Chapter 2
Historical Overview of Long Acting Injections and Implants

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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

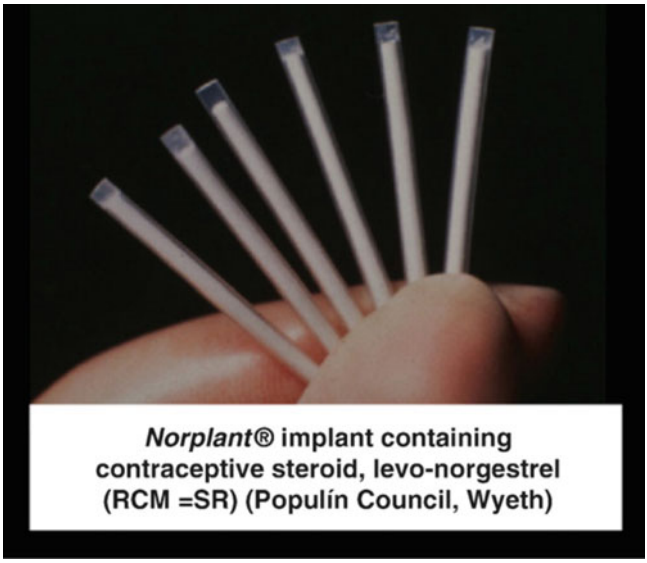

Fig. 2.1 Photograph of the Norplant® System (reprinted from [1] with permission from Elsevier)

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®).

In the late 1960s, Boswell and Scribner at Dupont developed microparticle and pellet depot delivery systems by adding drugs to PLA [15]. In parallel, in the 1970s, researchers at Southern Research Institute and the University of Alabama at Birmingham (UAB) (e.g., Cowser, Lewis and Beck) were investigating and clinically testing steroid-loaded PLGA microparticles for contraceptive drug delivery [Tice T (2008) personal communication]. Additionally, Gilding and Reed carried out important early studies on the properties and in vitro degradation of PLGA copolymers [16, 17].

While much of the early development of PLGA systems focused on small molecule drugs, a number of research groups and pharmaceutical companies began investigating the delivery of leutinizing hormone-releasing hormone (LHRH) analogues. In the late 1970s, under a Southern Research Institute project sponsored by Syntex, a Southern/Syntex team developed and patented long acting (1-month) PLGA microparticles for the delivery of LHRH [18]. In Europe in 1986, Debiopharm introduced a PLGA microparticle system for the delivery of triptorelin [D-Trp-6 LHRH; Decapeptyl®] as a treatment for prostate cancer. It was the first injectable, degradable microparticle depot drug delivery system to obtain regulatory approval and is still on the market today [Tice T (2008) personal communication]. Takeda Pharmaceutical Company (Takeda-Abbott Pharmaceutical Co. (TAP) in the United States) also developed a PLGA microsphere product for the delivery of a LHRH analogue (leuprolide, Lupron® Depot), licensing the Syntex patent [18] in addition to filing other patents. The Lupron Depot was introduced in the United States in 1989.

Additionally, implants composed of PLGA were investigated for a number of applications, including delivery of LHRH analogues. The Zoladex® implant (PLGA matrix system delivering the LHRH analogue goserelin) was developed for the treatment of prostate cancer, breast cancer and endometriosis, and was commercialized world-wide [20, 21].

Through the 1970s and 1980s, emulsion/solvent evaporation techniques or phase separation techniques were utilized to prepare microparticles for drug delivery applications. Gombotz and coworkers at Enzytech developed the Prolease® process in the early 1990s for fabricating PLGA microparticles. This process utilizes an ultrasonic sprayer and a liquid nitrogen/ethanol bath [22]. This process has been applied to the development of the Neutropin Depot (for delivery of the protein recombinant growth hormone) and Risperdal® Consta® (for delivery of risperidone, an antipsychotic drug).

In the 1970s, Heller and Choi at ALZA synthesized the first in a series of degradable polyorthoester (POE) polymers. Heller and coworkers continued to develop the POE family [23]. Recently (2009), a POE product delivering granisetron was submitted to the U.S. FDA for approval.

