Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 277 (2004) 133–139
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Chemistry of polymer biodegradation and implications on parenteral drug delivery

M. Acemoglu*

Process R & D, TRD-CHAD, Novartis Pharma AG, Basel CH-4002, Switzerland

Received 22 October 2002; received in revised form 9 January 2003; accepted 23 June 2003

Available online 12 April 2004

Abstract

Most polymeric implants are biodegraded by one of two common chemical degradation mechanisms: (i) hydrolysis and (ii) oxidation. The chemical structure is among the most important factors which affect the biodegradation of polymeric implants. Hydrolytic biodegradations are often accompanied by substantial decrease of pH, whilst oxidative biodegradation processes are usually very slow due to consumption of stoichiometric amounts of oxidising agents. A dramatic acceleration of the biodegradation can be expected, if the biodegradation can be initiated by catalytic amounts of oxidation agents. Poly(ethylene carbonate) (PEC) and poly(trimethylene carbonate) (PTMC) are presumably biodegraded by such catalytic oxidation processes. Their biodegradation shows all the characteristics of surface erosion. Poly(ethylene carbonate) is utilised as a surface eroding biocompatible polymer for controlled delivery of peptide and protein drugs.

Keywords: Chemical structure; Biodegradation; Hydrolysis; Oxidation; Surface erosion; Poly(ethylene carbonate) (PEC); Superoxide anion radical; Controlled release; Functional polycarbonates

1. Introduction

Polyesters, polyamides (Middleton and Tipton, 2000; Ikada and Tsuji, 2000; Göpferich, 1997, 1996; Williams, 1992; Bodmer et al., 1992; St. Pierre and Chiellini, 1986), poly(anhydrides) (Tamada and Langer, 1992; Peppas and Langer, 1993), poly(orthoesters) (Schwach-Abdellaoui et al., 1999; Ng et al., 1997; Heller and Himmelstein, 1985), poly(phosphazene)s (Ambrosio et al., 2002; Qiu and Zhu, 2000; Song et al., 1999; Crommen et al., 1992a, 1992b; Laurencin et al., 1987) and many other synthetic polymers are degraded by hydrolysis in vitro and in vivo and their degradation characteristics are well documented in the literature. It is noteworthy to mention that most of these polymers are carboxylic acid derivatives. However, polymers derived from carbonic acid show less tendency towards hydrolysis. Poly(urethane)s, poly(carbamate)s, poly(ether urethane urea)s, etc. are not degradable under hydrolytic conditions at physiological pH. They are known to be degraded by oxidation in vivo (McCarthy et al., 1997; Schubert et al., 1995).

The most important factor affecting the biodegradability of polymeric implants is the chemical structure: it is responsible for functional group stability, reactivity, hdrophilicity and swelling behaviour. Among other important factors are the physical and physico-mechanical properties, e.g. molecular weight (MW), porosity, elasticity, as well as the geometric

* Tel.: +41-324-5929; fax: +41-324-9536.
E-mail address: murat.acemoglu@pharma.novartis.com (M. Acemoglu).

0378-5173/$ – see front matter © 2004 Published by Elsevier B.V.
doi:10.1016/j.ijpharm.2003.06.002

form/morphology of the implant and the implantation site.

Degradations according to both hydrolytic and oxidative mechanisms show specific advantages and disadvantages for a given application. Degradation by hydrolysis is rather a fast process. The rate of the degradation can be fine tuned e.g. by the proper choice of molecular weight and by co-polymerisation of different monomeric units, providing different hydrolysis properties. However, hydrolysis of carboxylic acid derivatives such as polyesters and poly(anhydride)s may lead to local decrease of pH and thus causing problems in the case of acid sensitive drugs. Degradation by oxidation are intrinsically very slow processes. They can be observed in the form of surface cracking and pitting by active oxygen species. The attack proceeds mainly at soft segments, at positions alpha to an oxygen atom (McCarthy et al., 1997; Schubert et al., 1995). In most cases, stoichiometric amounts of oxidising agents would be needed for complete degradation; however, PMN's and macrophages usually produce the oxidising agents in small amounts. This is the reason for the very slow degradation in vivo of poly(urethane)s, poly(carbamate)s, poly(ether urethane urea)s, etc. Therefore, an increase of the rate of biodegradation can be expected in those cases, in which the biodegradation processes are initiated by catalytic amounts of oxidising agents.

