Review: Polymers for Absorbable Surgical Sutures—Part II
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3.4 Polyester-Carbonate Copolymers

Poly(glycolic acid) (PGA) sutures are routinely used for general and surgical specialties. They are more predictable with regard to tissue response and absorption profile than catgut sutures [27,36]. PGA sutures are also significantly stronger for a longer period of time than catgut sutures, which experience a greater rate of strength loss. However, PGA is a relatively rigid polymer and is supplied as a multifilament braid in sizes larger than 7-0. For reasons discussed earlier, strong, absorbable yet flexible monofilament sutures are more desirable.

In 1985, Davis and Geck introduced a new synthetic absorbable monofilament suture with the trade name of Maxon™ in an effort to provide a more desirable suture. The material is a copolymer produced by the ring opening polymerization of glycolide and trimethylene carbonate. The general structure is shown in Figure 3, and was reported to contain approximately 32.5 percent of trimethylene carbonate by weight [45]. Diethylene glycol was used as an initiator and stannous...
chloride dihydrate as the catalyst. A recent patent describes the manufacture of a triblock copolymer of glycolide and trimethylene carbonate where the center soft block was made predominantly of trimethylene carbonate and the end blocks were made predominantly of glycolide [46]. These polymers generally possessed fiber moduli of less than 500,000 psi.

The physical properties of a size 4-0 glycolide-trimethylene carbonate (GTMC) suture are given in Table 7. On the average, the straight and knot-pull strengths (psi) of these new sutures were greater than those for polypropylene and nylon sutures when tested directly out of the package [45].

The in vivo breaking strength profile of GTMC sutures was determined and compared to PGA sutures. The GTMC retained a greater percentage of its breaking strength as seen in Figure 4. At 28 days, GTMC sutures still retained an average of 59 percent of their original breaking strength, versus 13 percent for PGA sutures. Tissue reactions were reportedly not remarkable. Complete absorption of sizes 2-0 and 4-0 occurred between six and seven months was determined histologically. A pharmacokinetic study was conducted using 14C-labelled GTMC sutures in the subcutaneous tissues of rats. It was determined

Table 7. Typical physical properties of glycolide-trimethylene carbonate monofilament suture.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suture size</td>
<td>4-0</td>
</tr>
<tr>
<td>Diameter</td>
<td>0.224 mm</td>
</tr>
<tr>
<td>Knot-pull strength</td>
<td>57,000 psi</td>
</tr>
<tr>
<td>Knot-pull strength*</td>
<td>3.5 lb</td>
</tr>
<tr>
<td>Straight-pull strength*</td>
<td>88,000 psi</td>
</tr>
<tr>
<td>Straight-pull strength*</td>
<td>5.4 lb</td>
</tr>
<tr>
<td>Elongation to break</td>
<td>38%</td>
</tr>
<tr>
<td>Young's modulus</td>
<td>460,000 psi</td>
</tr>
</tbody>
</table>

\*Pounds force

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that urine and expired CO₂ were the principal excretory routes of the metabolites. The absorption of MAXON™ suture was reported to be essentially complete in six months.

The carbonate linkage had been suspected of being hydrolytically sensitive and predictions were made of its biodegradability [47]. Although not evaluated in fiber form, a preliminary report found poly-(ethylene carbonate) pellets to be absorbed in the rat peritoneal cavity, possibly relying on an enzymatic mode of degradation [48].

MAXON™ sutures seem to show improvements in the areas of tissue drag, knot slide down and knot tying characteristics when compared to the braided products. While providing increased tensile strength retention in vivo during the postoperative period, the monofilaments are stiffer than gut and require a longer period of time for total absorption of the foreign material.

3.5 Polylactide

Poly(lactic acid) or polylactide (PLA) has been considered as a synthetic, surgical repair material for many years [49,50]. In addition to the suture applications which will be discussed here, it has also been evaluated for use in orthopaedic surgery [51–55], in sustained release formulations [56,57], in microporous vascular prostheses [58–60], and as a mesh to facilitate dental extraction wound healing [61]. PLA was also investigated for biodegradable implants since its degradation product, lactic acid is a normal intermediate of carbohydrate metabolism (glycolysis). The early evaluations of PLA for surgical implants indicated no inflammatory reaction which provided evidence for its inertness and tissue receptivity.

High molecular weight PLA is synthesized by a ring opening polymerization of lactide in a manner similar to that of PGA (Figure 5)[49]. Lactic acid has one stereocenter which results in two enantiomers. When two lactic acid molecules combine to form the cyclic dimer, or the lactide, four possible stereoisomers can be formed. However, two of the possible stereoisomers are superimposable (i.e., the same compound) and form a meso compound. As shown in Figure 6, lactide can thus be obtained as the L,L or D,D enantiomers, commonly called L-lactide and D-lactide (which according to the Cahn-Ingold-Prelog system are called the (S,S) and (R,R) enantiomers, respectively) the meso compound (R,S), and a racemic or equimolar mixture of the L and D enantiomers, rac-lactide, commonly referred to as DL-lactide. Some care must be used in reading the literature since the meso- and rac-lactides have occasionally been confused and both have been referred to as DL-lactide.
Figure 5. Ring opening polymerization of lactide.