In the late 1980s, Dunn and coworkers at Southern Research Institute developed injectable, degradable drug depot systems of PLA or PLGA. These systems are in situ forming “implants” generated by subcutaneous or IM injections of drug/polymer/solvent formulations, with subsequent phase separation and solvent loss [24]. (This drug depot was extended into the clinic by Atrix, Inc. and has resulted in several

approved products, including the Eligard® system for the delivery of the LHRH analogue leuprolide; refer to the chapter on in situ forming systems).

Langer and coworkers developed a family of polyanhydride biodegradable polymers. The Gliadel® wafer utilizes this technology for the delivery of carmustine (BCNU) for the treatment of brain tumors (glioblastomas) [25]. Brem pioneered the clinical application of these systems and the product was approved by the FDA in 1996.

Thermally responsive, aqueous solutions of di-block and tri-block copolymers of PLGA–PEG were investigated by Kim and Byun at the University of Utah as degradable depot systems. These systems are trade named "Re-Gel®" (MacroMed, Inc.) and have been applied to the delivery of anticancer products and other drugs ([26]; refer to the chapter on in situ forming systems).

Another biodegradable polyester class based on copolymers of poly(ethylene glycol terephthalate) (PEG-T) and poly(butylene terephthalate) (PBT) was investigated for drug delivery applications by Feijen and coworkers at Twente University beginning in the 1990s [27]. A microparticle depot formulation of this copolymer and alpha interferon, trade named Locteron®, is currently under clinical investigation for the treatment of hepatitis [28].

2.5 Surface-Releasing Systems

Release of the anticoagulant heparin from polymer surfaces was an early, successful drug delivery system. Introduced into the clinic in the early 1960s, the concept was based on an ionic complex of heparin, an anionic polysaccharide, with a cationic surfactant that was hydrophobically imbedded in the surface of the polymer being "heparinized." The heparin was gradually released by exchange with the ions present in blood, thereby inhibiting coagulation of blood at the surface of the polymer until the heparin concentration decreased to low levels, usually after several days (refer to Plate and Valuev [29] for a review of heparinized surfaces).

A more recent application of drug-loaded surface coatings are the drug-eluting stents (DES) for the treatment of occluded or partially occluded arteries [30]. First approved in 2002, these stents have been one of the most successful recent drug delivery systems and have been widely adopted. The DES with the earliest regulatory approvals in the United States are the Cypher® stent (rapamycin, Johnson & Johnson) and the Taxus® stent (paclitaxel, Boston Scientific). These stents release smooth muscle cell (SMC) antagonists that retard SMC proliferation, the main cause of vessel stenosis. These DES are designed as matrix delivery systems; drug particles are blended with the polymer, which in the Cypher® stent is a polyblend of poly(butyl methacrylate) and polyEVA, while the polymer utilized in the Taxus® stent is a novel tri-block copolymer of polystyrene–polyisobutylene–polystyrene (SIBS). (Refer to the chapter on drug eluting stents).

DES are considered drug–device combination products, a product classification that overlaps with drug delivery systems and long acting implants.

Additional combination products that have been investigated include, among others, antibiotic impregnated bone cement matrices and implanted insulin pumps containing a glucose sensor that enables feedback control [31].

2.6 Nanotherapeutics, Conjugates, Liposomes, Micelles, and Targeting

Three key technologies: Three key scientific discoveries led to three key technologies that have been major factors in stimulating the growth in research and translational activity in nanotherapeutics. The first was the development of "PEGylation" technology in the late 1970s and early 1980s. The term "PEGylation" refers to polyethylene glycol-conjugated drugs or carriers. The second key development, "active targeting," was based on the concept of the "magic bullet," originally described by Ehrlich in the early 1900s. It became possible upon the discovery of monoclonal antibodies in the mid-1970s. (The use of a polyclonal antibody to target a drug was described in 1958 [32], while the use of monoclonal antibodies did not happen until after their discovery in 1975.) The famous peptide ligand, RGD [33], was also first described around the same time (in 1980). Active targeting was accomplished by attaching such targeting moieties directly to the drug or to its nanocarrier. The third key development was the discovery of the "enhanced permeation and retention effect" (EPR) in the early 1980s, wherein nanocarriers are entrapped within tumors. It is interesting that all three key technologies originated in the 1970s–1980s.

