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Recent developments in biodegradable synthetic polymers

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Abstract. This chapter reviews recent developments in biodegradable synthetic polymers focusing on tailoring polymer structures to meet material specification for emerging applications such as tissue engineered products and therapies. Major classes and new families of synthetic polymers are discussed with regard to synthesis, properties and biodegradability, and known degradation modes and products are summarized based on studies reported during the past 10–15 years. Polyesters and their copolymers, polyurethanes, polyphosphazenes, polyanhydrides, polycarbonates, polyesteramides and recently developed injectable polymer systems based on polypropylenefumarates, polyurethanes and acrylate/urethane systems are reviewed. Polyesters such as polyglycolides, polylactides and their copolymers still remain as the major class of synthetic biodegradable polymers with products in clinical use. Although various copolymerization methods have addressed needs of different applications, release of acidic degradation products, processing difficulties and limited range of mechanical properties remains as major disadvantages of this family of polymers. Injectable polymers based on urethane and urethane/acrylate have shown great promise in developing delivery systems for tissue engineered products and therapies.

Keywords: biodegradable polymers; polyurethanes; polyesters; tissue engineering; biocompatibility; biodegradation; injectable polymers; synthesis; mechanical properties; orthopedics; polyphosphazenes; polyanhydrides; polycarbonates; poly(ortho esters); copolymers

Introduction

A major drive for continued research to develop biodegradable synthetic polymers is the need for new materials with properties tailored to meet the biochemical and biomechanical requirements in the emerging technologies such as tissue engineering, regenerative medicine, gene therapy, novel drug delivery systems and implantable devices. Over the past 25 years, significant efforts have been devoted to the development of synthetic biomaterials, and a vast majority of these efforts have been focused on identifying ''off the shelf'' polymers that were biologically inert and stable in biological environments. Polysiloxanes, polyurethanes, polyesters and polyolefins are among the few families of synthetic polymers that are currently used in devices and prostheses implanted to help support the functions of organs and biological tissues. Recently, there has been a major shift in approach to repair/regenerate damaged tissues and organs. Instead of implanting permanent devices, a much better outcome could be expected for the patient if a temporary

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support is provided using a biodegradable polymer until the body can regenerate the damaged tissues and organs. A major challenge to the biomaterials researcher is the design of new materials that meets a number of demanding requirements in emerging technologies. The new material must support the tissue regeneration process while providing mechanical support and eventually degrades to non-toxic products with little or no harm to the body. Additionally, the polymers may be used as a cell delivery system using minimally invasive procedures in the development of advanced tissue engineered products and therapies. Accordingly, there is a need for new materials custom designed to fit varying needs of physicochemical properties necessary for the development of new products and therapies. The main aim of this review is to provide the readers with an update on recent developments in different classes of synthetic biodegradable polymers. While providing a brief introduction to chemistry and properties of major classes of synthetic biodegradable polymers, the review will focus on various copolymerization strategies, and new classes of biodegradable polymers reported in the literature over the last 10–15 years.

Polyesters

A number of families of synthetic biodegradable polymers are available for selection for a specific application. Among these poly(α-hydroxy acid esters) are the most widely investigated. Many review articles [1–7] have described the synthesis and properties of poly(glycolic acid) (PGA), poly(lactic acid) and their copolymers, the key members in this family. These polymers continue to be the most widely used synthetic biodegradable polymers in clinical applications. The major applications include resorbable sutures, drug delivery systems and orthopedic fixation devices, such as pins, rods and screws [7]. Despite some disadvantages, these polymers remain attractive because of their ease of degradation by hydrolysis of ester linkages and the degradation products are resorbed through metabolic pathways in some cases. They also have the potential to tailor the structure to alter degradation rates and mechanical properties by using various copolymerization strategies.

Poly(α-hydroxy esters)

Synthesis and properties: Poly(glycolic acid), poly(lactic acid) and their copolymers are among the most widely studied biodegradable polymers in the polyester family. Several excellent review articles have discussed synthesis, properties and biodegradation of poly(α-hydroxy esters) [1–7], and readers are referred to these reviews for more details.

PGA is a rigid thermoplastic material with high crystallinity (46–50%). The glass transition and melting temperatures of PGA are 36°C and 225°C, respectively. Because of high crystallinity, PGA is not soluble in most organic

solvents; the exceptions are highly fluorinated organic solvents such as hexafluoro isopropanol [7].

Although common processing techniques, such as extrusion, injection and compression molding can be used to fabricate PGA into various forms, its high sensitivity to hydrolytic degradation requires careful control of processing conditions [8,9]. Porous scaffolds and foams can also be fabricated from PGA, but the properties and degradation characteristics are affected by the type of processing technique. Solvent casting, particulate leaching method and compression molding are used to fabricate PGA based implants.

