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Jeremy C. Wright
Diane J. Burgess *Editors*

Long Acting Injections and Implants

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Long Acting Injections and Implants

Springer

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This book is dedicated to friends and family. Especially both editors dedicate the book to their respective parents (George Gartly Burgess and Violet Isobel Burgess; William C. Wright and Jenny J. Wright).

Preface

The evolving complexity of human therapeutics requires the development of novel drug delivery systems. This book encapsulates in a single volume the concepts essential for understanding the science and technology associated with the research and development of long acting injections and implants. It provides a comprehensive overview of the scientific and regulatory challenges associated with these delivery systems.

Critical contributions to this area are the array of formulations that make up the spectrum of long acting injections and implant dosage forms. These include microspheres, liposomes, in situ forming depots, suspensions, implants, lipophilic solutions, and osmotic implants. Such formulations have the potential to maintain therapeutic drug concentrations for durations from days to months, can be engineered to maintain characteristics such as zero-order or pulsatile drug release, and, in some cases (e.g., liposomes) can provide targeted drug delivery to the site of action. These attributes lead to increased patient compliance and convenience, reduced fluctuations in plasma profiles, and reduced plasma concentrations making it possible to administer higher drug concentrations to the site of action while reducing the overall dose. Thus, unwanted side effects can be minimized or reduced. In addition, long acting injections and implants can provide a means for the delivery of drugs that are subject to degradation in the harsh environment of the gastrointestinal tract, that undergo extensive first pass metabolism, or that exhibit poor bioavailability when such molecules are orally administered.

Long Acting Injections and Implants begins with chapters that provide basic concepts explained in a simple, clear, and concise manner. In subsequent chapters additional material, expansions on the basic scientific concepts underpinning research and development of such dosage forms, and examples of technological developments in this area are comprehensively reviewed and discussed. The introductory chapter provides a brief description of the types of systems and major areas of current application and research. The *Historical Overview* chapter provides a chronological overview of the historical developments associated with long acting injections and implants providing sufficient background to enable the reader to appreciate the historical development of the area and to use that knowledge as a foundation for the

development of the next generation of products. The *Host Response* chapter introduces the reader to the body's response to biomaterials/foreign bodies and the influence of environmental conditions on the design and development of long acting injections and implants. The *Anatomy and Physiology* chapter describes the biological features of the site of administration that are relevant to the development of long acting injections and implants. The following two chapters provide comprehensive information on drug candidates, clinical objectives, and disease states. The next series of chapters of the book focus on aspects related to the research and development of specific injection and implant dosage form types. In addition to the systems mentioned above, chapters are also provided on micro- and nanoemulsions, PEGylation of nanocarriers, self-assembling lipid formulations, microfabricated technologies, drug eluting stents, delivery of peptides and proteins, and delivery of vaccines. These overviews are followed by chapters that describe and discuss special considerations unique to the injection route including sterilization and in vitro release testing (and in vivo/in vitro correlation). In the final chapter of the book, an overview of the regulatory considerations associated with the registration of long acting injections and implants is provided.

Long Acting Injections and Implants has been written with the objective of both enlightening someone just starting in the field (e.g., a new scientist or experienced scientist switching fields) and while at the same time providing the in-depth knowledge that is beneficial for a skilled worker in the field. It is hoped that the reader will find this volume useful and intriguing for both the variety of scientific system types that provide long acting therapy and for the wide range of scientific and technical topics that are involved in the research, development, and registration of long acting injections and implants that provide state of the art therapy to patients.

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Chapter 1
An Introduction to Long Acting Injections and Implants

Diane J. Burgess and Jeremy C. Wright

Abstract This chapter provides an overview of the area of long acting injections and implants, summarizing the contents of the book. As appropriate, the reader is directed to the relevant chapters.

