6 CONTROLLED-RELEASE DRUG-DELIVERY FUNDAMENTALS

In the past, various herbal natural products have been used without molecular information on the bioactive molecules. All drug molecules currently in use are well characterized. The future of drug treatment relies on the use of drug-delivery construct (drug + drug-delivery module). It is the drug-delivery module that will deliver a specific amount of a drug at the right time to the right place. The delivery of drugs using drug-delivery modules is collectively known as controlled drug delivery.

I. REASONS FOR CONTROLLED-RELEASE DOSAGE FORMS

Before we go into the controlled drug-delivery technologies, we will briefly discuss the reasons for developing new drug-delivery systems rather than new drugs.

A. ALTERNATIVE TO THE DEVELOPMENT OF NEW DRUGS

1. Evaluation of New Drugs

Drugs are just chemical compounds at the molecular level. There are advantages and disadvantages of using drugs. The main advantage of using drugs is to cure diseases. This is the benefit of using drugs. The disadvantages are side effects often associated with using drugs. Sometimes the side effects can be serious and life threatening. This is the risk of using drugs. For the drugs to be truly useful for human applications, the benefit/risk ratio should be much greater than one. For many drugs this is not the case. Drugs such as anticancer agents have the benefit/risk ratio close to one.

The ideal drug is a drug which is selectively toxic to target cells (or tissues) but harmless to the host. Such a drug is called a "magic bullet." The benefit/risk ratio of the magic bullet is infinite, since the risk of using such a drug is none. Finding such a drug, however, is very difficult, if not impossible.

2. New Drug-delivery Systems for Existing Drugs

While developing new drugs is highly important for pharmaceutical companies, not every company can afford such costly drug development. As a result, more and more emphasis has been given toward the development of new drug-delivery systems for existing drugs. There are many existing

drugs which are not well utilized because of various shortcomings. New drug-delivery systems can reduce many limitations of the existing therapies to provide improvements in safety and efficacy (therapeutic ratio), pharmaceutical shortcomings (bad taste, poor stability, or gastric upset), and biopharmaceutical properties (absorption, distribution, toxicity, etc.). In addition, there is increasing awareness that drug release patterns of the same drug significantly affect therapeutic responses. For example, some drugs (*e.g.*, insulin) need to be delivered in a pulsatile fashion rather than continuously. New dosage forms are necessary to deliver such drugs in response to needs by the body.

Many drugs which are taken a few times daily by oral administration can be formulated into controlled-release dosage forms for once-a-day dosing. Such dosage forms would increase patience compliance significantly as well as patients' convenience. To change the dosage forms, efficacy study must be done. Diltiazem is a calcium-channel blocker which has been used for treating patients with chronic stable angina pectoris and hypertension. A new, once-daily, extended-release diltiazem hydrochloride formulation (Dilacor XR®, Rhône–Poulenc Rorer) was developed. Dilacor XR® is based on a novel drug-delivery system, the Geomatrix® (JAGO Research AG, Zollikon, Switzerland) controlled-release system, to deliver diltiazem at a constant rate for 24 h. The rate of diltiazem release was slower than the conventional dosage forms, and this resulted in the slower absorption rate from the GI tract. As doses of Dilacor XR® were increased from 120 mg/d to 540 mg/d, there were disproportionate increases observed in area under the curve, maximum peak plasma concentration, minimum peak plasma concentration, and average peak plasma concentration (Frishman, 1993). The efficacy of Dilacor XR® was examined in patients in a double-blind safety and efficacy dose-ranging study (Cutler *et al.*, 1995). Dilacor XR®, at 240-mg and 480-mg once-a-daily doses, significantly improved ($P < 0.05$) total exercise time during treadmill exercise tolerance testing after two weeks of treatment. The increasing doses of Dilacor XR® resulted in incremental improvements in exercise tolerance. Dilacor XR® also improved outpatient function, as assessed by frequency of anginal attacks, nitroglycerin use, and ambulatory electrocardiogram monitoring of ischemic events. New extended-release formulations of diltiazem, such as Dilacor XR® and Cardizem CD®, should significantly increase the bioefficacy, such as blood pressure control, owing to better patient compliance with a once daily regimen.

B. Extension of Product Life

New delivery systems can also extend the patent life of those drugs of which patent protection is expired. According to the Drug Price Competition and Patent Term Restoration Act (which was enacted in 1984), a new delivery system which makes a drug product a new or better therapy can protect the drug from generic competition for seven years and up to seventeen years. This exclusivity provision protects the new dosage form of the drug, provided that it is distinguishable from current therapy.