The preferred method for preparing high molecular weight PGA is ring-opening polymerization of glycolide (Fig. 1), the cyclic dimer of glycolic acid [10,11], and both solution and melt polymerization methods can be used. The common catalysts used include organo tin, antimony or zinc. If stannous octoate is used, temperature of approximately 175°C is required for a period of 2–6 h for polymerization. Although it is possible to synthesize these polymers by acid-catalyzed polycondensation of respective acids, the resulting polymers generally have a low molecular weight, broad molecular weight distribution and consequently poor mechanical properties [12].

The attractiveness of PGA as a biodegradable polymer in medical applications is that its degradation product glycolic acid is a natural metabolite. A major application of PGA is in resorbable sutures (Dexon, American Cyanamide Co.). Numerous studies [13,14] have established a simple degradation mechanism via homogeneous erosion. The degradation process occurs in two stages, the first involves the diffusion of water into the amorphous regions of the matrix and simple hydrolytic chain scission of the ester groups.

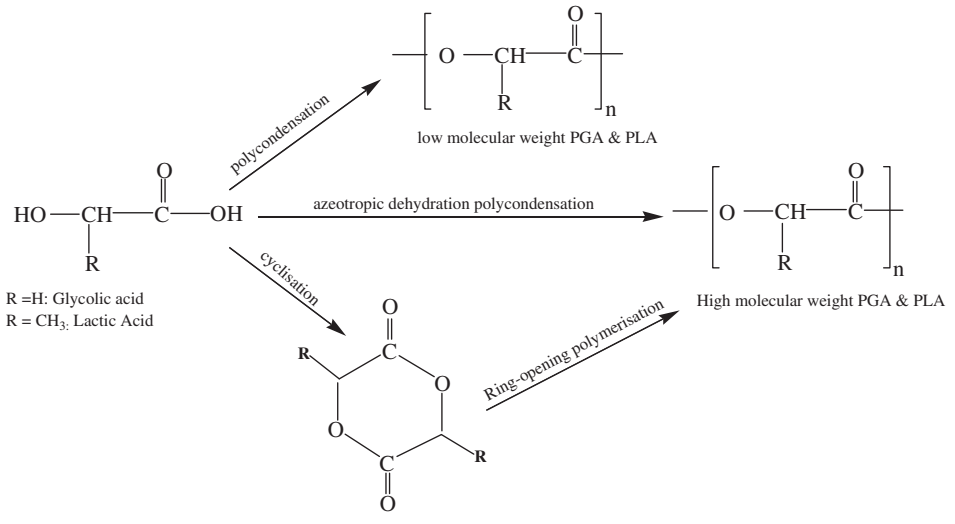


Fig. 1. Synthetic routes to poly(glycolic acid) and poly(lactic acid).

The second stage of degradation involves largely the crystalline areas of the polymer, which becomes predominant when the majority of the amorphous regions have been eroded.

In a study of Dexon sutures *in vitro*, the first stage degradation predominates during the first 21 days and a further 28 days for the degradation of the crystalline regions. After 49 days, the reported weight loss was around 42% with complete loss of mechanical properties. Because of the bulk degradation of PGA, there is a sudden loss of mechanical properties. Although the degradation product glycolic acid is resorbable at high concentrations, they can cause an increase of localized acid concentration resulting in tissue damage. The ultimate fate of glycolic acid *in vivo* is considered to be the conversion into carbon dioxide and water, with removal from the body via the respiratory system [15]. However, Hollinger [16] has suggested that only lactic acid (LA) follows this pathway, and that glycolic acid is converted into glyoxylate (by glycolate oxidase), which is then transferred into glycine after reacting with glycine transaminase.

Poly(lactic acid) is present in three isomeric forms D(−), L(+) and racemic (D,L), and the polymers are usually abbreviated to indicate the chirality. Poly(L)LA and poly(D)LA are semicrystalline solids, with similar rates of hydrolytic degradation as PGA. PLA is more hydrophobic than PGA, and is more resistant to hydrolytic attack than PGA. For most applications, the (L) isomer of LA is chosen because it is preferentially metabolized in the body. P(L)LA, poly(lactic–glycolic acid) (PLGA) copolymers and PGA are among the few biodegradable polymers with Food and Drug Administration (FDA) approval for human clinical use.

Both polycondensation and ring-opening polymerization methods (Fig. 1) are used to prepare polylactic acid, although the ring-opening polymerization of lactides is the preferred method as it provides high molecular weight polymer with good mechanical properties [1].

Mechanical properties of LA polymers can be varied to a large degree ranging from soft and elastic materials to stiff and high-strength materials by controlling the degree of crystallinity, molecular weight and forming stereo complexation of enantiomeric lactic acids. Semicrystalline PLA has an approximate tensile strength of 50–70 MPa, tensile modulus of 3 GPa, flexural modulus of 5 GPa and an elongation at break of 4% [17–19]. Superior mechanical properties have been achieved by stereo complexation of enantiomeric PLAs, and the improvement is ascribed to the formation of stereocomplex crystallites that acts as intermolecular cross-links [20].