Figure 4. Breaking strength retention of GTMC monofilament suture compared to PGA braided suture when implanted subcutaneously in rats. Reproduced with permission from Reference [45], Surgery, Gynecology & Obstetrics.
Figure 6. Stereoisomers of lactide monomer. Both the traditional D and L nomenclature and the IUPAC accepted Cahn-Ingold-Prelog nomenclature is given.

The melting point of PLA material can aid in the determination of the lactide in question if it is not specifically identified.

Most of the work conducted on lactide polymers or copolymers has been with L-lactide. These polymers will be referred to in this article as PLA and any use of the other isomers or forms will be specifically noted. Ring opening polymerization of L-lactide in the presence of a suitable catalyst is the preferred method of polymerization and yields high molecular weight polymers. A wide variety of catalysts have been used for this polymerization including stannous chloride [49,62,63], stannous octoate [64–66], tetraphenyl tin [49,67], zinc metal [68], and others [63,69].

Much work has been performed on the stereosequence distributions of the different lactides polymerized by different catalysts [62,68,70,71]. Many of the catalysts retain the configuration in the polymerization.
but redistribution may take place due to transesterification reactions. Poly(L-lactide) has an isotactic structure while poly(rac-lactide) is claimed to have a partially isotactic structure [62,70] and poly(meso-lactide) a partially syndiotactic structure [68], although the latter two are optically inactive.

Recently, poly(D-lactide) was synthesized using an aluminum porphyrin initiator [72,73]. This is of special note as the molecular weight distribution was narrow ($M_n/M_w = 1.12$). It appears that very little chain transfer occurs since the molecular weight can be closely controlled by the ratio of monomer to initiator concentrations. This “immortal” polymerization method is a carefully controlled synthesis of PLA and its copolymers which could expand the use of PLA for bioabsorbable medical devices.

The solution properties of the polylactides have been studied in more detail than for PGA because of the greater solubility of the polylactides in common organic solvents. Schindler and Harper [66] have established the Mark-Houwink equations for both poly(L-lactide) and racemic polylactide in benzene and chloroform at 30°C. Much of the published work of PLA has been performed in chloroform solutions. The Mark-Houwink relationship for poly(L-lactide) in chloroform at 30°C is given in the following equation:

$$\eta = 5.45 \times 10^{-4} M^{0.73}$$

Recently, PLA was synthesized in bulk at low catalyst concentrations at 100°C to produce a polymer with an intrinsic viscosity 13 dL·g⁻¹ and heat of fusion 64.7 J·g⁻¹. This is the highest intrinsic viscosity reported for PLA [74].

PLA has been converted into fibers by both melt spinning [50,75–78] and solution spinning [49,79,80] techniques. Because of its relatively high modulus, it has been considered mostly for multifilament braided suture applications. PLA has been melt-spun into fibers at 200°C and drawn to produce tensile strengths and moduli comparable to PGA fibers [75]. Melt spinning of the polymer resulted in a reduction of $M_n$ from $3.6 \times 10^4$ to $1.1 \times 10^4$. In vitro testing of bundled fibers in pH 7.4 phosphate buffer at 37°C showed that PLA is more resistant to hydrolytic degradation than PGA. A decrease in tensile strength was detected after five months and after nine months a decrease in tensile strength of about 20% was observed, however, no weight changes were detected at this time.

Solution spinning of PLA has recently been shown to generate fibers with tensile strengths up to 1.2 GPa (1.74 × 10⁶ psi) and Youngs
moduli in the range of 12–15 GPa (1.74 × 10⁶–2.18 × 10⁶ psi) [78–80]. These properties are considerably better than those reported for melt spinning. The fibers were spun from chloroform solutions (5–20%), which is a good solvent for PLA. A helical, threaded structure was observed for the undrawn fibers. The fibers were drawn at 200°C at ratios up to 20×. Although some of this surface structure was removed during drawing, the remaining surface structure was found to increase knot strengths over those of smooth surfaced fibers [79,80].

The fibers drawn at 20× showed a tensile strength of 1.2 GPa and a heat of fusion of 89.0 J·g⁻¹. The maximum draw ratio was considerably reduced when the fibers were extracted before hot drawing. This led the authors to conclude that a small amount of low molecular weight polymer in the fiber is required to obtain the high draw ratios which leads to the development of the higher tensile properties. The tensile strength of the fibers was independent of molecular weight in the range 1.8–3.0 × 10⁶, but increased linearly with molecular weight above this range. This break in behavior corresponds roughly to an intrinsic viscosity of 5.4 dL·g⁻¹.

Melt spinning of a high molecular weight polymer may be difficult since the high temperatures required to obtain a melt viscosity suitable for spinning could cause degradation of the polymer. Solution spinning may be the only method to obtain the higher tensile strengths reported by Gogolewski and Pennings [79]. Further work by these authors [80] showed that the in vitro rate of degradation could be accelerated and was comparable to commercially available synthetic absorbable sutures. This was accomplished by solution spinning PLA in the presence of various additives to produce a loose fibrillar structure. It was proposed that this type of structure enhanced the diffusion of body fluids into the fiber which led to an increased rate of absorption. This novel concept of increasing the degradation rate was demonstrated while the tensile and knot properties of the fibers were retained. Additional work could result in a greater use of PLA and its copolymers in designed absorbable devices.

