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Bioresorbable polymers in trauma and bone surgery

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Summary[1]

During the last few decades interest in resorbable polymeric materials has been steadily increasing. As with other materials for implantable devices, they have to satisfy several biological and technical requirements. Implants should maintain adequate mechanical properties *in vivo* for the time required and degrade at an effective rate. The conditions of polymer synthesis, further processing into implants and the sterilization process determine the mechanical properties of resorbable implants. Degradation of implants is manifested by implant fragmentation, strength loss and the decrease of polymer molecular weight. The rate of degradation and the tissue reaction are strongly affected by the material chemical composition and to some extent also by the mechanical properties.

Potentially, devices made from bioresorbable polymers can overcome problems associated with metal implants like stress protection, potential for corrosion, wear and debris formation, as well as the necessity of implant removal. Resorbable polymers have proven to be good materials for a range of devices in trauma surgery. However, modifications and optimizations are still required. Three-dimensional porous scaffolds in various geometrical forms offer a good potential for the manufacture of tissue-engineered implants in the future.

Keywords: resorbable polymers, bioresorbable, polyhydroxyacid, degradation, resorption
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Introduction

During the last few decades interest in resorbable materials, i.e. biomaterials which degrade *in vivo* to nonharmful by-products has been steadily increasing. Degradation products of such materials are usually present in the body as metabolites or constituents of the tissues. The early application of bioresorbable polymers almost exclusively for sutures (Dexon, Vicryl, Maxon, Monocryl, PDS, Polysorb, Biosyn) [1-8] is now widely expanded. Implants for trauma surgery (pins, screws, plates, dowels, anchors, membranes [9,10], drug carriers [11], delivery devices in gene therapy [12] and three-dimensional porous scaffolds in various geometrical forms (porous membranes, porous blocks (sponges), chips, beads (microspheres), fibrous structures such as fleeces and nonwoven mats) for tissue and organ substitutes and tissue-engineered implants are typical examples [13-18].

Materials for implants

As with other materials for implantable devices, bioresorbable polymers also have to satisfy several biological and technical requirements to qualify. Thus, they should not induce adverse inflammatory or foreign body reactions; be carcinogenic, mutagenic, or teratogenic; cause allergic, hypersensitive, or toxic responses; or activate the complement system [19]. They should be convertible into good quality and sterile implants using available processing and sterilization techniques. Implants should maintain adequate mechanical properties *in vivo* for the time required for bone fracture healing and degrade at a rate that allows for effective metabolism of degradation products. Among resorbable polymers for implants, polyhydroxyacids occupy the main

[1] Abstracts in German, French, Italian, Spanish, Japanese and Russian are printed at the end of this supplement.

Table 1: Degradation rates of various resorbable polymeric implants

Polymer (implant form)	Retained strength (%/week)	Total strength loss (months)	Complete resorption time (months)
Polydioxanone (sutures)	60/4 (40/6)	~2	6
Poly(glycolide-co-trimethylene carbonate) (sutures)	55/4 (14/7)	2.5	6
Polyglycolide (sutures)	30/2	1	4
Poly(glycolide-co-lactide)(sutures)	30/3	1	2
Poly(L-lactide) (solid, non-oriented)	40/8	3	1–72
Poly(L-lactide) (solid, oriented)	80/12 (65/25)	1–7	36–72[1)]
Poly(L/DL-lactide) 70/30% (solid, nonoriented)	40/12[1)]	3	24–36[1)]
Poly(L/DL-lactide) 80/20% (solid, nonoriented)	50/12[1)]	4	24–36[1)]
Poly(L/DL-lactide) 80/20% (porous membranes)	20/12[1)]	4	12–18

[1)] values to be proven by further experiments

position. These are mainly poly(L-lactide), poly(glycolide) and/or copolymers based on L-lactide, L/DL-lactide, DL-lactide, glycolide, trimethylene carbonate and ε-caprolactone. More recently, experimental polymers based on tyrosine carbonate have been suggested as materials for implants (Fig. 1).

