

KATARZYNA JELONEK^{1), *)}, JANUSZ KASPERCZYK^{1), 2)}

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Polyesters and polyester carbonates for controlled drug delivery

Part II. IMPLANTABLE SYSTEMS

Summary – Compared with injectable drug delivery systems (DDS), pharmaceutical implants can provide prolonged drug release, delivery of a higher amount of bioactive agent into the site of action and a higher local drug concentration. Simultaneously, these implants are simple to process and provide a reduction in drug toxicity that is typical for systemic administration. This article presents the composition, application and methods of processing of the implantable drug delivery systems that have already entered the market.

Keywords: polyesters, polycarbonates, controlled drug delivery.

POLIESTRY I POLIESTROWĘGLANY W SYSTEMACH KONTROLOWANEGO UWALNIANIA LEKÓW. CZ. II. IMPLANTOWANE SYSTEMY POLIMEROWE

Streszczenie – W porównaniu z systemami kontrolowanego uwalniania leku przeznaczonymi do iniekcji, implanty zapewniają wydłużony czas uwalniania leku, możliwość dostarczenia większej ilości leku do miejsca działania, wyższe miejscowe stężenie leku oraz ograniczenie, typowej dla podania systemowego, toksyczności leku. Zaletą jest także mało skomplikowany proces otrzymywania implantów polimerowych do zastosowań farmaceutycznych. W publikacji przedstawiono obecne na rynku implantowane systemy transportu leku, ich skład, zastosowanie oraz metody otrzymywania.

Słowa kluczowe: poliestry, poliestrowęglały, kontrolowane uwalnianie leków.

CONTROLLED DRUG DELIVERY SYSTEMS

Conventional therapeutic systems suffer from many drawbacks, including adverse effects, strongly fluctuating drug levels in the body, poor drug efficacy and poor patient compliance [1]. Additionally, there has been increased interest in drug delivery due to (i) the emergence of low-molecular-weight molecules and biomacromolecules with either poor aqueous solubility, poor tissue permeation, or both; (ii) the increased use of biological materials with poorly understood physical properties or questionable shelf life issues; and (iii) the realization that if the portion of the dose responsible for adverse events could be directed away from sites where they originate, toxic side effects would become less frequent, thus benefiting the therapeutic index [2]. Therefore, drug delivery technologies have evolved over recent decades, changing the methods of administration from simple tablets, liquids and injectables to complex systems employing polymers

and bioengineered products in order to optimize the therapeutic value of the active agents [3]. The first system of this type, the release of small drug molecules through a silica wall, was developed in 1960 by Judah Folkman [4]. However, the main problem with nondegradable implants is their retrieval after the treatment is completed. In the case of Norplant[®] (Wyeth-Ayerst), consisting of six small silica tubes with levonorgestrel used in prevention of pregnancy for up to five years, a decrease in demand for this product in the US has been observed since 1994. This decrease has been mainly attributed to the difficulties associated with removal of the implanted rods and publicity created by these clinical problems [5]. Consequently, there has been further progress with discovering the great potential of biodegradable polymers for biomedical and pharmaceutical applications. Progress in the technology of biodegradable polymers, especially related to the methods used for their synthesis, makes these polymers interesting for the fabrication of a tailored drug delivery system. Biodegradable aliphatic polyesters and polyester carbonates are widely used to form different types of injectable and implantable systems for the controlled release of pharmaceutical agents. However, the development of these systems is more complicated than that of non-biodegradable systems because parameters, such as the degradation kinetics of the polymer *in vivo*,

¹⁾ Centre of Polymer and Carbon Materials, Polish Academy of Sciences, 41-819 Zabrze.

²⁾ Department of Biopharmacy, School of Pharmacy, Medical University of Silesia, 41-200 Sosnowiec, Poland.