The therapeutic utility of many drugs can be enhanced by prolonged administration. Constant, extended drug levels at the site of action can improve efficacy and reduce side effects. A number of modalities can achieve sustained drug levels including: repeated oral administration, repeated topical (transdermal) administration, repeated pulmonary administration, repeated parenteral administration, delivery via infusion pumps, and long acting injections and implants. Long acting injections and implants offer a number of advantages (some of which are shared with other long acting administration modalities). First is extended duration of action. Repeated bolus administration of a drug (either oral or parenteral) can result in the classic "peak and valley" pattern of drug administration (see Fig. 1.1) wherein plasma C_{max} can exceed the toxic threshold (leading to undesirable side effects) and plasma C_{min} can fall below the minimum threshold for efficacy. Alternatively, prolonged, long acting drug delivery can result in steady levels that are maintained above the minimum threshold for therapeutic efficacy but below the toxic threshold, resulting in prolonged drug action (i.e., better pharmacodynamics) without unwanted side effects. For some therapies, side effects may be a matter of inconvenience to the patient, but for other therapies (e.g., cancer chemotherapy) the impact and potential benefits can potentially be much greater.

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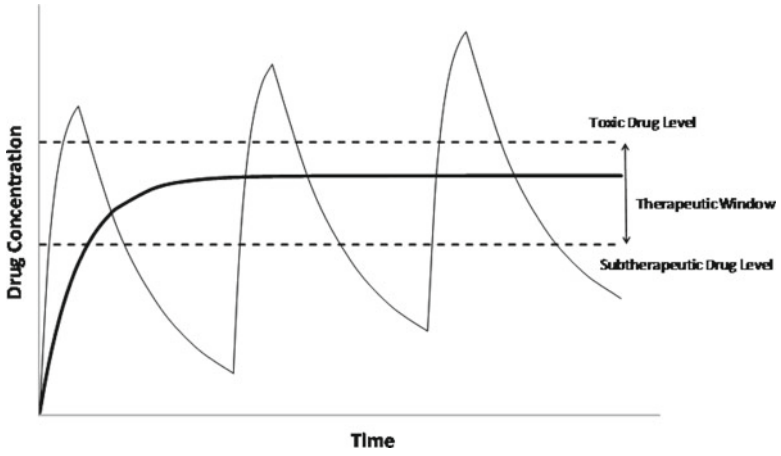

Fig. 1.1 Conceptual depiction of plasma drug concentrations after repeated administration from a conventional dosage form (*thin line*) and from a controlled release system (*bold line*)

Less frequent administration via long acting injections and implants can be significantly more convenient for the patient and the health care provider by reducing the number of times a drug must be administered. This reduced frequency of administration can result in savings for the health care system and can also enhance patient compliance with the therapeutic regimen (less skipped doses, etc.) thereby increasing the probability of the desired therapeutic outcome. Additionally, patient compliance can be enhanced when side effects are minimized by long acting injections and implants.

Parenteral administration may be the most logical or only choice for drugs with low oral bioavailability or extensive first pass metabolism. Long acting injections and implants may be applied to either systemic delivery of a drug (for example, systemic delivery of an antimetastatic chemotherapeutic agent) or applied to local delivery (for example, an analgesic system applied directly to a surgical incision or a chemotherapeutic system applied directly to a brain tumor site).

Sustained parenteral drug delivery (including long acting injections and implants) began to emerge as a subarea of pharmaceutics in the mid-twentieth century. Advances in pharmacokinetics and pharmacodynamics highlighted the need for sustained drug levels in plasma or in the target tissues in order to achieve the desired therapeutic response. The development of the field of long acting injections and implants was propelled by advances in pharmaceutical chemistry (including biotechnology) and advances in materials science, especially polymer technology. (See Chap. 2 for more information on the development of the field).

A wide variety of different types of long acting injections and implants have been designed and tested. New systems seem only to be limited by the extensive creativity of the innovators in this field and advancing scientific knowledge. Nevertheless, design of long acting systems requires knowledge of the physicochemical properties of

the system under development, the physicochemical properties of the drug being delivered, and the pharmacokinetic and pharmacodynamic properties of the drug, including toxicities associated with elevated drug levels. Drugs and diseases that have been treated or investigated for application of long acting injections and implants are discussed in Chaps. 5 and 6. Additionally, the body will respond to the administration of long acting injections and implants. The understanding of the foreign body response has progressed greatly, and the foreign body response must be considered in the development of long acting injections and implants. As is well known to those working in the field, even the administration of systems composed of materials considered to have good biocompatibility will engender some sort of foreign body response (see Chap. 3). Additionally, if the system is intended for producing sustained systemic levels of the drug, then the biological characteristics of the injection site that affect drug transport and uptake must be considered (see Chap. 4).