The solubility of LA polymers is highly dependent on the molar mass, degree of crystallinity and other comonomer units present in the polymer. Chlorinated or fluorinated solvents, dioxane, dioxalane and furane are good solvents for enantiomerically pure PLA. Poly(rac-lactide) and poly(meso-lactide) are soluble in a range of other organic solvents such as acetone, pyridine, ethylacetate, dimethylsulfoxide, dimethylformamide, etc., in addition

to the previously mentioned solvents. Södergård and Stolt [1] have recently reviewed the properties of LA polymers, and readers are referred to this article for more details.

Copolymers of α-hydroxy acids

Synthesis and properties: To address the material needs in drug delivery systems, tissue engineering and regenerative medicine, researchers have focused on developing various copolymer systems of α-hydroxy acids with other monomers. In addition to the copolymers of lactic and glycolic acids, the most frequently used other monomers for copolymerization include ε-caprolactone, δ-valerolactone, trimethylene carbonate (TMC) and 1,5-dioxepan-2-one.

The full range of copolymers of LA and glycolic acid has been investigated. The two main series are those of (L)LA/GA and (DL)LA/GA. Gilding and Reed [21] have shown that compositions in the 25–75% range for (L)LA/GA and 0–70% for the (DL)LA/GA are amorphous. For the (L)LA/GA copolymers, resistance to hydrolysis is more pronounced at either end of the copolymers compositions range [21–24]. The 70/30 GA/LA has the highest water uptake, hence the most readily degradable in the series. In another study, Miller *et al.* [22] have shown that the 50/50 copolymer was the most unstable with respect to hydrolysis. However, it is generally accepted that intermediate copolymers are very much more unstable than the homopolymers. The first commercial use of this copolymer range was the suture material Vicryl (Ethicon Inc.), which is composed of 8% (L)LA and 92% GA. The main application of (D,L-LA/GA) copolymer has been in the field of controlled drug release.

The degree of crystallinity and melting temperature of PLA polymers can be reduced by random copolymerization with other monomers which disrupts the crystallization ability of poly(lactide) segments. For example, a 50/50 copolymer of L-lactic acid and ε-caprolactone has shown to be largely amorphous with a common glass transition temperature of −15°C [25]. The average LA sequence length has been reported to have a large influence on both thermal and mechanical properties of the copolymers [26,27]. Likewise, copolymerization with 1,5-dioxepan-2-one [28] and TMC [29] lowers the crystallinity of PLA and consequently lower melting points.

Copolymerization with poly(ethylene glycol) (PEG) has been investigated to increase hydrophilicity of PLGA polymers, primarily targeting drug delivery applications. The choice of PEG as a precursor is largely due to its good biocompatibility and hydrophilicity. Chen *et al.* [30] and Kwon *et al.* have reported [31] the synthesis of thermo-sensitive triblock copolymers for protein delivery. PLGA–PEG–PLGA triblock copolymers can be made water soluble by using appropriate molecular weight PEG, and Choi *et al.* [32] have demonstrated that such copolymers can be used for sustained delivery of

peptides. Other studies have shown the usefulness of PLGA–PEG copolymers for stent-based controlled delivery of angiostatin [33], as excipients to enhance the gene transfection of various cationic vector systems [34], and delivery of plasmid TGF-beta 1 for diabetic wound healing [35]. Recently, Kumar *et al.* [36] and Huh *et al.* [37] have reviewed PLGA–PEG block copolymers for drug delivery applications, and these reviews cover a range of linear and star block copolymers based on PEG with PLA, PDLA and PCL.

In an attempt to improve cell attachment to PLGA copolymers, Yoon *et al.* [38] modified PLGA by attaching cell-adhesive peptides such as (R: Argenine; G: glycine; D: aspartic acid) RGD peptide and demonstrated significant improvement in cell attachment compared to unmodified polymer. The same group also investigated the effect of immobilization of hyaluronic acid (HA) and poly(L-lysine) to promote the regeneration of cartilage tissue [39,40].

Breitenbach *et al.* [41] have synthesized poly(vinyl alcohol) (PVA)-based branched polyesters bearing PLGA side chains, which are covalently attached via the hydroxyl groups in PVA. The hydrophilicity of the branched polymer system can be varied by varying the length of PLGA chains and exhibited different release profiles compared with unmodified polymer. An added advantage of these polymer systems is the apparent change in mode of degradation from bulk to surface erosion [42,43]. Further modification of these polymers by attaching sulfobutyl groups can create negatively charged polymers [44], while attachment of amino groups such as dimethylamino amine, etc. can generate positively charged copolymers.