Degradation of polyhydroxyacids

Polyhydroxyacids degrade to monomeric acids and subsequently to carbon dioxide and water. These are removed from the body via respiratory routes and kidneys (Krebs cycle). Degradation of implants from polyhydroxyacids *in vivo* proceeds via a random, bulk

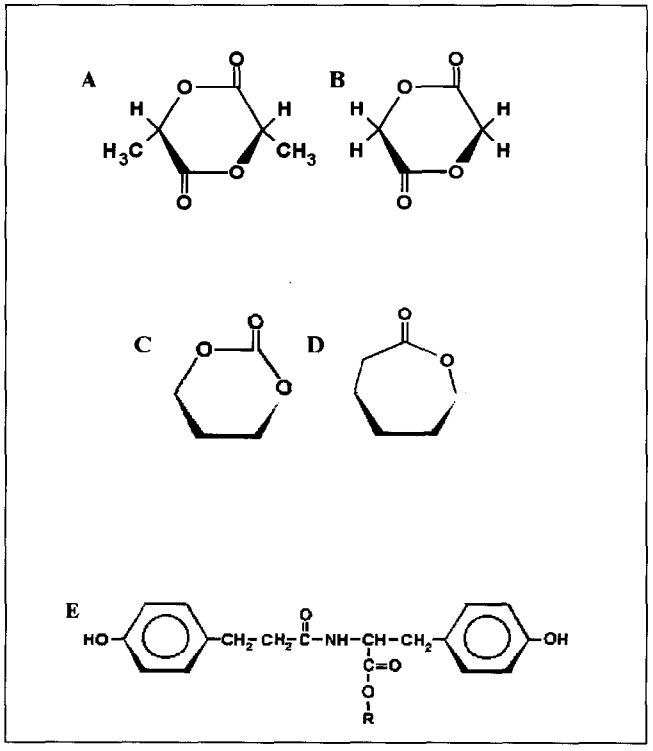

Fig. 1: Various monomer structures representing the basic elements for polymerization of resorbable polymer implant materials: A) glycolide, B) lactide, C) trimethylene carbonate, D) ε-caprolactone, E) tyrosine-derived diphenolic diol.

hydrolysis of ester bonds in the polymer chain. This is manifested by implant fragmentation, strength loss and the decrease of polymer molecular weight. Dissolution of low-molecular weight fractions, phagocytosis, lysis and enzymatic activity play a significant role at the final stage of material degradation. The rate of *in vivo* degradation of bioresorbable polymeric implants is strongly affected by the material chemical composition. By changing the proportions between the monomeric units constituting the polymer chain, it is possible to adjust the implant resorption time and to some extent also its mechanical properties. Other factors which affect *in vivo* degradation involve the implant's physical structure, molecular weight, polydispersity, chain orientation, crystallinity, the load (stress) acting on the implant, the implant mass, solidity, the presence of additives, and the site of implantation. In general, the increase of implant molecular weight, degree of orientation, crystallinity, mass, solidity and chain regularity decreases the rate of degradation. Highly vascularized implantation sites, an aggressive environment, load acting on the implant and the presence of additives accelerate degradation [9].

Bioresorbable internal fixation devices

Bone fractures are treated satisfactorily with rigid metal internal fixation devices which have a long clinical history, are reasonably cheap, and easy to produce and shape. Yet, large differences in Young's moduli between implants and bone, the reduction of the blood supply at the implantation site, stress protection, potential for corrosion, wear and debris formation, and the necessity of implant removal are often cited as drawbacks of these implants. In addition, in the craniofacial skeleton there are problems associated with implant extrusion, devascularization, palpability and migration. In children, local contour deformities in the bone adjacent to the plated area, plate intrusion due to appositional growth, and development of compensatory growth at sites distant to the site of fixation create problems. Thus, there is still a need for fixation devices which would be free from these

drawbacks. Such devices similar to the metal ones should ensure adequate bone fracture fixation, yet, they should transfer increasing load to bone, not affect skeletal growth, and not require removal. Potentially, such devices can be produced from bioresorbable materials including polymers, glasses, ceramics and composites based on these three classes of materials. However, as the problems associated with adequate adhesion between the polymeric matrix and the reinforcing inorganic component in the composite system do not seem to be satisfactorily solved yet, resorbable internal fixation devices are almost exclusively produced from polymers alone.

