Technical White Paper

Synthetic Absorbable Polyesters

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Polymers that are designed to degrade under physiological conditions are referred to as absorbable polymers. These polymers are sometimes also referred to as biodegradable or bioerodible or bioabsorbable polymers. Synthetic absorbable polymers are generally classified into the following categories:

(a) Polyesters
(b) Polyorthoesters
(c) Polyanhydrides
(d) Polyesteramides
(e) Polyoxaesters

Of these synthetic absorbable polymers, polyesters find numerous applications in medical, surgical and controlled delivery applications and are the key components of a majority of absorbable medical devices, ranging from sutures, staples, orthopedic screws and implantable surgical devices to tissue engineering scaffolds. Hence, the primary objective of this white paper is to provide the readers with an overview of the chemical and physical aspects of synthetic absorbable polyesters as well as their key applications.

Most of the synthetic absorbable polyesters are produced by ring opening homopolymerization or copolymerization of five key lactone–based, safe and biocompatible monomers. These are glycolide, L-lactide and its isomers, ε-caprolactone, p-dioxanone and trimethylenecarbonate (TMC). The structures and IUPAC names of these monomers are shown below in **Figure 1**.

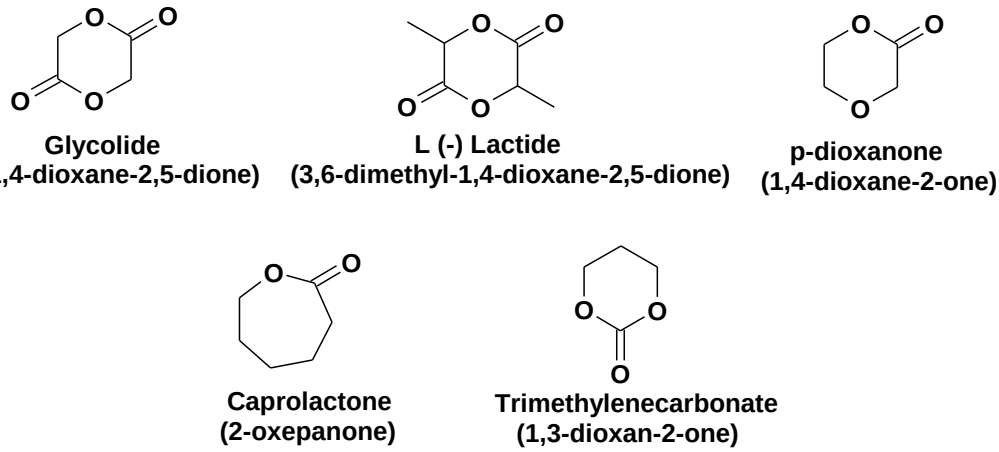


Figure 1. Five key monomers that are used extensively as precursors for synthetic absorbable polyesters.

Figures 2 and **3** depict the structures of homopolymers and copolymers, respectively, derived from the ring opening polymerization (ROP) of these monomers, and medical devices based on them. The ring opening (co) polymerization is carried out in the presence of a catalyst. Medical device applications of synthetic absorbable polyesters require the catalysts to be highly biocompatible and should not cause any immunogenic reactions when implanted inside the body. Although a number of catalysts can be used from a functional standpoint, specific tin catalysts have been used. This is because of their functional effectiveness in addition to their biocompatibility at the levels they are used. Stannous octoate, based on 2-ethylhexanoic acid, and stannous chloride dihydrate are the most commonly used catalysts for polymerization of these five key lactone monomers.