Ouchi and Ohya [45] have reported the synthesis of random and block copolymers of depsipeptide and L-lactide with reactive (ionic) side groups, comb-type PLA and branched PLA and PLA-grafted polysaccharides and PLA with terminal saccharide residues. These polymers have the potential to be used in drug delivery applications.

In summary, various copolymerization approaches have been used successfully to alter the mechanical properties and degradation rates to suit different applications of which drug delivery is the major application area of focus for copolymers of PLGA. Table 1 lists several commercially significant copolymers and recently developed copolymers with their potential applications.

Biodegradation and biocompatibility of poly(α-hydroxy esters): The degradation of PLA, PGA and PLA/PGA copolymers generally involves random hydrolysis of their ester bonds. PLA degrades to form LA, which is normally present in the body. This acid then enters tricarboxylic acid cycle and is excreted as water and carbon dioxide. No significant amounts of accumulation of degradation products of PLA have been reported in any of the vital organs [24]. Carbon^{13} labeled PLA has demonstrated little radioactivity in feces or urine indicating that most of the degradation products are released through respiration. It is also reported that in addition to hydrolysis PGA is

Table 1. Properties of copolymers based on α-hydroxy acids.

Copolymer	Major effect of the incorporation of comonomer	Degradation characteristics	Commercial products	Refs
Poly(lactic-*co*-glycolic acid) (PLGA)	Control degradation rates and mechanical properties	Composition dependent	Vicryl® (90% GA and 10% LA), Vicryl Rapid® (irradiated) Panacryl®, Polysorb®	[3,46,47]
Poly(glycolic acid-*co*-trimethylene carbonate) (PGA/TMC) and PGA/TMC/dioxane	To reduce rigidity of PGA and to reduce degradation rate	Half of mechanical strength is lost in 2 weeks	Biosyn®	[48,49]
Poly(glycolic acid-*co*-caprolactone)P(GA/CL)	Improve processability, degradation rates and tensile strength	120 days (in suture form) for complete degradation	Monocryl® (GA/CL:75/25)	[50]
P(GA/TMC/CL)	Increase degradation rate and processability	Half of mechanical strength is lost in 2 weeks	Monosyn®	[3]
P(LA/CL)	Improve processability, degradation rates and tensile strength	Half of mechanical strength is lost in 8 weeks	Used in veterinary applications	[51]
PLGA and PEG block copolymers	Increase hydrophilicity/degradation rate, drug compatibility	Dependent on the PEG content	Drug, peptide delivery	[31–37]
PVA–PLGA graft copolymers	Increase hydrophilicity and alter degradation mode. Can be modified to have cationic and anionic groups to accommodate different drugs	Dependent on PVA molecular weight and PLGA chain length	Drug delivery	[41–44]

also broken down by certain enzymes, especially those with esterase activity [52]. Glycolic acid also can be excreted by urine.

The rate of degradation, however, is determined by factors, such as configurational structure, copolymer ratio, crystallinity, molecular weight, morphology, stresses, amount of residual monomer, porosity and site of implantation.

Both *in vitro* and *in vivo* studies have been carried out to ascertain the biocompatibility of PLA and PGA. Many studies suggest that these polymers are sufficiently biocompatible [16,53] although certain studies [54–57] suggest otherwise. Recent studies have shown that porous PLA–PGA scaffolds may be the cause of significant systemic or local reactions, or may promote adverse responses during the tissue repair process. PLA–PGA copolymers used

in bone repair applications have shown to be biocompatible, non-toxic and non-inflammatory [16,53]. Since PLA–PGA have been used successfully in clinical use as sutures, their use in fixation devices or replacement implants in musculoskeletal tissues may be considered safe.

Concerns about the biocompatibility of these materials have been raised when PLA and PGA produced toxic solutions probably as a result of acidic degradation products [58]. This is a major concern in orthopedic applications where implants with considerable size would be required, which may result in release of degradation products with high local acid concentrations. Another concern is the release of small particles during degradation, which can trigger an inflammatory response. It has been shown that as the material degrades the small particles that break off are phagocytized by macrophages and multinucleated giant cells [59]. It was also noted that no adverse biological responses occur especially if the material volume is relatively small. In clinical studies where PGA was used as fracture fixation, foreign-body responses or osteolytic reactions have been reported [60–63].

Other polyesters

Polylactones

Synthesis and properties: Poly(caprolactone) (PCL) is the most widely studied in this family [64–65]. PCL is a semicrystalline polymer with a glass transition temperature of about–60°C. The polymer has a low melting temperature (59–64°C) and is compatible with a range of other polymers. PCL has relatively low tensile strength (23 MPa) but extremely high elongation at break (> 700%). PCL degrades at a much lower rate than PLA and is a useful base polymer for developing long-term, implantable drug delivery systems.