Some of the first implantable sustained release preparations involved compressed tablets of steroids, wherein the slow dissolution of the steroid from the tablet provided sustained release of the active agent. A significant improvement occurred due to advances in polymer technology, specifically the development of polymeric materials that possessed significant biocompatibility. It was recognized that a polymeric rate-controlling membrane (RCM) could be placed between the body and a drug reservoir, and this would lead to controlled release of the drug (RCM/reservoir drug delivery system). This led to the development of RCM drug delivery systems for ocular applications, intrauterine inserts, and, finally, to contraceptive implants such as the Norplant® system consisting of an outer cylindrical membrane of polydimethylsiloxane and the steroid levonorgestrel in the interior of the cylinder. An additional contraceptive implant utilizing similar design concepts is the Implanon®, which utilizes poly(ethylene-*co*-vinyl acetate) as the RCM for the delivery of etonogestrel. Implants utilizing a hydrogel RCM (Hydron® Implant) were also developed and applied to the delivery of the LHRH agonist, histrelin acetate. (See Chap. 2 for additional discussion of nondegradable implants).

Another subclass of RCM systems are the osmotic implant systems. In these systems, the RCM controls the rate of water diffusion into the system, with the delivery of an equal volume of the drug solution or suspension from the system reservoir. These systems yield steady, zero-order delivery of drugs. Use of a catheter with these systems can enable site-specific delivery of a therapeutic agent. The ALZET® pump was developed and commercialized for animal research applications and has been extensively applied in a wide range of investigational areas. Osmotic systems for human applications are based on a design with an outer cylinder of titanium (DUROS® implant) and a piston that separates the osmotic layer from the drug reservoir. DUROS implants have provided delivery of agents from 1 month to over 1 year for treatment of pain, cancer, diabetes, and hepatitis (see Chap. 17).

Lipophilic (oily) solutions and suspensions are one of the original dosage forms in this field. They contain an oil, such as sesame oil or castor oil, and the drug as either a solution or suspension. These depots can be quite elegant in design and

simple to manufacture. These systems have been applied to the delivery of a number of drugs (e.g., steroids, antipsychotics), with durations of action as long as 6 weeks. [See Chap. 7 on oily (lipophilic) solutions and suspensions].

Biodegradable polymers are inherently attractive for drug delivery applications because of two potential major attributes: first, if the polymer erodes only at the surface, then it would seem possible to engineer systems yielding nearly constant release. Second, the system can be expected to completely erode, thereby eliminating the need for a procedure to remove an implanted or injected system at the end of the delivery lifetime.

Biodegradable copolymers of lactic and glycolic acid (PLGA) have been extensively investigated for the delivery of a large number of drugs, including small molecules, peptides, proteins, vaccines, and other biomolecules. The degradation rates of these polymers can be modified by varying the ratio of lactic to glycolic acid in the copolymer.

The development of microspheres based on PLGA has been one of the major successful applications of long acting injections and implants. Microspheres can range in size from 1 to 999 μm. In general, microspheres are suspended in an aqueous vehicle prior to administration through a small gauge needle. The microspheres may have either a continuous polymeric matrix wherein the drugs are homogeneously dispersed or a shell-like wall surrounding the drug reservoir/core. The terms microspheres and microcapsules are often used synonymously. Research and development of PLGA-based microspheres has led to the regulatory approval and commercialization of a number of products including the Lupron Depot® (leuprolide), the Trelstar® depot (triptorelin), the Nutropin® depot (somatropin), and Risperal® Consta® (risperidone) for applications ranging from prophylactic treatment of prostate cancer to growth hormone deficiency to antipsychotic therapy (see Chap. 10).

Additionally, biodegradable implants composed of PLGA were investigated for a number of applications. The systems can be implanted via trocars or, if the implant size is small enough, these systems can be delivered via standard-sized needles. The Zoladex® implant (PLGA matrix system delivering the LHRH analog goserelin) was developed for the treatment of prostate cancer, breast cancer, and endometriosis and has been commercialized worldwide.

Other biodegradable polymers have also been investigated and utilized for the development of commercial products. Polyanhydride polymers are utilized for the Gliadel® wafer for the delivery of carmustine (BCNU) for the treatment of brain tumors (glioblastomas). The polyorthoester family of polymers has been widely investigated and regulatory approval has been sought for a product for the delivery of granisetron. (See Chap. 2 for additional discussion of biodegradable polymers).