Furthermore, hydroxyl-containing compounds are used as an initiator in the ring opening polymerizations. These compounds have either a single hydroxyl group, such as hexanol or dodecanol, or multihydroxyl groups such as ethylene glycol (diol) or glycerol (triol). Use of initiators with more than two hydroxyl groups results in the formation of branched polymers. The amount of initiator used for the fixed amount of monomer controls the final molecular weight of the polyester produced via ROP. The lower the amount of initiator used for a fixed amount of monomer, the higher is the molecular weight of the resulting polyester. These homopolymers and copolymers form the basis of number of

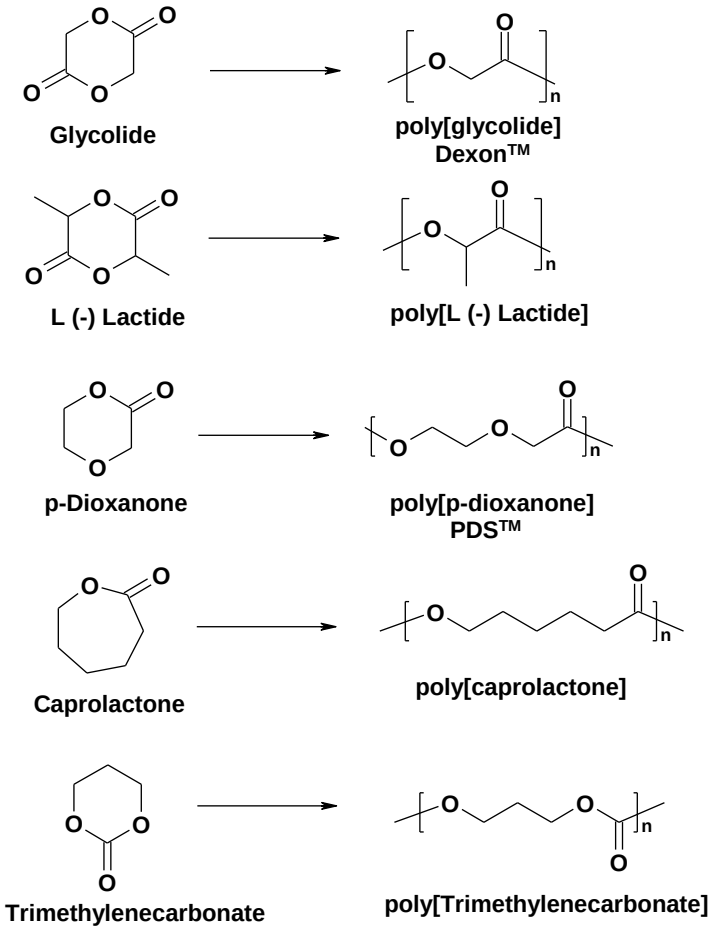


Figure 2. Synthetic absorbable homopolyesters.

absorbable products, including sutures, absorbable surgical devices and scaffolds for tissue engineering.

The three lactone monomers that are currently homopolymerized to produce absorbable polymers used in various biomedical and surgical applications are glycolide, L(-) lactide and p-dioxanone. Polyglycolide is the base material for suture sold under the trade name Dexon™. Similarly, poly[L(-) lactide] is used as a base material for various absorbable implantable surgical devices and poly (p-dioxanone), also referred to as PDS,™ is used both as a raw material for synthetic absorbable sutures and injection molding resin for absorbable implantable devices. Since poly[caprolactone] has relatively long absorption times and limited susceptibility to hydrolysis in the body, it generally does not find applications in implantable medical devices as a homopolymer. Rather, caprolactone is copolymerized with other key monomers to produce softer, more pliable absorbable materials suited to particular applications.

A number of absorbable products are based on copolymers derived from these five key monomers. For example, Vicryl™ suture, one of the largest selling braided sutures across the globe, from Ethicon Inc., is a 90/10 random copolymer of glycolide and lactide. Similarly, Monocryl™, another large selling monofilament suture from Ethicon Inc., is a copolymer of caprolactone and glycolide. The base copolymer material used for preparing Monocryl™ is formed in two steps via copolymerization of caprolactone and glycolide. The first step uses diol as an initiator, followed by further addition of glycolide to the prepolymer in a second stage polymerization step.