PLA is generally sterilized by ethylene oxide since both gamma and beta irradiation at the dose rates necessary for sterilization have been reported to degrade the polymer [51,81]. The extent of degradation by radiation may depend somewhat on the form of the sample. Radiolabelled studies of the biodegradation rate of lactide polymers and its copolymers with glycolide have been conducted by Brady et al. [82,83]. However, as Vert et al. [51,54] have pointed out, there is considerable scattering of the in vivo and in vitro data with regards to the strength retention and absorption characteristics of PLA. Generally, this is most
likely due to the variations in the starting material and the methods of processing. Specifically, these variations can result from differences in the methods of preparation, polymer molecular weight and molecular weight distribution, configurational structure and distribution, residual monomer, processing and annealing conditions, crystallinity, and sterilization techniques. Also, the final form of the polymer is important as a large bone plate will probably exhibit different absorption rates than a fine diameter filament. The more recent research for the polylactide family of polymers has been more cognizant of these variables which should lead to a better understanding of these polymers and their use in surgical products. Other new developments such as the recently reported stereo complex formation between poly(L-lactide) and poly(D-lactide) may also lead to useful surgical products [84].

Although the long absorption time of PLA has discouraged its use as a suture material, this has not precluded its use in other areas where an extended BSR profile is desired. For example, initial evaluations of bone plates for long bone fracture repair [51-55] have shown that these polymeric bone plates may have advantages over the metal plates for this application. A recent patent has also disclosed the use of poly(L-lactide) and poly(L-lactide-co-glycolide) 95/5 as an artificial absorbable ligament prosthesis. Benicewicz et al. [85] have described a fibrous, porous implant which provides a scaffolding for new tissue to form along the filaments of the prosthesis. It is believed that extremely fine diameter filaments (between about 3 and 15 microns) are desirable to maximize tissue ingrowth. For this application, the extended BSR exhibited by PLA or its previously mentioned copolymer is needed so that the rate at which the natural tissue is deposited about the absorbable fiber scaffold would be in concert with the rate of strength loss of the fiber. Braided devices were tested in rats to determine the BSR profile when these materials were made according to the methods described in the patent. These profiles are shown in Figure 7 for both the homopolymer and the 95/5 copolymer. In vitro (pH 7.27 phosphate buffer, 50°C) changes were also measured for molecular weight (as measured in terms of inherent viscosity), loss of breaking strength, and loss of weight.

3.6 Poly(p-Dioxanone)

The inherent stiffness of PGA and its copolymers precludes these polymers from being used as monofilament sutures in all but the smaller diameter sizes. Recently, it was announced that a novel synthetic polymer was being made into absorbable flexible monofilament
Figure 7. In vivo breaking strength retention for PLA, curve A; and poly(L-lactide-co-glycolide) 95/5, curve B. Reference [85].

Figure 8. Ring opening polymerization of p-dioxanone.
sutures of all sizes [86,87]. Poly(p-dioxanone) can be prepared by the ring opening polymerization of dioxanone in the presence of a suitable catalyst [86–89] (Figure 8). The polymer is melt spun, drawn and oriented, and may be heat treated or annealed to produce effective fibers. These fibers are flexible and suitable for monofilament sutures even in larger diameters. The homopolymer has a glass transition temperature in the range of –15°C to –20°C and melts at approximately 110°C. The Youngs modulus is 250,000 psi, compared to >1,000,000 psi for monofilament PGA and the copolymer polyglactin 910. The straight tensile strength for a size 2-0 (13 mil diameter) suture is 80,000 psi. Copolymers of poly(p-dioxanone) with glycolide and lactide have also been reported [90,91]. The copolymers of p-dioxanone and glycolide are crystalline copolymers that reportedly combine the fast absorbing characteristics of glycolide with the good pliability (low Youngs modulus) of poly(p-dioxanone).

The poly(p-dioxanone) suture (PDS™) has been reported to degrade in the body by simple hydrolysis mechanisms. It is characterized by an extended in vivo breaking strength retention profile. The average breaking strength following subcutaneous implantation in rats is given in Figure 9. Data for PGA and polyglactin 910 sutures are included for comparison. Molecular weights of the monofilament sutures were also measured as a function of time in vivo and the degree of reduction in molecular weight was found to be approximately parallel to the BSR (Table 8). This parallel relationship was also true for the in vitro (pH 7.27 buffer, 37°C) data. The degradation, both in vivo and in vitro, occurs through a nonenzymatic hydrolysis of chemical bonds. In vivo absorption of PDS™, as measured by the reduction of the average cross-sectional area of suture remaining and recovery of radiolabel from radiolabeled suture, was found to be virtually complete within 180 days, versus 60 to 90 days for polyglactin 910 and greater than 120 days for PGA suture when tested similarly. The 14C-labeled study showed that 14C did not accumulate in the tissues or organs, but was excreted via urine, feces and carbon dioxide. Copolymers of p-dioxanone and 2,5-morpholinedione (substituted or unsubstituted) have been found to exhibit accelerated absorption characteristics while still retaining good strengths [92].