In situ forming systems have been developed by a number of investigators. These systems can be injected through standard syringe needles but then gel or form viscous depots once injected. Drug release through the depot is thus sustained for periods of time from days to months. Major examples of these dosage forms include the Atrigel® system (based on PLGA copolymers), the SABER™ system (based on sucrose acetate isobutyrate) and the ReGel® system [based on polyethylene glycol (PEG)–PLGA copolymers]. These systems have been applied to cancer therapy, analgesia, and other areas (see Chap. 9).

Liposomes constitute another system for injectable drug delivery. Liposomes are self-closed structures composed of one or more curved lipid bilayers (lamella) that entrap part of the solvent into their interiors and are usually spherical in shape. Hydrophilic groups of the lipids are on the outside and inner surfaces of the lamella, hydrophobic groups are in the interior of the lamella. Liposomes can be utilized for drug delivery either by loading the drug into the interior of the liposome or into the lamella. Additionally, PEG can be covalently attached to the lipid molecules that constitute the lamella (termed a "Stealth" liposome) and this modification extends the circulating half-life. The most notable example of long-circulating liposomes is Doxil®, a PEGylated liposome product containing doxorubicin. Liposome formulations of doxorubicin exhibit reduced toxicity and a higher efficiency as a result of passive tumor targeting via the "Enhanced Permeation and Retention (EPR)" effect. The EPR was discovered by Maeda and coworkers who discovered that a nanoscale construct accumulated or was trapped within tumor tissue. They concluded that the vasculature in the tumors was "leaky" and the lymph drainage system was not yet functioning efficiently. (See Chaps. 2 and 11 for additional information).

An additional application of lipids involves lipid-based liquid crystalline (LC) phases that can be formed by molecular self-assembly. These systems consist of specific liquid mixtures of naturally occurring polar lipids and small amounts of solvents (FluidCrystal® Injection depot). The systems can be injected subcutaneously or intramuscularly. Upon contact with the aqueous fluids present in the tissue, the lipids self-assemble into reversed LC phases, thereby effectively entrapping dissolved or dispersed drugs. Drugs can be released over periods of days to months. The system is applicable to the delivery of small molecule drug substances, peptides, and proteins (see Chap. 16).

Liposome and microspheres are dispersed in a liquid carrier prior to injection. There are a number of other dispersed long acting injection systems, including aqueous suspensions, emulsions, nanosuspensions, and surface-modified nanocarriers.

Sustained release formulations of sterile aqueous suspensions (particle size of 0.1 μm or greater) are generally intended for injection by the subcutaneous, intramuscular, or intra-articular routes. Compared to aqueous solution formulations, aqueous suspension formulations can be relatively fast releasing or exhibit sustained release with readministration intervals from hours to months, depending on the formulation and the properties of the active ingredient. A number of formulation parameters must be assessed to prepare a formulation that exhibits acceptable functionality in the hands of the user. Additionally, an understanding of the rate limiting step in the absorption of the active into the systemic circulation (or target site for local delivery) is required to optimize the formulation and the delivery of the active. Examples of active ingredients formulated as aqueous suspensions include steroids and antibiotics (see Chap. 8).

Micro- and nanoemulsions may be utilized to overcome formulation challenges such as solubilization of poorly aqueous-soluble drugs and/or protection of drugs susceptible to hydrolysis. Emulsions may be oil-in-water (O/W) or water-in-oil (W/O) or multiple emulsions (O/W/O and W/O/W). Emulsions are thermodynamically unstable; however, emulsion stability can be substantially improved using suitable emulsifiers and viscosity-enhancing agents. The method of preparation can

affect the droplet size distribution and, hence, the stability. Drug release rates from emulsion systems are determined by both the carrier and the drug characteristics. A number of emulsion systems have been commercialized (see Chap. 12).

Nanosuspensions represent another possible approach to the problem of drug candidates that are poorly soluble in water and exhibit poor bioavailability. Nanosuspensions are generally considered as consisting of particles with mean diameters below 1,000 nm. Nanoparticles may be produced via techniques that are applicable to most drug candidates and amenable to scale-up. Nanoparticulate formulations have been approved for antipsychotic therapy (Invega Sustenna®) and for the treatment of breast cancer (Abraxane®, a nanoparticle formulation of paclitaxel with albumin which provides for targeted delivery of the chemotherapeutic to the tumor through albumin mediated uptake) (see Chap. 13).