Procardia® (nifedifine) is a calcium channel antagonist used for the treatment of hypertension. Recently, its patent was expired and therefore any companies can produce generic products containing the same active drug. Pfizer introduced the same drug in a new controlled-release delivery system, called "OROS® (Oral Osmotic Tablet)," which provides 24-h release after oral administration. The new product is called Procardia XL® and is a substantial improvement from the previous conventional tablet dosage form. The generic products must match the pharmacokinetic profile of Procardia XL® to be approved by FDA. The pharmacokinetic study may only require clinical study with twenty-five patients. If a generic product is available, pharmacists have to recommend them by law. If the pharmacokinetic profile is not the same, then the product is not considered generic. It is a new product that must be prescribed to be used. As we will learn in later chapters, mimicking the pharmacokinetic profiles of the drug delivered by OROS® is not easy to reproduce using other types of drug-delivery system. This is a good example of the triumphant of the controlled-release drug-delivery systems.

Recently, a new controlled-release product called Adalat CC® (nifedifine extended release tablet) was introduced. Adalat CC® is a new controlled nifedifine delivery system based on a dissolution controlled release from a coat-core tablet. In an open, randomized crossover study, the pharmacokinetics of Adalat CC® were compared with those of Procardia XL® 60 mg. Each was administered once-daily for 5 d to 24 young, healthy male and female volunteers whose nifedipine plasma levels and blood pressure responses were measured. As shown in Figure 6.1 (left), the pharmacokinetic profile of Adalat CC® is quite different from that of Procardia XL®. The steady state plasma nifedipine levels were not equivalent. The AUC for Adalat CC® was 845 ng/h/mL as compared to 670 ng/h/mL for Procardia XL®. Although a greater bioavailability was observed with Adalat CC®, it had wider range of drug concentration (*i.e.*, greater peak–trough ratio) during the 24-h period. However, as shown in Figure 6.1 (right), this pharmacokinetic difference between Adalat CC® and Procardia XL® was not reflected in either the systolic or diastolic blood pressure responses of the twenty-four volunteers. Since the ultimate goal of taking nifedifine is to control the blood pressure, the pharmacodynamic profile was more important in this case than the pharmacokinetic profile.

C. Delivery of Newly Developed Protein Drugs

In the past, most drugs were low molecular weight drugs which could be easily synthesized in the laboratory. The drugs which are being developed nowadays are mostly large molecules such as peptide and protein drugs which were used to be extracted from the animal tissues. They can be produced in large quantities by genetic engineering techniques. Human insulin was the first recombinant therapeutic protein drug approved by FDA in 1982. Since then, numerous genetically engineered protein drugs, such as human growth hormones, interferons, erythropoietin, hepatitis B

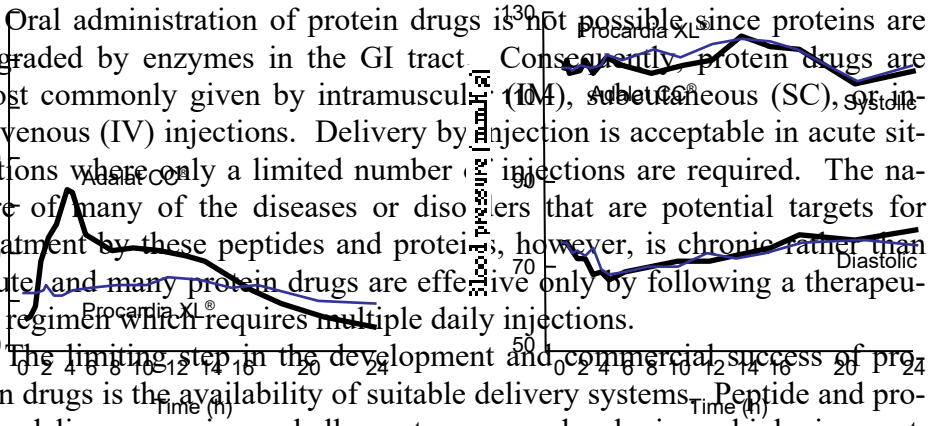

Figure 6.1 Comparisons of pharmacokinetic (left) and pharmacodynamic (right) profiles between Adalat® CC 60 mg and Procardia XL® 60 mg in healthy volunteers.

vaccine, or tissue plasminogen activator, have been approved. Delivery of this new class of drugs requires new delivery systems.

