (1984).

7. Milo Gibaldi and Donald Perrier. Pharmacokinetics, 2nd edition (Marcel Dekker, New York), pp. 188-194 (1982).

8. Theeuwes F and Bayne W. Dosage for index: an objective criterion for evaluation of controlled drug delivery systems. J Pharm Sci, 66(10):1388-1392 (1977).

9. Vittaz M, Bazile D, Spenlehaue G, Verrecchia T, Veillard M, Puisieux F and Labarre D. Effect of PEO surface density on long-circulating PLA-PEO nanoparticles which are very low complement activators. Biomaterials, 17(16):1575-1581 (1996).

10. Benahmed A, Ranger M, Leroux J. Novel polymeric micelles based on the amphiphilic diblock copolymer poly (N-vinyl-2-pyrrolidone)-block-poly (DL-lactide). Pharm Res, 18(3):323-328 (2004).

11. Lysenko EA, Trusov AN, Chelushkin PS, Bronich TK, Kabanov AV, and Zezin AB. Mixed micelles based on cationic and anionic amphiphilic diblock copolymers containing identical hydrophobic blocks. Polymer Sciences Series A, 51(6):606-615 (2009).

12. Ouchi T and Ohya Y. Macromolecular prodrugs. Progress in polymer science, 20(2):211-257 (1995).

13. Thatte S, Datar K and Ottenbrite RM. Perspectives on: polymeric drugs as delivery systems. J Bioactive and Compatible Polymers, 20(6):585-601 (2005).

14. Buprenorphine. Http: //en/Wikipedia.org/wiki/Buprenorphine (dated:28/02/2010).

15. Tice TR, Staas JK, Ferrell TM and Markland P. Injectable opioid partial agonist or opioid antagonist microparticle compositions and their use in reducing consumption of abused substances. US patent 6495155 (2002).

16. Drizen A, Rothbart P, Nath GM. Sustained release delivery system. US patent 6335035 (2002).

17. Goodson JM, Holborow D, Dunn RL, Hogan P and Dunham S. Monolithic tetracycline-containing fibers for controlled delivery to periodontal pockets. J Periodontol, 54(10):575-579 (1983).

18. Bodomeier R, Oh K and Chen H. The effect of the addition of low molecular weight poly (DL-lactide) on drug release from biodegradable poly (DL-lactide) drug delivery systems. Int J Phar, 51:1-8 (1989).