Since nanoparticulate pharmaceutical carriers are often rapidly cleared from the body, can be unstable at physiological conditions, and may be taken up by the mononuclear phagocytic system, surface modification is often used to extend the carrier lifetime. A number of synthetic polymers have been investigated as surface modifiers, with PEG being highly favored because of a number of attractive properties. Additionally, a targeting ligand can be attached to a PEGylated nanocarrier, especially if the receptor is overexpressed in the target tissue, as occurs for certain cancer cells (see Chap. 14).

Initially long acting implants and injections were developed for small molecule drugs. With the development of techniques for producing commercially significant quantities of peptides and proteins, investigations were launched into the design of systems for peptides and proteins, oftentimes exploiting and adapting existing technologies. These efforts resulted in the development of a number of techniques or systems for the delivery of peptides and proteins as long acting injections and implants. Included in these techniques/systems are synthesis of drug substance analogs with improved pharmacokinetic characteristics, the addition of high molecular weight entities (such as PEG) to the drug substance to modify release characteristics and the ADME profile and incorporation of the peptide or protein in a long acting drug delivery system. Examples of long acting drug delivery systems include PLGA microspheres and PLGA implants (especially for LHRH analogs), osmotic implants for peptide and protein delivery, in situ gelling systems, and self-assembling lipid systems. (See the chapters on the individual technologies and Chap. 20 for additional information).

As noted above, the covalent linking of polyethylene glycol ("PEGylation") to protein and other molecules has been a major area of research and development over the last several decades. Examples of commercial products resulting from these efforts include PEG-interferons (Pegasys®, PEG-Intron®) and PEG-GCSF (Neulasta®) among others. PEGylation results in an extended circulation half-life, although usually with some loss of activity and binding affinity. Overall, there is an improvement in product performance. Additionally, PEGylation has the potential to reduce immunogenicity. The attached PEG moieties can be either linear or branched and may attach to multiple sites on the protein. Thus, it is possible for PEGylation to yield mixtures of conjugate isomers; current development favors PEGylated molecules with minimized heterogenicity (see Chaps. 15 and 20).

Another area of biomolecule delivery that has been investigated is the sustained release of stable vaccine antigens. Vaccines are considered to be one of the most safe and effective medical interventions currently available. Micro- and nanoparticles prepared from PLGA represent a promising delivery system for vaccine antigens and have been shown to improve immunogenic responses in mammals relative to administration of soluble antigen. These systems have the potential to eliminate the need for booster vaccinations. Moreover, PLGA microparticles can trap and retain the vaccine antigens in local lymph nodes and protect them from proteolytic degradation, ensuring longer stimulation by the antigen. Development of PLGA protein antigen vaccine systems requires careful optimization of the microencapsulation method and selection of PLGA type and excipients. Because of cost considerations, the first clinical use of this dosage form for vaccines may be for treatment of diseases such as cancer instead of prophylactic immunization in healthy patient populations (see Chap. 21).

A major advance for "implantable" systems has been the development of drug-eluting stents (DES). Stents are tiny metal wire structures intended to keep arteries open following balloon angioplasty. While bare metal stenting produced improvements in restenosis rates compared to balloon angioplasty alone, a fairly high restenosis rate was still observed. DES that slowly release a potent antirestenotic drug were introduced to the market in 2002 and have resulted in very significant decreases in restenosis rates compared to bare metal stents. The first two commercially available DES were the CYPHER® Stent (a sirolimus-eluting stent marketed by Cordis Corporation) and the TAXUS® Stent (a paclitaxel-eluting stent by Boston Scientific). These DES consist of a metal stent that has been coated with the antirestenotic drug dispersed in polymer matrix. DES have been very successful and widely adopted. In addition to the CYPHER and TAXUS stents, DES have been introduced by other manufacturers. The ultimate stent design might be a fully bioresorbable DES and this concept is under investigation (see Chap. 19).