2.6.1 PEGylation

PEGylation was developed to enhance both the circulation time and the stability (against enzyme attack or immunogenic recognition) of recombinant protein drugs [34]. Enzon, a pioneering PEGylation company, was founded in the beginning of the 1980s. The first products were PEGylated enzymes such as asparaginase and glutaminase, which metabolize asparagine and glutamine, essential nutrients for leukemic cancer cells. These products were followed by PEGylated interferons and PEGylated G-CSF (refer to the chapters on protein and nanocarrier PEGylation for additional information).

2.6.2 Enhanced Permeation and Retention Effect

The "Enhanced Permeation and Retention" effect, or EPR, was discovered by Maeda and coworkers in 1984. The team was conducting animal studies with a novel polymer–drug conjugate, styrene-maleic anhydride (SMA) conjugated to

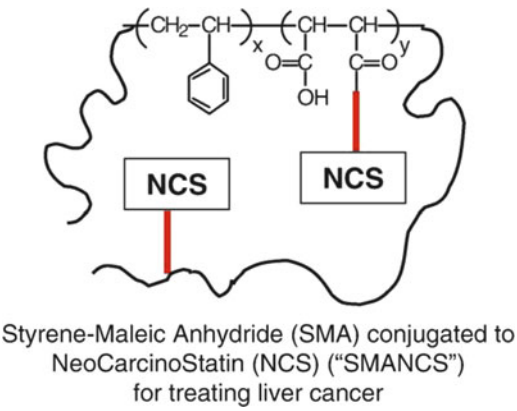

Fig. 2.2 Diagram of "SMANCS" (polymer–drug conjugate of poly(styrene-comaleic anhydride) (SMA) and NeoCarcinoStatin (NCS)) (reprinted from [1] with permission from Elsevier)

neocarcinostatin (NCS), an anticancer peptide drug (Fig. 2.2). They bound a blue dye to albumin and discovered that it accumulated in the tumor tissue of an experimental animal. Maeda concluded that the rapidly forming vasculature in such solid tumors was "leaky" and the lymph drainage system was not yet functioning efficiently, causing the entrapment of the nanoscale albumin–dye complex within the tumor tissue. They also injected SMANCS and saw the same effect [35].

2.6.3 Liposomes and Micelles

Liposomes were first described by Bangham in the 1960s. Their potential for drug delivery led to research in this area, wherein hydrophilic drugs could be loaded in the aqueous core of the liposome, or hydrophobic drugs could be loaded in the lipid bilayer shell [36]. Woodle and Martin at Liposome Technologies Inc. (LTI) developed a PEGylated liposome-doxorubicin product, with PEG being grafted to the lipid components of the liposome's lipid bilayer. The product, termed a "Stealth®" liposome and trade-named Doxil®, exhibited enhanced circulation times and accumulation in tumor tissues. It was approved by the FDA in 1995 for the treatment of AIDS-related Kaposi's sarcoma (Fig. 2.3) ([37]; also refer to the chapter on liposomes).

Another nanocarrier, polymeric micelles, were developed for drug delivery in 1990. Kataoka, Okano and Yokoyama synthesized A–B block copolymers of a block of a partially butylated aspartic acid that was conjugated to a PEG block. These copolymers spontaneously formed PEGylated polymeric micelles above a very low critical micelle concentration (CMC). The micelles had a PEG corona with a hydrophobic butyl aspartate core. Small hydrophobic drugs could be loaded into the core, either by physically loading or by conjugating the drug to the amino acid's remaining pendant acid groups. Additionally, the terminal OH groups of the PEGs