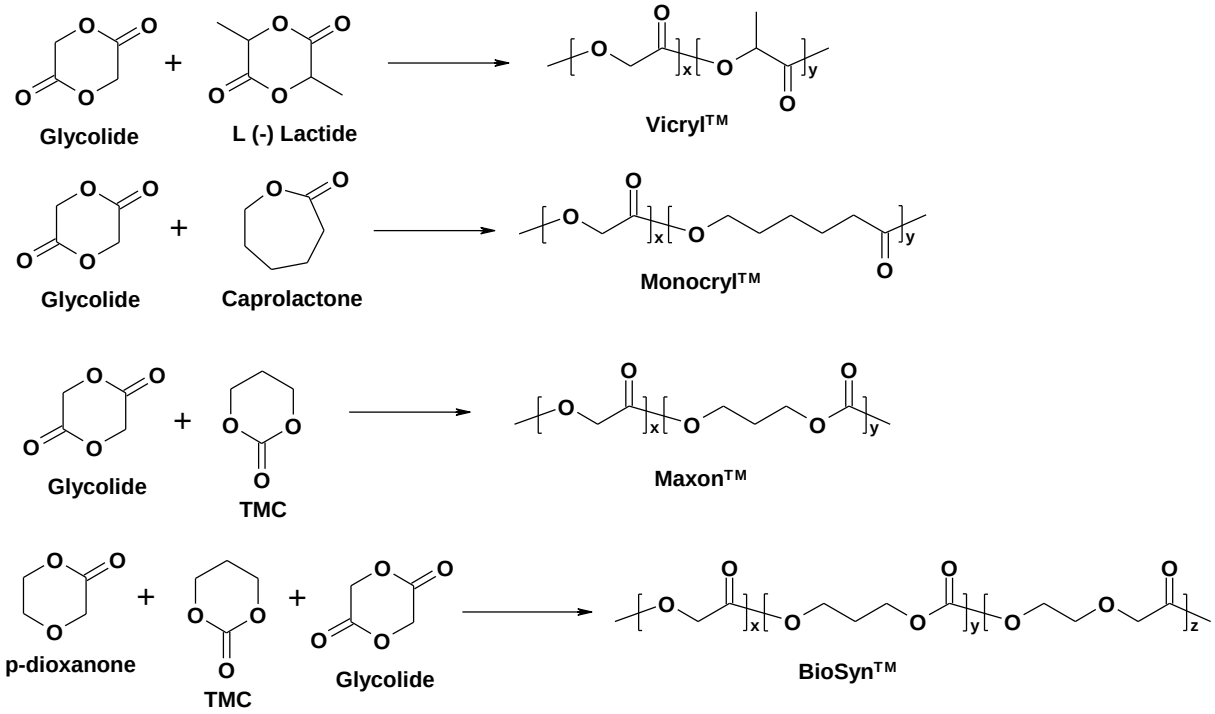


Figure 3. Absorbable copolymers and commercial products.

These ring-opening polymerizations can be carried out in bulk (i.e., without any solvent) or in solution. Nevertheless, solution polymerization has found little or no use in commercial production. This is attributed to the difficulty of removing the residual solvent to the acceptable level. The majority of the synthetic absorbable (co) polyesters are commercially produced via solventless-melt, ring-opening polymerizations at high temperatures in the presence of tin catalyst. Nevertheless, solution polymerization is very useful for preparing polyesters with very low polydispersity, and allows for efficient heat removal.

What is the key structural component of all these absorbable polyesters?

Careful investigation of the structural formula of absorbable polymers, as shown below in **Figure 4,** revealed the presence of an oxygen atom next to the alpha carbon of an aliphatic ester group, which imparts to them the absorbable (hydrolysable) property.