DES are considered combination products (drug + device) by regulatory agencies, a product classification that overlaps in some aspects with drug delivery systems and long acting implants. Examples of other combination products that have been investigated include antibiotic-impregnated bone cement matrices and implanted insulin pumps containing a glucose sensor that enables feedback control. While combination products are not discussed in extensive detail in this book, combination products are expected to expand as an area of investigation and product development, borrowing concepts and technologies from long acting injections and implants.

Another intriguing area for the development of long acting injections and implants involves utilization of the microfabrication technologies originally developed for the semiconductor industry. These technologies can be exploited in a number of ways. Implantable, addressable arrays with microreservoirs of drug can be implanted and drug release triggered electronically. Alternatively, the microfabrication technologies can be utilized to produce particles of uniform shape and size (and perhaps uniform surface properties) that can be exploited for various drug delivery applications (see Chap. 18).

There are a number of other important considerations required for development of a long acting system, obtaining approval from the appropriate regulatory authorities and for distribution into widespread commercial application so that patient therapy can be improved. Some of these considerations are unique to injections and implants (as compared to topical and oral delivery).

First, systems must be sterile. Sterilization may be achieved through terminal methods, such as irradiation or steam autoclave, or systems may be produced via an aseptic process. Because of its lower sterility assurance level, aseptic processing is less favored by regulatory agencies. Some innovative paradigms for achieving sterilization are under development, which may aid the commercial development of long acting injections and implants. In addition to sterility, systems must also meet requirements for endotoxin levels. These and other considerations are described in more detail in Chap. 22.

Second, a major advantage of long acting implants and injections is their ability to maintain a relatively constant drug concentration at the site of interest. In vitro drug release testing is of substantial utility for the development of new long acting implant and injection systems provided that there is correspondence between the in vivo performance of the systems and the in vitro test results. Establishment of an in vivo/in vitro correlation for drug release can thus help streamline system development and is also of substantial utility for regulatory approval and quality control of products via specifications on in vitro drug release. There are various in vitro release testing methods, which can be chosen based on availability, dosage form specifications, and drug properties. These methods are categorized into three groups: sample and separate, flow through, and dialysis. Although there are currently no standard methods for in vitro release testing of controlled release parenterals, standard dissolution apparatus specified by the US Pharmacopeia have been adapted in some cases and the development of compendial monographs is possible (see Chap. 23).

Finally, new parenteral products must be shown to be safe and effective via appropriately controlled clinical studies, resulting in the submission of a New Drug Application in the United States or other appropriate submission in other regions and countries. For these regulatory applications, specifications need to be developed to ensure consistent product performance across batches and throughout the shelf life of that product. This in turn necessitates an appreciation of the physiological variables and critical quality attributes that influence product performance. Some of these critical attributes may differ among the various types of long acting injection and implant systems described in this book. The assessment of critical quality attributes and manufacturing processes provides the basis for establishing appropriate quality standards for new drug products. Chapter 24 provides an overview of the questions and background information that regulators may consider when reviewing long acting injection and implant products.

As described above, the field of long acting injections and implants encompasses a wide range of system types and enables the delivery of drugs from days to years. A number of very innovative and commercially successful products have been developed, which have provided improved therapy through more precise control of drug levels and better patient compliance with the therapy regimen. It is expected

that additional innovative products will be developed and gain regulatory approval, many of them based on the science and technology described in this book. While it is difficult to precisely predict the future, it seems reasonable to assume that, in addition to products based on more mature technologies, nanoscale systems, targeted systems, and more combination products will enter the market place. Better test methods for drug release will be developed and the activity in this field will result in increasing regulatory guidance and scrutiny.

Chapter 2
Historical Overview of Long Acting Injections and Implants

Jeremy C. Wright and Allan S. Hoffman

Abstract Long acting injections and implants emerged as a sub-area of pharmaceutics in the twentieth century, with companies dedicated to the field being established in the 1960s and 1970s. The field contains a wide range of system types. This chapter summarizes the historical development of the field, including rate-controlled membrane concepts, biodegradable polymer concepts, surface-releasing systems, liposomes, targeted/nanoscale systems, and microelectronic systems.

2.1 Introduction

Sustained parenteral drug delivery began to emerge as a clearly defined sub-area of pharmaceutics in the middle of the twentieth century. The development of the field has been significantly influenced by advances in pharmacokinetics and pharmacodynamics, which served to highlight the need for controlled, extended drug delivery and sustained drug plasma/tissue levels in achieving desired therapeutic responses.