The poly(p-dioxanone) sutures are sterilized with ethylene oxide [86]. Williams, et al. [93] have reported that γ-irradiation lowered the tensile strength of PDS™ fibers and made them more susceptible to hydrolysis. Chain scission predominantly occurred when PDS was irradiated from 5 to 20 Mrad. The susceptibility of the polymer to γ-irradiation chain scission was probably due to the inherent chemical structure of
the material. Koelmel et al. [94,95] have investigated the incorporation of certain moieties into poly(p-dioxanone) which impart enhanced resistance to degradation by γ-irradiation. A base polyester was reacted with p-dioxanone monomer to produce copolymers that can be sterilized by γ-radiation while still retaining a desirable level of physical and biological properties. Examples of the base polyesters, containing glycolate ester linkages, are shown in Figure 10. These are similar in chemical structure to the nonabsorbable, radiation sterilizable poly(ethylene terephthalate).

3.7 Polyhydroxybutyrate

Poly[(R)-β-hydroxybutyrate] (PHB) is a highly crystalline, optically active, natural polyester that can be isolated from a large number of
Table 8. In vivo and in vitro breaking strengths and molecular weight changes for size 2-0 monofilament poly(p-dioxanone) suture.

<table>
<thead>
<tr>
<th>Post Implantation Time, Weeks</th>
<th>Breaking Strength, %</th>
<th>Molecular Weight* (% of Original)</th>
<th>Breaking Strength, %</th>
<th>Molecular Weight* (% of Original)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>63.120 (100)</td>
<td>100</td>
<td>63.120 (100)</td>
</tr>
<tr>
<td>1</td>
<td>85</td>
<td>53.280 (64)</td>
<td>85</td>
<td>54.225 (86)</td>
</tr>
<tr>
<td>2</td>
<td>81</td>
<td>47.950 (76)</td>
<td>76</td>
<td>43.685 (69)</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>44.110 (70)</td>
<td>66</td>
<td>45.955 (73)</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>33.150 (52)</td>
<td>61</td>
<td>30.530 (48)</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>23.105 (37)</td>
<td>42</td>
<td>20.170 (32)</td>
</tr>
</tbody>
</table>

* Determined from inherent viscosity measurements
Reproduced with permission from Reference [86]. Surgery, Gynecology & Obstetrics

Microorganisms. The polymer is accumulated by these bacteria as an energy reserve material and found as granules within the microbial cells. In 1982, ICI, in association with Marlborough Biopolymers announced the development of a pilot scale fermentation process to produce this polymer [96]. Random copolymers of 3-hydroxybutyrate with 3-hydroxyvalerate may also be produced by bacteria and are known by the trade name Biopol® [97]. The general chemical structure of these copolymers is shown in Figure 11. The bacterially produced random copolymers are crystalline at all accessible compositions [98], i.e., up to

\[
\begin{align*}
\text{O} & - \text{C} - \text{CH}_2 - \text{O} - \text{CH}_2 - \text{C} - \text{O} - \text{CH}_2 - \text{CH}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & - \text{C} - \text{O} - \text{CH}_2 - \text{C} - \text{O} - \text{CH}_2 - \text{CH}_2 \\
\end{align*}
\]

Figure 10. Examples of base polyesters used to improve the radiation resistance of poly(p-dioxanone).
47 mol% 3-hydroxyvalerate (HV) units. The copolymers undergo a transition at approximately 30 mol% HV units which represents a change from the PHB crystalline lattice to the PHV crystalline lattice which appears as a pseudoeutectic in the melting point and enthalpy of fusion versus copolymer composition plots. Recent attempts to produce the complete range of copolymer compositions by coordination polymerization of β-lactones have resulted in low yields of stereoregular material [99].

One bacteria, Alcaligenes eutrophus, is claimed to produce PHB with such efficiency that approximately 80% of its cell mass is PHB polymer [100]. Various conditions for the cultivation of the microorganisms and the procedures for extracting the polymer from the remainder of the cell mass have been reported [101–105]. The microbially produced polymer has an average degree of polymerization in the range 5,000–12,000 [100], which corresponds to molecular weights of several hundred thousand, although higher molecular weights have been reported [106]. The physical properties have been widely studied including crystal structure [107,108], thermal property [98,109–112], optical rotary dispersion [113–116], and microstructure [117]. The general physical properties have been compared to those of polypropylene (Table 9). PHB has also been reported to be biodegradable in soil [100]. A process for the production of PHB fibers has been claimed and some fiber properties were reported [118].

Table 9. Comparison of physical properties of PHB and polypropylene.

<table>
<thead>
<tr>
<th>Property</th>
<th>PHB</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystalline melting point °C</td>
<td>175</td>
<td>176</td>
</tr>
<tr>
<td>Crystallinity, %</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>5 × 10^5</td>
<td>2 × 10^5</td>
</tr>
<tr>
<td>T_m, °C</td>
<td>15</td>
<td>−10</td>
</tr>
<tr>
<td>Density, g·cm⁻³</td>
<td>1.250</td>
<td>0.905</td>
</tr>
</tbody>
</table>

Reproduced with permission from Reference [100]. Society of Chemical Industry
The biodegradability of PHB makes it a candidate as an absorbable suture material. Monofilaments of PHB and two PHB-HV copolymers were tested for retention of properties in vitro in phosphate buffer, pH 7.2, at 37°C. Little degradation of the homopolymer monofilament either in vitro or in vivo was observed [119]. After 182 days in vivo (subcutaneously in rats), the SEM appearance of the PHB homopolymer monofilament was identical to the original sample. It was also reported that no weight changes were recorded in vivo or in vitro at any period (testing was conducted as long as 182 days). When the PHB monofilament was irradiated with 10.0 Mrad of γ-irradiation, mechanical properties were lost after seven days in vivo while the in vitro tensile properties changed very little. Two different mechanisms (enzymatic versus simple hydrolytic) were proposed for the degradation (in vivo versus in vitro) and that γ-irradiation may assist the in vivo degradation by initially reducing the molecular weight.