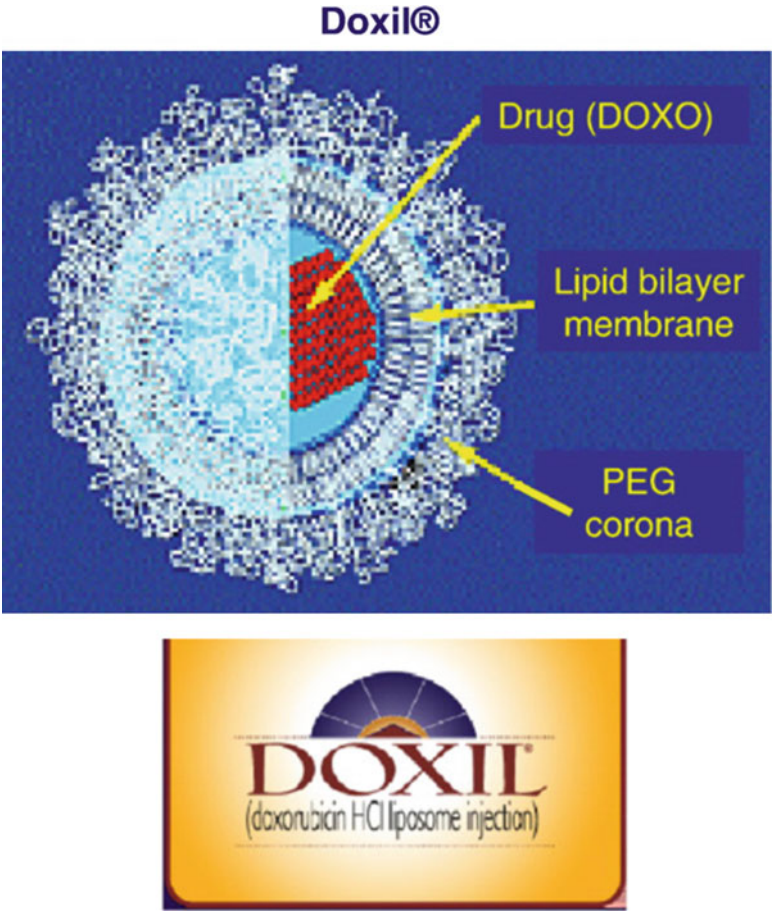

Fig. 2.3 Schematic of the PEGylated lipsome Doxil®, which contains the anticancer drug doxorubicin (reprinted from [1] with permission from Elsevier)

could be coupled to cell-specific ligands for targeted delivery (Fig. 2.4) [19, 38, 39]. Independent of Kataoka et al.'s work, drug-loaded PEGylated micelles based on the Pluronic® family of PEO-PPO-PEO tri-block copolymers were investigated by Kabanov and coworkers [40]. A number of different PEGylated micelles are now under clinical investigation for the delivery of small molecule drugs.

2.6.4 Polymer–Drug Conjugates, Targeting and Nanotherapeutics

The concept of polymer–drug conjugates or "nanotherapeutics" independently arose at several research centers in the mid to late 1970s. In the mid-1970s, PEGylated protein drugs were being synthesized and tested by Davis and

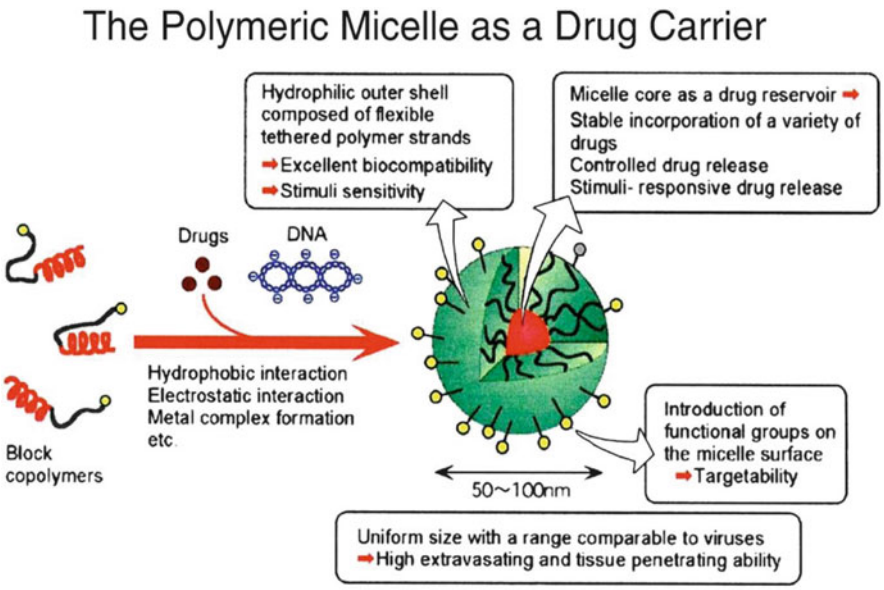

Fig. 2.4 Diagram of the PEGylated polymeric micelle drug carrier (reprinted from [1] with permission from Elsevier)

