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Biodegradable polymers as biomaterials

Lakshmi S. Nair[a], Cato T. Laurencin[a,b,c,*]

[a]*Department of Orthopaedic Surgery, The University of Virginia, VA 22903, USA*
[b]*Department of Biomedical Engineering, The University of Virginia, VA 22903, USA*
[c]*Department of Chemical Engineering, The University of Virginia, VA 22903, USA*

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Abstract

During the past two decades significant advances have been made in the development of biodegradable polymeric materials for biomedical applications. Degradable polymeric biomaterials are preferred candidates for developing therapeutic devices such as temporary prostheses, three-dimensional porous structures as scaffolds for tissue engineering and as controlled/sustained release drug delivery vehicles. Each of these applications demands materials with specific physical, chemical, biological, biomechanical and degradation properties to provide efficient therapy. Consequently, a wide range of natural or synthetic polymers capable of undergoing degradation by hydrolytic or enzymatic route are being investigated for biomedical applications. This review summarizes the main advances published over the last 15 years, outlining the synthesis, biodegradability and biomedical applications of biodegradable synthetic and natural polymers.

Keywords: Biodegradable; Polymers; Biomaterials; Hydrolytic degradation; Enzymatic degradation

Contents

*Corresponding author. The University of Virginia, 400 Ray C. Hunt Drive, Suite 330, Charlottesville, VA 22903, USA. Tel.: +1 434 243 0250; fax: +1 434 243 0252.
E-mail address: ctl3f@virginia.edu (C.T. Laurencin).

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1. Introduction

The last two decades of the twentieth century saw a paradigm shift from biostable biomaterials to biodegradable (hydrolytically and enzymatically degradable) biomaterials for medical and related applications [1–3]. The current trend predicts that in the next couple of years, many of the permanent prosthetic devices used for temporary therapeutic applications will be replaced by biodegradable devices that could help the body to repair and regenerate the damaged tissues. There are several reasons for the favorable consideration of biodegradable over biostable materials for biomedical applications. The major driving force being the long-term biocompatibility issues with many of the existing permanent implants and many levels of ethical and technical issues associated with revision surgeries.

Even though the biomedical applications of enzymatically degradable natural polymers such as collagen dates back thousands of years, the application of synthetic biodegradable polymers started only in the later half of 1960s [4]. However, the past two decades saw the development of a range of new generation synthetic biodegradable polymers and analogous natural polymers specifically developed for biomedical applications. The driving force is, in part, due to the emergence of novel biomedical technologies including: tissue engineering, regenerative medicine, gene therapy, controlled drug delivery and bionanotechnology, all of which require biodegradable platform materials to build on.

The slow evolution in the development of biodegradable biomaterials can be attributed to several unique challenges in developing resorbable clinical materials compared to developing commodity polymers. A biomaterial can be defined as a material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body [5]. The essential prerequisite to qualify a material as a biomaterial is biocompatibility, which is the ability of a material to perform with an appropriate host response in a specific application. The tissue response to an implant depends on a myriad of factors ranging from the chemical, physical and biological properties of the materials to the shape and structure of the implant. In the case of biodegradable biomaterials, their active biocompatibility must be demonstrated over time. The chemical, physical, mechanical and biological

properties of a biodegradable material will vary with time and degradation products can be produced that have different levels of tissue compatibility compared to the starting parent material.

Some of the important properties of a biodegradable biomaterial can be summarized as follows [6]:

- The material should not evoke a sustained inflammatory or toxic response upon implantation in the body.
- The material should have acceptable shelf life.
- The degradation time of the material should match the healing or regeneration process.
- The material should have appropriate mechanical properties for the indicated application and the variation in mechanical properties with degradation should be compatible with the healing or regeneration process.
- The degradation products should be non-toxic, and able to get metabolized and cleared from the body.
- The material should have appropriate permeability and processibility for the intended application.

Some of the inherent properties of polymeric biomaterials that can have an affect on their biocompatibility include: material chemistry, molecular weight, solubility, shape and structure of the implant, hydrophilicity/hydrophobicity, lubricity, surface energy, water absorption, degradation and erosion mechanism.

Given the complexity and the range of applications polymeric biomaterials are currently used, there is not just one polymeric system available that could be considered as an ideal biomaterial. This underlines the need for developing a wide range of biodegradable materials available for implant fabrication that can appropriately match the specific and unique requirements of each individual medical application.

Current efforts in biodegradable polymer synthesis have been focused on custom designing and synthesizing polymers with tailored properties for specific applications by: (1) developing novel synthetic polymers with unique chemistries to increase the diversity of polymer structure, (2) developing biosynthetic processes to form biomimetic polymer structures and (3) adopting combinatorial and computational approaches in biomaterial design to accelerate the discovery of novel resorbable polymers.

Biodegradable polymeric materials are being investigated in developing therapeutic devices such as temporary prostheses, three-dimensional porous structures as scaffolds for tissue engineering and for pharmacological applications, such as drug delivery (both localized and targeting systems). Some of the current biomedical applications of biodegradable polymeric materials include: (1) large implants, such as bone screws, bone plates and contraceptive reservoirs, (2) small implants, such as staples, sutures and nano- or micro-sized drug delivery vehicles, (3) plain membranes for guided tissue regeneration and (4) multifilament meshes or porous structures for tissue engineering [7]. A tissue engineering approach uses a biodegradable construct to assemble cells in three-dimensions to ultimately develop into functioning tissue. Polymeric materials with a wide range of mechanical and degradation properties are required to mimic the properties of various tissues. In controlled drug delivery, bioactive agents are entrapped within a biodegradable polymer matrix from which they are released in an erosion- or diffusion-controlled fashion or a combination of both. The release characteristics of the bioactive agents can be effectively modulated by suitably engineering the matrix parameters.

Due to the versatility of polymeric materials, they are rapidly replacing other material classes, such as metals, alloys and ceramics for use as biomaterials. In 2003, the sales of polymeric biomaterials exceeded $7 billion, accounting for almost 88% of the total biomaterial market for that year [8]. It is predicted that by 2008, the biocompatible materials market will reach $11.9 billion suggesting a huge market for polymeric biomaterials in the coming decades.

2. Biodegradable polymers

Both synthetic polymers and biologically derived (or natural) polymers have been extensively investigated as biodegradable polymeric biomaterials. Biodegradation of polymeric biomaterials involves cleavage of hydrolytically or enzymatically sensitive bonds in the polymer leading to polymer erosion [9]. Depending on the mode of degradation, polymeric biomaterials can be further classified into hydrolytically degradable polymers and enzymatically degradable polymers. Most of the naturally occurring polymers undergo enzymatic degradation.

Natural polymers can be considered as the first biodegradable biomaterials used clinically. The rate of *in vivo* degradation of enzymatically degradable

polymers however, varies significantly with the site of implantation depending on the availability and concentration of the enzymes. Chemical modification of these polymers also can significantly affect their rate of degradation. Natural polymers possess several inherent advantages such as bioactivity, the ability to present receptor-binding ligands to cells, susceptibility to cell-triggered proteolytic degradation and natural remodeling. The inherent bioactivity of these natural polymers has its own downsides. These include a strong immunogenic response associated with most of the polymers, the complexities associated with their purification and the possibility of disease transmission.

Synthetic biomaterials on the other hand are generally biologically inert, they have more predictable properties and batch-to-batch uniformity and they have the unique advantage having tailored property profiles for specific applications, devoid of many of the disadvantages of natural polymers. Hydrolytically degradable polymers are generally preferred as implants due to their minimal site-to-site and patient-to-patient variations compared to enzymatically degradable polymers [9]. The successful performance of the first synthetic poly(-glycolic acid) based suture system during the late 1960s led to the design and development of a new array of biodegradable polymers as transient implants for orthopaedic and related medical applications. Extensive research has gone since then to custom designing biodegradable polymer systems with predictable erosion kinetics as drug/gene delivery vehicles or as scaffolds for tissue engineering. For applications that need materials with a certain level of biological activity, strategies to incorporate biological motifs onto synthetic polymers in the form of hybrid materials have also been developed.

The objective of this review is to highlight the current status of biodegradable polymers for various biomedical applications including transient implants, drug delivery vehicles and tissue engineering scaffolds. This review covers the general synthesis, biodegradation, biocompatibility and potential biomedical applications of some of the most promising polymeric biomaterials used today.

The polymeric biomaterials discussed in this review have been broadly classified into hydrolytically degradable polymers and enzymatically degradable polymers placing emphasis on the mode of degradation for the corresponding polymers.

3. Hydrolytically degradable polymers as biomaterials

Hydrolytically degradable polymers are polymers that have hydrolytically labile chemical bonds in their back bone. The functional groups susceptible to hydrolysis include esters, orthoesters, anhydrides, carbonates, amides, urethanes, ureas, etc. [10].

Two general routes are used to develop hydrolytically sensitive polymers for biomedical applications. They are step (condensation) polymerization and addition (chain) polymerization including ring-opening polymerization. Step process is used to prepare a variety of hydrolytically sensitive polymer classes, such as polyanhydrides, poly(ortho esters) and polyurethanes. Ring opening polymerization (ROP) is an extensively investigated polymerization route to develop hydrolytically sensitive polymers, including the poly(α-esters) and polyphosphazenes. Radical polymerization mostly results in the formation of non-degradable polymers; however, recent studies have demonstrated the feasibility of developing synthetic degradable polymers or cross-linked gels by radical polymerization processes. In addition, several polymers developed by microbial bioprocess are gaining significant interest as biodegradable polymers. The following sections discuss some of the most promising hydrolytically sensitive synthetic polymers developed and their biomedical applications.

3.1. Poly(α-esters)

Poly(α-ester)s are thermoplastic polymers with hydrolytically labile aliphatic ester linkages in their backbone. Although all polyesters are theoretically degradable as esterification is a chemically reversible process, only aliphatic polyesters with reasonably short aliphatic chains between ester bonds can degrade over the time frame required for most of the biomedical applications. Poly(α-esters) comprise the earliest and most extensively investigated class of biodegradable polymers. The uniqueness of this class of polymers lies in its immense diversity and synthetic versatility. Poly(α-ester)s can be developed from a variety of monomers via ring opening and condensation polymerization routes depending on the monomeric units. Bacterial bioprocess routes can also be used to develop some poly(α-ester)s. Various synthetic routes for developing polyesters have been recently reviewed by Okada et al. [11].

Among the class of poly(α-ester)s, the most extensively investigated polymers are the poly(α-hydroxy acid)s, which include poly(glycolic acid) and the stereoisomeric forms of poly(lactic acid). The first synthetic suture material was successfully developed based on the glycolides in late 1960s. Several other aliphatic polyesters were developed since then as biodegradable biomaterials and are attracting significant attention as biomaterials due to their good biocompatibility and controllable degradation profiles. The class of poly(α-ester)s now include poly(α-hydroxy acids) and other ester polymers with and without oxygen atom adjacent to the α-carbon of the acid moiety. Fig. 1 shows some of the commercially developed meniscus repair devices based on poly(α-ester)s [12].

Polyesters can be synthesized by the polycondensation of difunctional monomers such as the self-condensation of hydroxy acids, diacids with diols, diacid chlorides with diols or by the ester interchange reaction of diesters and diols. However, since it is difficult to achieve high molecular weight polymers by the polycondensation route, it has not been extensively investigated for developing biomaterials [13].

ROP of cyclic lactones has developed into the most effective one pot polymerization route to develop high molecular weight homo- and co-polyesters. The advantages of ROP over polycondensation route as a commercially viable process are: milder reaction conditions, shorter reaction times, the absence of reaction by-products and the ability of using even six or seven membered lactones [14]. During ROP, specific initiator molecules such as hydroxyl containing molecules, can control the molecular weight of the polymers. The rate of polymerization can be controlled by the application of a wide-range of biocompatible catalytic systems, such as stannous octoate and 2-ethylhexanoic acid. To further improve their biocompatibility, several solvent-less polymerization routes have been developed. Table 1 shows the structure of various cyclic lactones and their corresponding homopolymers. The most extensively studied monomers for aliphatic polyester synthesis for biomedical applications are lactide, glycolide and caprolactone [15]. In addition to cyclic lactones, cyclic anhydrides can also undergo ROP to form polyesters. Enzymatic polyesterification of bacterial origin is yet another elegant method for developing polyesters [16].

Poly(α-ester)s mainly under go bulk erosion i.e., the polymeric matrices degrade all over their cross-section and have erosion kinetics that are non-linear and usually characterized by a discontinuity [17]. Several excellent reviews have been published on the degradation mechanism of poly(α-ester)s [7,18–21]. Both homo-polymers and co-polymers of poly(α-ester)s have been investigated as potential biomaterials for a variety of biomedical applications. The following section will review the synthesis and biomedical applications of some of these polymers.

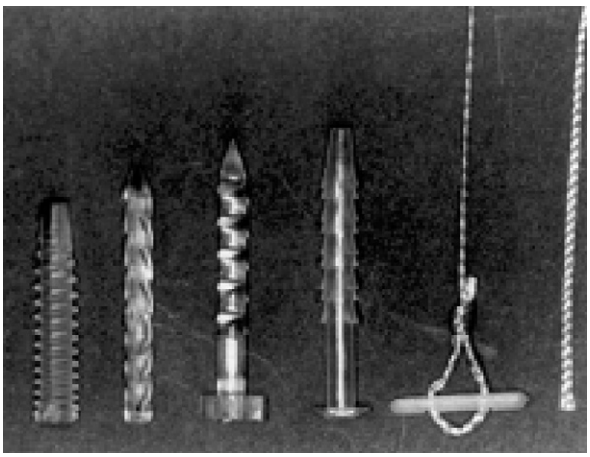


Fig. 1. Some of the commercially developed poly ester-based meniscus repair devices. (*Left to right*) Mitek Meniscal Repair system, Clearfix Screw, Arthrex Dart, Bionx Meniscus Arrow, Linvatec Biostinger, Smith & Nephew T-fix, 2-0 Ethibond suture. Reprinted from Ref. [12] with permission from Elsevier.

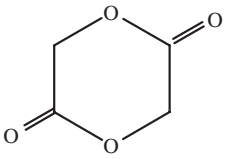
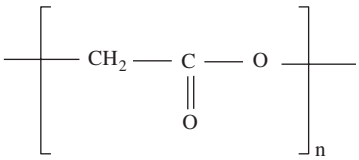
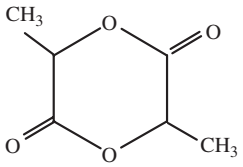
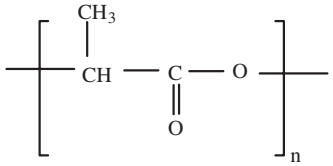
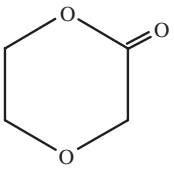
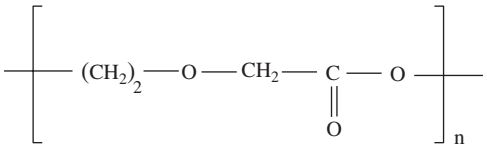
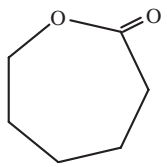
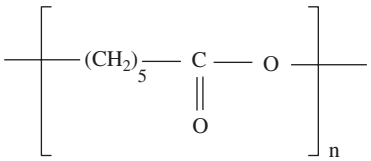
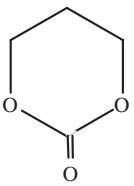
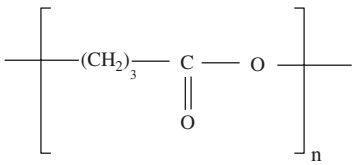
3.1.1. Polyglycolide

Polyglycolide can be considered as one of the first biodegradable synthetic polymer investigated for biomedical applications. Polyglycolide is a highly crystalline polymer (45–55% crystallinity) and therefore exhibits a high tensile modulus with very low solubility in organic solvents. The glass transition temperature of the polymer ranges from 35 to 40 °C and the melting point is greater than 200 °C.