Detailed hydrolytic degradation studies on copolymers containing up to 20% hydroxyvalerate (HV) units have been conducted on films and discs prepared by solvent casting, cold and hot pressing, and injection molding [120]. The effects of copolymer composition, molecular weight, pH and temperature on the degradation rates were reported based on weight loss and water uptake measurements, together with goniophotometric, surface energy, and scanning electron microscope studies. This study has confirmed that under conditions where molecular weight and composition of the copolymers are chosen to produce acceptable mechanical properties, the degradation rates are markedly slower than the commercially available suture materials.

Although PHB polymer produces an exceptionally mild foreign body response, its purported total absorption time of several years for a monofilament surgical suture [97] is much longer than the present commercial absorbable sutures. It would be interesting to investigate the absorption and BSR properties of PHB if tested as a fine diameter multifilament suture. The greater hydrolytic stability of the PHB-HV copolymers could be useful in other surgical and orthopedic devices such as bone plates, screws, and pins, where a material is desired that combines the extended retention of physical properties with eventual absorption by the body. These natural copolymers could be very useful in such applications.

3.8 Chitin

Chitin, poly[β-(1,4)-N-acetyl-D-glucosamine], Figure 12, is an abundant naturally occurring polysaccharide which constitutes the main
structural element of the outer shells of crustaceans. Because of its abundance in nature, there have been many proposed industrial and medical applications [121–126]. Interestingly, chitin has been reported to accelerate wound healing [127–129]. Chitin is known to be degraded by lysosomal enzymes and is reportedly nontoxic [130]. Chitin is commonly found in nature surrounded by a protein sheath and must be isolated from this and other biological components of the animal. Different purification techniques and different sources of the natural chitin may lead to difficulties in producing a standard, uniform material.

Recent work has shown, that despite the problems associated with chitin, fine fibers of suitable tensile strength can be produced. For example, chitin fiber has been produced by wet-spinning a dope solution using a mixed solvent consisting of a 50/50 w/w trichloroacetic acid/methylene chloride [131]. These fibers have a dry tensile strength of 4.1 g/d (single filament 1.16 dpf). A braided suture can be made with USP size 4-0. When tested on the back muscle of a rabbit, the silk-like suture was easy to handle and exhibited the following knot tenacity retention ratio: 5 days (76%), 10 days (52%), 20 days (13%), 30 days (0%).

Multifilament fibers can also be spun from amide-LiCl solvents [130]. Fibers spun from amide solvent were made into sutures with USP size 4-0 and they possessed dry straight breaking loads of 2.25 ± 0.05 kg, which is approximately the same as Dexon™ and much stronger than catgut [132]. The mechanical properties of these sutures are compared in Table 10 to the properties of Dexon™ and catgut. The straight strength of chitin and catgut sutures is greater in dry conditions than in wet conditions, although the knot strength of chitin sutures is about the same in dry or wet conditions. In wet conditions, the knot strength of chitin sutures is considerably greater than catgut but less than Dexon™. Toxicity tests were negative for acute toxicity, pyrogenicity and mutagenicity.

As stated earlier, lysosomal enzymes may play an important role in the in vivo degradation of chitin materials (as demonstrated by the
in vitro generation of N-acetylglucosamine in lysozyme solution). Changes in the tensile strength retention in different biological fluids and tissue is given in Figure 13. In rabbit dorsum muscle, both chitin and Dexon™ sutures lost their strength at 24 to 28 days. In calf serum, chitin sutures still retained 35% of their original strength while Dexon™ and catgut had lost all of their strengths at 20 days. In gastric juice of pH 1.2, chitin sutures experienced an initial rapid decrease in strength. In canine bile, chitin sutures decreased in strength slowly and still retained 71% of their initial strength after 21 days. In human pancreatic juice, chitin sutures retained virtually all of their initial strength after 11 days while Dexon™ had only 32% of its initial strength. In human infected urine, chitin sutures retained 80% of their initial strength, far more than either Dexon™ or catgut sutures.

It was reported that chitin sutures were absorbed in about four months in rat muscles [132]. It appears that chitin absorbable suture materials are still undergoing testing and evaluation and, to the author’s knowledge, a commercial chitin surgical suture is not yet available.