Regardless of the exact chemical mechanism, biodegradation can be characterised by two surface-related phenomena: (a) bulk erosion and (b) surface erosion. In case of bulk erosion, degradation proceeds throughout the polymer matrix and immediate drop of MW is observed, whilst the mass loss is retarded (lag-time). In the case of surface erosion, the biodegradation proceeds exclusively at the surface. A fast onset of mass loss can be observed and the MW of the residual mass remains constant until complete disappearance of the implant.

2. Results and discussion

Poly(ethylene carbonate) (PEC) (Inoue et al., 1969a,b; Kawaguchi et al., 1983) and poly(trimethylene carbonate) (PTMC) (Zhu et al., 1991) are carbonic acid derivatives, known to be degradable in vivo. PEC was reported to be degradable also in vitro

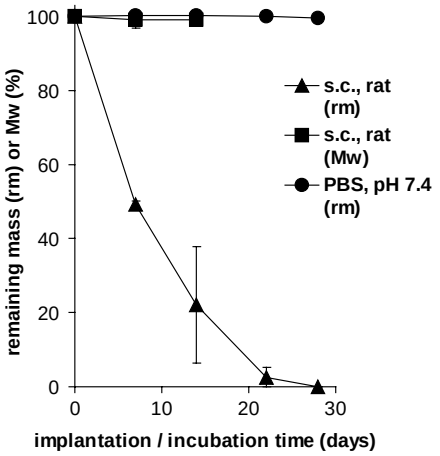


Fig. 1. In vivo surface erosion of PEC implants (s.c. in rats, MW: 350 kDa).

by the hydrolytic enzyme pronase (Imai et al., 1974). The mechanism of the biodegradation of high purity, high molecular weight PEC (Acemoglu et al., 1997; Stoll et al., 2001) was re-investigated. PEC was found to be not degradable in vitro, neither in PBS buffer, nor by many hydrolytic enzymes, such as pronase, pronase E, pronase containing bovine serum albumine or fibronectin, lipases, esterases, chymotripsin, trypsin, papain, collagenase, horse serum/sheep blood and rat blood in Alsever's solution. In vivo in rats, PEC showed clean surface erosion: s.c. implants of PEC disappeared within 3–4 weeks, whilst the molecular weight of the polymer mass remained unchanged during the whole period of biodegradation (Fig. 1).

Most interestingly, the biodegradation of low molecular weight PEC samples (MW <100 kDa) was strongly suppressed, whilst all samples having MW >150 kDa were biodegraded by clean surface erosion. Our investigations suggest a superoxide anion radical induced chain reaction as mechanism for the biodegradation of PEC. The following observations would be in accordance with such a mechanism:

(i) The biodegradation of PEC is cell mediated. Biodegradation of implants in membrane cages was clearly suppressed in comparison to free samples (Fig. 2).
(ii) PEC induces the production of superoxide anion radicals by PMN's in vitro (Fig. 3).

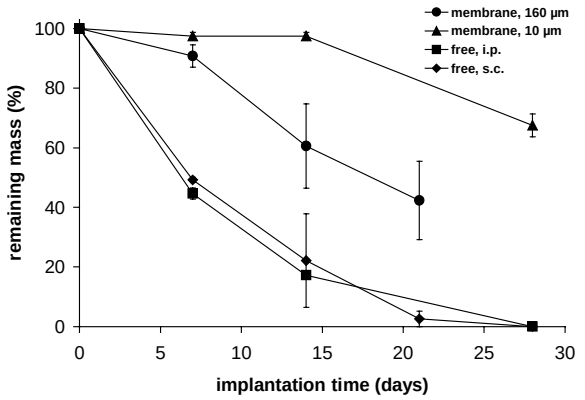


Fig. 2. Biodegradation of PEC samples incorporated in membrane cages (s.c.) as compared to free samples (s.c. and i.p.).