Oral administration of protein drugs is not possible since proteins are degraded by enzymes in the GI tract. Consequently, protein drugs are most commonly given by intramuscular (IM), subcutaneous (SC), or intravenous (IV) injections. Delivery by injection is acceptable in acute situations where only a limited number of injections are required. The nature of many of the diseases or disorders that are potential targets for treatment by these peptides and proteins, however, is chronic rather than acute, and many protein drugs are effective only by following a therapeutic regimen which requires multiple daily injections.

The limiting step in the development and commercial success of protein drugs is the availability of suitable delivery systems. Peptide and protein delivery remains a challenge to anyone developing a biologic agent, whether vaccine, monoclonal antibody or enzyme inhibitors. There is an urgent need for development of alternative delivery route as well as controlled-release systems to fully realize the potential utility of peptides and protein drugs. New delivery systems for the nontraditional routes of administration with the ability of self-regulating delivery are necessary for those drugs if they are to be useful in treating chronic disease.

II. ADVANTAGES AND DISADVANTAGES OF CONTROLLED-RELEASE DOSAGE FORMS

A. ADVANTAGES

1. Maintenance of Optimum Drug Concentrations

Maintaining the drug concentration between the minimum effective and toxic levels is important but often times difficult. Multiple, successive administration of conventional dosage forms tend to result in overdose and underdose (see Figure 1.1).

The ratio between the maximum safe concentration (C_{max}) and the minimum effective concentration (C_{min}) is known as the therapeutic index (TI).

$$TI = \frac{C_{max}}{C_{min}}$$

Table 6.1 lists TI values of selected drugs. For the drugs with high TI (such as chlorpheniramine), conventional multiple, successive administration may be all right, since overdosing and/or underdosing are not likely to occur. For the drugs with low TI (such as phenobarbital), however, it is highly possible to have overdosing and/or underdosing. Even slight overdosing may result in the drug concentration at the toxic range and underdosing may result in no bioactivity at all.

In addition to TI, another parameter known as "dosage form index (DI)" is also commonly used to evaluate the performance of the dosage forms. DI is defined as the ratio of the maximum (C'_{max}) to the minimum (C'_{min}) concentration achieved during a dose cycle.

$$DI = \frac{C'_{max}}{C'_{min}}$$

It is most desirable to have a DI as small as possible for any dosage forms. Having small DI values is especially important for controlled-release dosage forms.

2. Improved Efficiency of Treatment with Less Amount of Drug

Since controlled-release dosage forms provide steady level of drug concentration for longer period of time than traditional dosage forms, they can result in more prompt alleviation of the symptoms and cure of the disease. Thus, the total amount of drug necessary to cure the disease is less than that required by the traditional dosage forms.

3. Minimized Side Effects

Since the controlled-release dosage forms can maintain the effective drug concentration in blood for long period of time, the possibility of having toxic drug levels as well as subtherapeutic drug levels can be eliminated.

Table 6.1 Therapeutic Index Values of Selected Drugs

Drug	TI
Theophylline	∞
Triphenylamine	19,000
Diphenhydramine	2,300
Chlorpheniramine	1,400
Penicillin	>100
Acetaminophen	20–40
Barbiturates	2–7
Quinidine	2–3
Digitoxin	1.5

For example, transdermal patches eliminate problems associated with overdosing and underdosing of the drug. The side effect of clonidine can be reduced by lowering the daily dose and thus eliminating peak concentrations using the controlled-release transdermal patches. Estradiol is used therapeutically for systemic estrogen replacement for postmenopausal women and prevention of osteoporosis. A once-daily oral bolus of estradiol is compared to "hitting the liver with a hammer" every 24 h (Berner & Kydonieus, 1996). Such side effect of estradiol was also reduced by using transdermal delivery systems which lowers the daily dose of estradiol for metabolism during the first pass through the liver.

4. Less Frequent Administration

Improving adherence to treatment regimen may be as important as the development of new biomedical treatment techniques. The studies on the effect of the dosage regimen for hypertensives, antiasthmatics, allergenics, diabetes, cancer, and ulcer patients showed that once a day medication gave the best patient compliance (Berner & Kydonieus, 1996).

Controlled-release dosage forms have increased duration of therapeutic effects following a single administration. Controlled-release dosage forms are ideal for long-term delivery of drugs with very short half-lives. For example, the half-lives of nitroprusside and nitroglycerin are only a few minutes. This means that the effect of each dose last only several minutes, and patients have to take the drugs quite often. Transdermal controlled-release systems can increase the duration of action of such drugs up to 24 h.