3.9 Polyesteramides

A new class of absorbable polymers was synthesized with the goal of combining the excellent fiber, film, and molding properties of nylon (polyamides) with the degradability of PGA by introducing hydrolytically unstable ester linkages into the polyamide structure [133–

<table>
<thead>
<tr>
<th>Suture Property</th>
<th>Chitin 4-0</th>
<th>Dexon™ 4-0</th>
<th>Catgut 4-0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Straight pull</td>
<td>Dry</td>
<td>2.25 ± 0.05</td>
<td>2.35 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>Elongation (%)</td>
<td>12.3 ± 0.8</td>
<td>25.3 ± 1.3</td>
</tr>
<tr>
<td>Wet</td>
<td>Strength</td>
<td>1.96 ± 0.06</td>
<td>2.33 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>Elongation</td>
<td>21.2 ± 1.8</td>
<td>24.8 ± 1.8</td>
</tr>
<tr>
<td>Knot pull</td>
<td>Dry</td>
<td>1.21 ± 0.05</td>
<td>1.47 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>Elongation</td>
<td>12.6 ± 0.7</td>
<td>23.9 ± 0.9</td>
</tr>
<tr>
<td>Wet</td>
<td>Strength</td>
<td>1.25 ± 0.09</td>
<td>1.48 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>Elongation</td>
<td>18.9 ± 1.2</td>
<td>24.1 ± 1.5</td>
</tr>
</tbody>
</table>

(n = 10, mean ± SD)
Reproduced with permission from Reference [132], Japan Surgical Society
Figure 13. Breaking strength retention of chitin, Dexon™, and catgut sutures in (a) rabbit dorsum muscle, (b) calf serum, (c) dog gastric juice, (d) dog bile, (e) human pancreatic juice, and (f) human infected urine. Reproduced with permission from Reference [132], Japan Surgical Society.
These polyesteramides were prepared in a two-step procedure shown in Figure 14. The first step involved the condensation of a linear aliphatic diamine with two moles of glycolic acid to form a diamidediol monomer, I. The diol containing the preformed amide linkages was polyesterified with a diacid chloride in chlorobenzene to produce the polyesteramides, II. This simple polymer structure allowed for many variations in \( x \) and \( y \), as well as many copolymer variations. These variations in structure also produced a wide range of BSR profiles.

Monofilaments were melt spun from many of the copolymers prepared with these compositions. These fibers had reported tenacities as high as 6.53 g/den. The \textit{in vivo} BSR profiles were determined on monofilament fibers (2-0 U.S.P. suture size) implanted subcutaneously in mice \cite{133}. As mentioned previously, the BSR composition was varied widely and could be tailored to produce sutures whose strength retention was greater or less than the commercial PGA-based sutures.

\[
\begin{align*}
H_2N\{(CH_2)_y\}NH_2 + 2\text{HO-CH}_2\text{-COOH} & \xrightarrow{\Delta, H_2O} \text{HO-CH}_2\text{-C-NH\{(CH}_2\_y\}NH\text{-C-CH}_2\text{OH}} \\
\text{I} \\
\begin{align*}
\text{HO-CH}_2\text{-C-NH\{(CH}_2\_y\}NH\text{-C-CH}_2\text{OH} + Cl\cdot\{(CH}_2\_x\}\cdot Cl & \xrightarrow{\phi\cdot Cl, HCl} \\
\text{HO-CH}_2\text{-C-NH\{(CH}_2\_y\}NH\text{-C-CH}_2\text{-O-C\{(CH}_2\_x\}Cl}\_n \\
\text{II}
\end{align*}
\]

\textbf{Figure 14.} Two-step procedure for the preparation of absorbable polyesteramides.
These data are shown in Table 11 and Figure 15. These polymers were reported to be useful for absorbable surgical staples and for nerve repair devices [136–138].

The in vivo absorption properties (subcutaneous in rats) of the polysteramides were evaluated using polymers made from diamidediols labeled with carbon-14 in the hydroxyacetamide moiety [133, 139, 140]. The rate of absorption was not related to the rate of strength loss (BSR). For the polymer II (x = 2, y = 12 or Sample A in Table 11), it was estimated that approximately three years would be required for total absorption. However, the polymer that was formed from a shorter diamine (x = 2, y = 6 or Sample E in Table 11) was absorbed in nine months. It was reported that there was no significant accumulation of radioactivity in any of the peripheral tissues at any time and no evidence of toxicity or adverse tissue reaction. This difference in absorption times was related to the solubility of the diamidediol monomer. The y = 12 monomer was water insoluble, in contrast to the other homologs which were at least sparingly soluble. Labeled diamidediol monomer implant studies confirmed this general behavior. For polymers with shorter diamide diols, the monomer presumably was readily removed from the implant site and resulted in shorter absorption times. Based on the results reported these polymers continue to be viable candidates for further development as sutures and other bioabsorbable polymer applications.

4.0 RESEARCH POLYMERS

There are a large number of polymeric systems that have been claimed to be biodegradable in the body and thus useful for absorbable suture materials. Many of these claims are made as possibilities for a new polymer or copolymer rather than the ultimate goal of the research or a conclusion based upon experimental evidence.

Initial investigations of polymers for absorbable sutures must include a test of its eventual absorption and breaking strength retention characteristics in addition to its ability to be transformed into a fiber with potential useful physical properties. The ability of a polymer or copolymer to form useful fibers is a particularly important criterion for the development of surgical sutures. Additional tests must then be conducted to evaluate efficacy and safety.

In this section a brief survey is made of some of the polymers or copolymers in the research stage that have been or are being evaluated for absorbable suture materials. This is intended to be instructive in some of the directions of research in this area and not comprehensive.
Table 11. Chemical composition of polyesteramide fibers tested in vivo.