In spite of its low solubility, this polymer has been fabricated into a variety of forms and structures. Extrusion, injection and compression molding as well as particulate leaching and solvent casting, are some of the techniques used to develop polyglycolide-based structures for biomedical applications [22].

Due to its excellent fiber forming ability, polyglycolide was initially investigated for developing resorbable sutures. The first biodegradable synthetic suture called DEXON® that was approved by the United States (US) Food and Drug Administration

Table 1
Structure of cyclic lactones and corresponding homopolymers

Cyclic lactone	Linear homopolymer
 Clycolide	 Poly(glycolide)
 Lactide	 Poly(lactide)
 Dioxanone	 Poly(dioxanone)
 Caprolactone	 Poly(caprolactone)
 Trimethyl carbonate	 Poly(trimethylene carbonate)

(FDA) in 1969 was based on polyglycolide. Non-woven polyglycolide fabrics have been extensively used as scaffolding matrices for tissue regeneration due to its excellent degradability, good initial mechanical properties and cell viability on the matrices. A polyglycolide non-woven fabric-fibrin glue composite matrix is currently undergoing clinical trials. It is being investigated as a biocompatible dural substitute due to its excellent skin-closing ability without requiring

sutures and its ability to help regenerate biological tissue [23].

Polyglycolide shows excellent mechanical properties due to its high crystallinity. A self reinforced form composed of polyglycolide is stiffer than any other degradable polymeric system used clinically [24] and has been shown to exhibit a modulus of approximately 12.5 GPa [25]. Due to its good initial mechanical properties, polyglycolides have been investigated as bone internal fixation devices (Biofix®).

Polyglycolide is a bulk degrading polymer, degrades by the non-specific scission of the ester backbone. The polymer is known to lose its strength in 1–2 months when hydrolyzed and losses mass within 6–12 months. In the body, polyglycolides are broken down into glycine which can be excreted in the urine or converted into carbon dioxide and water via the citric acid cycle [25].

The high rate of degradation, acidic degradation products and low solubility however, limit the biomedical applications for polyglycolide. Therefore, several copolymers containing glycolide units are being developed to overcome the inherent disadvantages of polyglycolide.

3.1.2. Polylactides

Unlike glycolide, lactide is a chiral molecule and exist in two optically active forms; L-lactide and D-lactide. The polymerization of these monomers leads to the formation of semi-crystalline polymers. The polymerization of racemic (D,L)-lactide and mesolactide however, results in the formation of amorphous polymers. Among these monomers, L-lactide is the naturally occurring isomer. Similar to polyglycolide, poly(L-lactide) (PLLA) is also a crystalline polymer (~37% crystallinity) and the degree of crystallinity depends on the molecular weight and polymer processing parameters. It has a glass transition temperature of 60–65 °C and a melting temperature of approximately 175 °C [15]. Poly(L-lactide) is a slow-degrading polymer compared to polyglycolide, has good tensile strength, low extension and a high modulus (approximately 4.8 GPa) and hence, has been considered an ideal biomaterial for load bearing applications, such as orthopaedic fixation devices. Some of the PLLA-based orthopaedic products include: the Phantom Soft Thread Soft Tissue Fixation Screw®, Phantom Suture Anchor® (DePuy), Full Thread Bio Interference Screw® (Arthrex), BioScrew®, Bio-Anchor®, Meniscal Stinger® (Linvatec), and the Clearfix Meniscal Dart® (Innovasive Devices).

PLLA can also form high strength fibers and was FDA approved in 1971 for the development of an improved suture over DEXON®. Due to the high strength of PLLA fibers, it has been investigated as scaffolding material for developing ligament replacement or augmentation devices to replace non-degradable fibers, such as Dacron [26,27]. Some PLLA fiber-based devices are currently under investigation as long-term blood vessel conduits [28]. An injectable form of PLLA (Sculptra®) has recently been approved by the FDA for the restoration or correction of facial fat loss or lipoatrophy in people with the human immunodeficiency virus.

However, being more hydrophobic than polyglycolide, the degradation rate of PLLA is very low. It has been reported that high molecular weight PLLA can take between 2 and 5.6 years for total resorption *in vivo* [15,29]. The rate of degradation however, depends on the degree of polymer crystallinity as well as the porosity of the matrix. Even though the polymer is known to lose its strength in approximately 6 months when hydrolyzed, no significant changes in mass will occur for a very long time. Therefore, several co-polymers of L-lactides with glycolides or DL-lactides are currently under investigation for the development of polymers with better property modulation. Thus Resomer® LR708 is a 70:30 amorphous copolymer of poly(L-lactide-*co*-DL-lactide) and is being extensively investigated as a bioresorbable implant material [30].

Poly(DL-lactide) (PDLLA) is an amorphous polymer due to the random distribution of L- and D-lactide units and has a glass transition temperature of 55–60 °C. Due to its amorphous nature the polymer shows much lower strength (~1.9 GPa) compared to poly(L-lactide). This polymer loses its strength within 1–2 months when hydrolyzed and undergoes a loss in mass within 12–16 months [25]. Being a low strength polymer with faster degradation rate compared to poly(L-lactide), it is a preferred candidate for developing drug delivery vehicles and as low strength scaffolding material for tissue regeneration.

Polylactides undergo hydrolytic degradation via the bulk erosion mechanism by the random scission of the ester backbone. It degrades into lactic acid a normal human metabolic by-product, which is broken down into water and carbon dioxide via the citric acid cycle [25].

3.1.3. Poly(lactide-co-glycolide)

Among the co-polyesters investigated, extensive research has been performed in developing a full range of poly(lactide-*co*-glycolide) polymers (PLGA). Both L- and DL-lactides have been used for co-polymerization. In the composition range of 25–75%, poly(L-lactide-*co*-glycolide) forms amorphous polymers. Miller et al. have shown that the 50/50 poly(lactide-*co*-glycolide) is very hydrolytically unstable and the resistance to hydrolytic degradation was found to be more pronounced at either end of the co-polymer composition range [22,31]. The intermediate co-polymers were found to be much more unstable compared to the homopolymers. Thus, 50/50 poly(DL-lactide-*co*-glycolide) degrades in approximately 1–2 months, 75/25 in 4–5 months and 85/15 in 5–6 months [32].

Different ratios of poly(lactide-*co*-glycolides) have been commercially developed and are being investigated for a wide range of biomedical applications. PuraSorb®PLG is a semicrystalline bioresorbable co-polymer of L-lactide and glycolide with a monomer ratio of 80L:20G [33]. A co-polymer containing 90% glycolic acid (GA) and 10% L-lactic acid (LA) was initially used for the development of the multifilament suture Vicryl®. A modified version of the suture, Vicryl Rapid®, is currently on the market, which is an irradiated version of the suture to increase the rate of degradation. PANACRYL® is another commercially developed suture from the co-polymer with a higher LA/GA ratio in order to decrease the rate of degradation. Several co-polymers have subsequently been developed for the fabrication of monofilament sutures. These include poly(glycolide-*co*-trimethylene carbonate) and poly(glycolide-*co*-caprolactone) containing hard and soft segments along the polymer backbone for property modulation. Other applications of PLGA are in the form of meshes (Vicryl Mesh®), suture reinforcements, skin replacement materials and duramater substitutes. The tissue engineered skin graft (Dermagraft®) use a Vicryl Mesh® as the scaffolding structure.

PLGA has been shown to under go bulk erosion through hydrolysis of the ester bonds and the rate of degradation depends on a variety of parameters including the LA/GA ratio, molecular weight, and the shape and structure of the matrix. The major popularity of these biocompatible co-polymers can be attributed in part to their approval by the FDA for use in humans, its good processibility which enables fabrication of a variety of structures and forms, controllable degradation rates and their success as biodegradable sutures compared to the earlier suture materials. As such, there has been extensive investigation into its use as an ideal biomaterial for temporary medical applications, such as controlled drug/protein delivery systems and as scaffolds for tissue engineering.

PLGA demonstrates good cell adhesion and proliferation making it a potential candidate for tissue engineering applications. Various studies have been performed so far using micro- and nano-fabrication techniques to form three-dimensional scaffolds based on PLGA [34–37]. Fig. 2 illustrates three structures developed from PLAGA using various micro- and nano-fabrication techniques.

Another application of biodegradable PLGA is for use in guided tissue regeneration by providing a permeable material for space preservation. A composite PLGA-collagen matrix is currently in the market (CYTOPLAST Resorb®) as a guided tissue regeneration membrane. LUPRON DEPOT® is a drug delivery vehicle composed of

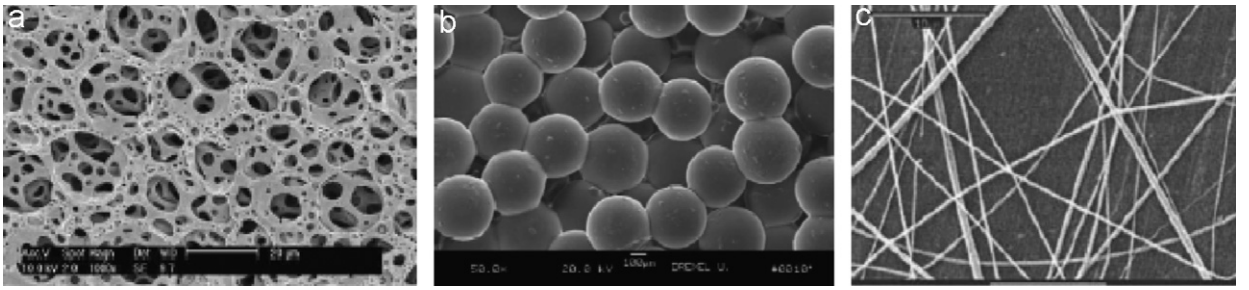


Fig. 2. Porous three-dimensional structures developed from PLGA using (a) gas foaming (reprinted from Ref. [35] with permission from Elsevier), (b) microsphere sintering (reprinted from Ref. [36] with permission from Elsevier) and (c) electrospinning (reprinted from Ref. [37] with permission from Wiley Interscience).

PLGA used for the release of a gonadotropin releasing hormone analog for prostate cancer and endometriosis.

Several drug delivery vehicles composed of PLGA, such as microspheres, microcapsules, nanospheres and nanofibers have been developed for the controlled release of drugs or proteins. Depending on the nature of the PLGA used, the drug or protein has been shown to have varying extents of interactions with the base polymer resulting in rapid or prolonged release profiles [38]. However, due to the bulk degradation of the polymers, the achievement of zero-order release kinetics from these polymer matrices has been found to be difficult. Another concern with using PLGA as a protein delivery vehicle is the possibility of protein denaturation within the delivery vehicle due to the bulk degradation mechanism of the polymer and the acidic degradation products produced. This has led to the search for surface eroding polymers as ideal candidates for developing drug delivery vehicles. Surface eroding polymers have a greater ability to achieve zero-order release kinetics for molecules delivered from the matrix and are able to protect hydrolytically sensitive molecules by encapsulation.

3.1.4. Polydioxanone

Although biodegradable polylactides and glycolides have allowed for the development of versatile resorbable multifilament sutures for biomedical applications, much research has gone into developing materials that would facilitate the formation of monofilament sutures. Multifilament sutures have a higher risk of infection associated with their use and causes a greater amount of friction when penetrating tissues. Polydioxanone (PDS) was the material of choice for the first commercially developed monofilament suture under the trade name of PDS® in the 1980s. In addition to sutures, PDS has also been investigated for several orthopaedic applications as fixation screws for small bone and osteochondral fragments (Orthosorb Absorbable Pins®) [39]. PDS is a colorless, semicrystalline polymer prepared by the ROP of *p*-dioxanone (Table 1). The polymer exhibits a very low glass transition temperature ranging from −10 °C to 0 °C. Being a polyester, it undergoes degradation by the non-specific scission of the ester back bone. However, due to the high crystallinity and hydrophobicity of the polymer, it can be considered a slow to moderately degrading polymer. In the body, PDS is broken down into glycoxylate and excreted in the urine or converted into glycine and subsequently into carbon dioxide and water similar to polyglycolides [25]. The modulus of PDS is very low (approximately 1.5 GPa) compared to polyglycolides. The polymer is known to lose its strength within 1–2 months and its mass within 6–12 months by hydrolytic degradation [25].

3.1.5. Polycaprolactone

Polycaprolactone (PCL) (Table 1) is a semicrystalline polyester and is of great interest as it can be obtained by the ROP of a relatively cheap monomeric unit 'ε-caprolactone'. The PCL is highly processible as it is soluble in a wide range of organic solvents, has a low melting point (55–60 °C) and glass transition temperature (−60 °C) while having the ability to form miscible blends with wide range of polymers. The polymer undergoes hydrolytic degradation due to the presence of hydrolytically labile aliphatic ester linkages; however, the rate of degradation is rather slow (2–3 years). Due to the slow degradation, high permeability to many drugs and non-toxicity, PCL was initially investigated as a long-term drug/vaccine delivery vehicle. The long-term contraceptive device Capronor®, is composed of this polymer and has been developed for the long-term zero order release of levonorgestrel [40]. PCL has low tensile strength (approximately 23 MPa) but an extremely high elongation at breakage (>700%) [22]. Extensive research is ongoing to develop various micro- and nano-sized drug delivery vehicles based on PCL [41]. Due to its excellent biocompatibility, PCL has also been extensively investigated as scaffolds for tissue engineering. A recent study demonstrated the feasibility of using a composite matrix composed of PCL and hyaluronic acid as a potential meniscus substitute [42]. Composites of PCL with calcium phosphate based ceramics are also currently being investigated as suitable scaffolds for bone tissue engineering [43].

Due to the slow degradation rate of PCL, several co-polymeric systems containing PCL have been investigated to improve the properties of the native polymer. Co-polymers of ε-caprolactone with DL-lactide have yielded materials with more rapid degradation rates. Similarly, a co-polymer of ε-caprolactone and glycolide resulted in fibers that were less stiff compared to those made of polyglycolide and are currently on the market as a monofilament suture (MONACRYL®). Another bioresorbable multiblock co-polymer composed of

ε-caprolactone, glycolide, lactide and poly(ethylene glycol) units has been developed as a drug delivery vehicle for small and medium sized biologically active molecules (SynBiosys®).