^{*)} Corresponding author: e-mail address: katarzyna.jelonek@cmpw-pan.edu.pl

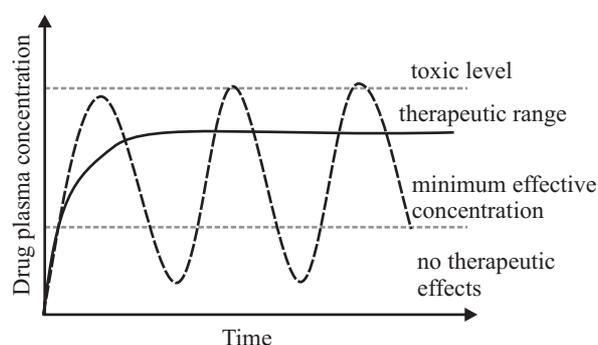


Fig. 1. Comparison of plasma drug concentration profiles after doses of a conventional drug delivery system (---) and a controlled drug delivery (—)

biocompatibility and repetition in processing, must be considered as well [1]. Thus, there are some biodegradable drug delivery systems currently on the market, but there are still many challenges to consider and overcome in order to develop biodegradable implants that are able to provide prolonged drug delivery release within the therapeutic range for effective treatment.

A comparison of drug concentration profiles after doses of a conventional drug delivery system and a controlled drug delivery system is presented in Fig. 1.

In conventional oral drug delivery systems, the drug is released from the dosage form within a short period of time. The activation and action of the therapeutic agent is controlled by its absorption into the systemic circulation. An increase in drug concentration at the site of action requires higher doses of the drug, resulting in greater concentrations of the drug in the systemic circulation. In the case of controlled drug delivery systems, the therapeutic agent is kept at a sustained level that is optimal for therapy, which enables the elimination of high concentrations of drugs that exceed the maximum safe plasma con-

centration at a sub-therapeutic level that is insufficient to render a therapeutic response [6]. Thus, controlled drug delivery technology is concerned with the systematic release of a pharmaceutical agent to maintain a therapeutic level of the drug in the body for a sustained period of time. The main aim is to optimize the doses and duration of the therapeutic agent, which subsequently improves therapeutic effects and decreases adverse effects [7].

There are many advantages of biodegradable controlled drug delivery systems in comparison with traditional dosage forms [1, 6, 8–10]:

- an increased specificity of systemic or local drug administration;
- an increased efficiency of sensitive drugs (peptides, proteins, enzymes) caused by local administration; a maximization of the efficacy-dose relationship;
- the maintenance of drug concentration within an optimal therapeutic range for a prolonged duration of treatment;
- a reduction of adverse side effects;
- a decrease of doses and an enhancement of patient compliance;
- no requirement for post-treatment removal because the drug carrier degrades to non-toxic products, which are metabolized or eliminated from the body.

The biodegradable materials must be properly selected to eliminate the possible drawbacks of biodegradable controlled drug delivery systems, which include the toxicity of application materials that are not completely biocompatible; irritation after the incorporation of a polymeric delivery system and higher cost [1]. Implantable or injectable drug delivery systems produced from biodegradable polymers are intended for parenteral administration — subcutaneous, intramuscular, intravenous or intraperitoneal [11]. The injectable drug delivery systems do not require a surgical incision, which is a great advan-

Table 1. Examples of currently marketed microspheres obtained from aliphatic polyesters

Name of product	Drug carrier	Therapeutical agent	Application
Lupron Depot®	PLAGA or PLA (dependent on the release period (1, 3 and 4 months))	leuprorelin acetate	endometriosis, prostate cancer, precocious puberty in children
Prostap® 3	P(D,L-LA)	leuprorelin acetate	metastatic prostate cancer
Sandostatin® LAR	PLAGA-glucose	octreotide acetate	acromegaly, diarrhea and flushing episodes associated with metastatic carcinoid
Somatuline® LA	PLGA	lanreotide acetate	acromegaly
Decapeptyl®	PLAGA	triptorelin pamoate	prostate cancer
Decapeptyl® SR	PLA or PLGA	triptoreline	
Telstar Depot®	PLAGA	triptoreline	prostate cancer
Nutropin Depot®	PLAGA	somatotropin	long-term treatment of growth failure due to a lack of adequate endogenous GH secretion
Suprecur® MP	PLAGA	buserelin	endometriosis
Arestin®	PLAGA	minocycline	periodontitis
Risperdal Consta®	PLAGA	risperidone	schizophrenia

tage. Injectable drug delivery systems include microspheres, nanospheres, polymeric micelles, polyerosomes and conjugates. Examples of commercially available microspheres obtained from aliphatic polyesters are presented in Table 1 [5, 6, 12–15].