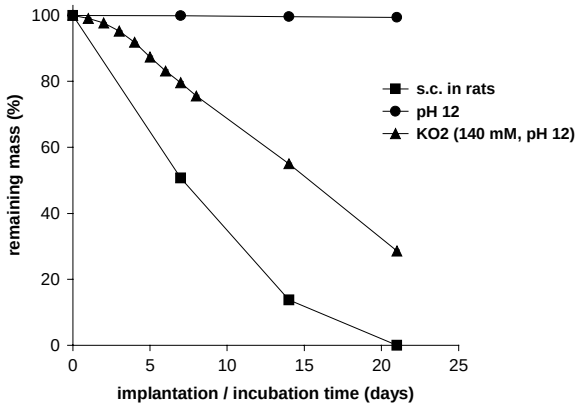


Fig. 4. In vitro degradation of PEC in buffered superoxide anion radical solution.

(iii) PEC is degraded by superoxide anion radicals in vitro (Fig. 4).
(iv) The biodegradation of PEC is much faster than other poly(alkylene carbonate)s and is too fast for a stoichiometric oxidation reaction.

Based on the results discussed above, a chain reaction mechanism can be proposed for the biodegradation of PEC in vivo (Scheme 1). Superoxide anion radicals, according to an anionic- or radical-based mechanism can initiate the proposed chain reaction. Ethylene carbonate is the product of degradation in both cases.

Additional support for the proposed mechanism is provided by a comparison of the biodegradation properties of PEC with PTMC. If the proposed biodegradation mechanism is correct, then the biodegradation of PTMC must be much slower than PEC. Based on semi-empirical AM1 calculations, the formation of the five-membered ring ethylene carbonate is favored both by kinetics and thermodynamics over the formation of the six-membered ring trimethylene carbonate by 3.1 and 2.9 kcal/mol, respectively (Fig. 5).

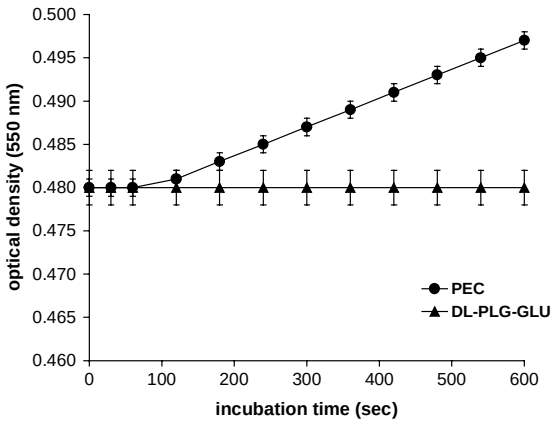
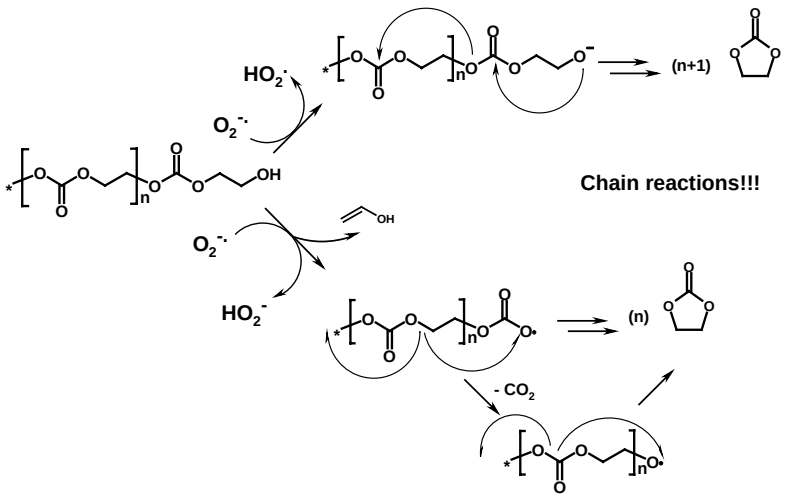


Fig. 3. Cellular superoxide anion radical production in the presence of PEC in vitro, as compared to DL-PLG-GLU as reference.

Indeed, the biodegradation of PTMC is much slower than PEC. After 6 months, only ca. 60% of a PTMC implant is biodegraded (s.c. in rats, Fig. 6). However, the biodegradation proceeds by surface erosion and the MW of the remaining implant mass remains unchanged during the whole biodegradation period.