Tissue reaction to resorbable polymers

Tissue reaction to resorbable polymeric implants is much dependent on the material chemical composition, its degradation rate and toxicity of degradation products. Physical factors, which affect tissue response to implants include, their shape, physical structure, the mass of the implant, the stress at the implantation site and the micromotions at the implant tissue interface. Large bulky implants from fast degrading polymers may cause more pronounced inflammation than small implants from slowly degrading polymers. Inflammatory response may be intensified as a result of implant positional instability invoking micromotions. A typical soft tissue reaction to fast resorbing implants from polyglycolide or poly(glycolide-co-lactide) is manifested by the formation of a fibrous capsule containing mononuclear cells, polymorphonuclear leucocytes and lymphocytes, occasional giant cells, and fibroblasts. Histocytes, large multinucleated giant cells, macrophages and fat cells are found at the later stages of degradation. Soft tissue reaction to slow degrading polymers, such as polylactides, is mild and may involve fibroblasts, histocytes, foreign body giant cells and macrophages and no lymphocytic or plasmacytic infiltration up to 4 years after subcutaneous implantation [20,21]. It should be mentioned, however, that in some publications the presence of lymphocytes, mast cells, plasma cells, eosinophils, and lymphoid cells has also been reported. The differences in purity (catalyst residues, the nonreacted monomer, a low molecular weight fraction present initially in a raw material or formed in the implant during processing) may be the reason for the reported variations in tissue response to polylactides. Bone reaction to polylactides is in general good if the implant is properly designed, produced from a suitable polymer, and surgical technique is adequate. Reported cases of sterile cyst formation are more frequent for implants from fast degrading poly(glycolide) than from polylactides [22] and may have their origin in inadequate implant purity, bone overdrilling or implant positional instability promoting micromotions at the bone-implant interface.

Mechanical properties of resorbable polymeric implants

The commercial resorbable implants available at present have a tensile strength of about 36%, a flexular strength of 54% and an elastic modulus under tension of 4% of those of stainless steel.

Table 2: Mechanical properties of polylactide implants

Production technique	Bending (flexular) strength (MPa)	Elastic modulus under bending (GPa)
Injection-moulding	80–140	5– 6
Melt-extrusion	80–150	5– 7
Solid-state extrusion	150–350	7–14
Bone	100–200	7–40

The conditions of polymer synthesis and further processing into implants strongly affect the molecular weight, chain orientation, crystallinity and purity of implants. All these factors determine the mechanical properties developed in the implants. The higher the molecular weight, chain orientation, crystallinity and material purity, the better mechanical properties can be achieved. It should be kept in mind, however, that increasing these physical properties increases the time required for complete implant resorption. Hence, a proper balance between all these factors is required to obtain resorbable implants with satisfactory mechanical properties, yet acceptable, not too long resorption times.

Processing and sterilization of bioresorbable polymeric devices

Commercial, solid resorbable polymeric devices for internal fixation are mainly produced from the melt by injection-moulding, compression-moulding or melt-extrusion. Orienting of polymer molecules in these objects can additionally enhance their mechanical properties. This is usually achieved by stretching of objects with small cross-sections, e.g. fibres, or so-called solid-state or ram extrusion of objects with large cross-sections, e.g. elements for screws, pins or plates. In the latter process, the objects are pulled or pushed through the nozzles with smaller cross-sections. This results in the reduction of the implant cross-section associated with orientation of polymer molecules in the drawing direction. Melt-processing of resorbable polymers usually results in a substantial reduction of polymer molecular weight and mechanical properties of the implants. This is why the mechanical properties of resorbable internal fixation devices available at present are far from ultimate. This calls for new technologies allowing for processing of resorbable polymers into high-strength, high-modulus implants.

Porous implants (membranes and sponges) can be produced from the melt or from solution. Both techniques have their limitations. As mentioned above, melt-processing causes material degradation. The use of low-toxicity blowing agents or gases mainly results in foams with predominantly closed-cell structures. Solution-processing requires dissolving of polymer in a suitable solvent to obtain solutions with the required concentration. The pores in polymer matrix can be developed by nonwoven web-spinning, salt-leaching, leaching of polymeric or monomeric additives, phase-inverse process or freeze-drying. Although solution processing does not affect the polymer molecular properties, the scaffold post-treatment procedure (salt extraction, rinsing) will affect its surface properties and in consequence, the interaction with cells and tissues.

Yet, another problem relates to sterilization of resorbable implants. High-energy irradiation causes extensive material degradation and loss of mechanical properties. Ethylene oxide sterilization does not practically affect mechanical and molecular properties of resorbable polymers, but there are concerns about ETO residues and environmental problems. New sterilization techniques for resorbable polymeric implants such as the treatment with low-temperature plasmas of various gases are still under investigation.