Before the advent of advanced drug-delivery systems, such as the Geomatrix system (see later chapters) used for extended-release diltiazem, once-daily oral dosing was achieved by simply increasing the total dose of drug administered. As you already know, a higher dose results in a higher peak concentration; the drug elimination is usually first-order (*i.e.*, independent of the concentration). Thus, the higher peak concentration means longer therapeutically effective blood levels. For example, therapeutically effective blood levels can be maintained twice longer by simply doubling the dose administered. The problem, however is that a high loading dose may limit the usefulness of the drug because of a potential for a higher incidence of side effects at the elevated concentrations. The controlled diltiazem delivery systems are designed specifically to provide continuous release of the drug over a 24-h period. This allows once-daily administration of the drug and maintains therapeutic blood levels without a dramatic initial peak in blood levels.

5. Increased Patient Convenience and Compliance

With the advent of potent new drugs, noncompliance has become the most important limiting factor in the management of diseases. Improving adherence to treatment regimen may be as important as developing new drugs.

Many new transdermal therapeutic systems deliver drugs for 24 h and up to 7 d. Using such transdermal patches is obviously much more con-

venient than taking drugs several to dozen times a day. Each patch of Catapres® TTS (Transdermal Therapeutic System) provides continuous systemic delivery of clonidine for seven days at an approximately constant rate for treatment of hypertension. Once-a-week application of the 0.1-mg/day system results in constant clonidine levels in plasma which correspond to the trough levels of an oral dose of 0.1 mg given twice daily (Berner & Kydonieus, 1996). Seven day efficacy after each transdermal application versus 8 or 12 h efficacy with use of tablets provides substantial advantage in convenience. It also allows control the hypertension with a lower daily dosage of clonidine and reduced side effects such as drowsiness and dry mouth.

The Norplant® birth control system delivers levonogestrel, a contraceptive agent, for up to 5 y once implanted into the body. What could be more convenient than that? The failure rate of the implant in the first year is known to be only 0.2% (Barnhart, 1991). Developing once-a-day oral dosage form would benefit patients a lot, since it eliminates multiple (sometimes 4–6) administration of the drug to the patients in a given day.

Multiple administration is a problem particularly to the elderly patients or patients like me who do not have good memory. To aid such patients, a little gadget was made to display the time that the previous pill was taken (more precisely the time that the vial was open last) on the cap of the drug-containing vials.

6. Application to the Pharmacokinetic and Pharmacodynamic Research

The use of controlled-release dosage forms which can release drugs at the same rate for long periods of time eliminates the problems associated with irregular administration of the drugs. This is particularly good for the study of pharmacokinetic and pharmacodynamic properties of the drug. Simply speaking pharmacokinetic is the study on what the body does to the drug, while pharmacodynamics is the study on what the drug does to the body. As shown above in Figure 6.1, the pharmacokinetic profile may be very much different from pharmacodynamic response.

It is noted that there are cases where prolonging blood levels of the drug has no therapeutic advantages. For the drugs in the following examples, making controlled-release formulation is pointless.

a. Drugs with a long half-life so that frequent dosing is unnecessary (*e.g.*, diazepam and amitriptyline).
b. Drugs of which maintained effect is undesirable (*e.g.*, prednisolone)
c. Drugs which require immediate effect (*e.g.*, hypnotics).

B. DISADVANTAGES

1. Relatively High Production Costs

The overall cost for curing the disease (including the cost for doctors, nurses, pharmacists, and other health care personnel) may be substantially smaller with controlled-release dosage forms than with conventional dos-

age forms. This is true despite the fact that the controlled-release dosage forms is more expensive to produce than conventional dosage forms. The reason is that with controlled-release dosage forms patients may recover faster and save time for themselves and others.

The use of more expensive controlled-release dosage forms by the patients is a different story, however, if patients have to pay for them from their own pocket. Ocusert® is a controlled-release product which delivers pilocarpine at the constant rate for up to 7 d when placed in the eye. It looks like half of contact lens and can be used as if half-sized contact lens. Maintaining the constant pilocarpine level for up to 7 d by one application is supposed to be much better than applying eye drops of pilocarpine every 6 h. The transient high levels of pilocarpine following the use of eyedrops can cause severe visual difficulties. Despite the great advantage of Ocusert, its use has been limited by the patients mainly owing to the fact that patients have to pay higher price for it.