In the 1960s and 1970s, companies dedicated to controlled delivery were established (e.g., Alza, Elan). The field of long acting injections and implants consists of trends and technological developments that converge, diverge and sometimes reconverge, somewhat reconfigured. Two major trends have been the development of pharmaceutical chemistry (including biotechnology) and advanced materials science, especially polymer technology.

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The field has encompassed dissolution-controlled systems, liposomes and micelles, oleaginous depots, membrane rate-controlled implants, micro- and nanoparticles, extended circulation conjugates and in situ forming systems. Some of these systems "borrow" concepts or materials from another class, with the objective of providing long acting therapy. Systems in this field include those that provide zero-order (constant rate) delivery of drugs and sustained-release systems that provide long acting therapy, though not necessarily at a constant rate. Long acting injections and implants can provide systemic, local, or targeted therapy. Systems can also be viewed as macroscale, microscale, or nanoscale [1]. This chapter provides an overview of the historical development of this field with an emphasis on systems that have achieved clinical or commercial success; individual following chapters provide more details on key system types.

2.2 Early History

By the 1930s, it was recognized that implanted pellets containing hydrophobic compounds could provide sustained release of drugs [2]. Examples of these pellet systems included pellets containing estradiol for the treatment of prostate cancer and pellets containing testosterone for the treatment of testosterone deficiency [3].

Additionally, it was recognized that depot formulations of drugs or esters with very low water solubility could also provide extended delivery. These depots often utilized oleaginous vehicles. Examples include procaine penicillin G in an aqueous vehicle and fluphenazine decanoate in a sesame oil vehicle as an antipsychotic preparation ([3–5]; oil-based solutions and suspensions are discussed further in the chapter on oily (lipophilic) solutions and suspensions).

In the early 1960s, T. Higuchi presented the now classic "Higuchi model" [6]. While originally for release of drug dispersed in an ointment, the model was subsequently applied to the release of drugs from a variety of matrix systems. The Higuchi model (2.1) indicates that extended drug release will be observed from solid drug dispersed in a matrix, but will vary with (time)$^{1/2}$:

$$M_t / M_\infty = 2\left\{DC_s(2C_0 - C_s)t\right\}^{1/2} / C_0 l \tag{2.1}$$

In this equation, C_0 is the total concentration, D is the diffusivity and C_s is the solubility of the drug in the matrix. The surface area and thickness of the depot are denoted by A and l, respectively. Equation (2.1) describes release from a rectangular slab, so that $M_\infty = Al\,C_0/2$. It should be noted that the above model is for a drug delivery system where the rate of diffusion of the drug through the system matrix is the rate-controlling phenomena. The form of the model given above assumes that there is rapid transport of the drug through any diffusional boundary layer at the surface of the system.

2.3 Rate-Controlling Membrane Concepts

In the mid-1960s, while circulating rabbit blood inside a Silastic® (silicone rubber) arterio-venous shunt, Folkman discovered that if the tubing was exposed to anesthetic gases on the outside, the rabbits would fall asleep [7]. He proposed that short, sealed segments of such tubing containing a drug could be implanted and form the basis of a constant rate drug delivery system [8].

Further work in the 1960s and 1970s led to the establishment of the rate-controlling membrane (RCM)/reservoir drug delivery system (DDS) concept as yielding a constant delivery rate and producing a zero-order, flat pharmacokinetic profile. The first commercial RCM product was the Ocusert® that was developed and commercialized in the early 1970s by ALZA Corporation for the treatment of glaucoma. It was an elliptical-shaped planar system that was inserted into the cul-de-sac of the eye and delivered pilocarpine at a controlled rate for 1 week. The product utilized poly(ethylene-co-vinyl acetate) (polyEVA) as the RCM, thereby introducing this versatile material for controlled-release applications. This product was followed by the Progestasert® (also ALZA Corporation), a T-shaped device that was inserted into the uterus and released progesterone for a 1-year period for contraception. The RCM of this system was also polyEVA, further demonstrating the utility of this polymer [9]. Subsequently, the Population Council developed a contraceptive subcutaneous implant system comprised of six silicone rubber tubes (crosslinked polydimethylsiloxane) containing the steroid levo-Norgestrel. The system was trade named the Norplant® (Fig. 2.1) and has a 5-year delivery duration. It was introduced