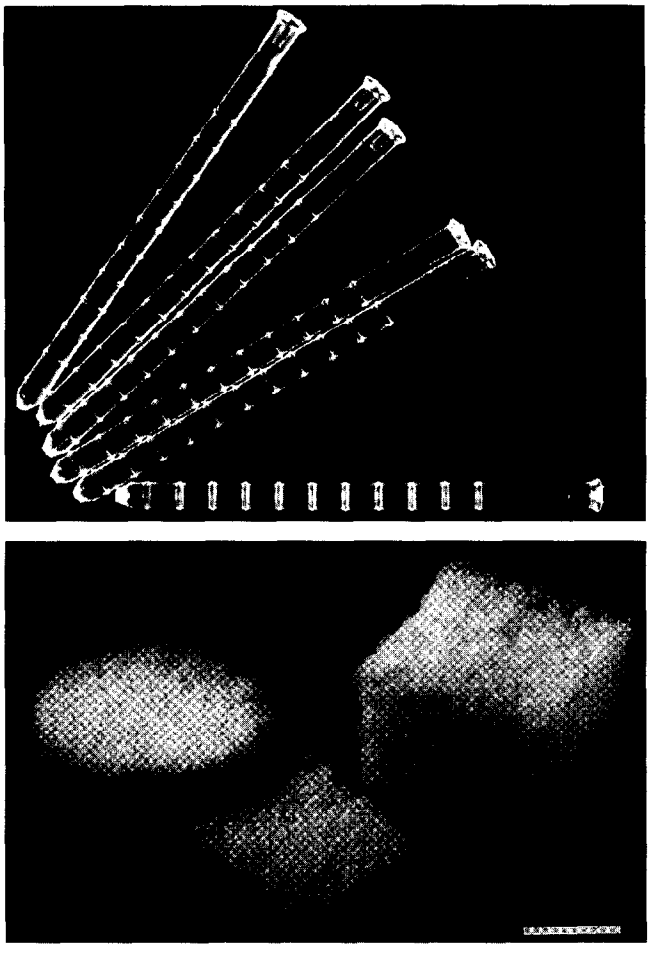

Fig. 2: The Polypin™ representing a commercially available, resorbable polylactide implant, which is used for operative fixation of fractures subjected to slight biomechanical stress, like apical fragments at the radius head or osteochondral fractures at the talar dome or femoral condyle (top) and overall view of three-dimensional, as-prepared, porous scaffolds of different shape are supposed to be used in future in various applications (scale bar = 10 mm; down).

Nevertheless, quite a number of implants made from resorbable polymers are commercially available nowadays (Fig. 2). Sutures are used for the repair of soft tissues; pins and screws in diameters ranging from 1.5 to 5.0 mm are used for the fixation of bone flakes in limited load bearing fractures, e.g. forearm fractures; small plates and screws are applied in craniofacial surgery; interference screws and staples are used in knee surgery for the re-attachment of cruciate ligaments; harpoon devices are used for meniscus tears; anchors are inserted into the bone to enable the anchorage of sutures which attach tendons, ligaments or joint capsules to bone. In hip joint replacement, resorbable plugs are inserted into the femoral diaphysis as cement flow stoppers. In oral surgery, membranes are used in guided tissue regeneration with the aim of inducing sufficient bone stock for dental implant anchoring. Membranes may be held in place with resorbable dowels. However, the very promising three-dimensional, porous scaffolds with potential in lost tissue and/or internal organ substitution, in cell culture and tissue regeneration for the manufacture of tissue-engineered implants or other future applications are still at the research or development stage and are not yet ready for standard clinical use.

Concluding remarks

Resorbable polyhydroxyacids have proven to be good materials for a range of implantable devices. Existing production technologies require modification to obtain high-strength, high-modulus internal fixation devices with predetermined molecular characteristics. A new class of resorbable polymers should be developed allowing for the preparation of resorbable implants with adequate mechanical properties and preferably a resorption time of 1 to 2 years. Such a degradation time frame might allow for the effective metabolism of degradation products and reduce the chance of their local accumulation. Resorbable internal fixation devices can effectively supplement existing metal ones.