A study was done to explore the therapeutic substitution of a less expensive but equally effective antihypertensive agent by assessing patient outcome. The medication with hypertension was changed from once-daily diltiazem hydrochloride (Cardizem CD) or nifedipine (Procardia XL) to felodipine (Plendil®) (Landry *et al*., 1996). The final dose was titrated based on home and office blood pressure measurements assessed over subsequent follow-up clinic visits. The systolic and diastolic pressures improved after the medication change (systolic: 150 mm Hg versus 144 mm Hg; diastolic: 92 mm Hg versus 87 mm Hg). The results indicated that 80% of the cohort switched successfully to felodipine, and a yearly savings potential for the institution which conducted the study was estimated to be $72,000 (Landry *et al*., 1996). If more expensive controlled-release dosage forms are covered by insurance, more of them will be accepted by patients. But, then not everybody in the United States has the health insurance.

2. Leakage of Drug Mass (Dose Dumping)

Since controlled-release dosage forms are designed for long-term delivery, the amount of drug contained in the dosage form is much higher than a single dose of conventional dosage forms. If the drug reservoir of the delivery module is damaged and release the drug all at once, the drug concentration may go above the toxic level. The issue of dose dumping has to be considered in the design of controlled-release dosage forms.

3. Necessity of Surgical Operation

Many controlled-release dosage forms are designed to be implanted into the body by either surgical operation or injection. Those devices require surgical operation for implantation as well as removal at the end of the device lifetime. To avoid removal by surgical operation, many controlled-release devices are made biodegradable.

4. Difficulty of Stopping Drug Release

In some instances the drug release from controlled-release devices may have to be stopped. In that situation, those controlled-release dosage forms (such as injected biodegradable microparticles and orally administered dosage forms) make it difficult to shut off the drug release. There is no control over the drug release once they are administered.

5. Biocompatibility of the Controlled-Release Devices

This is a very important issue and we have a separate section for this subject.

III. BIOCOMPATIBILITY OF CONTROLLED-RELEASE DOSAGE FORMS

A. BIOMATERIALS AND BIOCOMPATIBILITY

1. Biomaterials

All the materials we use in our daily life are perfectly suited to their functions. This is simply because humans transform raw materials into materials with special properties that we need. Several thousand years ago, humans found that clay changed into a hard, brittle substance (ceramic) by heating, or baking. This process was used to make bowls, cups, and bricks. Later humans could extract iron from iron-containing rocks, and much later made steel and alloys. The modern era of polymers (or plastics) began in the 1840s when the first synthetic polymer, cellulose nitrate, was made. Since then, polymers became important resources for making replacements of many damaged and/or diseased body parts.

Biomaterials are any materials which are designed to restore, augment, or replace the natural functions of the living tissues or organs in the body (see Table 6.2). Simply speaking, biomaterials are those which become a part of the body either temporarily or permanently. Biomaterials can be classified into metals (e.*g*., stainless steels, CoCr alloys, Ti and its alloys), ceramics (*e.g*., nonabsorbable bioceramics, biodegradable or absorbable ceramics, bioactive or surface-reactive ceramics), composites (*e.g*., particulate composites, fibrous composites, porous materials polymers), and polymers. Biomaterials can be applied for soft tissue replacements (such as blood-interfacing implants), hard tissue replacements (such as dental implants, bone repair and joint implants), and orthopedic prosthesis fixations (such as mechanical fixation, bone cement fixation, porous ingrowth fixation, direct bonding of implant and bone).

Table 6.2 Selection of Biomaterials in Early Days

Polymer	Original Applications	Biomaterials applications
Polyetherurethane	Ladies girdle	Total artificial heart
Cellulose acetate	Sausage casing	Dialysis tubing
Dacron	Clothing	Vascular graft
Silicone rubber	Lubricant	Breast gel implant

Biomaterials are used not only for prosthetic applications but also for diagnostic and therapeutic application. Many controlled-release dosage forms which use polymeric systems are often implanted into the body for long period of time. For this reason, many polymeric controlled-release dosage forms can be regarded as biomaterials. Sometimes, biomaterials of which main function is not drug delivery can contain drugs for long-term delivery of certain drugs to the surrounding environment. For example, it is common to include antibiotics into heart valves or catheters to prevent bacterial infection on the surfaces.