PCL is prepared by the ring-opening polymerization of the cyclic monomer ε-caprolactone. Catalysts such as stannous octoate are used to catalyze the polymerization and low molecular weight alcohols can be used as initiator which can also be used to control the molecular weight of the polymer [66,67]. The other polyesters in the lactone family include poly(3-hydroxybutyrate) (PHB), poly(3-hydroxyvalerate) and poly(valerolactone). Among these PHB is the most investigated for biomedical applications. The polymer can be synthesized by ring-opening polymerization or by microbial methods. PHB is a stiff and brittle polymer with tensile strength of about 40 MPa [68].

Biodegradation and biocompatibility of polylactones: The homopolymer has a degradation time of the order of 2–3 years [64,69,70]. PCL with an initial average molecular weight of 50,000 takes about 3 years for complete degradation *in vitro* [71]. The rate of hydrolysis can be altered by copolymerization with other lactones, for example, a copolymer of caprolactone and valerolactone degrades more readily [72]. Copolymers of ε-caprolactone with DL-lactide have been synthesized to yield materials with more rapid

degradation rates (e.g., a commercial suture MONOCRYL, Ethicon) [70]. PCL is considered a non-toxic and a tissue compatible material [69].

Blends with other polymers and block copolymers and low molecular weight polyols and macromers based on caprolactone backbone are a few of the possible strategies to explore this class of polymers for various applications.

Poly(ortho esters)

Synthesis and properties: Poly(ortho esters) are another class of synthetic biodegradable polymers developed and investigated for applications such as drug delivery in ocular, burns treatment, management of post-operative pain and orthopedic applications. Heller *et al*. [73,74] have reported on the development of several families of poly(ortho esters) with different mechanical properties and degradation rates. The polymers are relatively easily synthesized by reacting a diol and a diketene and proceeds virtually instantaneously after addition of a trace amount of an acidic catalyst [75]. Polyols based on lactides can be copolymerised to increase degradation rates. Poly(ortho ester)s degrade by surface erosion, and the incorporation of lactide units allows the control of degradation rate. The degradation of the lactide segment releases lactic acid, which catalyze the degradation of the ortho ester groups [75]. Block copolymers of poly(ortho esters) and PEG can form micelles useful in drug delivery applications.

Biocompatibility and degradation: Biocompatibility of different poly(ortho esters) has been demonstrated. For example, in ophthalmic drug delivery tests, the polymer was well tolerated and showed no significant inflammatory reaction [76]. Recently, a GMP toxicology study on one poly(ortho ester) was concluded for products under development for post-surgical pain treatment, osteoarthritis and ophthalmic disease. In orthopedic applications, preliminary *in vivo* studies have shown that poly(ortho ester) to increase bone growth in comparison to PLGA [77].

Polyanhydrides

Synthesis and properties: Polyanhydrides are one of the most extensively studied [78–82] classes of biodegradable polymers with demonstrated biocompatibility and excellent controlled release characteristics. Polyanhydride synthesis, properties and biodegradation have been reviewed recently [78–80]. Langer [83] in 1980 was the first to exploit hydrolytic instability of aliphatic polyanhydrides for sustained release of drugs. Owing to the hydrophobic nature, polyanhydrides degrade by surface erosion [81] that makes them very attractive for controlled-release applications. Polyanhydride-based drug delivery systems have been utilized clinically [84].

Diacids or diacid chlorides are the most commonly used monomers for the synthesis of polyanhydrides [78,79]. Melt condensation, ring-opening polymerization, interfacial condensation and dehydrochlorination have been

used for polyanhydride synthesis [85,86]. Figure 2 illustrates the dehydration of a mixture of diacids by melt polycondensation [87]. The dicarboxylic acid monomers are converted into the mixed anhydride of acetic acid by reflux in excess acetic anhydride. High molecular weight polymers are prepared by melt polycondensation of prepolymer in vacuum under nitrogen sweep. Typical temperatures employed in melt polycondensation are in the range 150–200°C. Catalysts such as cadmium acetate, earth metal oxides and diethyl zinc/water, have been used to catalyze polycondensation reaction. For thermally sensitive monomers, solution polymerization using a range of solvents has been reported [88–90]. Figure 3 shows several common diacid monomers used in the synthesis of polyanhydrides.

Langer and coworkers [87,88] have synthesized polyanhydrides from sebasic acid and bis(*p*-carboxyphenoxy)methane for drug delivery applications. This polyanhydride is used to deliver carmustine, an anticancer drug, to sites in the brain where a tumor has been removed. The degradation products are

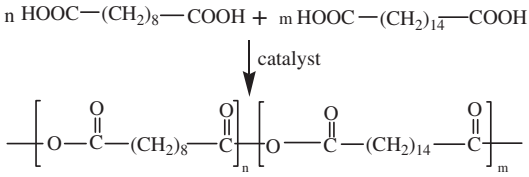
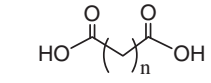
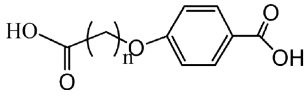


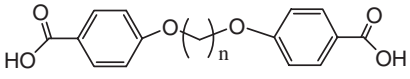
Fig. 2. Polyanhydrides from dehydration of dicarboxylic acids.