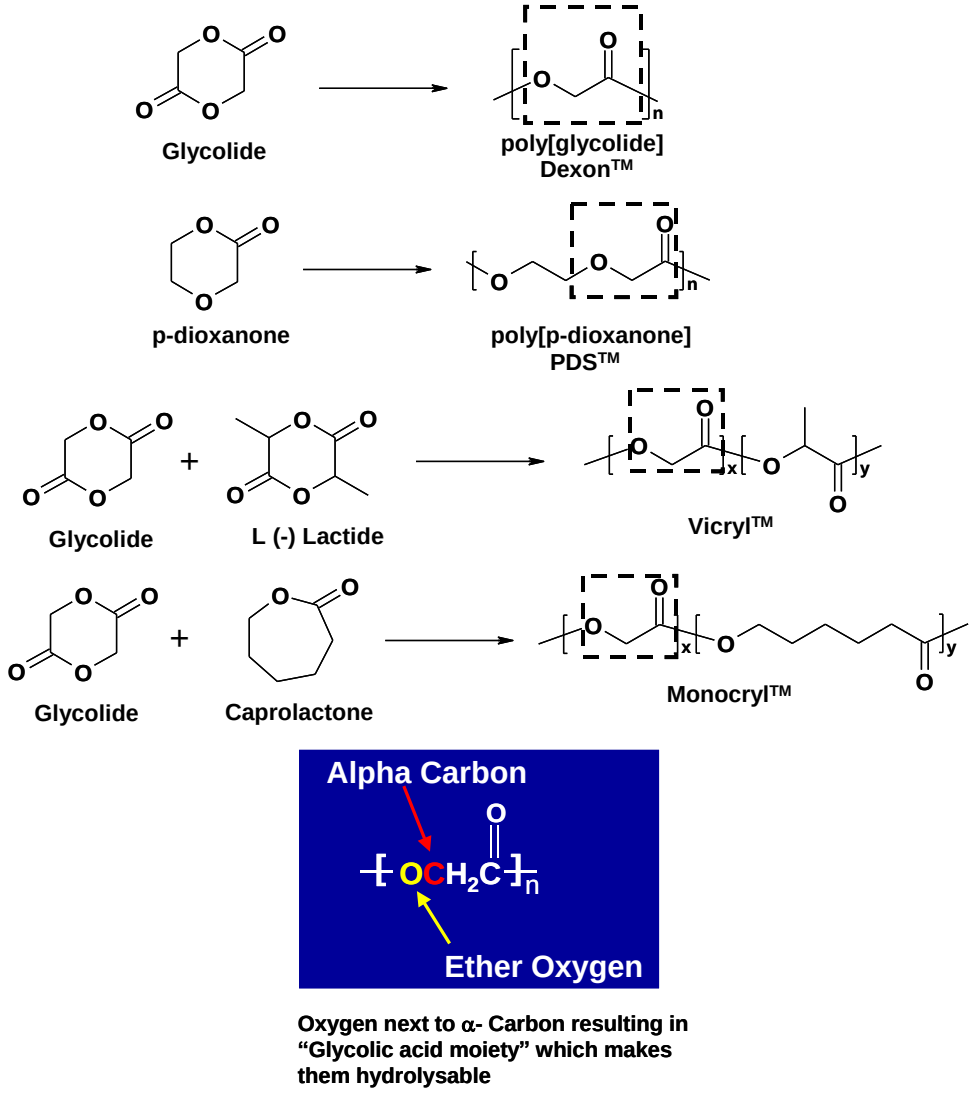


Figure 4. Key structural component of synthetic absorbable polyesters.

Typically, the rate of hydrolysis of the homopolymers follows the order:
poly(glycolide)> poly(p-dioxanone)> poly(lactide)> poly(caprolactone).

Residual monomers

Since most of the synthetic absorbable polyesters are formed by ring-opening polymerization, the resulting polyesters may coexist with about 1-10% of their monomers as a result of thermodynamic equilibrium between monomer and polymer. The extent of the equilibrium, and hence the amount of residual monomer in the polymer, depends on a number of factors, including the size of the ring, steric hindrance, presence of heteroatoms, reaction temeperatures and the polymer processing conditions. For example, a ring with high strain energy will usually have a relatively fast rate of polymerization and hence a low monomer concentraion at equilibrium. This is best exemplified by comparing glycolide and lactide monomers. The two methyl groups on the carbon atom alpha to the ester group result in the stabilization of the lactide ring and hence less ring strain when compared to glycolide. This results in the lactide being a slower reacting monomer than the glycolide and hence in a higher equilibrium monomer level (2-7%) of lactide at higher temperature as compared to glycolide (1-3%).