3.1.6. Poly(trimethylene carbonate)

High molecular weight flexible poly(trimethylene carbonate) (PTMC) (Table 1) can be obtained by the ROP of trimethylene carbonate. Being an elastomeric aliphatic polyester with excellent flexibility and poor mechanical strength, PTMC has been investigated as a candidate implant material for soft tissue regeneration. Low molecular weight PTMC on the other hand, has been investigated as a suitable material for developing drug delivery vehicles. Unlike the previously described polyesters, PTMC undergoes surface degradation with the rate of *in vivo* degradation was found to be much higher than *in vitro* degradation. This is presumably due to the contribution of *in vivo* enzymatic degradation process [44]. The low mechanical performance of the homopolymer significantly limits its applications and consequently, several co-polymers were developed with other cyclic lactones. Thus, polyglyconates have been developed as block co-polymers of trimethylene carbonate and glycolides for use as flexible suture materials (Maxon®) and orthopaedic tacks and screws (Acufex®). BioSyn® is a terpolymer composed of glycolide, trimethylene carbonate and dioxane that has reduced stiffness and degrades within 3–4 months and has been used as suture materials.

3.1.7. Bacterial polyesters

Bacterial polyesters are naturally occurring biodegradable polyesters produced by many bacteria as their energy source. The most common polymer among this class is poly(3-hydroxybutyrate) (PHB), which was discovered in 1920 as produced by the bacteria "*Bacillus megaterium*" (Fig. 3). Since then, it was discovered that several other bacterial strains could produce the same polymer. PHB is a semi-crystalline isotactic polymer that undergoes surface erosion by hydrolytic cleavage of the ester bonds and has a melting temperature in the range of 160–180 °C [16]. In addition to a bacterial synthetic route, several chemical synthetic routes have been developed for PHB synthesis. Shelton et al. [45], demonstrated that the ROP of optically active β-butyrolactone can result in the formation of PHB, which is identical to the bacterial PHB. The co-polymers of PHB and 3-hydroxyvalerate P(HB-HV) have similar semi-crystalline properties as PHB; however, the melting temperature is lower depending on the HV content [46]. The polymer shows glass transition temperature in the range of −5 to 20 °C. Both PHB and P(HB-HV) have been found to be soluble in a wide range of solvents and can be processed into different shapes and structures, such as films, sheets, spheres and fibers. Since the homopolymer PHB is a tough, brittle polymer, the less brittle and tougher co-polymer has more potential as a biomaterial. Another unique property of P(HB-HV) is its piezoelectricity which makes it a potential candidate for orthopaedic applications since electrical stimulation is known to promote bone healing. It has also been investigated as a material for developing bone pins and plates [46].

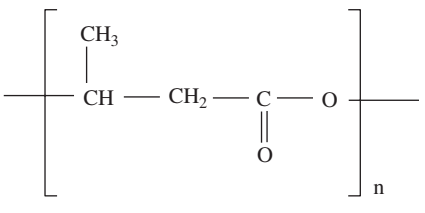


Fig. 3. Structure of poly(3-hydroxybutyrate) PHB.

The hydrolytic degradation of PHB results in the formation of D-(−)-3-hydroxy-butyric acid which is a normal constituent of blood (concentrations between 0.3 and 1.3 mM). However, PHB has a rather low degradation rate in the body compared to synthetic polyesters presumably due to its high crystallinity. The co-polymer, P(HB-HV), being less crystalline undergoes degradation at a much faster rate, however, no correlation has been found between the degradation rate and the amount of HV in the co-polymer. The mass loss of this polymer follows a zero-order release kinetics and this property along with its hydrophobic nature indicate that this polymer primarily undergoes surface erosion. This property makes it an ideal candidate for developing drug delivery vehicles that can achieve zero-order drug release. The *in vivo* degradation of these polymers is slow, although not many degradation studies have been performed. As such, PHB and P(HB-HV) may be potential biodegradable candidates for long term implants. Attempts are currently underway to increase the rate of degradation of these polymers by blending them with more hydrophilic polymers or other low molecular weight additives to increase water penetration and facilitate degradation [47].

3.2. Polyurethanes

Biostable polyurethanes and poly(ether urethanes) have been extensively investigated as long term medical implants, such as cardiac pacemakers and vascular grafts due to their excellent biocompatibility and mechanical properties. Based on the good biological performances of biostable polyurethanes and their synthetic versatility, attempts were made to develop biodegradable polyurethanes. Polyurethanes are generally prepared by the polycondensation reaction of diisocyanates with alcohols and/amines [48]. However, due to the toxicity of common diisocyanates such as 4,4′-methylenediphenyl diisocyanate (MDI) and toluene diisocyanate (TDI), other biocompatible aliphatic diisocyanates have been investigated for the development of biodegradable polyurethanes. Lysine diisocyanate (LDI), and 1,4-diisocyanatobutane (BDI) are a few. Degradable poly(ester urethanes) were developed by reacting LDI with polyester diols or triols based on D,L-lactide, caprolactone and other co-polymers having a wide range of properties [49]. In these biodegradable polyurethanes, aliphatic polyesters such as lactide/glycolide copolymers or polycaprolactones form the soft segments and polypeptides form the hard segments [50]. Another unique feature of the peptide-based polymer systems is that active moieties such as ascorbic acid and glucose can be incorporated into the polymer which could potentially promote cell adhesion, viability and proliferation without any adverse effect [51]. A biodegradable elastic poly(ester urethane) (Degrapol®) is being used to develop highly porous scaffold for tissue engineering application [52].

Injectable biodegradable polymers are attractive materials as they can alleviate many of the challenges associated with current surgical techniques and pre-fabricated tissue engineered implants. Several biodegradable injectable hydrogels systems have been developed; however, only very few studies have been performed at developing injectable materials suitable for orthopaedic applications. These materials would require the additional property of having good mechanical properties and controlled degradability. A unique injectable, two component LDI-based polyurethane system that cures in situ was recently developed for orthopaedic applications (PolyNova®). This self-setting system can be administered arthroscopically in liquid form and polymerizes at physiological temperature in situ to provide appropriate bonding strength and mechanical support comparable to or superior to widely used bone cements. This material has also been shown to promote favorable cell adhesion and proliferation [53].

3.3. Poly(ester amide)

Due to the hydrogen bonding ability of the amide bonds and biodegradability imparted by the ester bonds, these co-polymers have good mechanical and thermal properties. The degradation of poly(ester amides) has been shown to take place by the hydrolytic cleavage of the ester bonds, leaving the amide segments more or less intact. The good mechanical properties of poly(ester amides) derived from symmetrical bisamide-diols and succinyl chloride led to its investigation as a potential bioresorbable suture materials. Different water soluble bisamide-diols have also been prepared from glycolic acid and diaminoalkanes containing 2–12 methylene groups [54]. Attempts were also made to increase the degradation rate of poly(ester amides) by incorporating amino acid units in the polymer backbone. CAMEO® is a poly(ester amide) blend based on leucine or phenylalanine that is currently being developed for the site specific delivery of small hydrophobic drugs and peptides.

3.4. Poly(ortho esters)

The disadvantages of bulk eroding biodegradable polymers for use as drug delivery vehicles has led to the search for more hydrophobic polymers with hydrolytically sensitive backbones that could under go surface erosion. Poly(ortho esters) were developed by the ALZA corporation (Alzamer®) as a hydrophobic, surface eroding polymer designed specifically for drug delivery applications. Although the ortho ester linkages are hydrolytically labile, the polymer is hydrophobic enough such that its erosion in aqueous environments is very slow. The unique feature of poly(ortho esters) is that in addition to its surface erosion mechanism, the rate of degradation for these polymers, pH sensitivity, and glass transition temperatures can be controlled by using diols with varying levels of chain flexibility. The pH sensitivity of the poly(ortho esters) has lead to the development of several drug delivery systems using this polymer. The rate of drug release is predominantly controlled by the rate of polymer hydrolysis through the use of acidic or basic excipients. By now four different classes of

poly(ortho esters) have been developed [55]. Fig. 4 shows the structures of different types of poly-orthoesters. Poly(ortho ester) I (POE I) is synthesized by the transesterification between a diol and diethoxytetrahydrofuran. One of its hydrolysis products, γ-hydroxybutyric acid, has an autocatalytic effect on the further degradation of the polymer. Poly(ortho ester) II (POE II) was synthesized to overcome the autocatalytic effect of POE I and its degradation products are neutral molecules. Poly(ortho ester) II is synthesized by the reaction of diols with diketene acetal 3,9-bis(ethylidene 2,4,8,10-tetraoxaspiro[5,5]undecane). The degradation rate of this polymer can be modulated by adding acid excipient such as itaconic and adipic acids. Poly(ortho ester) III (POE III) is synthesized by the direct polymerization of a triol with an orthoester. In this case, the polymer chains are highly flexible making the polymer a gel-like material at room temperature. The viscous nature allows for the incorporation of therapeutic agents into the polymer matrix without the need for solvents. The release of 5-flurouracil from this polymer matrix has been demonstrated to follow a zero-order release kinetics and has been extensively investigated for ocular applications [56,57]. However, the gel-like consistency and the technical difficulties in scaling up the synthetic procedure are the limitations of POE III. This led to the development of POE IV. Poly(ortho ester) IV was developed as a modification of poly(ortho ester) II to allow for an appreciable degradation rate without the addition of an acid excipient. This was achieved by incorporating short segments based on lactic or glycolic acid into the polymer backbone. Upon exposure to aqueous environments, the latent acid will undergo hydrolysis, and the liberated lactic or glycolic acid will catalyze further polymer hydrolysis. The rate of degradation for these polymers can also be finely controlled to vary from a few days to

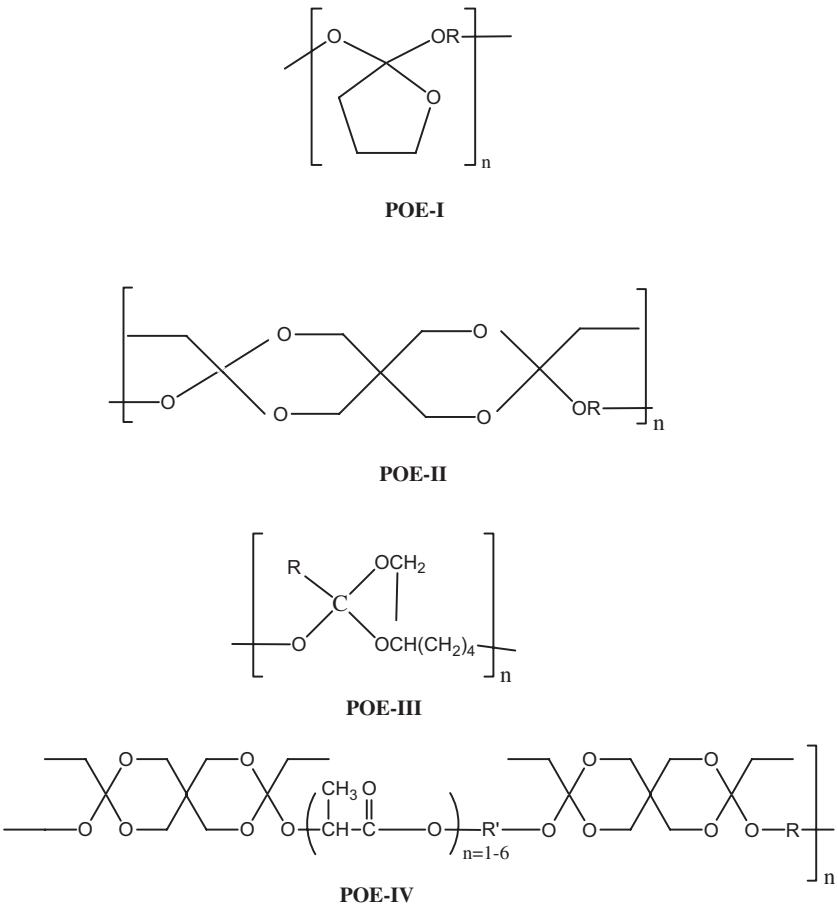


Fig. 4. Structures of different poly(ortho ester)s.

several months by changing the amount of the acid segment in the polymer backbone. Additionally, by varying the nature of the diols, solid materials or soft gel-like materials can be obtained. Extensive biocompatibility evaluations of POE IV have been performed, which demonstrate the good biocompatibility of the polymer. Thus, among the four different classes of POEs, POE IV has been considered to be the biomaterial with greatest potential having not only a scalable synthetic procedure, but also the ability to provide well-controlled release profiles for a wide range of pharmaceutical agents, including proteins [56].

3.5. Polyanhydrides

Polyanhydrides can be considered as the most extensively investigated biodegradable surface eroding polymers specifically designed and developed for drug delivery applications. Polyanhydrides are one of the most hydrolytically labile polymers due to the highly sensitive aliphatic anhydride bonds on the polymer backbone. The hydrolytically labile backbone coupled with the hydrophobicity of the polymer precludes water penetration into the matrix allowing polyanhydrides to truly undergo surface erosion. The aliphatic polyanhydrides were developed in 1932 as a fiber forming polymer for textile applications [58]. Due to its hydrolytic instability and surface eroding nature, Langer et al., investigated this class of polymers as candidate materials for controlled drug delivery applications in 1980s [59]. In 1996, this material was approved by the US FDA, as a drug delivery vehicle following extensive *in vitro* and *in vivo* drug release and biocompatibility evaluations [9].

Polyanhydrides are synthesized via melt condensation of diacids/diacid esters, ROP of anhydrides, interfacial condensation, dehydrochlorination of diacids and diacid chlorides or by the reaction of diacyl chlorides with coupling agents such as phosgene or diphosgene [60,61]. A variety of catalyst systems for polymerization have been identified, which has enabled the synthesis of high molecular weight polyanhydrides. Both homo- and co-polyanhydrides having different properties have been developed by the melt condensation method. Aliphatic homo-polyanhydrides, such as poly(sebacic anhydride) (PSA), have been found to have limited applications due to their crystalline structure and fast degradation. Several co-polymers of sebacic anhydride and hydrophobic aromatic co-monomers have been investigated to develop polymeric systems with controllable degradation rate and processibility.

Polyanhydrides are generally classified as surface eroding polymers because they undergo a linear mass loss during erosion. However, studies have shown that their degradation is not strictly limited to the surface of the polymer matrix and additional studies have tried to elucidate other parameters that affect polyahydride degradation [62–64].

The most extensively investigated polyanhydride is poly[(carboxy phenoxy propane)-(sebacic acid)] (PCPP-SA). Fig. 5 shows the structure of P(CPP-SA). The polymer has been found to exhibit a zero-order release of incorporated drug over periods of time ranging from days to years depending on the ratio of the co-monomers used and the molecular weight of the polymer. The degradation products of the polymers have been found to be non-toxic and biocompatible [9,59,65,66]. This polymer was been approved by the US FDA for use as a localized delivery vehicle for the controlled delivery of the chemotherapeutic agent BCNU for the treatment of brain cancer (Gliadel®). A co-polymer of 1:1 sebacic acid and erucic acid dimer has been found to be useful as a potential delivery vehicle for gentamicine (Septacin®) in the treatment of osteomyelitis [67]. The *in vivo* drug release of Septacin® in rats demonstrated extremely low gentamicin plasma levels, indicating a low systemic exposure

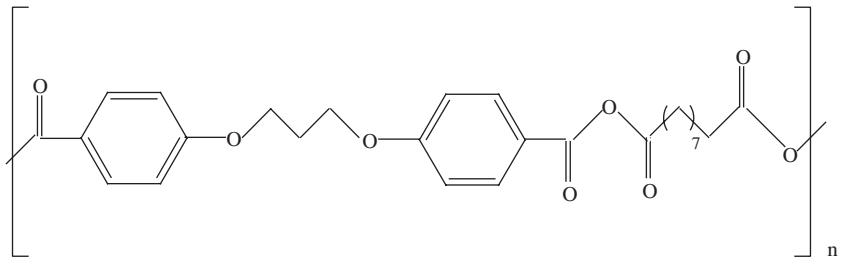


Fig. 5. Structure of poly[(carboxy phenoxy propane)-(sebacic acid) P(CPP-SA).

to the drug. Septacin® has also showed efficacy in rat skin-abscess and horse joint infection models. A recent human trial has corroborated the results of the prior animal studies, confirming the potential use of this polymer drug-delivery system.