2. Biocompatibility

Biomaterials should perform with an appropriate host response in a specific application without toxic, inflammatory, carcinogenic, and immunogenic responses. Appropriate host response ranges from inertness and no interaction to one of positive interaction. In general, the body's reaction to implants is to extrude them from the body or form a sheath-like capsule around the implants if they cannot be removed. The injury created by the implantation procedure usually results in inflammation which can be defined as the local reaction of vascularized tissue to injury.

The success in the applications of biomaterials relies heavily on the biocompatibility of biomaterials. Biocompatibility is the appropriate biological performance, both local and systemic, of a given polymer in specific applications. A clear, specific and absolute definition of biocompatibility does not exist at this time. The numerous and interdisciplinary factors must be used to describe the biocompatibility of a given polymer in a given application for a given duration. The following few examples describe how important the biocompatibility issue is for the development of controlled-release dosage forms which are designed to be implanted inside the body.

B. Silicone Gel Breast Implant

The importance of biocompatibility cannot be overemphasized. Recent highly publicized controversy on silicone gel-filled breast implants is a case in point. A total of some two million women have received various types of breast implants since they were introduced in the early 1960s for cosmetic and reconstructive purposes. The outer layer of silicone gel breast implant is made of crosslinked poly(dimethyl siloxane) (PDMS, 10%) outer layer (10%, crosslinked) and the inner side is filled with PDMS oil. In 1992 FDA pulled silicone gel implants used for cosmetic breast enlargement off the market based on widespread reports of adverse reactions and insufficient evidence of the implants' safety (Wilkinson, 1998). Since then, most of the implants have been made of a saline-filled silicone rubber envelope.

The typical tissue reaction around any implanted biomaterial is the formation of thin fibrous capsule similar to scar tissue. Scar tissue was formed on the surface of silicone gel implant, and the contraction of the fibrous capsule often causes painful breast hardening and deformity. The formation of fibrous membrane capsule around the implants is an attempt

by the body to extrude the implant. Some silicone implants were coated with polyurethane foam featuring micro pillars which was designed to disrupt the fibrous capsule architecture and prevent the formation of scar tissue. Initially the approach was hailed as the brilliant way to overcome the scar tissue formation. The polyurethane foam, however, was slowly degraded in the body, and the degradation products such as 2-toluenediamine was known to be carcinogenic. Furthermore, the silicone shell of the implant ruptured in many cases to release silicone oil into the body. Once released from an implant, silicone gel was observed to migrate as far away as the fingers and down into the groin of some women, and this might have led to granulomas, chronic inflammation, migration of silicone through the skin, and gel infiltration of nerves, causing numbness or pain. Such leakage was blamed for harmful immune reactions and a cause of cancer. More and more studies on the effects of silicone gel implants have consistently shown, however, that there was no direct link between implants and autoimmune disease. This does not mean there is no possibility of a new, undefined disease. Dow Corning, the largest U.S. maker of breast implants declared bankruptcy in May, 1995 because of the billions of dollars of health claims from implant recipients. Dow Corning was able to receive nearly $1.6 billion from the more than 100 insurers including Allstate Insurance, Home Insurance, and Employers Insurance of Wausau that had written policies covering Dow Corning between 1962 and 1985 (Rouhi, 1999). Whether the silicone gel leaked from the implants is responsible for all the problems or not, it is clear that the lack of biocompatibility of the silicone gel implants resulted in one of the most disastrous medical incidents in recent history.

C. NORPLANT

Norplant® is contraceptive device developed by the Population Council and Wyeth–Ayerst Laboratories (A division of American Home Products Corp. of Philadelphia). Norplant is made of six silicone rubber tubes which can be implanted under the arm by a simple surgical operation. Each silicone rubber tube is about the size of a match stick. The six tubes release progestin at a constant rate for up to 6 y. FDA recommended using it only for 5 y.

Before the introduction in the United States, Norplant® was tested on half a million women in fifteen countries. None of the women in the program reported any life-threatening problems. Consequently, the product was approved by FDA. During use in the United States, problems of using Norplant have surfaced one by one. Although the problems were limited to rather a small percentage of women, they were nevertheless serious. Some women with implanted Norplant reported problems with scar tissue formation—the same problem seen with the silicone gel breast implant. Owing to the scar tissue formation around Norplant, the removal of Norplant was difficult in many women and in some cases silicone rubber tubes were not found in the implant site at all. Norplant is working well for many and highly effective. Relatively small problems like capsule formation around the implanted Norplant and subsequent problems in cer-

tain number of women jeopardize the whole field of contraceptive development. Because of the potential lawsuits against their products, many industries are away from biomedical business. Considering the fact that there have not been any new contraceptive devices since the introduction of the pill, one could argue that the real losers in the end would be women who would otherwise use new, more convenient contraceptive dosage forms.