The monomer-polymer equilibrium is temperature dependent, too. Hence, as the temperature increases, even though the rate of reaction increases, the equilibrium is shifted more and more towards the monomer. Excessively high processing temperatures may result in monomer formation during the molding or extrusion process. The presence of excess residual monomer can change the material's mechanical and hydrolytic degradation properties, processing behaviour, shelf life and hence the ultimate functional performance of the absorbable medical device. Thus, these materials should be synthesized and processed at the lowest (optimal) temperatures possible.

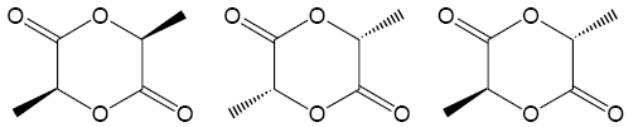
Specific synthetic absorbable polyesters

The following section provides an overview of the synthetic absorbable polyesters prepared via ring opening polymerization that are currently being used or investigated for use in numerous medical device, controlled drug delivery and regenerative medicine applications. These applications include: wound closure (sutures, staples, tissue adhesives, sealants); orthopedic fixation devices (pins, rods, screws, tacks, ligaments); cardiovascular and drug delivery applications (drug eluting stents, absorbable stents, grafts); and regenerative medicine applications (tissue engineering scaffolds).

Polyglycolide (PGA). Polyglycolide is prepared by the ring-opening polymerization of glycolide monomer. Glycolide monomer is synthesized by the back-biting depolymerization of low molecular weight polyglycolic acid prepared via polycondensation process. The back-biting depolymerization results in the formation of glycolide. Ring opening polymerization provides high-molecular weight polyglycolide,

the simplest linear aliphatic polyester. Polyglycolide was originally used to manufacture the first totally synthetic absorbable suture, marketed as Dexon in the 1970s by Davis and Geck, Inc. The high crystallinity of PGA (40-55%) limits its solubility in most organic solvents with the exception of highly fluorinated organic solvents such as hexafluoroisopropanol and hexafluoroacetone. PGA exhibits a high melting point (220-225°C) and a glass-transition temperature of 35-40°C. Although fibers from PGA exhibit high tensile strength and modulus, they are too stiff to be used as sutures except in the form of braided material. A typical suture braid prepared from PGA loses about 50% of its strength after 2 weeks and 100% at 4 weeks, and is completely absorbed in 3-4 months. In order to reduce the stiffness of the fibers, glycolide is copolymerized with other monomers such as caprolactone and trimethylene carbonate. For example, glycolide has also been polymerized with TMC and *p*-dioxanone to form a terpolymer suture Biosyn™ that absorbs within 3-4 months and offers reduced stiffness compared with pure PGA fibers.

Polylactides (PLA). The term polylactides refers to a family of materials with a wide range of physical and mechanical properties depending upon the stereochemistry of the starting lactide monomer**.** Lactide is the cyclic dimer of lactic acid that exists as three stereoisomers, L(-)-lactide, D(+) lactide and meso lactide. L(-)-lactide and D(+) lactide are optical isomers. L(-)-lactide is the naturally occurring isomer, and DL-lactide (meso



L,L-lactide 97-98 °C | D,D-lactide 97-98 °C | D,L-lactide 43-46 °C

lactide) is the synthetic blend of D(+)-lactide and L(-)-lactide. Poly(L(-)-lactide) and poly(D(+) lactide homopolymers are crystallizable and exhibit melting transitions between 170 and 182ºC. Poly(L(-)-lactide) is a semicrystalline (~37% crystallinilty) polymer with a melting point of 175-178°C and a glass-transition temperature of 60-65°C. Furthermore, it has a high tensile strength and low elongation, and it has a high modulus that makes it suitable for load-bearing applications as in sutures or absorbable orthopedic devices. In contrast to L(-)-PLA, poly(dl-lactide) (DL-PLA) is an amorphous polymer, comprised of both isomeric forms of lactide distributed in a random manner. This results in lower tensile strength, higher elongation, and a much more rapid degradation time for DL-PLA in comparison to L(-)-PLA, making it more attractive as a carrier for controlled release of drugs. The complete absorption of L(-)-PLA requires more than 2 years and is much slower than that of DL-PLA. In order to decrease the absorption times of implantable devices incorporating L(-)-PLA, copolymers of L(-)-lactide and dl-lactide have been prepared.