In addition to aromatic co-monomers, highly hydrophobic aliphatic linear fatty acid dimers (FAD) have also been investigated for developing slow degrading polyanhydrides [68]. The degradation rate of these fatty acid polymers can be further modulated by using non-linear fatty acid dimers [63]. Due to the availability of a wide range of diacid monomers, different types of polyanhydrides with ether, ester and urethane linkages were also developed [69].

3.6. Poly(anhydride-co-imide)

Although polyanhydrides were found to be ideal candidates for drug delivery applications due to their surface eroding properties, the mechanical performance of these polymers were found to be less than optimal for load bearing applications, such as for orthopaedic implants. The Young's modulus for poly[1,6-bis(carboxyphenoxy) hexane] is only 1.3 MPa, which is well below the modulus for human cancellous bone [70]. The search for high strength polyanhydrides with surface eroding properties has led to the development of poly(anhydride-*co*-imides) due to the imide segments in the polymer back bone imparting unusual strength. The poly(anhydride-*co*-imides) were found to under go degradation via the anhydride bonds first, followed by the hydrolysis of the imide bonds [71]. Laurencin et al., have investigated the mechanical performance and biocompatibility of a wide range of poly(anhydride-*co*-imides), such as poly[pyromellitylimidoalanine-*co*-1,6-bis(*p*-carboxyphenoxy) hexane] (PMA ala:CPH) (Fig. 6) as scaffolds for bone tissue engineering applications [72,73]. The osteocompatibility of these polymers were investigated using a rat tibial model. It was shown that the untreated defects healed in 12 days. In comparison, the defects treated with poly(anhydride-*co*-imides) produced endosteal bone growth as early as day 3 and formed bridges of cortical bone around the implanted matrices by day 30 demonstrating the good osteocompatibility of the matrices [73]. The good mechanical performance of these polymers has also been demonstrated. Polymers based on succinic acid trimellitylimidoglycine and trimellitylimidoalanine have compressive strength on the order of 50–60 MPa suggesting their suitability for orthopaedic applications [70].

3.7. Cross-linked polyanhydrides

Another approach investigated to increase the mechanical strength of polyanhydrides is by incorporating acrylic functional groups in the monomeric units to form injectable photocrosslinkable polyanhydrides. Injectable anhydrides can be used for filling irregularly shaped bone defects or for soft tissue repairs that require materials with a liquid or putty-like consistency, which can set and be molded into a desired shape under physiological conditions. Fig. 7 shows the structure of the polymers poly(sebacic acid)(PSA) and poly(1-3-bis(*p*-carboxyphenoxy)propane) (PCPP) and poly(1-6-bis(*p*-carboxy phenxoy)hexane) (PCPH). The hydrolytic degradation products of these polymers are nontoxic and composed of the corresponding diacid molecules and water-soluble linear methacrylic acid molecules. Different types of initiator-accelerator systems and energy sources have been investigated to develop crosslinkable matrices with appropriate thickness for orthopaedic applications. The most effective composition for the photopolymerization of these polymers was found to be 1.0 wt% camphorquinone (CQ) and 1.0 wt% ethyl-4-*N*,*N*-dimethyl aminobenzoate (EDMAB) with 150 mW/cm^2 of blue light. As in the case of polyanhydrides, the mechanical strength and degradation rate of the crosslinked polyanhydrides has been found to depend on the nature of the monomeric units. A compressive strength similar to the lower range of

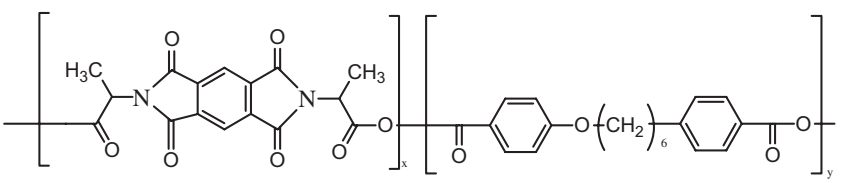


Fig. 6. Structure of poly[pyromellitylimidoalanine-*co*-1,6-bis(*p*-carboxyphenoxy) hexane].

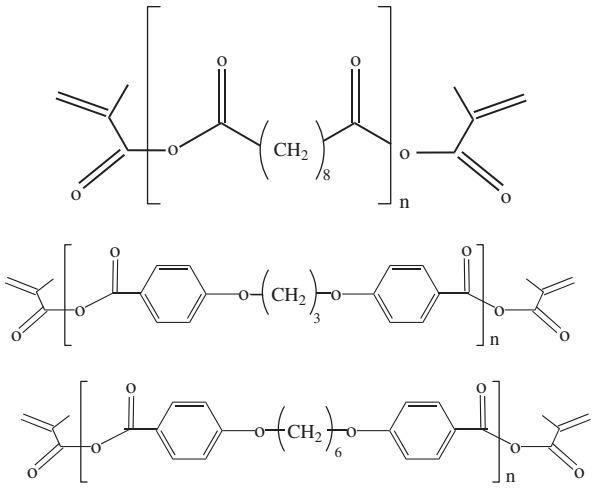


Fig. 7. Structure of photocrosslinked polymers (a) poly(sebacic acid) (PSA), poly(1-3 bis(*p*-carboxyphenoxy)propane) (PCPP) and (c) poly(1-6 bis(*p*-carboxy phenxoy)hexane) (PCPH).

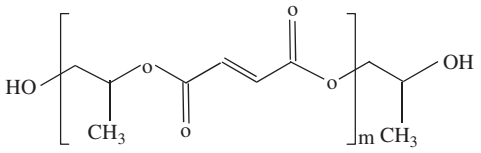


Fig. 8. Structure of polypropylene fumarate.

cancellous bone (30–40 Mpa) has been reported for this class of polymers [75].

3.8. Poly(propylene fumarate)

Another injectable biodegradable high-strength polymeric biomaterial developed for orthopaedic applications is the co-polyester poly(propylene fumarate (PPF) (Fig. 8). Several routes, including the transesterification of fumaric diester, can be used to synthesize linear PPF. These synthetic procedures have been extensively reviewed by Peter et al. [76].

PPF is known to under go bulk erosion via hydrolysis of the ester bonds and the degradation time depends on several parameters, such as molecular weight, type of cross-linker, and cross-linking density. The degradation products are fumaric acid, a naturally occurring molecule found in the tricarboxylic acid cycle and 1,2 -propane diol, a common diluent of drug formulations. The molecular weight of linear PPF has been found to be rather low, while one unique feature of this polymer is the presence of unsaturated fumarate groups on the polymer back bone which can be used to further cross link the polymer to improve the material properties [77].

Several attempts have been made to develop mechanically competent biodegradable systems for orthopaedic applications by cross-linking PPF or by developing composites using ceramic materials. Cross-linked PPF was developed by co-polymerizing with acrylic monomers, such as methyl methacrylate or *N*-vinyl pyrolidone, using different types of polymerization initiators. The cross-linked matrices demonstrated a compressive strength in the order of 1–12 MPa depending on the composition and conditions of polymerization [76]. Composites of PPF with ceramics, such as tricalcium phosphate or calcium sulfate, created high strength matrices (2–30 MPa) suitable for orthopaedic applications [77]. These cross-linked polymer matrices also supported good cell viability and could function as a growth factor delivery system making them promising candidates for bone tissue engineering applications.

3.9. Pseudo poly(amino acid)

Poly(amino acid)s are ubiquitous, naturally-occurring biodegradable polymers; however, their application as a biomaterial has been limited due to immunogenicity and poor mechanical performances. To overcome these limitations, attempts have been made to develop pseudo amino acids composed of amino acids linked by non-amide bonds such as esters, imino carbonates and carbonates. One of the most extensively investigated system is the tyrosine-derived poly(amino acids) using desaminotyrosyl-tyrosine alkyl esters as the building blocks (Fig. 9). Due to the aromatic backbone, these polymers show good engineering properties and therefore could serve as a mechanically-competent, biodegradable polymer system for load bearing biomedical applications.

Tyrosine-derived polycarbonates are a versatile polymer class in which the glass transition temperatures (50–90 °C) and the mechanical properties (strength 50–70 Mpa, stiffness 1–2 Gpa) can be easily tailored by varying the pendant alkyl chain [78]. These polymers have been found to be amorphous, hydrophobic and undergo slow hydrolytic degradation at physiological temperature. The *in vitro* degradation products were found to be desaminotyrosyl-tyrosine and alcohol, *in vivo* the

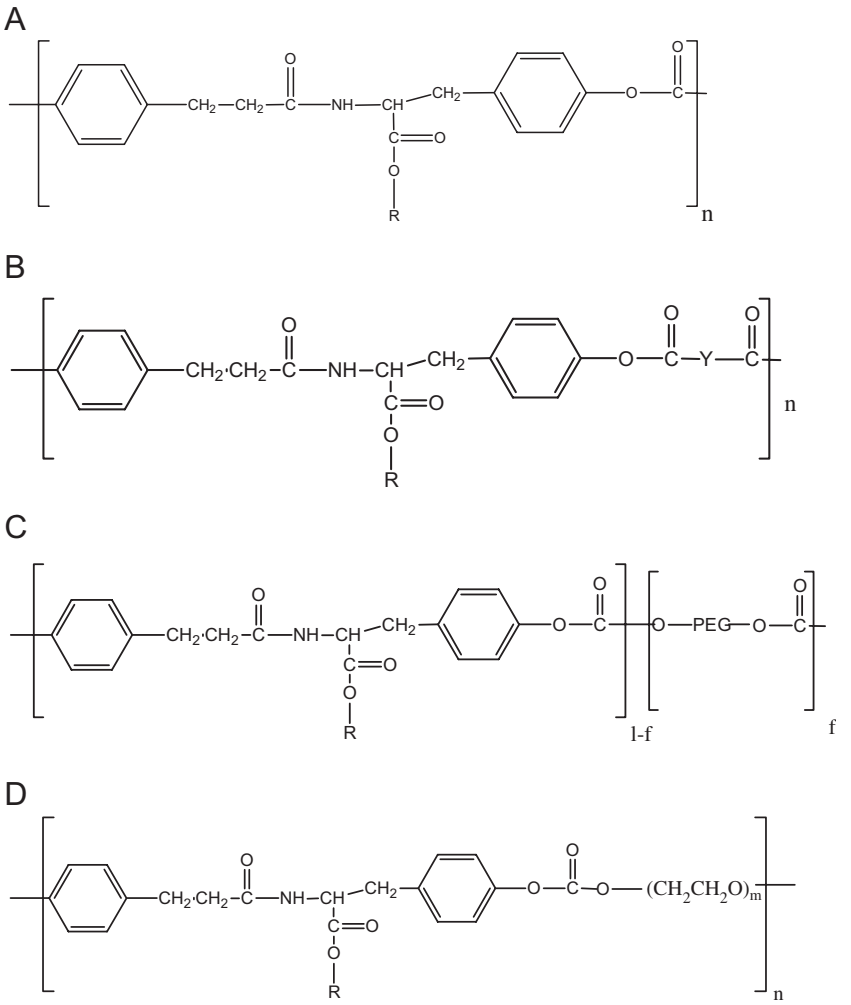


Fig. 9. Chemical structures of (A) tyrosine derived polycarbonates, (B) tyrosine derived polyarylates, (C) tyrosine containing poly(DTR-PEG carbonate) and (D) tyrosine containing poly(DTR-PEG ether).

degradation products undergo further enzymatic degradation to form desaminotyrosine and tyrosine. The good *in vitro* and *in vivo* osteocompatibility and mechanical properties of carbonate polymers make them suitable candidates for developing long-term orthopaedic implants. The carbonate polymers have already been investigated as candidate materials for fracture fixation pins [79].

One significant difference between PLLA and tyrosine-derived carbonates is in their water absorbtivity. The tyrosine-derived polymers do not to take up more than 5% water even at later stages of degradation and are able to maintain their shape for a longer period of time. PLLA on the other hand swell significantly with time. Another unique advantage of tyrosine-derived carbonate is that because of their hydrophobic degradation products, the polymer experiences a mass loss only at the very end of the degradation process. PLLA shows significant mass loss when the molecular weight reaches the threshold value of 20,000. The low acidity of the degradation products of tyrosine-derived carbonate compared to PLLA is another significant advantage. In a study that compared the acidic degradation products of different polymers, it was reported that poly(glycolic acid), poly(lactic acid), poly (DTE adipate) and poly(DTE carbonate) give rise to 15.5, 11.4, 6.4, and 2.6 mEq of acid per gram of the polymer [80].

An unique feature of poly(desaminotyrosyl-tyrosine ethyl ester) is its ability to form high strength fibers by melt extrusion (ultimate tensile strength of

230 Mpa and Young's moduli of 3.1 Gpa) with better mechanical properties than PLLA. After 30 weeks of incubation in water, these fibers retained 87% of the strength, whereas PLLA fibers decreased to 7% of its initial strength after 2 weeks of incubation [81]. Different tyrosine carbonate blend systems are currently under development each having unique cellular responses for use as ideal candidates for tissue engineering applications [82].

Tyrosine-derived polyarylates are soft elastomeric forms of pseudo(amino acids) having faster degradation rates than the carbonates. One unique feature of this class of polymer is the predictability of properties, such as glass transition temperature, hydrophobicity/hydrophilicity, crystallinity which tend to vary with the number of carbon or oxygen atoms in the polymer backbone or pendent chains. This allows for the development of polymers with a wide spectrum of properties from soft and elastomeric to strong materials, as well as from amorphous to liquid crystalline materials [83].

Tyrosine containing poly(DTR-PEG carbonate) and poly(DTR-PEG ether) have also been developed as highly hydrophilic, water-soluble polymers based on tyrosine. These polymers are biocompatible and degradable and have potential applications as drug delivery vehicles and as thromboresistant coatings.

3.10. Poly(alkyl cyanoacrylates)

Poly(alkyl cyanoacrylate)s (PCA) form the major class of biodegradable acrylate polymers used for biomedical applications. Poly(alkyl cyanoacrylates) have so far been investigated as excellent synthetic surgical glue, skin adhesive and an embolic material. Poly(alkyl cyanoacrylates) can also be considered to be one of the first biodegradable polymers used for developing nanoparticles for drug delivery application. Fig. 10 shows the structure of PCA. These are neutral polymers prepared by the anionic polymerization of alkyl cyanoacrylic monomers with a trace amount of moisture as the initiator. The uniqueness of poly(cyano acrylates) is the instability of the carbon–carbon sigma bond on polymer backbone. The hydrolytic sensitivity of the backbone has been attributed to the high inductive activation of methylene hydrogen atoms by the electron withdrawing neighboring groups.

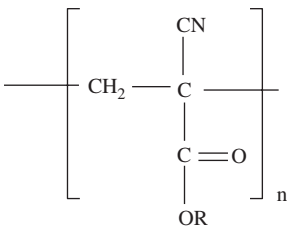


Fig. 10. Structure of poly(alkyl cyano acrylate).