<table>
<thead>
<tr>
<th>Sample</th>
<th>R₁</th>
<th>R₂</th>
<th>Initial Tenacity (g/denier)</th>
<th>% Tensile Strength Retained 4 Weeks Post Implantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>(CH₂)₁₂</td>
<td>(CH₂)₂</td>
<td>3.15</td>
<td>87.4</td>
</tr>
<tr>
<td>B</td>
<td>(CH₂)₁₂</td>
<td>(CH₂)₂</td>
<td>6.53</td>
<td>96.5</td>
</tr>
<tr>
<td>C</td>
<td>(CH₂)₁₂</td>
<td>(CH₂)₂</td>
<td>4.67</td>
<td>76.6</td>
</tr>
<tr>
<td>D</td>
<td>(CH₂)₁₂</td>
<td>(CH₂)₂</td>
<td>4.11</td>
<td>79.4</td>
</tr>
<tr>
<td>E</td>
<td>(CH₂)₁₂</td>
<td>(CH₂)₂</td>
<td>3.60</td>
<td>64.0</td>
</tr>
<tr>
<td>F</td>
<td>(CH₂)₁₂</td>
<td>(CH₂)₂</td>
<td>2.50</td>
<td>0.0</td>
</tr>
<tr>
<td>G</td>
<td>(CH₂)₁₂</td>
<td>(CH₂)₂</td>
<td>0.82</td>
<td>0.0</td>
</tr>
<tr>
<td>H</td>
<td>Dexon™</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Vicryl™</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>Chromic catgut</td>
<td></td>
<td>4.10</td>
<td>28.7</td>
</tr>
</tbody>
</table>
Figure 15. Breaking strength retention of monofilament polyesteramides when implanted subcutaneously in mice. A–G refer to polymer compositions denoted in Table 11. Reproduced with permission from Reference [133], Plenum Press.

A common approach that will become evident is the technique of copolymerization to modify an already existing polymer (e.g., PGA) and impart new properties to the copolymer (e.g., radiation sterilizability, high compliance, slower/faster BSR and absorption).

Poly(ε-caprolactone) is an aliphatic polyester which has been evaluated mostly for drug release applications since its absorption rate is generally considered to be too slow for absorbable suture applications [141–144]. This problem has been partially solved by copolymerization with glycolide [145–147] and lactides [148–149]. The block copolymers of ε-caprolactone and glycolide have been converted into low Young's modulus (less than 250,000 psi) fibers that are suitable as monofilaments which are absorbed in vivo in about 120 days. Copolymers of ε-caprolactone and rac-lactide were made via an anionic polymerization using a new bimetallic μ-oxoalkoxide catalyst [150,151] to generate well-defined block copolymers with narrow molecular weight distributions [149,152]. The degradation times of the block copolymer films in deionized water at 50°C ranged from several months to three years depending on the molar ratio of the monomers. The full scope of using
anionic or living polymerization techniques has not been fully explored in the field of absorbable polymers.

The current commercially available synthetic absorbable sutures are sterilized by ethylene oxide. It would be desirable from a safety and economic point of view to be able to sterilize absorbable sutures by radiation methods. However, radiation sterilization has not been practical since it causes an unacceptable degree of deterioration in the tensile properties and in the in vivo performance of these polymers. Several methods have now been disclosed for improving the resistance to gamma radiation [94,153–155]. These methods generally involved reacting glycolide, lactide or p-dioxanone with a base polyester containing aromatic moieties. The aromatic nature of the polymer chain is often associated with improved protection against gamma radiation. These absorbable copolymers were claimed to be radiation sterilizable and retained good tensile and in vivo properties.

The seven membered ether-lactone, 1,5-dioxepan-2-one, was synthesized and copolymerized with lactide, glycolide and ε-caprolactone [156–159]. The copolymers could be extruded into monofilaments with useful tensile properties. The absorption via intramuscular implantation in rats is dependent upon the copolymer composition.

An entirely new class of polymers has been prepared from 3- and 3,6-unsymmetrically substituted 1,4-dioxane-2,5-diones [160,161]. These new monomers were polymerized to give absorbable fibers. The polymers were found to have mostly regular spacings of the side chains and were more crystalline than the randomly sequenced polymers. The absorption of these polymers was confirmed by in vivo tests (subcutaneously in rabbits).

Shalaby and Jamiolkowski [162–165] investigated the use of homopolymers and copolymers of poly(alkylene oxalates) for absorbable surgical devices. The polymers were melt spun and oriented to produce fibers with good tensile properties, suitable as monofilaments. In vivo (intramuscularly in rats) and in vitro tests showed that these fibers absorbed with a minimal degree of adverse tissue reaction. The rate of tensile strength loss and absorption was regulated by the choice of diol(s). Absorption rate ranges were obtained that could be broadly classified from relatively fast to slow. Some highly crystalline isomorph copolyoxalates were also reported.