Compared to injectable drug delivery systems, pharmaceutical implants can provide a prolonged drug release, the delivery of a higher amount of bioactive agent into site of action and a higher local drug concentration. Some of these implants are produced in shapes that facilitate injection. Simultaneously, they provide a reduction of drug toxicity that is typical of systemic administration and the simplicity of processing [6, 16, 17]. There are two types of biodegradable implants: matricial (monolithic) and reservoir systems. In the matricial system, the polymer degrades slowly under physiological conditions, and the drug is released during polymer degradation or by diffusion through pores in the matrix. In reservoir systems, the process of membrane degradation is generally slower than in drug diffusion [16].

Implantable drug delivery systems are usually produced in the form of cylinders, pellets, discs and films [18]. Elongated implant shapes (cylinders, tubes) are the most frequently used for subcutaneous administration. The implants may release drugs for months or up to years. A prolonged sustained drug release is advantageous mainly in the case of steroids or anticancer drug release [19, 20].

Biodegradable, injectable, *in situ*-forming drug delivery systems represent an alternative to solid implant parenteral depot systems. Injectable gel-forming matrices offer several advantages over systems shaped into their final form before implantation — ease of administration (they do not require a surgical procedure for placement or local anesthesia), compatibility with a broad range of pharmaceutical compounds (water soluble and insoluble compounds, high and low molecular weight agents), even less complicated fabrication (various agents may be incorporated by simple mixing) and less stressful manufacturing conditions for sensitive molecules. Therefore, injectable gel-forming matrices may be very attractive for protein delivery and could possibly extend the patent life of protein drugs. Additionally, when they are used to fill a cavity or a defect, their flowing nature enables a good fit [21–23].

PROCESSING METHODS OF BIODEGRADABLE IMPLANTS WITH DRUGS

The polymers selected for parenteral administration must fulfill several requirements, including biocompatibility, drug compatibility, suitable degradation kinetics and mechanical properties as well as ease of processing [24]. Implantable drug delivery systems can be formed by (i) compression molding of the polymer and drug mixture (the drawback of this method is the risk of thermal degradation of the polymer); (ii) extrusion may be used

to form needle-like implants; (iii) a casting method is used to form polymer films (the polymer and drug are dissolved in a proper solvent, cast on a flat surface or into a mold and left for solvent evaporation) [18]. The temperature used for compression molding and extrusion depends on the polymer morphology — in the case of crystalline polymers, it is usually higher than the melting point of the polymer (T_m), and in the case of amorphous polymers, it is higher than the glass transition temperature (T_g). Producing implants with the use of solvents requires conditions that enable complete solvent evaporation to ensure a lack of toxicity of the final product [11].

Injectable *in situ*-forming implants may be classified according to their mechanism of depot formation: thermoplastic pastes, *in situ* cross-linked polymer system, *in situ* polymer precipitation and thermally induced gelling system [21]. The concept of *in situ*-forming devices based on polymer precipitation was first developed by Dunn and co-workers in 1990. This type of device requires the dissolution of a water-insoluble and biodegradable polymer in a biocompatible organic solvent in which a drug is added, and the drug forms a solution or suspension after mixing. After injection into the body, the water-miscible organic solvent dissipates, and water penetrates into the organic phase, which leads to phase separation and precipitation of the polymer, forming a depot at the site of injection. This method is designated AtrigelTM technology [21, 5–28]. The Atrigel system is protected by 33 patents in the United States and 35 patents in the rest of the world [25].

The idea of thermally induced gelling systems is based on polymers that show abrupt changes in solubility as a function of environmental temperature. Thermo-sensitive biodegradable triblock copolymers were developed of the ABA and BAB type, where A denotes the hydrophobic polyester block and B denotes the hydrophilic poly(ethylene glycol) block. These low-molecular-weight polymers are water-soluble and yield a temperature-dependent reversible gel-sol transition. The ReGel[®] formulation, which consists of an ABA-triblock copolymer (PLGA-PEG-PLGA) in phosphate-buffered saline (pH 7.4) (23 % w/w) has entered the market [21].