Owing these interesting and unique properties, PEC was utilised as matrix for the controlled release of the peptide and protein drugs, octreotide and hIL-3, respectively. For this purpose, the drugs were incorporated into PEC microparticles at ca. 1% loading and the microparticles were pressed into tablets. The tablets were implanted s.c. in rats and rabbits. In all cases, a linear correlation between drug release and mass loss of the implant was observed (Fig. 7), confirming the drug release by surface erosion of PEC in vivo.

The drug release from tablet implants was determined by analysis of the drug content in the residual tablet masses. The hIL-3 content was analysed by two different methods, HPLC and ELISA bioanalytics, respectively. Good correlation was found between the results of both analytical methods (Fig. 8).



Scheme 1. Proposed chemical mechanism for the biodegradation of PEC in vivo.

The differences in the drug release from a surface eroding polymer (PEC) and a bulk eroding polymer (DL-PLG-GLU) are demonstrated in Fig. 9. Formulations of hIL-3 in PEC and DL-PLG-GLU were implanted s.c. in rats and the drug release was followed by determination of the drug content in the residual polymer mass during a period of 21 days. In the case of the surface eroding PEC, a linear correlation between the polymer mass loss and hIL-3 release was observed. Twenty-one days post-implantation, ca. 60% of the hIL-3 was released and ca. 70% of the implant mass had disappeared. There was good correlation between HPLC and ELISA analysis in this case. In the case of DL-PLG-GLU, ca. 60% of hIL-3 was released according to HPLC and only 30% mass loss was observed after 21 days. However, in parallel experiments in vitro, no hIL-3 could be detected by ELISA, neither in the buffer solution nor in the residual mass analysis. Therefore, hIL-3 must be damaged in the DL-PLG-GLU matrix, possibly by acid catalysed hydrolysis.

This comparison clearly demonstrates the superiority of PEC as matrix for controlled release: the biodegradation of PEC leads to neutral degradation products, e.g. ethylene carbonate, which can be further hydrolysed to ethylene glycol and carbon dioxide.

The facile and favorable formation of the five-membered carbonate ring can also be observed in the case of functional polycarbonates bearing free hydroxy substituents: poly[(hydroxymethyl)ethylene

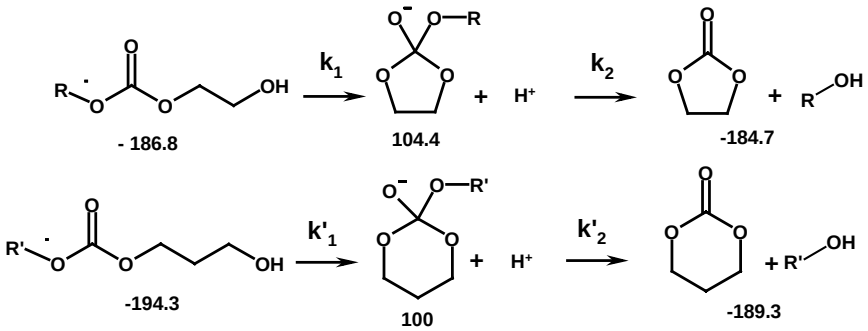


Fig. 5. Formation energies for the formation of ethylene carbonate and trimethylene carbonate (values in kcal/mol).

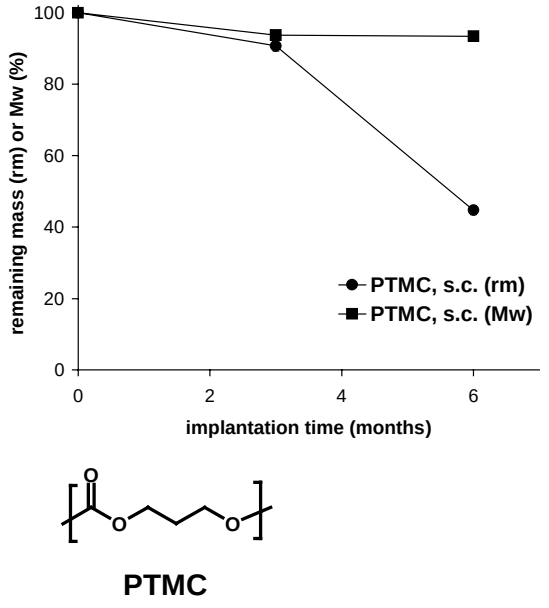


Fig. 6. In vivo degradation of PTMC implants (s.c. in rats).