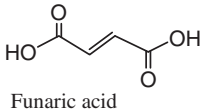
n=4: Adipic acid
n=8: Sebasic acid



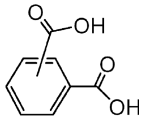
n=1: p-carboxyphenoxy acetic acid (CPA)
n=4: 5-(p-carboxyphenoxy)valeric acid
n=7: 8-(p-carboxyphenoxy)octanoic acid



n=1: bis(p-carboxyphenoxy)methane(CPM)
n=31,3-bis(p-carboxyphenoxy)propane



Funaric acid



meta=isophtahalic acid
para=terephthalic acid

Fig. 3. Dicarboxycylic acid monomers useful in preparing biodegradable polyanhydrides.

non-toxic and have controlled surface erosion degradation mechanism that allows delivery of drugs at a known rate.

Aliphatic polyanhydrides such as those based on sebasic acid or adipic acid are brittle, crystalline and soluble in common organic solvents and generally have fast degradation rates [91,92]. Aromatic polyanhydrides are crystalline with high melting temperatures (> 200°C), insoluble in most organic solvents and degrade slowly [93]. Various copolymerization approaches using mixtures of different diacids as well as the incorporation of fatty acids, polyether segments, photo cross-linkable groups and blends of polyanhydrides have been employed to modify degradation rates and mechanical properties [78].

Polyanhydrides have limited mechanical properties that restrict their use in load-bearing applications such as in orthopedics. For example poly[1,6-bis(carboxyphenoxy) hexane] has a Young's modulus of 1.3 MPa [94,95], which is well below the modulus of human cortical bone (40–60 MPa). To combine good mechanical properties of polyimides with surface-eroding characteristics of polyanhydrides, poly(anhydrides-*co*-imides) have been developed [96,97], particularly for orthopedic applications. Examples include poly[trimellitylimidoglycine-*co*-bis(carboxyphenoxy)hexane] and poly[pyromellitylimidoalanine-*co*-1,6-bis(carbophenoxy)-hexane] [97,98]. These poly(anhydride-*co*-imides) have significantly improved mechanical properties, particularly compressive strengths. Materials with compressive strengths in the 50–60 MPa range has been reported for poly(anhydrides-*co*-imides) based on succinic acid trimellitylimidoglycine and trimellitylimidoalanine [97]. The degradation of these copolymers occurred via hydrolysis of anhydride bonds, followed by the hydrolysis of imide bonds.

Photo cross-linkable polyanhydrides have also been developed for use in orthopedic applications, particularly focusing on achieving high mechanical strength [90]. The systems developed are based on dimethacrylated anhydrides. For example, dimethacrylate macromers based on sebacic acid and 1,6-bis(*p*-carboxyphenoxy)hexane have been reported [90,99]. Both ultraviolet (UV) and visible light curing methods have been investigated with these macromonomers. The most effective means of photopolymerization of these macromonomers was found to be 1.0 wt% camphorquinone and 1.0 wt% ethyl-4-*N*,*N*-dimethyl aminobenzoate with 150 mW/cm^2 UV power source. Combination of redox type and visible initiation has provided means of achieving efficient curing of thick samples.

Depending on the monomers used, the mechanical properties as well as degradation time can be varied. Compressive strengths of 30–40 MPa, and tensile strengths of 15–27 MPa, similar to those of cancelleous bone, have been reported [100].

Biocompatibility and biodegradation of polyanhydrides: Polyanhydrides are biocompatible [101], have well-defined degradation characteristics and have been used clinically in drug delivery systems [94]. Polyanhydrides degrade by hydrolysis of the anhydride linkage and generally undergo a linear mass loss

during erosion. The hydrolytic degradation rates can be altered by simple changes in the polymer backbone structure by choosing the appropriate diacid monomers. Poly(sebasic acid) degrades quickly (about 54 days in saline), while poly(1,6-bis(-*p*-carboxyphenoxy)hexane degrades much more slowly (estimated 1 year). Accordingly, combinations of different amounts of these monomers would result in polymer with degradation properties custom-designed for a specific application [102].

Minimal inflammatory responses to sebacic acid/1,3-bis(*p*-carboxyphenoxy)propane (SA/CPP) systems have been reported when implanted subcutaneously in rats up to 28 weeks. Loose vascularized tissue had grown into the implant at 28 weeks, with no evidence of fibrous capsule formation [101]. No data have been reported about polymer sterilizability and heat generation during polymerization. A 12-week study using 2–3 mm diameter full thickness defect in the distal femur of rabbits showed good tolerance of the SA/CPP polymer system and osseous tissue in the outer zone of some implants [101].