Poly(cyano acrylates) are one of the fastest degrading polymers having degradation times ranging from few hours to few days. The degradation rate for these polymers depends on the length of the alkyl side groups. The lower alkyl derivatives, such as poly(methyl cyano acrylate), degrade within hours in an aqueous environment; however, it leads to toxic degradation products such as cyanoacetic acid and formaldehyde. Most of the research in this area has therefore been concentrated on higher alkyl derivatives, such as octyl and isobutyl cyanoacrylates. Due to the fast polymerization rate, these monomers have also been investigated as tissue adhesives. Dermabond® (2-octyl cyanoacrylate) has been approved by the US FDA as a tissue adhesive for topical skin application. Poly(alkyl cyanocrylates) have also been extensively investigated for use as gene delivery vehicles and are considered to be unique matrices for the delivery of oligodeoxynucleotides (ODN) due to the unique hydrophobic interactions the matrix has with ODN [84].

Extensive research has gone into PCA nanoparticles as drug delivery vehicles following the studies by Couvreur in late 1970s. PCA nanoparticles have several advantages over other polymeric nanoparticles such as easy preparation, high utility size ranges, absence of solvent residues, ability to form stealth nanoparticles and the ability of PCA to absorb or encapsulate a wide range of drug or protein molecules [85]. As such, several PCA based nanoparticles are currently undergoing late stage clinical trials for cancer therapy [86].

3.11. Polyphosphazenes

In addition to organic polymers, several inorganic or inorganic–organic hybrid polymers have also been investigated as potential biodegradable biomaterials. Polyphosphazenes are hybrid polymers with a backbone of alternating phosphorus and nitrogen atoms containing two organic side groups attached to each phosphorus atom. Fig. 11 shows the general structure of polyphosphazenes where R represents a variety of organic or organometallic side groups. Although polyphosphazenes were

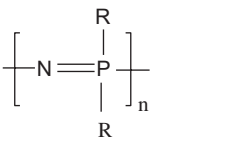
developed during late 1960s by Allcock et al. [87,88], biodegradable polyphosphazenes were developed only within the past two decades by the same group. Biodegradable polyphosphazenes are quite distinct from other biodegradable polymers due to its unprecedented functionality, synthetic flexibility and adaptability for various applications.

The phosphorous nitrogen backbone is hydrolytically stable and forms the backbone of more than 500 different types of polyphosphazenes synthesized so far [87]. However, the incorporation of certain groups, such as amino acid esters, glucosyl, glyceryl, glycolate, lactate and imidazole, has been found to sensitize the polymer backbone to hydrolysis.

The most extensively investigated route for polyphosphazene synthesize is based on the two-step preparative protocol outlined in Scheme I. In this method, a reactive macromolecular intermediate, poly(dichlorophosphazene) (Scheme I; 2) is first produced by the ROP of the cyclic trimer, hexachloro cyclotriphosphazene (Scheme I; 1). The chlorine side units in this polymer are subsequently replaced by any of a broad range of organic side groups [87]. The ROP of 1 is now a well-developed process. Another synthetic route developed for the synthesis of polyphosphazenes with well-controlled structure is the living cationic polymerization process. It involves a catalyzed condensation of the monomer, $(CH_3)_3Si–N=PCl_3$ (Scheme I; 3) with a loss of $(CH_3)_3SiCl$. The living polymerization can take place at room temperature and gives polymers with controllable chain lengths and narrow molecular weight distribution. The "living" character of the polymerization process also allows the preparation of phosphazene-based block co-polymers.

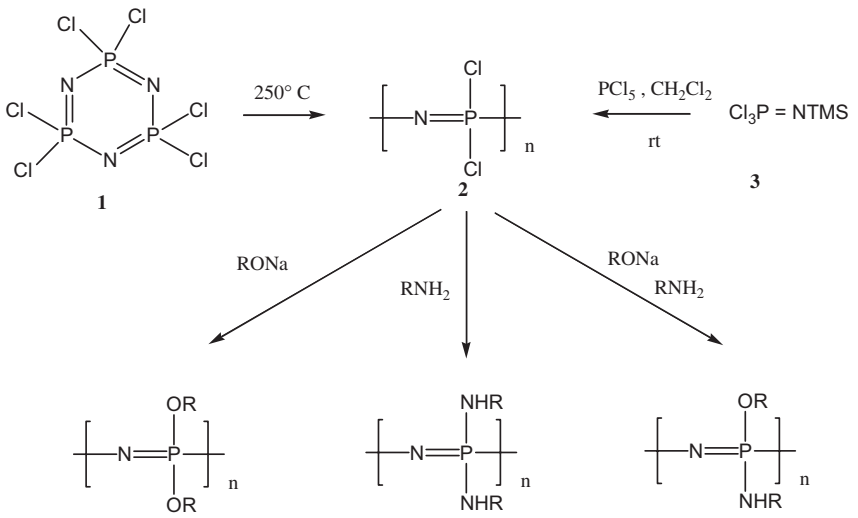
The unique feature of the phosphorous-nitrogen backbone of polyphosphazenes is its unusual flexibility. Therefore, the side groups play a curcial role in determining the properties for these polymers. This allows for the possibility of designing and developing polymers with highly controlled properties such as extent of crystallinity, solubility, appropriate thermal transitions and hydrophobicity/hydrophlicity. In the case of biodegradable polyphosphazenes, the side groups control the rate of degradation for the polymers. Thus, polymers can be designed with appropriate degradation profile ranging from few hours to years by varying the side group chemistry [40].

Among the different classes of degradable polyphosphazenes investigated, poly[(amino acid ester) phosphazenes] have been met with the most success in terms of potential biomedical applications. All of the amino acid ester substituted polyphosphazenes



R = Organic groups,
Organometallic groups

Fig. 11. General structure of polyphosphazene.



Scheme I. Synthesis of polyphosphazene.

were found to be degradable with the rate of degradation varying with the type of amino acid esters used. Among the amino acid esters investigated, polyphosphazenes substituted with glycine ethyl ester shows the fastest degradation [65,66]. Unlike polyesters, the amino acid ester polyphosphazenes undergo degradation to form neutral and non-toxic products such as phosphates, ammonia and the corresponding ester side groups. This unique property of polyphosphazenes has been recently utilized to form self-neutralizing blend systems by combining polyphosphazenes with poly(lactide-*co*-glycolide) [89]. Another unique feature of polyphosphazenes, is that they undergo both surface and bulk erosion making the drug release profile from these matrices significantly different from other polymers. Although polyphosphazenes have not been extensively investigated as drug delivery vehicles, studies so far show the potential of biodegradable polyphosphazenes as drug delivery vehicles due to their excellent biocompatibility, unique functionality, matrix permeability and the ability to control the rate and mode of degradation [88].

The *in vitro* and *in vivo* biocompatibility of biodegradable polyphosphazene have been extensively investigated by Laurencin et al. [40,90–94]. Most of the amino acid ester polyphosphazenes elicited minimal to mild tissue responses when implanted subcutaniously in a rat model. Fig. 12 illustrates the histology showing a minimal tissue response to two different types of amino acid ester polyphosphazenes [90].

Many of the amino acid ester polyphosphazenes have shown excellent osteocompatibility and have been investigated as matrices for bone tissue engineering [95]. Recently a polyphosphazene-self setting calcium phosphate composite cement system has been developed by taking advantages of the favorable interactions between polyphosphazene side groups and calcium phosphate ceramics [96–99]. Due to the flexible backbone, most of the amino acid ester polyphosphazenes are soft elastomeric polymers and have limitations to its use as a biomaterial for load bearing applications.

3.12. Polyphosphoester

Polyphosphoesters form another interesting class of phosphorus containing polymers developed as biomaterials. Polyphosphoesters were developed in 1970s by Penczek and his colleagues [100]. The unique property of the synthetic biodegradable polyphosphoesters is their good biocompatibility and similarity to biomacromolecules, such as nucleic acid.

The polyphosphoesters can be developed by a variety of synthetic routes including ring opening, poly condensation and polyaddition reactions. Several other mechanisms have also been proposed [100,101]. Fig. 13 shows the general structure of polyphosphoester, where R and R' can be varied to develop polymers with a wide range of physicochemical properties as in the case of polyphosphazenes. The term polyphosphoesters is commonly used to characterize several classes of polymers that have phosphoester bonds in their backbone including polyphosphites (Fig. 13, $R' = H$), polyphosphonates (Fig. 13 $R' =$ alkyl/aryl group) and polyphosphates (Fig. 13 $R' =$ aryloxy/alkoxy group).

Polyphosphoesters degrade under physiological conditions due to the hydrolytic and enzymatic cleavage of the phosphate bonds in the backbone. The ultimate breakdown products of these polymers are phosphate, alcohol and diols. Varying either the

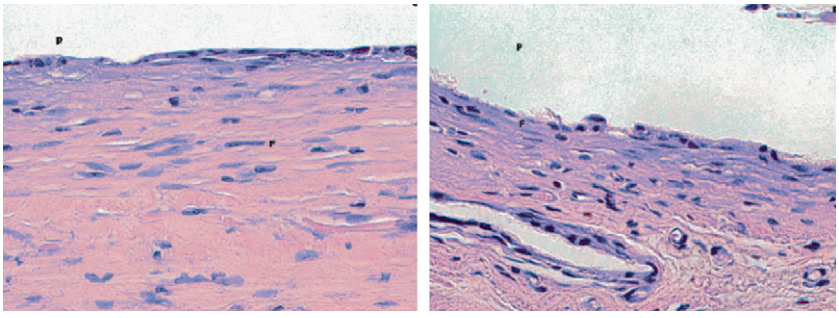


Fig. 12. Micrographs showing rat subcutaneous tissue response to poly[(ethyl alanato)$_{50}$(methyl phenoxy)$_{50}$]phosphazene and poly(ethyl alanato)$_{50}$ (phenylphenoxy)$_{50}$]phosphazene after 12 weeks of implantation. P—polymer; N—neutrophils; F—fibrous tissue ($\times 40$). Reprinted from Ref. [90] with permission from Wiley Interscience.

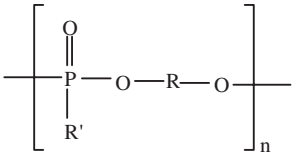


Fig. 13. Structure of polyphosphoesters.

backbone or side chain organic components can readily alter the physico-chemical properties of these polymers. The pentavalency of the phosphorous atoms, as in the case of polyphosphazenes, allows for chemical linkages to be made between drugs or protein molecules and the polymer backbone, thereby enabling the development of novel polymer pro-drugs. Most of these polymers demonstrate good *in vitro* cytocompatibility and good *in vivo* tissue compatibility as evidenced by low fibrous tissue encapsulation of the implanted polymer.

The synthetic flexibility of polyphosphoesters allows for the development of co-polymers with other monomers, such as DL-lactide to form poly(lactide-*co*-ethyl phosphate). The percentage of DL-lactide in the co-polymer can be controlled by varying the ratio between the monomers and the propylene glycol initiator. This is done during the synthesis of the lactide prepolymer prior to the chain being extended by ethyl-phosphorodichloridate [102]. The glass transition temperature of the co-polymers was found to be inversely proportional to the weight percentage of the phosphoester segment. The co-polymers were also found to be more hydrophilic due to the presence of ethylphosphate groups in the backbone. These copolymers show a two phase degradation profile compared to polylactide, which has been attributed to the hydrolysis of the phosphates versus lactide functional groups. The neutral co-polymer has been investigated as a potential candidate for drug delivery applications. Poly(lactide-*co*-ethyl phosphate) demonstrated a near zero-order release profile of chemotherapeautic drugs, such as paclitaxel. The sustained release formulation PACLIMER® microspheres contains 10% (w/w) paclitaxel and has undergone Phase I human clinical trials for the treatment of ovarian and lung cancer. Results demonstrated the ability of this delivery system to deliver chemotherapeutic agents in a sustained manner, while maintaining appropriate biodegradation and biocompatibility. This polymer is also currently under investigation as a scaffold for tissue engineering applications.

Water-soluble cationic polyphosphoesters including polyphosphates and polyphosphoramidates have been investigated as gene carriers [103]. These polymers were found to bind plasmid DNA, form complexes or nanoparticles and efficiently trasfect many cell lines. The cytocompatibility of these cationic polymers have also been demonstrated in various cell cultures. These polymers undergo hydrolytic degradation at 37 °C due to the hydrolytic cleavage of the phosphoester bonds in the backbone as well as the side chains. Due to the chemical reactivity of the polymer, the conjugation of specific ligands, endolysolytic elements or nuclear localization signals to the polymer is possible to enhance their transfectin efficiency. By incorporating cross-linkable moieties along the side chain of water-soluble polyphosphoesters biodegradable crosslinkable structures can be developed as injectable tissue engineering scaffolds [104].

4. Enzymatically degradable polymers as biomaterials

4.1. Proteins and Poly(amino acids)

Proteins, the major structural components of many tissues are essentially amino acid polymers arranged in a three-dimensional folded structure and are one of the most important class of biomolecules identified. Being a major component of the natural tissues, proteins and other amino acid-derived polymers have been a preferred biomaterial for sutures, haemostatic agents, scaffolds for tissue engineering and drug delivery vehicles. Furthermore, protein based biomaterials are known to under go naturally-controlled degradation processes [105].

The human body is capable of synthesizing a wide range of proteins in which the precursor molecules pass through four major stages in becoming functional proteins. The first step involves the formation of the primary structure where, a linear sequence of various amino acids is held together by peptide bonds. The constituent amino acids then participate in hydrogen bonding to form the secondary structure of protein. The linear primary structure arranges itself in the most stable structures—an α-helices or β-pleated sheets. These secondary structures then join together to form three-dimensional tertiary structures which in turn interact with other protein chains to form the more

refined three-dimensional quaternary structure of a multi-unit protein [106].

4.1.1. Collagen

Collagen is the most abundant protein present in the human body being the major component of skin and other musculoskeletal tissues. Collagen is a rod-type polymer nearly 300 nm long with a molecular weight of 300,000. There have been more than twenty two different types of collagen identified so far in the human body, with the most common being Type I–IV. Type I collagen is the single most abundant protein present in mammals and is the most thoroughly studied protein. The Type I collagen is composed of three polypeptide subunits with similar amino acid compositions. Each polypeptide is composed of about 1050 amino acids, containing approximately 33% glycine, 25% proline and 25% hydroxyproline with a relative abundance of lysine.

The subunit chains of collagen are synthesized from free amino acids in the body and undergo transcription, translation and post-translation modification processes in appropriate cells such as fibroblasts and osteoblasts. The primary structure of these proteins is composed of repeating triplets of $(\text{Glycine-X-Y})_n$, where X and Y are often proline and hydroxyproline. The repeating sequence is responsible for the helical structure and the inherent and predictable mechanical strength of collagen [107]. The glycine content accounts for the flexibility of the collagen chain—increased glycine gives rise to more flexibility. Ten of these polypeptide chains form the α-chain of collagen which arranges to form the right handed helical secondary structure. A left handed, triple helical tertiary collagen structure is formed from the arrangement of three secondary structures. The smallest repeating units (glycine molecules) have been found to cluster towards the inside of the triple helix [108]. The procollagen molecules are secreted into the extracellular space where they spontaneously self-assemble to form higher order structures, sometimes followed by further modifications, such as cross-linking. The formed fibrils are oriented differently in different types of tissues to give them the appropriate mechanical strength.