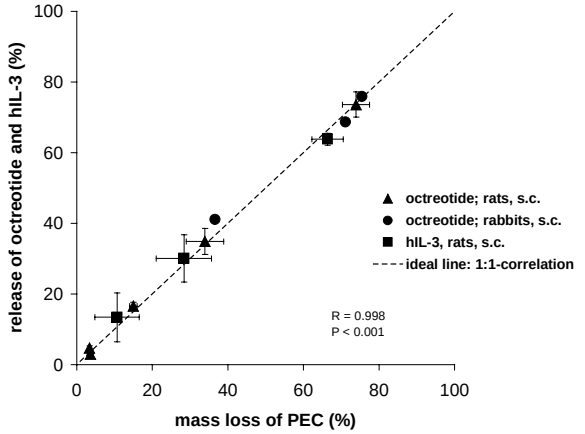


Fig. 7. Correlation of polymer degradation and drug release from PEC tablets in rats and rabbits (s.c., ca. 1% drug loading).

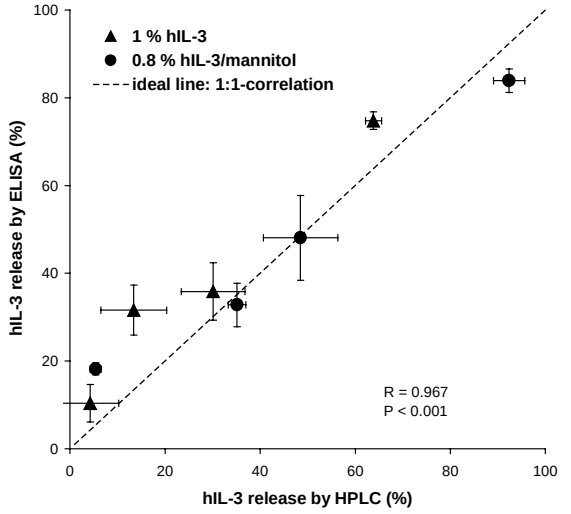


Fig. 8. Correlation of HPLC and ELISA bioanalytics for hIL-3 from PEC tablets.

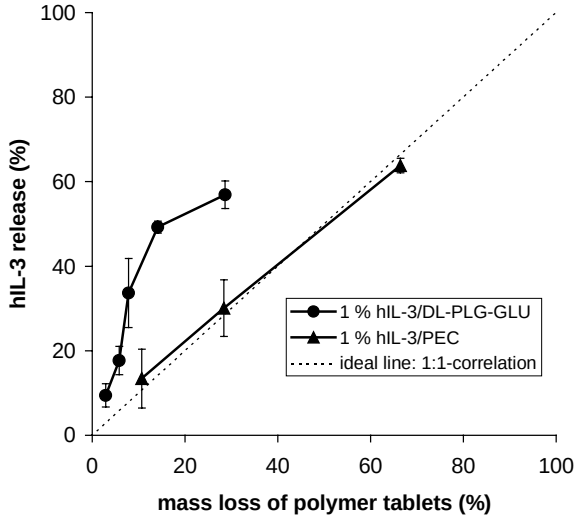
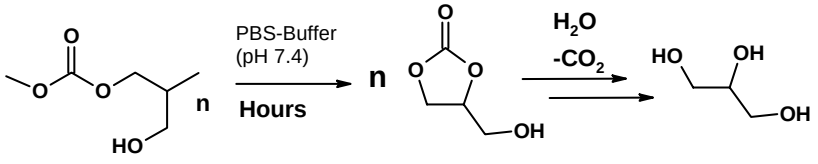
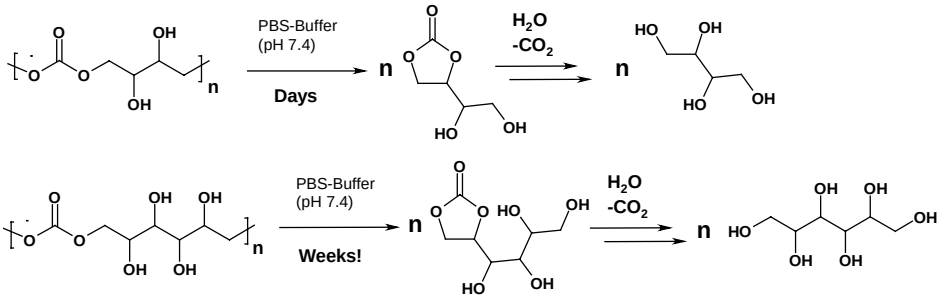


Fig. 9. Correlation of mass loss and hIL-3 release from sustained release formulations with PEC and DL-PLG-GLU after s.c. implantation in rats.