APPLICATION OF BIODEGRADABLE CONTROLLED DRUG DELIVERY IMPLANTS

Controlled delivery of anticancer drugs

The aim of developing these new technologies is to improve overall survival and quality of life by increasing the bioavailability of drugs to the cancerous tissues, increasing drug solubility and minimizing systemic side effects. The implants with anticancer drugs are intended to be administered intra-tumorally or adjacent to the cancerous tissue. These technologies have been embodied in a variety of forms, such as drug-eluting films, gels, wafer, rods and particles [18]. Delivery systems that provide the

targeting and release of drugs in controlled manner are particularly useful for chemotherapy, where local delivery of cytotoxic drugs to the tumor site may improve patient outcome and potentially overcome limitations associated with systemic administration [3].

Developed in the early 1980s, the Gliadel Wafer is perhaps the most studied and most successful drug delivery implant for the treatment of recurrent brain cancer. A dime-sized biodegradable polyanhydride wafer contains chemotherapeutic carmustine and is used for the treatment of high grade malignant glioma [29–31]. However, biodegradable polyesters are the largest group considered to be used as a vehicle for anticancer drugs.

One example is the Zoladex[®] system, where an implantable cylinder (approximately 1 mm in diameter and 10 mm in length) is used for the subcutaneous controlled delivery of goserelin acetate, a potent biosynthetic analog of GnRH (gonadotropin releasing hormone) treatment for patients with prostate cancer [5, 32, 33]. The system composed of 50:50 PLGA delivers approximately 3.6 mg of drug for over a 1-month period or 10.6 mg for over 3 months [5].

There are also two anticancer in situ-forming implants on the market. The first of these implants is known as Eligard[™] and uses Atrigel[™] as a drug delivery system. This system consists of LHRH (luteinizing hormone releasing hormone) agonist leuprolide acetate and P(D,L-LA-co-GA) dissolved in *N*-methyl-2-pyrrolidone (NMP) [22, 28]. The composition of the system depends on the drug dose and length of release (Table 2) [34].

OncoGel[™], the formulation of paclitaxel in the ReGel[®] system was designed for the local delivery of

therapeutic agents. Anatomical and physiological barriers in the eye, including the corneal epithelium and conjunctival clearance mechanisms, afford protection against the entry of xenobiotics. These barriers also greatly impede the entry of drugs to the posterior segment, making it difficult to achieve the necessary therapeutic drug concentration [35]. Novel drug-delivery systems are required to overcome the anatomical and physiological barriers of the eye and to improve patient safety and compliance. The advantages of biodegradable implants include overcoming the blood-retina barrier, allowing drug delivery at the therapeutic levels directly into the target site, prolonged drug delivery, and the reduction of the side effects frequently observed with intravitreal injections and systemic administration [36, 37]. A biodegradable intravitreal implant, Ozrudex[®] / Posurdex[®], has been approved for the treatment of macular edema, retinal vein occlusion, and non-infectious uveitis. The implant is composed of PLGA and releases dexamethasone over four to six weeks. It is also in phase III clinical trials for the treatment of macular edema caused by diabetes [36, 37]. Surodex[®] is another PLGA implant; it contains 60 µg of dexamethasone and is currently undergoing phase III clinical studies. This implant is intended for use in avoiding inflammation after cataract surgery [36, 38].

Antibacterial implants

Polymeric materials of synthetic origin are also considered as drug delivery systems for various antibiotics. Two systems based on Atrigel[®] technology have entered the market — Atridox and Atrisorb D. Atridox[®] is a sub-

Table 2. Composition of Eligard[®] (according to ref. [34])

	ELIGARD [®] 7.5 mg	ELIGARD [®] 22.5 mg	ELIGARD [®] 30 mg	ELIGARD [®] 45 mg
Composition of copolymer (D,L-lactide to glycolide ratio)	50:50 copolymer containing carboxyl end groups	50:50 copolymer with hexandiol	75:25 copolymer with hexandiol	85:15 copolymer with hexandiol
Approximate injection volume	0.25 ml	0.375 ml	0.5 ml	0.375 ml
Duration of drug release	1 month	3 months	4 months	6 months

paclitaxel to solid tumors to provide targeted cytotoxicity without systemic toxicities associated with conventional systemic paclitaxel delivery [3, 31]. ReGel[®] provides the controlled release of paclitaxel for over 50 days and a greater than 400-fold enhancement in the solubility of this drug (>10 mg/cm³) [31].