Collagen undergoes enzymatic degradation within the body via enzymes, such as collagenases and metalloproteinases, to yield the corresponding amino acids. Due to their enzymatic degradability, unique physico-chemical, mechanical and biological properties collagen has been extensively investigated for biomedical applications. Collagen is mostly soluble in acidic aqueous solutions and can be processed into different forms such as sheets, tubes, sponges, foams, nanofibrous matrices, powders, fleeces, injectable viscous solutions and dispersions. Studies have also shown that the degradation rate of collagen used for biomedical applications can be significantly altered by enzymatic pre-treatment or cross-linking using various cross-linking agents.

Collagen is one of the primary initiators of the coagulation cascade and its high thrombogenicity has led to its application as a haemostatic agent. Several collagen-based hemostats are currently on the market or undergoing clinical trials for multiple surgical indications. Some of these include sealant consisting of bovine collagen and bovine thrombin (Sulzer-Spine® Tech) used for cardiovascular and spinal surgical procedures, CoStasis® Surgical Hemostat which is composed of bovine microfibrillar collagen, bovine thrombin combined with autologous plasma, and Floseal®, a high viscosity gel haemostatic agent composed of collagen-derived particles and tropical bovine-derived thrombin.

Since collagen forms the major component of the extracellular matrix and serves as a natural substrate for cell attachment, proliferation and differentiation, renewed interest in collagen as an ideal matrix material for tissue engineering and wound dressing application has occurred. Promogran®, a novel spongy collagen matrix containing oxidized cellulose has been recently introduced in US and European market for treating exuding diabetic and ulcer wounds [109]. An FDA approved bilayer skin substitute (Integra® Dermal Regeneration Template), currently in the market for full thickness or deep partial thickness thermal injury, is composed of a dermal layer of crosslinked bovine collagen and glycosaminoglycan and an epidermal layer of polysiloxane [110,111]. Other FDA approved collagen-based wound dressings are Biobrane® and Alloderm®, which are, acellular collagen matrices obtained from chemically processed human cadavers. In addition to these acellular collagen-based products, several bioengineered skin equivalents have also been commercially developed. TransCyte® consists of porcine, dermal collagen-coated polymer substrates seeded with allogenic human keratinocytes which deposit extracellular matrix components. Orcel® and Apligraf® are other FDA approved collagen-based bilayer dressings seeded with live human keratinocytes and

fibroblasts for the treatment of chronic ulcers. Other collagen-based dressings have been recently reviewed by Purna and Babu [112].

Due to the high reactivity of collagen it can be cross-linked by a variety of cross-linking agents such as difunctional or multifunctional aldehydes, carbodiimides, hexamethylene-diisocyanate, polyepoxy compounds and succinimidyl ester polyethylene glycol. Cross-linking can also occur by thermal or high-energy irradiation, as well as by chemical modification, such as succinylated collagen to form collagen gels for use as carriers for drug delivery and as scaffolds for tissue engineering. Furthermore, the extent of drug release from these collagen matrices can be controlled by varying the physical properties of the gel such as porosity, density and degradation rate.

Collagen has been extensively investigated for the localized delivery of low molecular weight drugs including antibiotics. Several collagen-based gentamicin delivery vehicles are currently on the market world-wide (Sulmycin®-Implant, Collatamp®-G). This delivery system shows a prolonged local delivery of antibiotics with very low systemic exposure. Recently, another prolonged antibiotic collagen delivery system (Septocoll®) has been approved to prevent infection of collagen hemostatic sponge by incorporating two gentamicin salts having different solubilities [113]. Several composite systems of collagen and synthetic polymers are also currently under investigation as drug delivery devices [114].

Cross-linked absorbable collagen sponges are also used as clinical trials as protein carrier vehicles. Bioactive proteins, such as recombinant human bone morphogenic protein (rhBMP-2), was incorporated in collagen matrices to achieve sustained release of the protein due to favorable interactions of the collagen matrix with the protein [115]. This combination product is recently approved by the US FDA to be used in conjunction with a titanium interbody spine fusion cage for anterior lumbar spinal fusion (InFUSE® Bone graft/LT-CAGE® Lumbar Tapered Fusion Device) and is approved in Europe (InductOs®) for the treatment of acute tibia fractures in adults.

In addition to its use as a protein delivery vehicle, collagen has also been investigated for gene and plasmid DNA delivery [116]. Due to the injectability of a collagen matrix, collagen has been shown to retain the gene vector/plasmid DNA and protect them from immunological or enzymatic reactions of the body.

Absorbable collagen sponges, due to their excellent biocompatability, biodegradability and porous structure have been extensively investigated as a scaffolding material for accelerated tissue regeneration. Duragen® is a suture-free, three-dimensional-collagen matrix graft developed for spinal dural repair and regeneration is currently undergoing late stage clinical trial [117].

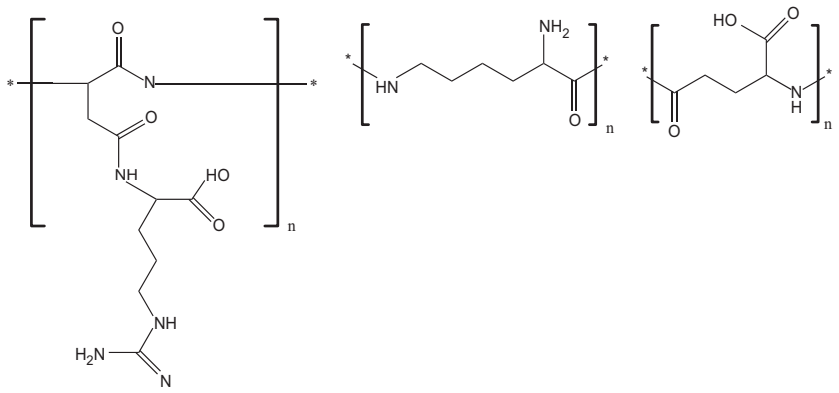
Similarly, a composite of fibrillar collagen, hydroxyapatite and tricalcium phosphate (Collagraft®) has been FDA approved for use as a biodegradable synthetic bone graft substitute. Several forms of collagen are currently being investigated as scaffolds for cardiovascular, musculoskeletal and nervous tissue engineering [118].

The major sources of collagen currently used for biomedical applications are bovine or porcine skin or bovine or equine Achilles tendons. One disadvantage of these collagen-based biomaterials, which is a limiting factor for the wide-spread clinical application is their mild immunogenicity imparted by the composition of the terminal region and the antigenic sites in the central helix. The immune response has been found to vary depending on the species from which collagen has been isolated, processing techniques and the site of implantation. Other concerns include, the high cost of pure collagen, variable physico-chemical and degradation properties and the risk of infectious diseases transmission due to the allogenic or xenogenic origin of the material. Several recombinant systems are currently under development to produce human sequence collagen to overcome some of the limitations of using animal-derived collagen [119].

4.1.2. Natural poly(amino acids)

Natural poly(amino acids) are biodegradable ionic polymers that differ from proteins in certain aspects. Natural poly(amino acids), such as cyanophycin, poly(ε-L-lysine) and poly-γ-glutamic acid are mainly composed of one type of amino acid. These molecules exhibit polydispersity and in addition to α-amide linkages, they exhibit other types of amide linkages that involve β- and γ-carboxylic groups as well as ε-amino groups [120]. Scheme II shows the structure of cyanophycin, poly(ε-L-lysine) and poly-γ-glutamic acid.

Poly-γ-glutamic acid (γ-PGA) is an anionic, water-soluble biodegradable homo-polyamide produced by microbial fermentation and is composed of D- and L-glutamic acid units connected by amide



Scheme II. Structure of cyanophycin, poly((ε-L-lysine), poly-γ-glutamic acid.

linkages between α-amino and γ-carboxylic acid groups. This biodegradable polymer was first isolated in 1937 by autoclaving capsules of *Bacillus anthracis*. [121]. Later, it was discovered that several other *Bacillus* species were capable of secreting the polymer into culture growth medium as well as nematocysts of the eukaryotic organism Hydra (*Hydrozoa*, *Cnidaria*). [122,123]. An investigation of the polymer composition revealed it to be a co-polymer with different proportions of enantiomeric L- and D-glutamic acid [124].

Several modified forms of γ-PGA has been developed so far as drug delivery vehicles, tissue engineering scaffolds and as thermosensitive polymers. Poly(-γ-glutamic acid) benzyl ester (γ-PBG) was developed by Kishida et al. as a carrier vehicle for 5-fluorouracil. This polymer degrades very slowly in phosphate buffer solution (pH 7.4) and shows a diffusion-controlled release pattern that is pH dependent [125].

The high functionality of γ-PGA makes it a promising material for developing bioactive scaffolds for tissue engineering application. Matsusaki et al. demonstrated the feasibility of developing bioactive fibroblast growth factor-2 coupled biodegradable substrates using poly(-γ-glutamic acid)-sulfonate (γ-PGA-S) polymer. The modified polymer has several advantages over natural sulfonated polymers (e.g., heparin), such as the ability to control the content of sulfonate group, low anticoagulant activity and the ability to enhance FGF-2 activity [126]. Thermosensitive polymers have been known to exhibit unique changes in their hydration properties following temperature changes and are considered to be nano-engineered intelligent materials for biomedical applications. Shimokuri et al. [127], developed a thermosensitive polymer by controlled propylation of poly(-γ-glutamic acid). Their studies showed that at appropriate levels of propyl esterification, the polymer could exhibit a hydrophobic-hydrophilic balance suitable for thermosensitivity.

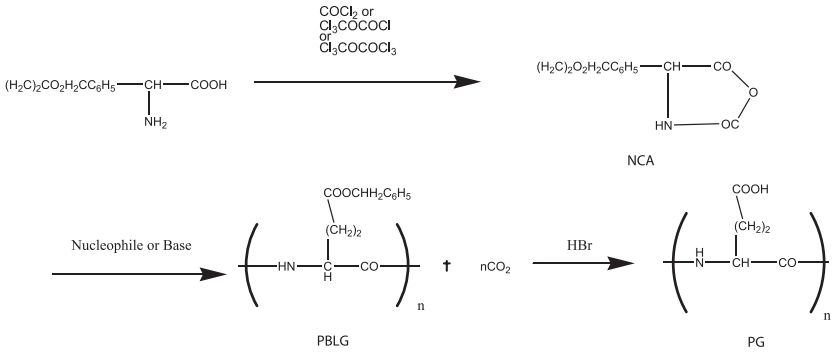
Being a natural polymer, γ-PGA is an ideal biomaterial; however, due to its limited availability, not many studies have been performed so far.

Similar to to γ-PGA, poly L-lysine is of bacterial origin and is currently being investigated as scaffold material for tissue engineering and as drug delivery vehicles due to its ability to form biocompatible hydrogels [128]. Poly(L-lysine) is known to have antibacterial, antiviral and antitumour activity and is considered to be a potential candidate for developing drug carrier vehicles. The cytotoxicity of the polymer due to the very high positive charge limits its applications however.

Cyanophycin, is a comb-like polypeptide isolated from cyanobacteria that contains α-amino-α-carboxy-linked L-aspartic acid residues representing the poly(α-L-aspartic acid) backbone and L-arginine residues bound to the β-carboxylic groups of aspartic acids making it a highly polydisperse polymer [129]. However, studies on the applications of cyanophycin as a biomaterial have been limited.

4.1.3. Synthetic poly(amino acids)

4.1.3.1. Poly (L-glutamic acid). Poly(L-glutamic acid) (L-PGA) is structurally different from γPGA and is composed of naturally occurring L-glutamic acid residues linked together through amide bonds. Several synthetic routes have been investigated for the synthesis of L-PGA; however, the triethylamine initiated polymerization of the *N*-carboxyanhydride (NCA) of γ-benzyl-L-glutamate is the most widely



Scheme III. Synthesis of poly(L-glutamic acid).

used route [130]. Studies on developing a biosynthetic route to form monodisperse L-PGA have also been performed by expressing artificial genes encoding the polymer in bacterial strains [131]. In addition, novel synthetic strategies for developing L-PGA-based polymers with unique architectures, such as star polymers and polymers with varying compositions (e.g., di and multiblock polymers) are being developed that could provide interesting physical and biological properties [130]. Scheme III shows the synthesis of L-PGA.

Poly(L-glutamic acid) has been found to be highly susceptible to degradation by lysosomal enzymes. The degradation product is monomeric L-glutamic acid, which makes them ideal candidates as biodegradable biomaterials. A biodistribution study demonstrated that at a molecular weight of 11,000, the polymer can be largely recovered in the kidneys and urine with minimal retention in other tissues [130]. Also, several *in vivo* studies have been performed that demonstrate the good biocompatibility and non-immunogenicity of L-PGA [130].

Poly L-glutamic acid has several unique properties that make them attractive candidates as polymeric biomaterials. The polymer is highly charged at physiological pH and has been identified as a unique gene/plasmid delivery vehicle. A recent study using a rodent model has shown that sodium poly-L-glutamate enhanced the expression of the reporter gene SEAP up to eight-folds after an intra-muscular injection when compared to the plasmid in saline. Using quantitative PCR analysis of DNA extracted from muscles at various time points, the authors have shown that the amount of plasmid retained was approximately three-fold higher for plasmid formulated with poly-L-glutamate compared to plasmids in saline after electrophoration-mediated DNA delivery [132].

The α-carboxylate side chains of L-PGA are highly reactive and can be chemically modified to introduce various bioactive ligands or to modulate the physical properties of the polymer.

L-PGA has also been extensively investigated for developing polymeric drugs by conjugating anticancer drugs to the polymer backbone. The conjugation has been shown to significantly increase the aqueous solubility, plasma distribution time and tumor distribution of the drugs [130,133]. The high functionality of L-PGA also enabled the development of biodegradable MRI contrast agents [134].

Additionally, L-PGA has been investigated as an attractive biodegradable biological adhesive and hemostat, by chemically cross-linking gelatin [135]. L-PGA based adhesives demonstrated better soft tissue binding and hemostatic properties compared to fibrin glue in studies using animal models. Another promising bioadhesive is composed of porcine collagen and L-PGA and has been found to be superior to fibrin glue in sealing air leakage from the lungs [136].

4.1.3.2. Poly(aspartic acid). Poly(aspartic acid) (PAA) is synthesized from aspartic acid by thermal polymerization [137]. PAA is a highly water-soluble ionic polymer with a carboxylate content much higher that poly(glutamic acid). Fig. 14 shows the structure of aspartic acid.

Polyaspartic acid has also been found to undergo biodegradation by lysosomal enzymes. Several block copolymers with aspartic acid and other synthetic biodegradable polymeric moieties have been developed to form core forming micellar nanostructures for use as smart drug delivery vehicles. Many of these systems are currently undergoing late stage clinical trials [138]. Due to the polymer's high functionality,

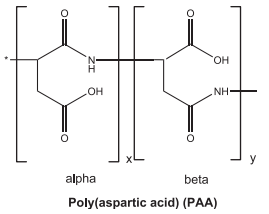


Fig. 14. Structure of poly(aspartic acid).

several chemically modified forms of PAA are also being considered as potential biomaterials. α,β-poly(*N*-2-hydroxyethyl)-D,L aspartamide (PHEA) is a synthetic water-soluble and biocompatible polymer extensively investigated as a plasma expander. This polymer was developed by simple aminolysis with an ethanolamine of a polysuccinimide (PSI). This polymer can also be converted into a hydrogel by high-energy radiations and is currently being investigated for various biomedical applications [139].