Poly(ε-caprolactone). Poly(ε-caprolactone) is prepared via ring-opening polymerization of ε-caprolactone, a water soluble monomer. It is a semicrystalline polymer with a melting point of 60-64°C and a glass-transition temperature of -60°C. Due to the long degradation time of poly(ε-caprolactone), on the order of two years, copolymers have been synthesized to accelerate the rate of bioabsorption. For example, copolymers of ε-caprolactone with glycolide or dl-lactide result in materials with more-rapid hydrolytic degradation rates. Furthermore, it is generally used to reduce the stiffness of the pure polyglycolide polymer. For example, Monocryl,™ sold as a monofilament suture by Ethicon, Inc., is a block copolymer of ε-caprolactone with glycolide, and has reduced stiffness compared to Dexon™ which is a prepared from polyglycolide homopolymer.

Poly(p-dioxanone). Poly(p-dioxanone) is prepared via ring-opening polymerization of *p*-dioxanone. It is the base material for the monofilament synthetic suture PDS,™ marketed by Ethicon Inc. Poly(p-dioxanone) has a low melting temperature of approximately 110 to 115°C and exhibits a low glass transition temperature of about –10°C. This material has approximately 55% crystallinity. It is the low glass transition temperature of poly(p-dioxanone) and its ability to be crystallized, coupled with its biocompatibility, that resulted in its application as a monofilament suture and other absorbable devices that can be flexed without breaking. The PDS™ suture retains 50% of its initial breaking strength after 3 weeks and is absorbed within 6 months, providing an advantage over Dexon™ or other products for slow-healing wounds. Poly(p-dioxanone) is not as thermally stable as other synthetic absorbable polyesters. This is attributed to the monomer-polymer equlilibrium being more favourable to the monomer than polymer. Hence, poly(p-dioxanone) is processed at the lowest possible temperature to prevent depolymerization back to monomer. Furthermore, during the synthesis of poly(p-dioxanone) polymer by solid–state polymerization, the reaction temperature is kept lower than the melting point of the forming polymer. Moreover, the unreacted residual monomer is removed by volatilization under vacuum at temperatures lower than the melting point of poly(p-dioxanone) polymer.

Poly(lactide-co-glycolide). In order to expand the utility of lactide and glycolide monomers beyond their homopolymer use and to extend the bandwith of homopolymer properties, a number of copolymers of glycolide with both L(-)-lactide and DL-lactide have been developed. These copolymers have found numerous applications in medical device and controlled drug delivery applications. For example, a copolymer of 90% glycolide and 10% l-lactide was developed by Ethicon as an absorbable suture material, under the trade name Vicryl™. Similarly, Monocryl,™ sold as a monofilament suture by Ethicon, Inc., is a block copolymer of ε-caprolactone with glycolide, and has reduced stiffness compared to Dexon,™ which is a prepared from a polyglycolide homopolymer.

Sterilization

Medical devices based on or incorporating synthetic absorbable polyesters cannot be sterilized by autoclaving. This is attributed to the limited dimensional stability and high susceptibility of these materials to undergo hydrolytic degradation at high temperatures, resulting in the loss of mechanical properties and functional performance. The methods

that are generally used to sterilize these medical devices include gamma or e-beam irradiation or exposure to ethylene oxide (EtO) gas. Although gamma and e-beam irradiation are convenient methods for sterilization, they cause a drop in the molecular weight, and degradation of mechanical properties and functional performance, especially at doses above 2 Mrad. Hence, exposure to EtO is the most popular method used to sterilize medical devices incorporating synthetic absorbable polyesters. Nevertheless, great care must be taken to ensure that all the gas is removed from the device before final packaging because the highly toxic EtO can present a safety hazard. Furthermore, the temperature and humidity conditions should also be considered for sterilization. Temperatures must be kept below the glass-transition temperature of the polyester to prevent dimensional changes in devices during sterilization.