Polycarbonates

Synthesis and properties: Polycarbonates are another class of synthetic polymers explored as biodegradable polymers. Aliphatic polycarbonates such as poly(trimethylene carbonate) degrade under physiological conditions. Most aliphatic polycarbonates become extremely soft in the temperature range 40–60°C and weak mechanical properties make them less attractive for use in most applications. One advantage of polycarbonates is their degradation products, most cases the corresponding diols are less acidic than those produced by degradation of polyesters such as poly(lactic acid). Recent studies [103–108] have focused on developing aliphatic polycarbonates with functional groups which allow modification of degradation rate and mechanical properties, targeting drug delivery and tissue engineering applications.

Polycarbonates are generally prepared by reacting diol compounds with cyclic carbonates or with phosgene (Fig. 4). Several studies have focused on strategies to increase degradation rates by incorporating pendant hydroxyl, carboxyl and amino groups [108–110] to increase hydrophilic character of the polymer. A series of amphiphilic graft polymers of poly(2,2-dimethyltrimethylene carbonate) (PDTC) and poly-α-β-(*N*-2-hydroxyethyl)-L-aspartamide (PHEA) have been reported [108,109], to increase the hydrophilicity and degradation rate. The hydrophilicity of graft polymer increased with increasing HEA content, and consequently the water absorption level of the polymer. Cholesteryl end-capped polycarbonates have also been reported [110,111] by ring-opening polymerization without catalyst in different molecular weight range. Such polymers are expected to have promising applications in tissue engineering.

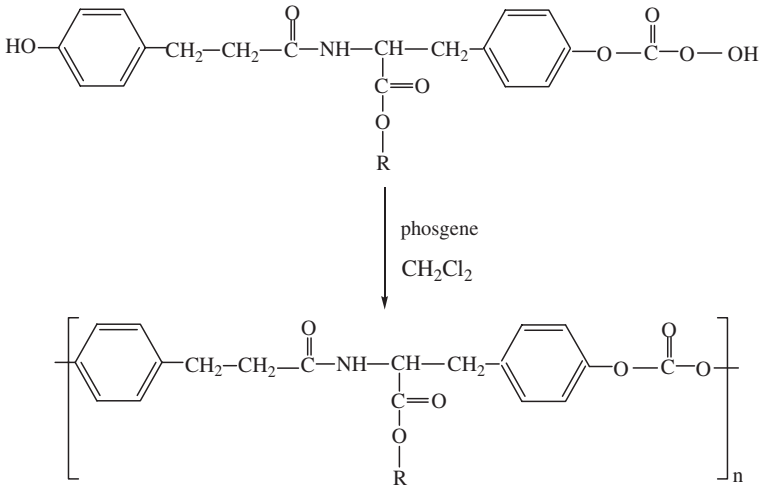


Fig. 4. Synthetic route to prepare polycarbonates.

Biocompatibility and biodegradation: Tyrosine-based polycarbonates have been reported as other promising degradable polymers for use in orthopedic applications [99,112–114]. These polymers posses three potentially hydrolyzable bonds: amide, carbonate and ester. Studies have shown [99] that the carbonate group hydrolyzes at a faster rate than the ester group, and the amide bond is not labile *in vitro*. Since the hydrolysis of the carbonate groups yields two alcohols and carbon dioxide, the problem of acid bursting seen in polyesters is alleviated. By variation of the structure of the pendant R group, polymers with different mechanical properties, degradation rates as well as cellular response could be prepared. Polycarbonate having an ethyl ester pendant group has shown to be strongly osteoconductive and good bone apposition, and possesses sufficient mechanical properties for load bearing bone fixations. *In vivo* studies have demonstrated that the polymer was biocompatible and promoted significant bone growth [99,114].

Polyesteramides

Synthesis and properties: Polyesteramides have both amides as well as ester linkages which attributes amphiphilicity and biodegradability [115–118]. They are designed to couple the excellent mechanical properties of polyamides and the biodegradability of polyester [119]. Owing to the polar nature of amide groups and their ability to form hydrogen bonds, these polymers exhibit good thermal and mechanical properties even at low molecular weight. On the other hand, hydrolytically degradable ester bond provides

biodegradability to the polymer. Another advantage of this class of polymers is the ability to incorporate α-amino acids, which provides sites for enzyme-induced biodegradation [117].