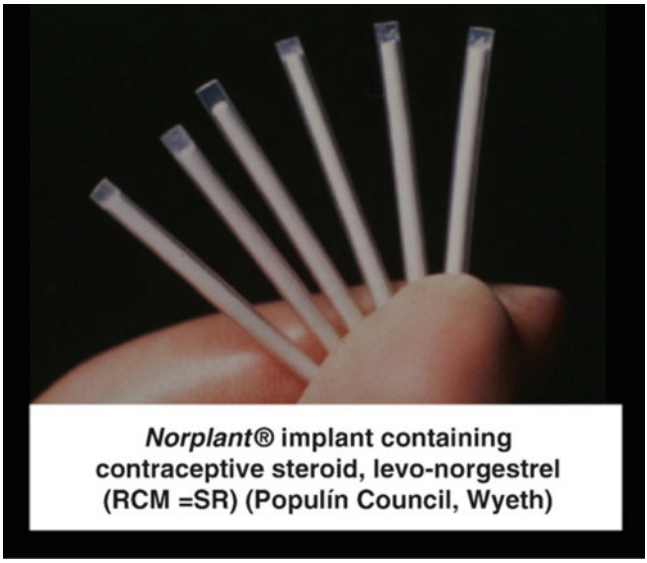

Fig. 2.1 Photograph of the Norplant® System (reprinted from [1] with permission from Elsevier)

in certain countries in 1983, but it was not until 1990, that Norplant was approved in the United States. Later in the United States, Norplant became associated with removal problems due to operator inexperience leading to poor insertion technique and thereby resulting in explantation difficulties. Norplant® was withdrawn from the U.S. market in 2002, but is still available in other countries. Organon has recently developed a similar system (Implanon®), using polyEVA as the RCM for the delivery of etonogestrel for up to 3 years. Implanon was approved by the FDA in 2006. Additionally, following the ALZA work with polyEVA, the polymer was investigated for protein delivery but was not commercialized for this application [10].

Additionally, implants utilizing a hydrogel RCM were investigated leading to the development of the Hydron® Implant, a nondegradable reservoir implant capable of long-term (1 year or longer) delivery. This technology has been utilized for the delivery of the LHRH agonist, histrelin acetate for the treatment of precocious puberty (Supprelin® LA) and for prostate cancer (Vantas®) (http://www.endo.com, accessed July 2010) (see Sect. 2.4 for other delivery systems for LHRH analogues).

The osmotic pump is a variant of the rate-controlled membrane system. Building on earlier work [11] and beginning in the 1970s and continuing into the 1990s, Theeuwes and coworkers at Alza developed a family of osmotic pump systems. This work led first to the development of the ALZET® pump that provides zero-order delivery when implanted into research animals [12] and subsequently to the DUROS® osmotic implant system for human therapy ([13]; also see the chapter on systems based on osmosis). Both of these systems are zero-order, diffusion-controlled systems with RCMs, but the difference is that in the osmotic systems the RCM controls a constant rate of water diffusion into the system, forcing an equal volume of the drug solution or suspension out of the system reservoir through the delivery orifice. The RCM in the ALZET pump is based on cellulose esters (e.g., cellulose acetate), while the RCM in the DUROS system is polyurethane.

2.4 Biodegradable Polymer Concepts

Biodegradable polymers are inherently attractive for drug delivery applications because of two potential major attributes: first, if the polymer erodes only at the surface, then it would seem possible to engineer systems yielding sustained or constant release. Second, for parenteral applications, the system can be expected to completely erode, thereby eliminating the need for a procedure to remove the system at the end of the delivery lifetime.

Investigations of biodegradable polymers of poly(hydroxy acids) for drug delivery applications began in the 1960s and 1970s and the polymers continue to be utilized today. These polymers were developed for sutures in the 1960s and 1970s. Schmitt and Polestina at Davis & Geck (Cyanamid Co.) synthesized poly(glycolic acid) (PGA) for use as a degradable suture [14]. Ethicon added lactic acid to the composition, licensed the PGA technology from Davis and Geck, and introduced the degradable poly(lactic-co-glycolic acid) (PLGA) suture (Vicryl®).