D. Self-Regulating Insulin Delivery Devices

For the diabetic patients, nothing could be better than replacing multiple, daily injections of insulin with controlled-release drug-delivery systems which sense the blood glucose level to release appropriate amount of insulin and automatically shut-off the insulin release once the glucose level is lowered to a desirable level. Currently, technology is such that we can make a controlled-release device which has a glucose sensing capability and controlling insulin release. The problem of using such systems clinically is that the biocompatibility of such systems is not good enough. For example, the glucose sensor which functions perfectly in the laboratory for a long period of time does not work more than 12 h or so when implanted under the skin. The proteins and cells adhere to the surface of the sensor and the sensor immediately starts losing the sensitivity. In another approach, pancreatic cells were encapsulated in polymeric microspheres to prevent immune rejection before implanting in the body. While the clinical study on such approaches has been successful, the issue of biocompatibility of such a dosage form for long-term application has not been resolved. For implanted insulin delivery systems, we may face the same problem we had with Norplant of silicone gel implant.

Biofilms colonize on many surfaces including teeth, contact lenses and urinary catheters. Biofilms are the main cause of infection in the patients who use the biomaterials. Biofilms are slime-enclosed communities of microorganisms in complex and tenacious films (Costerton & Stewart, 2001). To form biofilms, bacteria manufacture hundreds of proteins that are not found in free-floating cells, for extracellular matrix. It is nearly impossible to eradicate with conventional antibiotics. Quite often antibiotics and germ-fighting cleansers fail to pierce the film. Before antibiotics, penicillin for example, diffuse into a biofilm, the enzymes released by the microbial cells degrade them, and thus antibiotics can never reach the deeper layers of a biofilm. Even in places where an antimicrobial agent penetrate biofilms and kill most of the cells, the few cells remaining after the aggressive antibiotic therapy can restore the biofilm to its original state in a matter of hours. This is partly because surviving bacteria can use dead ones as nutrients.

The issue of biocompatibility for the controlled-release dosage forms has not been extensively dealt with in the scientific community, and so by the public. This is mainly due to the fact that all the efforts so far have been focused on the development of drug-delivery systems with specific release properties. As we get over those technological problems, we real-

ize that there are other important problems we have to face and overcome. One of them is the biocompatibility problem.

E. THE BIOMATERIALS ACCESS ASSURANCE ACT OF 1998

Law said that even if a material is used as a minor portion of the device, the company can be sued if the device does not work. Because of this, big companies, such as DuPont, withdrew all of their biomedical polymers from market. Lack of biomaterials and biomaterials research will make the development of new biomaterials very slow, and as a result, it is the public who will be suffered by the lack of good biomaterials in the end. To alleviate this particular problem, Congress passed a new law. On July 30, 1998, Congress passed the Biomaterials Access Assurance Act, and the bill was signed into law (Public law 105–230) by President on August 13, 1998 (Costerton & Stewart, 2001). The bill protects certain raw materials and parts suppliers from liability for harm caused by a medical implant, and this certainly will help to ensure the continued availability of life-saving and life-enhancing medical devices, such as heart valves, jaw implants, artificial hips, and other medical devices (including many not yet imagined). This Act helps remove the roadblock of developing new medical devices (*i.e.*, the supply of raw materials used to make medical devices) since it will prevent misdirected lawsuits. Before the Biomaterials Access Assurance Act, biomaterials suppliers have been included in lawsuits, even though their own materials were not dangerous or faulty. It was reported that DuPont has been sued 651 times in 41 states over 10 y because it sold "less than $100 worth of Teflon" that was subsequently used in jaw implants. The law is intended to protect the suppliers of raw materials and component parts used to manufacture implantable medical devices from the costs of defending themselves in lawsuits brought against the devices that contain their materials (Costerton & Stewart, 2001). The law made it clear that, in most instances, the suppliers of biomaterials used in medical devices such as implants are not liable for damages allegedly caused by such devices if they met the contract specifications for the biomaterial. It is the manufacturers and the sellers of the devices that are liable. It is interesting to note that the bill's provisions specifically do not apply to suppliers of silicone gel and silicone envelopes used in breast implants (Wilkinson, 1998).