4.1.4. Elastin

Elastin is a major protein component of vascular and lung tissue and is mainly responsible for the unusual elastic properties of these tissues. Elastin is a highly cross-linked insoluble polymer composed of a number of covalently bonded tropoelastin molecules. The tropoelastin molecules are produced intracellularly by smooth muscle cells and fibroblasts and are cross-linked extracellularly to form a secondary structure with β-turns [140]. The tropoelastin is composed of several repeating sequences of the pentapeptide VPGVG, the hexapeptide APGVGV, the nonapeptide VPGFGVGAG and the tetrapeptide VPGG. Among these, the pentapeptide VPGVG recurs up to 50 times in a single molecule. *In vivo* biocompatibility studies have shown that elastin elicit immune response to the same extent as collagen implants. This property, along with the insolubility of native elastin limits its biomedical applications [140]. Elastin shows minimal interaction with platelets and hence has been evaluated as biological coatings for synthetic vascular grafts [141]. To overcome the limitation of insolubility, synthetic elastin has been developed from recombinant human tropoelastin [142]. The tropoelastin solution can be transferred to appropriate molds and allowed to coaservate and cross-link at 37 °C. The formed matrices were found to have good mechanical and biological properties making them promising elastic biomaterials for appropriate applications [140].

Another interesting property of elastic and tropelastin is their ability to undergo folding when the temperature is increased above 25 °C. This is due to their transition from a disordered form to an ordered form at higher temperature called inverse temperature transition (ITT). Due to the unique thermal transition properties of tropelastin and its synthetic analogs, they have been extensively investigated as a smart, injectable drug delivery systems [140].

4.1.5. Elastin-like peptides

Elastin-like polypeptides (ELP) are artificial polypeptides composed of the pentapeptide repeats (VPGXG) of human topoelastin except the fourth amino acid. The X in ELP stands for a guest residue that can be any amino acid except proline. The main properties of ELP are derived from the naturally occuring protein, elastin. ELPs have been found to have excellent biocompatibility, non-immunogenic properties and degradation products composed of natural amino acids that are non-toxic. Similar to topocollagen, ELPs also exhibit a reversible ITT. ELPs can also respond to other stimuli such as pH, ionic strength, and light by the incorporation of appropriate guest residues in the molecule at the fourth position [143]. Initially, the monomers, oligomers and high polymers of these molecules were chemically synthesized. However, with the advancements in molecular biology these molecules can be bioproduced using genetic engineering technique. ELPs can be recombinantly synthesized as monodisperse polymers in *E. coli* by the over-expression of a synthetic gene. Due to its injectability and phase transition under mild conditions, ELP has been extensively investigated as a drug carrier vehicle [144]. ELPs are also currently being investigated as potential biomaterials for cartilage tissue engineering. The shear modulus of cross-linked ELP was found to be similar to normal cartilage and the dynamic shear modulus of the gel increased from 0.28 to 1.7 kPa after seeding with chondrocytes for 4 weeks in culture. This indicates the feasibility of remodeling ELP matrices by the deposition of functional cartilage extracellular matrix components [145]. Also, due to the synthetic versatility of ELP, tailored substrates can be developed for engineering various tissues by incorporating specific cell binding epitopes in ELPs [146]. Thus, the incorporation of RGD peptide into an ELP has significantly enhanced cell adhesion and spreading on ELP hydrogel matrices.

4.1.6. Albumin

Albumin is the most abundant protein in human blood plasma accounting to almost 50% of total plasma mass. Albumin is a water soluble-protein with a molecular weight of 66 kDa. The primary function of albumin is to carry hydrophobic fatty acid molecules around the blood stream and maintain blood pH. The preproalbumins are synthesized in the liver and undergo further processing before getting released into the circulatory system. The composition of albumin is characterized by a low content of tryptophan and methionine and a high content of cystine and charged amino acids, such as aspartic and glutamic acids, lysine and arginine. Studies have shown that almost all tissues in human body have the ability to degrade albumin, making it a highly preferred degradable biopolymer for medical applications [147]. Due to its solubility and the presence of functional groups along the polymer chain, albumin can be easily processed into various shapes and forms such as membranes, microspheres, nanofibers and nanospheres. Due to its excellent blood compatibility, albumin has been extensively investigated as a carrier vehicle for intravenous drug/gene delivery [148]. Albumin has also been investigated as coating materials for cardiovascular devices [149]. Albumin-based surgical adhesives have also been approved by the FDA for reapproximating the layers of large vessels, such as aorta, femoral and carotid arteries (CryoLife Inc.) and are composed of bovine serum albumin, gelatin and glutaraldehyde.

4.1.7. Fibrin

Fibrin is a biopolymer similar to collagen that is involved in the natural blood clotting process. Fibrin is derived from fibrinogen, which is a 360 kDa protein composed of three pairs of polypeptide chains. The structure can be divided into three major sections consisting of a central domain composed of fibrinopeptide E with two pairs of fibrinopeptide A and B molecules and two terminal domains of fibrinopeptide D. In the presence of the enzyme thrombin, spontaneous fibrillogenesis occurs due the cleavage of fibrinopeptide A and B to form a linear fibril. These fibrils undergo lateral association to form fibers of varying diameters ranging from 10 to 200 nm depending on the environmental conditions. The fibrin clot, once formed, can undergo degradation called fibrinolysis in the body initiated by a complex cascade of enzymes present in the human body [150].

Fibrin is one of the earliest biopolymers used as biomaterials. This is due to the excellent biocompatibility, biodegradability, injectability and the presence of several extracellular matrix proteins, such as fibronectin, that favorably affects cell adhesion and proliferation. One of the first products developed from fibrin was a fibrin sealant. Various fibrin sealant products are being used clinically worldwide for hemostasis and tissue sealing applications in various surgical procedures. Due to its injectability and biodegradability, fibrin has also been investigated as a carrier vehicle for bioactive molecules. It has been found that proteins interact differently with fibrin clots, with certain growth factors demonstrating a strong interaction with fibrin matrices [151]. Several cross-linking techniques are also currently under investigation to control the release profile of bioactive molecules from the fibrin matrix. Fibrin matrices have also been found to be excellent cell carrier vehicles. Bioseed® is a fibrin-based product obtained by mixing keratinocytes with fibrin and is used to treat chronic wounds. A unique feature of fibrin-based cell carriers is that the matrix properties can be optimized for each different cell type [152].

4.2. Polysaccharides

Polysaccharides are macromolecules formed from many monosaccharide units joined together by glycosidic linkages. Polysaccharides are gaining renewed interest as biomaterials due to the growing body of literature pointing to their unique biological functions ranging from cell signaling to immune recognition. This combined with new synthetic routes currently available to modify polysaccharides or synthesize oligosaccharide moieties, biodegradability and ability to fabricate appropriate structures, make them one of the most important and extensively investigated natural biomaterials.

4.2.1. Polysaccharides of human origin

4.2.1.1. Hyaluronic acid. Hyaluronic acid (HA) was first isolated in 1934 from the vitreous humor of the eye by Meyer and Palmer [153]. This biopolymer has steadily raised interest as a unique biomaterial since its discovery.

Hyaluronic acid is a member of the glycosaminoglycan family, which are linear polysaccharides consisting of alternating units of *N*-acetyl-D-glucosamine and glucuronic acid, and are found in virtually every tissue in vertebrates. HA can be

considered to be the largest glycosaminoglycan having molecular weights up to several millions. Unlike other members of the glycosaminoglycan family present in the human body, such as chondroitin sulfate, dermatan sulfate, keratin sulfate and heparin sulfate, HA is not covalently bond to proteins. HA is water-soluble and forms highly viscous solutions with unique viscoelastic properties. HA can form three-dimensional structures in solution with extensive intramolecular hydrogen bonding. It has been reported to be present at high concentrations in synovial fluid and vitreous humor and significantly contributes to the viscoelastic properties of these tissues. Furthermore, HA plays an important structural role in a variety of tissues including articular cartilage, the nucleus pulposus, skin, the cervis, and the glycocalyx of endothelial cells. Fig. 15 shows the structure of HA.

It has been reported that half of the body's total HA content is present in the skin and the half-life of this polymer varies from a few minutes to weeks depending upon the tissue type.

Studies have elucidated that within the cells, HA is synthesized on the cytosal surface of the plasma membrane under the direction of three glycosyl transferases: hyaluronan synthase-1 (Has-1, Has-2 and Has-3 [154]. Among these, Has-2 is the principal enzyme responsible for HA synthesis during embroyogenesis; however, specific roles played by Has1 and Has3 are not yet clear [155].

The traditional sources for HA isolations are rooster combs and bovine vitreous humor. However, using bioprocess methods for HA synthesis is gaining interest and several bacterial fermentation processes are currently under development.

HA can undergo degradation within the body by free radicals, such as nitric oxide and MMPs found in the extracellular matrix, followed by endocytosis. It can also undergo digestion by lysosomal enzymes to form mono and disaccharides, which can be further converted into ammonia, carbon dioxide and water via the Krebs cycle [156].

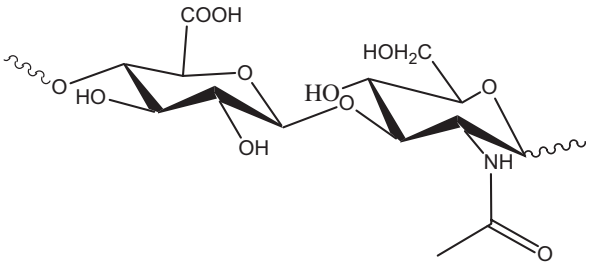


Fig. 15. Structure of HA.

In earlier studies, HA was considered to be a passive structural component of connective tissues; however, later studies revealed it to be actively involved in many biological processes such as modulating cell migration and differentiation during embryogenesis, regulating extra cellular matrix organization and metabolism, as well as playing important roles in metastasis, wound healing and inflammation [157].

Since HA is produced by cells during early wound healing, this polymer has been extensively investigated for wound dressing applications. Other unique properties of HA include its ability to promote angiogenesis, to modulate wound site inflammation by acting as a free radical scavenger, and to be recognized by receptors on a variety of cells associated with tissue repair [154]. Due to the high functionality and charge density of HA, it can be cross-linked by a variety of physical and chemical methods [158]. Modified HA, such as esterified derivatives like ethyl/benzyl esters (HYAFF®) and cross-linked hyaluronic acid gels have been extensively investigated for wound dressing application. These chemical modifications have also been found to significantly reduce the degradation rate of the polymer.

The benzyl esters (HYAFF®) undergo hydrolytic degradation via ester bonds in the absence of enzymatic activity with degradation times varying from 1–2 weeks to 2–3 months, depending on the degree of esterification. The de-esterified polymers are more hydrated and soluble and resemble native HA [159,160].

HA also plays an important role in tissue repair by promoting mesenchymal and epithelial cell migration and differentiation, thereby enhancing collagen deposition and angiogenesis. This property, in addition to its immunoneutrality makes HA an ideal biomaterial for tissue engineering and drug delivery applications. Its aqueous solubility allows HA to be fabricated into different types of porous and three-dimensional structures for these applications. Thus a viscous formulation of HA containing fibroblast growth factor (OSSIGEL®) is undergoing late stage clinical trial as a synthetic bone graft to accelerate bone fracture healing. Similarly HYAFF® 11 is currently been used as a carrier vehicle for a variety of growth factors and morphogens as well as bone marrow stromal cells. In a study that compared HYAFF® 11 with an absorbable

collagen sponge as a carrier vehicle for osteoinductive protein, recombinant human bone morphogenetic protein-2 (rhBMP-2) revealed a better healing response with HYAFF®11 carrier than collagen [161]. HA-based materials have also replaced collagen-based materials as injectable soft tissue fillers [162]. High molecular weight viscous HA solutions (AMVISC® and AMVISC® PLUS) are being used as a vitreous humor substitute as well as to protect the sensitive eye tissue during cataract extraction, corneal transplantation and glaucoma surgery. Viscous HA solutions (SYNVISC®, ORTHOVISC®) are clinically used as a synovial fluid substitute to relieve pain and improve join mobility in osteoarthritis patients [163]. A recent animal study demonstrated the advantages of exogenous HA in treating vascular diseases [164].

4.2.1.2. Chondroitin sulfate. Studies have shown that an important phase of wound healing involves the secretion of glycosaminoglycans by fibroblast cells to form a hydrophilic matrix suitable for remodeling while healing. A recent study using rat embryonic fibroblast cells showed that the majority of the glycosaminoglycan chains synthesized were chondroitin sulfate, suggesting the significance of this natural polymer for use in biomedical applications [165]. Fig. 16 shows the structure of chondrotin sulfate.

Chondrotin sulfate is the major component of aggrecan, the most abundant glycosaminoglycan found in the proteoglycans of articular cartilage. Studies have shown that CS can stimulate the metabolic response of cartilage tissue and has anti-inflammatory properties [166]. It is also involved in intracellular signaling, cell recognition and the connection of extracellular matrix components to cell-surface glycoproteins [167].

Chondrotin sulfate consists of a repeating unit formed by *N*-acetyl galactosamine (GalNAc) and glucuronic acid (GlcA) modified by sulfation, where the position of sulfation varies with the type of CS [168]. In mammals chondroitin sulfate disaccharides have been found to be monosulfated in the 4th or 6th position of the GalNAc residue or disulfated in the 2nd and 6th position of the GlcA and GalNAc or in the 4 and 6 positions of GalNAc residue [169]. The enzymes responsible for these modifications are chondroitin sulfotransferases.

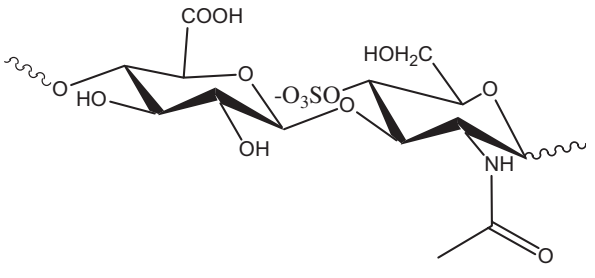


Fig. 16. Structure of chondroton sulfate.