Scheme 2. Degradation of poly[(hydroxymethyl)ethylene carbonate].



Scheme 3. Degradation of functional polycarbonates from threitol and mannitol.

carbonate] (Takanashi et al., 1982) was found to be unstable and to decompose spontaneously to form hydroxymethyl-ethylenecarbonate as the primary degradation product (Scheme 2). Subsequent slow hydrolysis of hydroxymethyl-ethylene carbonate gives glycerol and CO_2 as final degradation products.

More stable, functional polycarbonates were obtained by introduction of conformational barriers against the formation of the five-membered carbonate ring: polycarbonates from threitol and mannitol, containing secondary hydroxy groups as substituents, were much more stable than poly[(hydroxymethyl)-ethylene carbonate] (Acemoglu et al., 1995). This stability may be attributed to the higher conformational barrier for the formation of the five-membered carbonate ring in these cases. The polymer chain must rotate and assume a certain conformation to enable the formation of the five-membered carbonate rings by the secondary hydroxy substituents (Scheme 3).

3. Conclusions

Poly(ethylene carbonate) and poly(trimethylene carbonate) have been shown to biodegrade in vivo by surface erosion, according to a superoxide anion radical initiated chain reaction mechanism. The biodegradations of PEC and PTMC are the first examples of oxidation initiated catalytic degradation processes, consuming only catalytic amounts of the oxidation agent. PEC was successfully utilised as matrix for the controlled release of the peptide and protein drugs, octreotide and hIL-3, respectively.

Acknowledgements

Valuable contributions to this work by Drs. G.H. Stoll, F. Nimmerfall, S. Bantle, D. Bodmer, M. Ausborn, T. Gengenbacher, P. Floersheim and Messrs. J. Munzer and R. Trommer is gratefully acknowledged.

References

Acemoglu, M., Bantle, S., Mindt, T., Nimmerfall, F., 1995. Novel bioerodible poly(hydroxyalkylene carbonate)s: a versatile class of polymers for medical and pharmaceutical applications. Macromolecules 28, 3030–3037.

Acemoglu, M., Nimmerfall, F., Bantle, S., Stoll, H., 1997. Poly(ethylene carbonate)s, Part I: Syntheses and structural effects on biodegradation. J. Control. Release 49, 263–276.

Ambrosio, A.M.A., Allcock, H.R., Katti, D.S., Laurencin, C.T., 2002. Degradable polyphosphazene/poly(α-hydroxyester) blends: degradation studies. Biomaterials 23, 1667–1672.

Bodmer, D., Kissel, T., Traechslin, E., 1992. Factors influencing the release of peptides and proteins from biodegradable parenteral depot systems. J. Control. Release 21, 129–137.

Crommen, J.H.L., Schacht, E.H., Mense, E.H.G., 1992a. Biodegradable polymers. I. Synthesis of hydrolysis-sensitive poly[(organo)phosphazenes]. Biomaterials 13, 601–611.

Crommen, J.H.L., Schacht, E.H., Mense, E.H.G., 1992b. Biodegradable polymers. II. Degradation characteristics of hydrolysis-sensitive poly[(organo)phosphazenes]. Biomaterials 13, 511–520.

Göpferich, A., 1996. Mechanisms of polymer degradation and erosion. Biomaterials 17, 103–114.

Göpferich, A., 1997. Polymer bulk erosion. Macromolecules 30, 2598–2604.

Heller, J., Himmelstein, K.J., 1985. Poly(ortho ester) biodegradable polymer systems. Methods Enzymol. 112, 422–436.

Ikada, Y., Tsuji, H., 2000. Biodegradable polyesters for medical and ecological applications. Macromol. Rapid Commun. 21, 117–132.

Imai, Y., Kojima, K., Watanabe, A., Masuhara, E., 1974. Study of the reaction between living tissue and polymer materials. Jinko Zoki 3, 212–215.