IV. DEVELOPMENT OF CONTROLLED-RELEASE DOSAGE FORMS

While the polymeric materials have been an essential component in the controlled-release dosage forms, the development of such dosage forms requires more than mixing drugs with polymeric materials. It requires careful planning with considerations on the following factors.

A. FACTORS TO CONSIDER

1. Medical Rationale

The controlled-release dosage forms should have impact on at least one of the following aspects: (1) drug efficacy; (2) drug safety; and (3) patience compliance. By having a controlled-release dosage forms, a drug must increase its efficacy and/or safety. Making patients more compliant can also be a good reason to develop controlled-release dosage forms.

Patients who undergo major surgery often faces an additional ordeal of sever pain that may last a long time ranging from months to years. Effective (*i.e.*, timely and proper) treatment of pain not only spares patients' suffering but also leads to faster, more complete recovery resulting in lower cost of health care. For treating acute pain, morphine is still one of the most useful drugs, but it has not been properly used owing to its addictive nature. The fear of addiction by overdose resulted in undermedication of patients in most cases, despite evidences that morphine and other opioids almost never lead to addiction when used for pain treatment. The best pain management may be to deliver enough amount of painkiller when patients need it, instead of delivering a certain dose several times a day. An approach, called patient controlled analgesia, allows patients to administer a dose of painkiller using advanced devices, such as electronically controlled pumps (*e.g.*, Panoject™) that have safeguards to prevent overuse. Other patient-controlled pain-killer devices include a transdermal patch (from Alza Corp.) delivering fentanyl for up to 72 h, allowing chronic pain suffers to sleep through the night (Bylinsky, 1994). DepoMorphine™ (SkyePharma: San Diego, CA; formerly DepoTech) is a sustained-release encapsulated dosage form under development which delivers morphine sulfate for the treatment of post-surgical pain (Verma R K & Garg, 2001).

2. Drug Input Rate

The target pattern of drug input rate can be established from various requirements of a drug, such as indication, safety, pharmacokinetics, and pharmacodynamics. The best input rate is the one which counteracts the drug elimination rate.

3. Biological Interface

The controlled-release dosage forms should have minimum impact on the body. The formation of scar tissue capsules around the implanted devices, such as silicone rubber tubes, is not desirable at all. In the case of transdermal patches, the adhesive should have acceptable adhesion to the skin while providing user comfort. In addition, cosmetic acceptability is also an important consideration.

4. Cost Effectiveness

Although the cost of the dosage form may increase, the controlled-release dosage forms may decrease the frequency of dosing and the side effect. Thus, the overall cost is reduced. The controlled-release dosage forms

should maximize the therapeutic benefit and minimize the cost of therapy (*i.e.*, increase the benefit/cost ratio).

B. Example of Transdermal Patch Development

Let's use Nicoderm® transdermal patch developed by Alza and licensed to Marion Merrell Dow as an example.

1. Medical Rationale

Nicotine is highly potent. Thirty milligrams of nicotine are toxic. It is also highly water-soluble and permeates through skin quite well. Thus, the transdermal patch can significantly improve the safety and the efficacy of nicotine.

2. Drug Input Rate

For many, nicotine level has to be above a certain level for 24 h. The transdermal patch should have a rapid onset of action after application to mimic smoking. The nicotine level does not have to be high so that the nicotine input level from the transdermal patch can be low. The drug input rate was controlled by the rate controlling polymer membrane.

3. Biological Interface

Membrane layers were cut into individual patches by die cutting. Thus, the edges are not sealed. Loss of 20% of nicotine by diffusion through edges; but, it does not cause any harm to the skin and to the patient. After all, delivery of nicotine through the skin is the goal, and the absorption of the nicotine released through edges should not be a problem.

4. Cost Effectiveness

The cost of Nicotine patches is rather high, but the desire to quit smoking makes cost not a factor.

V. STERILIZATION OF MEDICAL DEVICES

If controlled-release dosage forms need to be sterilized, one of the methods listed in Table 6.3 can be used.

Table 6.3 Examples of Sterilization Methods

Gamma sterilization
E-beam sterilization
Ethylene oxide sterilization
H_2O_2 vapor sterilization
Low temperature H_2O_2 plasma (*e.g.*, STERRAD® Sterilization System)
Intense pulsed light sterilization
Gas plasma-based sterilization (*e.g.*, Plazlyte® System)

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