Polyethylene terephthalate) is a polyester commonly used in the manufacture of nonabsorbable sutures. A series of modified polyesters, based on the copolymers of PET and poly(ethylene oxide) (PEO) have been synthesized and show some evidence of in vitro degradation [166,167]. The copolymers contained 50–70 weight percent PEO. The
physical properties of this biodegradable elastomer were compared to those of commercially available nonbiodegradable polyurethanes and polysiloxanes. The mechanism and rate of in vitro degradation was reported as a function of time, pH and exposure to selected enzymes. Although a simple hydrolytic mechanism does explain the degradation of these copolymers, enzymes were shown to have an effect on the degradation. Sterilization was best achieved by dry heat or ethylene oxide since 60Co gamma irradiation at 2.5 Mrads dosage caused a ~50% reduction in weight average molecular weight.

Casey and Huffman [168] reported on block copolymers of PGA and PEO. These were prepared by transesterification of PGA and hydroxyl-terminated poly(alkylene glycols). This was followed by the addition of an aromatic orthocarbonate such as tetra-p-tolyorthocarbonate which acted as a chain extender and reduced the brittleness of the resulting fibers. Monofilaments produced by this method exhibited a lower tensile modulus than monofilament of PGA homopolymer, which resulted in increased flexibility. The copolymers were claimed to be biodegradable but specific details of the strength retention or absorption were not given.

Schmitt and Polistina [169] synthesized a series of poly(aminotri-azoles) from aliphatic acid dihydrazides. These film-forming polymers were evaluated in rabbits up to 180 days and found to be at least partially degraded provided the nitrogen content was between 31.5 and 35.5% by weight.

A logical approach to the design and synthesis of biodegradable polymers has been to start with materials or monomers that are found in nature or that can be degraded into natural materials. There have been reports of biodegradable polymers derived from tartronic acid [170], aspartic acid [171], and other Krebs-Cycle dicarboxylic acids and diols [172], although much of this work is in the early stages of research. Huang et al. [173-175] have conducted extensive work in modifying biodegradable polymers to improve their physical properties to produce useful biodegradable plastics, films, and fibers. They have also designed, synthesized, and tested new polymers with desirable physical properties that might be biodegradable. Much of this work has been oriented towards enzymatic degradation.

Synthetic inorganic fibers are also undergoing evaluation as absorbable materials. The chemical composition of Phosphate Fiber™, developed by Monsanto [176], is approximated by the formula 2CaO·Na2O·3P2O5 and has the empirical formula of calcium sodium metaphosphate, CaNa(PO3)2. This crystalline fiber is claimed to consist of long, parallel, polyphosphate chains held together ionically by the
calcium and sodium cations. Biomedical applications of these and similar fibers have been claimed [177] and their fiber tensile properties seem appropriate for absorbable composite applications such as bone fixation devices.

4. CONCLUSIONS

There is still much work to be done in extending the spectrum of degradation times and profiles needed for absorbable surgical devices. Even within the existing spectrum of materials used for absorbable sutures, there are needs for materials with more desirable physical properties, such as high strength, low modulus polymers for monofilament sutures.

At each level of participation in the absorbable surgical suture market (the manufacturer, hospital, surgeon and patient) the criteria of an ideal universal suture differs widely. It is further differentiated by surgical specialty and new technologies such as surgical stapling and ligating devices. It is not likely that any one suture material will find universal appeal and capture 100% of the market. This would be very desirable from the standpoint of nursing personnel, hospital purchasing agents, and surgical supply dealers whose tasks and inventories would be tremendously simplified and who would enjoy significant cost reductions as a result.

Most manufacturers' perspective is oriented towards the generation of new products to maintain competitive positions with technological superiority. They too, however, shoulder the burden of thousands of needle–suture combinations to meet the wide range of demands and procedures of the surgical specialties. The development of radiation sterilizable absorbable materials will remain a high priority in achieving cost savings within the industry.

Perhaps the ideal suture from a theoretical point of view would be one that had both nonabsorbable and absorbable properties. In the future this may come in the form of a polymer which would resist degradation indefinitely until exposed to a unique inert activating agent applied either topically or systemically to initiate rapid strength loss and degradation into readily metabolized byproducts without complications. The use of non-damaging wavelengths in the electromagnetic spectrum might be used in vivo to produce similar accelerations with an appropriately targeted absorbable polymer. Such mechanisms would permit the surgeons to determine when or if they wanted the suture to absorb. Several companies have utilized radiation treated ab-
sorbables with accelerated absorption profiles to develop new potential applications in plastic surgery, fat closure, and episiotomy closure.

Other potential ideal developments would include malleable absorbable polymers with sufficient strength to duplicate the performance of stainless steel staples without an increase in size. The use of staplers for wound closure continues to grow dramatically due to the time savings involved. Several manufacturers have developed absorbable staples and clips but their acceptance has been retarded by the significant size difference in absorbable clips and staples when compared to their stainless steel counterparts. Secondly, injection molding of absorbable polymers for these applications results in a larger mass to be degraded and may significantly extend the total absorption time over an absorbable suture counterpart.

The potential use of absorbable polymers in the fabrication of bone plates, screws and other internal fixation devices has previously been alluded to and is the subject of ongoing evaluations.

Finally, the use of pharmoactive agents in conjunction with sutures, while not new may be accelerated through new advances in such areas as epithelial growth factors, wound healing accelerators, and antibiotics. The use of absorbable polymers as drug release agents for indications other than wound closure has stimulated further research.

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LITERATURE (PART II)