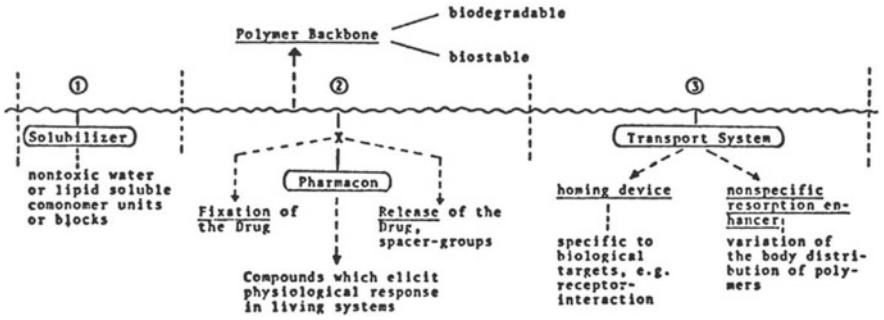

Fig. 2.5 Schematic from Ringsdorf [41] illustrating proposal for the concept of the "complete" polymer–drug construct, including targeting (reprinted from [1] with permission from Elsevier)

Aubuchowski in the United States. In 1975 in Mainz, Germany, Ringsdorf independently outlined the concept of a targeted, polymer–drug conjugate (Fig. 2.5) [41]. Independent of those scientists, and also in the mid-1970s, Kopecek in Prague described the conjugation of drugs to their new polymer carrier, poly(hydroxypropyl methacrylamide) (PHPMA). A drug was conjugated to PHPMA by pendant, degradable peptide linkages. Later, in collaboration with Duncan, the tetrapeptide linkages were designed to be degradable by a lysosomal enzyme, cathepsin B [42–44]. The polymer synthesis and characterization were conducted in Prague while the conjugate's

drug action was tested in the UK in collaboration with Duncan and Lloyd (Interestingly, Kopecek was introduced to Duncan and Lloyd by Ringsdorf). Rihova in Prague found PHPMA to be nonimmunogenic, and Cassidy, a UK clinician, led the clinical investigations, which included doxorubicin and other small molecule anticancer drugs. Active targeting for liver cancer therapy was accomplished with ligands such as galactose, a membrane receptor ligand for hepatocytes. This international success story has significantly influenced the field of nanoscale polymeric therapeutics and several reviews have been published [45, 46].

Albumin-drug carriers have also been developed. These drug nanocarriers are, in some senses, similar to PEGylated drug nanocarriers. Abraxane® (Abraxis Bioscience) is a nanoparticle of albumin and paclitaxel (http://www.drugs.com/pro/abraxane.html, accessed 28 Aug 2010) that has received regulatory approval for the treatment of breast cancer.

2.7 Microelectronic/Microfabricated Technologies

In the period from 1960 to the present, microelectronic technology has experienced a huge growth in capacity and almost unimaginable reductions in size and cost. For drug delivery, the technology was initially applied via improved control and capabilities for pump systems. In the 1990s, Langer, Cima, Santini and coworkers applied microelectronic chip technology to implantable drug delivery via a chip containing addressable, drug-filled reservoirs covered with a film that could be disintegrated via electric current [47]. This type of system can provide a variety of drug delivery patterns. Sensing elements may also be included in the microelectronic system, thereby enabling feedback controlled drug delivery. Since the initial publications, the concept of microelectronic/microfabricated drug delivery systems has been investigated and extended by a number of investigators. (Refer to Chap. 18).

2.8 Conclusion

This chapter has attempted to provide an overview of the major developments in long-lasting injections and implants over the last 50 years or so. Polymer technology, pharmaceutical chemistry and biotechnology have enabled significant advances in the field, with products as diverse as nonerodible implants, erodible implants, microspheres, liposomes, targeted nanoparticles, and microelectronic implants. There have been significant benefits to the patient and to the practitioner in terms of efficacy, side effects, convenience, duration of therapy, and compliance with the treatment regimen. These historical systems can generally be characterized as macro- or microscale, but, as indicated above, work at the nanoscale has progressed into clinical applications.

Disclaimer

In a summary survey such as this chapter, it is impossible to describe every system developed since the mid-twentieth century and it is impossible to know of and include all such examples and to properly credit all the key people who helped to bring the various technologies and devices to the clinic. The authors apologize in advance for all omissions.

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