References

1. Kronenthal RL. Biodegradable polymers in medicine and surgery. In: Kronenthal R, Oser Z, Martin E. eds Polymers in medicine and surgery. New York: Plenum Press, 1975.
2. Hollinger JO. ed. Biomedical applications of synthetic biodegradable polymers. Boca Raton, FL: CRC Press, 1995.

3. Hermann JB, Kelly RJ, Higgins GA. Polyglycolic acid sutures. Arch. Surg. 1970;100: 486-490.

4. Frazza EJ, Schmitt EE. A new absorbable suture. J. Biomed. Mater. Res. Symposium 1971; 1: 43-58.

5. Conn JP, Oyasu P, Welsh M, Beal JM. Vicryl (Polyglactin 910) synthetic absorbable sutures. Am. J. Surg. 1974;128: 19-23.

6. Ray JA, Doddi N, Regula D, Williams JA, Melveger A. Polydioxanone (PDS), a novel monofilament synthetic absorbable suture. Surg. Gynecol. Obstet. 1981; 153: 497-507.

7. Katz AR, Mukherjee DP, Kaganov AL, Gordon S. A new synthetic monofilament absorbable suture made from polytrimethylene carbonate. Surg. Gynecol. Obstet. 1985; 161: 213-222.

8. Bezwada RS, Jamiolkowski DD, Lee IY et al. Monocryl® suture, a new ultra-pliable absorbable monofilament suture. Biomaterials 1995;16: 1141-1148.

9. Gogolewski S. Resorbable polymers for internal fixation. Clin. Materials 1992;10: 13-20.

10. Gogolewski S. Bioresorbable internal fixation devices – Mechanical properties and future trends in production technologies. In: Leung KS, Hung LK, Leung P.Ch. eds. Biodegradable Implants in Fracture Fixation. Hong Kong: Chinese Univ. Hong Kong & World Scientific Publ., 1994: 249-258.

11. Wise DL, Fellmann TD, Sanderson JE, Wentworth RL. Lactic/glycolic acid polymers. In: Gregoriadis G, ed. Drug Carriers in Biology and Medicine. London: Academic Press, 1979:237-270.

12. Rajasubramanian G, Meidell RS, Landau C et al. Fabrication of resorbable microporous intravascular stents for gene therapy applications. ASAIO J. 1994;40:5 84-589.

13. Gogolewski S, Pennings AJ. Resorbable materials of poly(L-lactide). III. Porous materials for medical applications. Colloid Polym. Sci. 1983;261: 477-484.

14. Gogolewski S, Pennings AJ, Lommen E, Nieuwenhuis P, Wildevuur ChRH. Growth of a neo-artery induced by a biodegradable polymeric vascular prosthesis. Makromol. Chem., Rapid Commun. 1983;4, 213-219.

15. Freed LE, Grande DA, Lingbin Z, Emmanual J, Marquis JC, Langer R. Joint resurfacing using allograft chondrocytes and synthetic biodegradable polymer scaffolds. J. Biomed. Mater. Res. 1994;28: 891-899.

16. Gugala Z, Gogolewski S. In vitro growth and activity of primary chondrocytes on a resorbable polylactide three-dimensional scaffold. J. Biomed. Mater. Res. 2000;49: 183-191.

17. Pineda LM, Büsing MC, Meinig RP, Gogolewski S. Bone regeneration with resorbable polymeric membrane. III. Effect of poly(L-lactide) membrane pore size on the bone healing process in large defects. J. Biomed. Mater. Res. 1996; 31: 385-394.

18. Gugala Z, Gogolewski S. Regeneration of segmental diaphyseal defects in the sheep tibiae using resorbable polymeric membranes. A preliminary study. J. Orthop. Trauma 1999;13: 187-195.

19. Lyman DJ. Biomedical Polymers. Rev. Macromol. Chem. 1966;1: 355-391.

20. Matlaga BF, Salthouse TN. Ultrastructural observations of cells at the interface of a biodegradable polymer: Polyglactin 910. J. Biomed. Mater. Res. 1983;17: 185.

21. Cutright DE, Hunsuck EE. Tissue reaction to the biodegradable polylactic acid suture. Oral Surg. 1971;31: 134.

22. Böstman OM, Pihlajamäki HK. Adverse tissue reaction to bioresorbable fixation devices. Clin. Orthop. 2000; 371: 216.