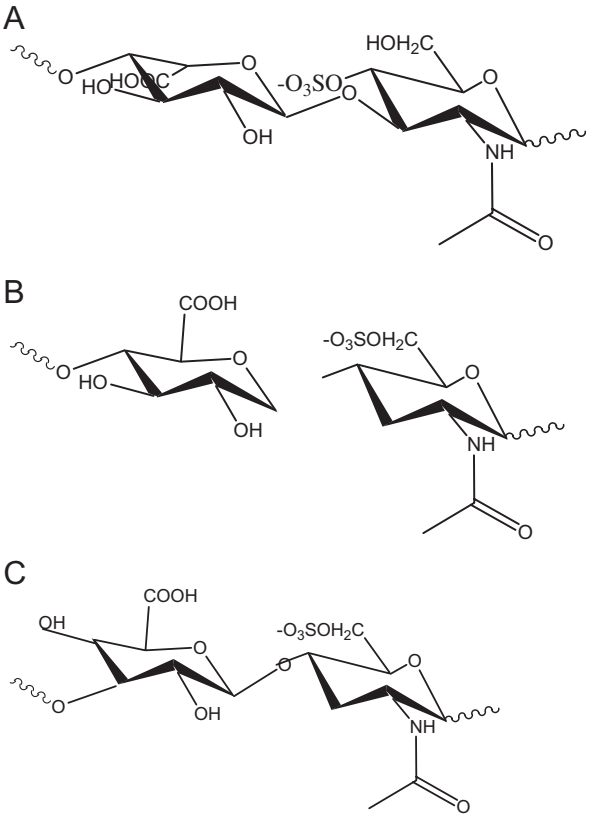
Due to its biocompatibility, non-immunogenicity and pliability, CS hydrogels have been extensively investigated for wound dressing applications [170]. Similar to HA, several physical and chemical crosslinking techniques have been developed for CS to form hydrogels for biomedical applications [171]. Since CS plays an important role in regulating the expression of the chondrocyte phenotype, it has been extensively investigated as a scaffolding material for cartilage tissue engineering. This is particularly important since studies have shown that successful cartilage regeneration can be achieved through the use of a tissue engineered implant, only if the seeded cells undergo normal proliferation and phenotype development within the biodegradable scaffold together with the production of a new cartilage-specific extracellular matrix. Several studies have investigated the efficacy of using composite scaffolds composed of CS and other biopolymers, such as collagen or synthetic biodegradable polymers, as scaffolds for cartilage tissue engineering. These studies have revealed a strong correlation between the use of CS and the bioactivity of the seeded chondrocytes [172].

Other natural bioactive polysaccharides that are being considered as potential biomaterials for various biomedical applications include heparin sulfate, keratin sulfate and dermatan sulfate (Scheme IV).

4.2.2. Polysaccharides of non-human origin

In addition to the glycosaminoglycans present in the human body, other types of polysaccharide molecules have also raised interest as biodegradable polymeric biomaterials. The most important members among this class are the cationic polymer chitosan, which originates from crutacian skeletons, and the anionic polymer alginic acid, derived from brown algae, both of which have been used as drug delivery vehicles [173]. One of the most extensively investigated polyelectrolyte complexes for biomedical applications involve chitosan and alginic acid. They are used as wound dressings and as drug as well as cell delivery vehicles [174].

4.2.2.1. Chitin and chitosan. Structurally chitosan is a linear polysaccharide consisting of β (1-4) linked D-glucosamine with randomly located *N*-acetyl-glucosamine groups depending upon the degree of deacetylation of the polymer. Chitosan is derived from chitin which is a fully acetylated polymer and forms the exoskeleton of arthropod. Fig. 17 shows the structure of chitosan. Chitosan has been found to be non-toxic after oral administration in humans and is an FDA approved food additive.



Scheme IV. Structures of glycosaminoglycans: (A) dermatan sulfate, (B) heparin sulfate and (C) keratin sulfate.

Enzymes, such as chitosanase, lysozyme and papain are known to degrade chitosan *in vitro* [175]. The *in vivo* degradation of chitosan is primarily due to lysozyme and takes place through the hydrolysis of the acetylated residues. The rate of degradation of chitosan inversely depends on the degree of acetylation and crystallinity of the polymer [176]. The highly deacetylated form exhibits the lowest degradation rates and may last several months *in vivo*. Apart from this, chemical modification of chitosan can significantly affect its solubility and degradation rate. In a study that compared the *in vivo* degradation of 85% deacetylated chitosan with isobutyl substituted chitosan (degree of substitution, approximately 40%) after implantation in the muscle pouch of mice demonstrated the faster degradation rate of substituted chitosan [177]. The faster degradation rate has been attributed to the deformation of strong hydrogen bonds present in chitosan. Azab et al. investigated the effect of cross-linking density on the *in vivo* degradation of chitosan gels. Various concentrations of glutaraldehyde were used to develop gels having varying cross-linking densities. The degradation rates of the gels were investigated following subcutaneous and intraperitoneal implantations in a rat model. The gels with lower cross-linking density (FDG) showed significant weight loss after 14 days of implantation; approximately 80% (subcutaneous) and approximately 91% (intraperitoneal). No significant decrease in weight was observed for highly cross-linked gels (SDG) after 14 days of implantation [178]. The study clearly showed the effect of cross-linking density and the site of

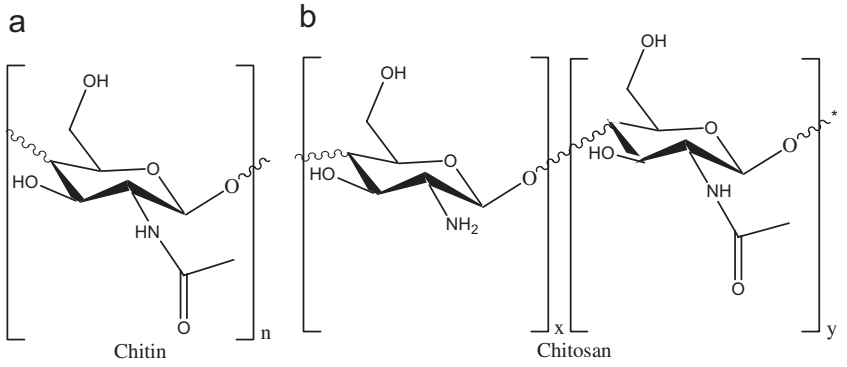


Fig. 17. Structure of chitosan.

implantation on the *in vivo* degradation of chitosan-based implants. *In vivo*, chitosan is also known to elicite minimal foreign body reactions with little or no fibrous encapsulation upon implantation. Fig. 18 shows the tissue responses to chitosan gels (FDG and SDG) when compared to biodegradable surgical suture Vicryl®. Chitosan gels elicited very minimal inflammatory response compared to Vicryl® which showed a pronounced inflammatory reaction [178].

Chitosan is soluble in weekly acidic solutions resulting in the formation of a cationic polymer with a high charge density and can therefore form polyelectrolyte complexes with wide range of anionic polymers [179].

Chitosan has structural similarities with glycosaminoglycans and hyaluronic acid present in human body and due to the presence of highly reactive amino groups along the polymer backbone, chitosan is susceptible to chemical or biological functionalization [180]. In fact, chitin and chitosan have shown to have stimulatory properties on macrophages, and chemoattractive properties on neutrophils [181]. These properties, along with its antibacterial, hemostatic properties give chitosan enourmous potential as a natural polymer for wound healing applications [182,183]. Furthermore, *in vivo* hydrolysis of chitosan and its derivatives by lysozyme gives rise to oligomers that activate the macrophages. The degradation leads to the formation of *N*-acetylglucosamine which is a major component of dermal tissues and its presence is essential for scar-less tissue repair. Thus, chitosan can potentially act as a wound healing accelerator as well.

The strong positive charges on chitosan makes it a very effective mucoadhesive as it can strongly interact with the negatively charged mucous membrane. Several chitosan-based bioadhesive drug/vaccine delivery systems are currently under development [184]. Due to is aqueous solubility chitosan can be fabricated into various structures and forms, such as gels, nanofibers nanospheres, microspheres and combined with its pH sensitivity, excellent biocompatibility and biodegradability, makes chitosan a promising candidate for developing drug delivery devices and as scaffolds for tissue engineering. Chitosan has the ability to condense DNA to form complexes and extensive research has gone into developing non-viral gene delivery vehicles [185]. Studies are currently being performed to evaluate the potential of using chitosan as a scaffolding material for engineering various tissues including cartilage, skin and bone [176].

Chitosan has the ability to act as a permeation enhancer through its interaction with the cell membrane resulting in a structural reorganization of tight-junction associated proteins. This, along with its mucoadhesive property, makes it a suitable candidate for use in both oral and nasal vaccination formulations. As such, several solution and microsphere vaccine formulations based on chitosan have been developed. Chitosan offers another advantage by being able to form micro/nanosphere formulations without the use of organic solvents, which maintains the immunogenicity of the antigens [186]. The high chemical reactivity of chitosan, has also led to several chitosan-drug conjugates for cancer therapy [187].

Chitosan was also used to develop injectable thermosensitive carrier material for biomedical applications [188,189]. Studies have shown that in the presence of certain phosphate salts, chitosan can undergo a temperature-controlled phase transition. Due to the mild gelling conditions, the hydrogel has been found to be a potential delivery vehicles for growth factors, small molecular weight drugs and cells for localized therapy.

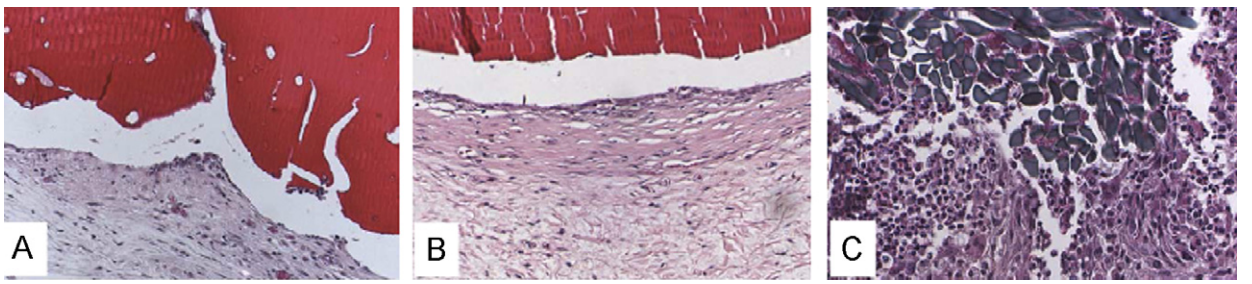


Fig. 18. Histological sections demonstrating minimal tissue response in the surrounding tissues: (A) SDG implant, (× 100), (B) FDG implant (× 100) and (C) chronic foreign body reaction in the tissues surrounding surgical sutures (× 200). Reprinted from Ref. [178] with permission from Elsevier.

4.2.2.2. Alginic acid. Alginic acid present within the cell walls and intercellular spaces of brown algae and has a structural role in giving flexibility and strength to marine plants. Due to its non-toxicity, alginate has been extensively used as a food additive and a thickener in salad dressings and ice creams.

Alginate is a non-branched, binary copolymer of (1-4) glycosidically linked β-D-mannuronic acid and α-L-guluronic acid monomers. The composition of alginate (the ratio of the two uronic acids and their sequential arrangements) varies with the source. Alginate is not a random copolymer, but instead, it is a block copolymer composed of two uronic acid with different block lengths and sequential arrangement. Fig. 19 shows the structure of alginic acid. Alginates are extracted from the algae using a base solution and then reacted with acid to form alginic acid. They are high molecular weight polymers having molecular weights up to 500 kDa. Aqueous solutions of alginates show non-Newtonian behavior similar to other glycosaminoglycans discussed earlier.

The high functionality of alginic acid makes it a favorable biopolymeric material for use in biomedical applications. The high acid content allows, alginic acid to undergo spontaneous and mild gelling in the presence of divalent cations, such as calcium ions. This mild gelling property allows the encapsulation of various molecules or even cells within alginate gels with minimal negative impact [190]. Furthermore, the carboxylic acid groups of alginic acid are highly reactive and can be appropriately modified for various applications. Fig. 20 shows various molded shapes made from aqueous alginic acid solution in the presence of calcium carbonate [191].

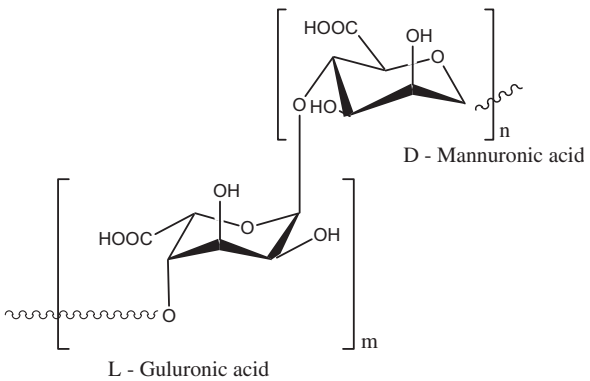


Fig. 19. Structure of alginic acid.

Even though alginates have been extensively investigated as biomaterials, one of the main disadvantages of using alginate-based materials is their inability to undergo enzymatic degradation by mammals. Studies are currently underway to develop degradable gels based on alginate. It has been found that ionically cross-linked alginates dissolve at neutral pH upon losing the divalent cross-linking cations and leads to uncontrolled and typically slow degradation *in vivo*. Developing alginate gels by gamma irradiation has been reported to be another elegant way for developing degradable alginate gels. It has been found that irradiation of high molecular weight alginate with doses below 8 Mrad cleave M-G residues in the polymer leaving the G block. The resulting polymers were found to degrade faster *in vivo* and get cleared from the body faster making it a potential scaffolding material for bone regeneration [192]. Another method to induce biodegradation to alginate-based materials is by chemical modification, which involves oxidation of the polymer backbone by periodate. The resulting hemiacetal ring change the urinate residue to an open chain and creates a hydrolytically labile bond and the rate of hydrolysis of the resulting polymer depends on pH and temperature [193]. Since the aldehyde groups are highly reactive they can be used to form chemically cross-linked degradable gels for cells or drug encapsulation.

Alginate has also been extensively investigated as a drug delivery device where in the rate of drug release can be varied by varying the drug polymer interaction as well as by chemically immobilizing the drug to the polymer back bone using the reactive carboxylate groups. The encapsulation of

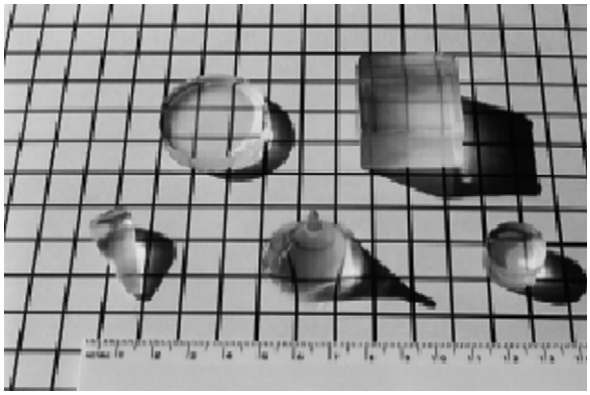


Fig. 20. Various shapes developed from alginate via calcium crosslinking. Reprinted from Ref. [191] with permission from Elsevier.

proteins and bioactive factors within ionically cross-linked alginate gels are known to greatly enhance their efficiency and targetability and as a result, extensive investigation has been undertaken to develop protein delivery systems based on alginate gels [194].

A disadvantage of using alginate-based gels, apart from their poor degradability, is poor cell adhesion on alginate gels. Recent studies; however, have shown the feasibility of developing alginate gels with good cell affinity. The modification of alginate with bioactive molecules, such as cell binding peptides is a versatile method for developing cell-binding hydrogels for use as scaffolds for tissue engineering.

5. Conclusions

Most of the biodegradable materials currently on the market are based on natural polymers such as collagen and synthetic polymers such as poly(α-esters). Advances in synthetic organic chemistry and novel bioprocesses are enabling the development of a wide range of novel polymeric materials as candidates for developing transient implants and drug delivery vehicles. The success of biodegradable implants lies in our ability to custom design or modify existing biomaterials to achieve appropriate biocompatibility, degradation and physical properties to elicit favorable biological responses.

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