Intraocular implants

Efficient drug delivery to the posterior eye is becoming increasingly vital with the escalating prevalence of posterior eye diseases and the development of novel the-

gingival controlled-release system consisting of: 450 mg of Atrigel[®] (36.7 % poly(DL-lactide) in 63.3 % of *N*-methyl-2-pyrrolidone; Syringe A) and 50 mg of doxycycline hydrochloride (equivalent to 42.5 mg of doxycycline; Syringe B). Upon contact with crevicular fluid, the liquid product solidifies and then allows for the controlled release of drugs for a period of 7 days. Atridox[®] is intended for use in the treatment of chronic adult periodontitis for an improvement in clinical attachment, reduction in probing depth, and reduction in bleeding and probing [39, 40]. Atrisorb D, a bioresorbable guided tissue regeneration (GTR) barrier, contains 4 % doxycycline [40].

Another type of system for the controlled release of antibiotics, obtained from aliphatic polyesters, involves coating the implants. Normally, antibiotics are administered systematically prior to surgery to prevent implant-related infection. However, due to the disturbed bony fractures and the local vascularity of trauma patients, an appropriate local antibiotic level might not be achieved by circulating antibiotics. Additionally, the systematically administered dosage is relatively high in comparison to the required local dosage at the implant-bone interface [40]. Therefore, locally implanted antibiotics support prophylaxis of implant associated infections. One concept for the prevention of device-related infections involves coating the devices with various substances, such as antibacterials, antiseptics and/or metals [41]. Implant coatings of titanium wires with gentamicin incorporated into PDLLA (10 % w/w) present a promising approach [42]. To date, the results suggest that the local application of gentamicin from PDLLA-coated implants might support systemic antibiotic prophylaxis in preventing implant-associated osteomyelitis [40].

Antirestenotic systems

Similarly, biodegradable and biocompatible coatings with drugs are also applied on the surface of a new generation of drug-eluting coronary stents. The aim of the local therapy is to control or reduce smooth muscle cell growth and migration, as well as to prevent inflammatory response, which are the predominant causes of neointimal proliferation and in-stent restenosis [43]. Metal stents, such as CoStar or Luc-Chopin, possess a biodegradable coating of antirestenotic drugs [44, 45]. Poly(L-lactide), poly(L-lactide-co- ϵ -caprolactone), and poly(ϵ -caprolactone) are the most often used polymers for the coating layer. The drug carrier must fulfill many requirements: it must provide a sustained release of the drug for at least 3 weeks after stent deployment, it must be biologically inert (e.g., non-thrombogenic, non-inflammatory) and sterilizable, it must follow the changes in stent configuration during expansion and deployment and it must be mechanically resistant to abrasion [46].

Contraceptive systems

Biodegradable polymers are also the most recent development in contraceptive drug delivery systems because they can provide a programmed rate of the release of steroids. Following implantation or injection, the devices can be used for three months or longer. For example, poly(ϵ -caprolactone), which is permeable to levonorgestrel, is believed to release the drug for at least a year at a constant diffusion-controlled rate, after which the device erodes away [47]. The Capronor system has already been in development. These implants, containing progestin, are implanted under the skin of the arm or hip, providing the gradual release of hormone for 12 to 18

months. Capronor II consists of two rods of poly(ϵ -caprolactone), each containing 18 mg of levonorgestrel. Capronor III is a single capsule of poly(ϵ -caprolactone-co-trimethylenecarbonate) filled with 32 mg of levonorgestrel. Both systems remain intact during the first year, so they can be removed if needed or begin to degrade over the second year [48].

CONCLUSION

There are many advantages to biodegradable pharmaceutical implants for prolonged drug release: the delivery of a higher amount of bioactive agent into the site of action, a higher local drug concentration, the reduction of drug toxicity that is typical for systemic administration and the simplicity of processing. These implants can be used for the controlled delivery of steroids, anticancer drugs, antibacterial drugs, and antirestenotic drugs. Although some products of this type have already entered the market, the process of development and commercialization of DDS is still quite slow, which can be assigned to the diversity of factors controlling the drug release that must be taken into account during the development of new biodegradable drug delivery systems.

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BAZĘ APARATURY DO OKREŚLANIA CHARAKTERYSTYKI I PRZETWÓRSTWA POLIMERÓW

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