Physical Properties

The physical properties of some of the synthetic absorbable homopolymers and copolymers are given below in **Table 1**.

Table 1. Physical properties of synthetic absorbable homopolymers and copolymers.

Polymer	Melting Point (°C)	Glass Transition Temp (°C)	Modulus (gPa)	Degradation Time (months)
PGA	225 to 230	35 to 40	7.0	3 to 4
L-PLA	173 to 178	60 to 65	2.7	> 24
DL-PLA	Amorphous	55 to 60	1.9	12 to 16
PCL	58 to 63	(-65) to (-60)	0.4	> 24
PDS-II	110 to 115	(-10) to 0	1.5	6 to 9
PGA-TMC	210 to 220	N/A	2.4	4 to 5
85/15 DL-PLG	Amorphous	50 to 55	2.0	5 to 6
75/25 DL-PLG	Amorphous	50 to 55	2.0	4 to 5
65/35 DL-PLG	Amorphous	45 to 50	2.0	3 to 4
50/50 DL-PLG	Amorphous	45 to 50	2.0	1 to 2

PCL=Poly(caprolactone), PLA=Poly(lactic acid), PGA=Poly(glycolic acid), PDS=Poly(p-dioxanone), PLG= Poly(lactide-co-glycolide)

Commercial Applications

Table 2 below depicts the examples of commercially available absorbable medical devices prepared using different homopolymers and copolymers.

Table 2. Selected examples of commercially available bioabsorbable medical devices.

Application	Trade Name	Composition	Manufacturer
Sutures	Monocryl	PCL-PGA	Ethicon
	Vicryl	PLA-PGA	Ethicon
	PDS-II	PDO	Ethicon
	Dexon	PGA	Covidien
	Maxon	PGA-TMC	Covidien
	BioSyn	PDS-PGA-TMC	Covidien
	PolySorb	PLA-PGA	Covidien
	Caprosyn	PGA-PCL-TMC-PLA	Covidien
Interference screws	Bioscrew	PLA	Linvatec
	Smart Screw	PLA	Bionx Implants
Mesh	Optima	LPLA-DLPLA	Inion
Pins and Rods	Biofix	PLA-PGA	Bioscience
	Orthosorb	PDS	Johnson & Johnson

PCL= Poly(caprolactone), PLA= Poly(lactic acid), PGA= Poly(glycolic acid), PDO= Poly(p-dioxanone)

Summary

A number of synthetic absorbable polyesters with varying hydrolytic degradation rates are commercially available. These absorbable polyesters include polyglycolide, polylactide, polycaprolactone, poly(p-dioxanone), poly(trimethylenecarbonate) and copolymers. These absorbable polyesters are key ingredients of number of commercially successful medical devices, such as sutures, suture anchors, screws, mesh, adhesion prevention barriers and implantable devices. Furthermore, they also find use in a number of controlled drug delivery and tissue engineering applications. The hydrolytic degradation property of synthetic absorbable co-polyesters is attributed to the presence of ester linkage in the polymer backbone. A number of medical device companies, such as Johnson & Johnson, Boston Scientific and Abbott laboratories, are using synthetic absorbable polyesters with varying physical and chemical properties to develop absorbable medical devices, e.g., absorbable stents.

How Bezwada Biomedical can help you engineer your success?

At Bezwada Biomedical, we understand the challenges and risks involved in bringing a highly differentiated and technically advanced bioabsorbable product to the market. By combining our years of experience and unequaled expertise in developing absorbable polymers, we evaluate the individual needs of our customers and develop smart, value added solutions ideally matched to their end-use requirements.

In addition to custom synthesized absorbable polymers, we also provide our customers with absorbable copolymers with varying compositions. These include copolymers of caprolactone, glycolide and lactide, and copolymers of p-dioxanone with caprolactone, lactide, and glycolide, among others.

Contact Us

For further information, please contact us at rao@bezwadabiomedical.com or visit us at www.bezwadabiomedical.com

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