Inoue, S., Koinuma, H., Tsuruta, T., 1969a. Copolymerisation of carbon dioxide and epoxide. J. Polym. Sci. B 7, 287–292.

Inoue, S., Koinuma, H., Tsuruta, T., 1969b. Copolymerisation of carbon dioxide and epoxide with organometallic compounds. Makromol. Chem. 130, 210–220.

Kawaguchi, T., Nakano, M., Juni, K., Inoue, S., Yoshida, Y., 1983. Examination of biodegradability of poly(ethylene carbonate) and poly(propylene carbonate) in the peritoneal cavity in rats. Chem. Pharm. Bull. 31, 1400–1403.

Laurencin, C.T., Koh, H.J., Neenan, T.X., Allcock, H.R., Langer, R., 1987. Controlled release using a new bioerodible polyphosphazene matrix system. J. Biomed. Mater. Res. 21, 1231–1246.

McCarthy, S.J., Meijs, G.F., Mitchell, N., Gunatillake, A.P., Heath, G., Brandwood, A., Schindhelm, K., 1997. In-vivo degradation of polyurethanes: transmission-FTIR microscopic characterization of polyurethanes sectioned by cryomicrotomy. Biomaterials 18, 1387–1409.

Middleton, J.C., Tipton, A.J., 2000. Synthetic biodegradable polymers as orthopedic devices. Biomaterials 21, 2335–2346.

Ng, S.Y., Vandamme, T., Taylor, M.S., Heller, J., 1997. Synthesis and erosion studies of self-catalyzed poly(ortho ester)s. Macromolecules 30, 770–772.

Peppas, N.A., Langer, R.S. (Eds.), 1993. Advances in Polymer Science (no. 107: Biopolymers I). Springer Verlag, Berlin.

Qiu, L.Y., Zhu, K.J., 2000. Novel biodegradable polyphosphazenes containing glycine ethyl ester and benzyl ester of amino acethydroxamic acid as cosubstituents: syntheses, characterization and degradation properties. J. Appl. Polym. Sci. 77, 2987–2995.

Schubert, M.A., Wiggins, M.J., Schaefer, M.P., Hiltner, A., Anderson, J.M., 1995. Oxidative biodegradation mechanisms of biaxially strained poly(etherurethane urea) elastomers. J. Biomed. Mater. Res. 29, 337–347.

Schwach-Abdellaoui, K., Heller, J., Gurny, R., 1999. Hydrolysis and erosion studies of autocatalysed poly(ortho ester)s containing lactoyl-lactyl acid dimers. Macromolecules 32, 301–307.

Song, S.C., Lee, S.B., Jin, J.I., Sohn, Y.S., 1999. A new class of biodegradable thermosensitive polymers. I. Synthesis and characterization of poly(organophosphazenes) with methoxy-poly(ethylene glycol) and amino acid esters as side groups. Macromolecules 32, 2188–2193.

St. Pierre, T., Chiellini, E., 1986. Biodegradability of synthetic polymers used for medical and pharmaceutical applications: Part 1. Principles of hydrolysis mechanisms. J. Bioact. Comp. Polym. 1, 467–497.

Stoll, G.H., Nimmerfall, F., Acemoglu, M., Bodmer, D., Bantle, S., Müller, I., Mahl, A., Kolopp, M., Tullberg, K., 2001. Poly(ethylene carbonate)s, Part II: Degradation mechanisms and parenteral delivery of bioactive agents. J. Control. Release 76, 209–225.

Takanashi, M., Nomura, Y., Yoshida, Y., Inoue, S., 1982. Functional polycarbonate by copolymerization of carbon dioxide and epoxide: synthesis and hydrolysis. Makromol. Chem. 183, 2085–2092.

Tamada, J., Langer, R., 1992. The development of polyanhydrides for drug delivery applications. J. Biomater. Sci., Polym. Ed. 3, 315–353.

Williams, D.F., 1992. Mechanisms of biodegradation of implantable polymers. Clin. Mater. 10, 9–12.

Zhu, K.J., Hendren, R.W., Jensen, K., Pitt, C.G., 1991. Synthesis, properties and biodegradation of poly(1,3-trimethylene carbonate). Macromolecules 24, 1736–1740.