Polycondensation of monomers with carboxyl, alcohol and amino functional groups are used to prepare polyesteramides. The availability of a range of suitable monomers, such as hydroxy acids, dicarboxylic acids, amino acids, diamines, amino alcohols and diols allows the preparation of a range of copolymers with different mechanical properties and biodegradability. Examples of biodegradable polyesteramides reported in the literature include polyesteramides based on ε-caprolactone and 11-aminoundecanoic acid [120], ε-caprolactone, 11-aminoundecanoic acid and ethylene glycol [121], adipic acid, caprolactam and 1-4 butanediol, and their branched polymers with glycerol as branching agent [120–127]. In addition, many amino acid and amino alcohol-based polyesteramides have also been reported in the literature [128–133]. Kise *et al.* [134] have reported synthesis and biodegradability of a series of novel polyesteramides based on alpha-amino acid, 2-aminoethanol and dicarboxylic acid chlorides.

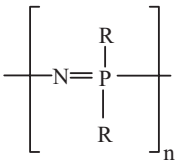
Synthesis of biodegradable polyesteramide microspheres based on ε-caprolactone and 11-amino undecanoic acid and their degradation properties have been reported by Qian *et al.* [135].

Degradable polyesteramides fibers based on 11-aminodecanoic acid have also been prepared by melt spinning. These fibers exhibited very high tensile strength (140 MPa) [136]. A biologically safe anti-corrosive coating based on a polyesteramide from *Pongamia glabara* oil has also been reported [137]. The solubility of these polymers is dependent on amino acid residues and they are generally soluble in highly polar solvents like formic acid and trifluroethanol and insoluble in non-polar solvents such as ethylacetate. Polyesteramide generally containing alpha-amino acid are soluble in chloroform [128,129], whereas those containing Gly residues are soluble in aprotic polar solvents such as DMF and DMSO.

Biodegradability: The ester group is the more readily hydrolyzable linkage in these polymers and amide linkages are not easily hydrolyzable due to strong hydrogen bonding and the associated crystallinity. Accordingly, polyesteramides with high level of amide linkages are extremely slow to degrade. The biodegradability of amino acid-based polyesteramides is depended on the specificity of enzymes to amino acid derivatives. The degradability of these polymer was reported low when L-Ala and L-Val was introduced into the polymers [134]. Kim *et al.* [138] have reported the relationship between hydrophilicity and biodegradability of polyesteramides. Branched polyesteramides degraded slowly in PBS and hydrolysis was reported primarily on ester bonds. Branching of polyesteramide have been reported to substantially enhance hydrolysis both in alkaline and in PBS solution [139].

Polyphosphazenes

Synthesis and properties: Polyphosphazenes are a relatively new class of biodegradable polymers, distinct from other classes of biodegradable polymers due to their synthetic flexibility and versatile adaptability for applications. Polyphosphazenes are high molecular weight, essentially linear polymers with an inorganic backbone consisting of alternating phosphorous and nitrogen atoms bearing two side groups attached to each phosphorous atom.



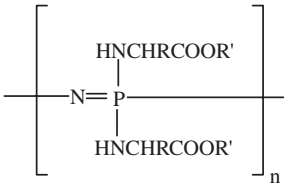
R = alkoxy, aryloxy or amino groups

(I)

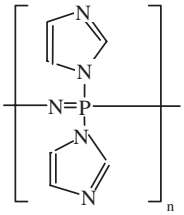
Although the early attempts to synthesize polyphosphazene dates back to 1895 by Stokes [140], the first successful synthesis of poly(dichlorophosphazene) was reported by Allcock and Kugel [141] in 1965. Different polyphosphazenes are synthesized by means of macromolecular substitution reactions carried out on a reactive polymeric intermediate, poly(dichlorophosphazene), $(NPCl_2)n$. This intermediate is prepared by thermal ring-opening polymerization of hexachlorotriphosphazene. The poly(dichlorophosphazene) is hydrolytically unstable due to the high reactivity of P–Cl bonds. Allcock's group utilized the high reactivity of the P–Cl bond to synthesize a range of hydrolytically stable poly(organophosphazenes) by replacing chlorine atoms with alkoxide or aryloxide [142], primary or secondary amines [143] or organometallic reagents [144]. The polyphosphazenes consist of over 700 different polymers with the general structure (I) [145]. The substituents on phosphorous influence the properties of these polymers and their typical properties include biocompatibility, flexibility, high dipole moment, broad range of glass transition temperature, chemical inertness, elastomeric properties, flame-retardancy, mechanical strength and solvent permeability.

It has been reported recently that by substituting with appropriate side groups, polyphosphazenes could be rendered biodegradable. Examples of such side groups include amines, amino acid esters, glucosyl, glyceryl, lactate or imidazolyl units [146–148]. Among these, aminoacid ester substituted polymers have been the most widely investigated as biodegradable polymers. Phosphazenes with amino acid esters (II) [149–151] and imidazole (III) have shown excellent hydrolytic degradability. The hydrolytic stability can be

modulated by cosubstituting with less hydrolytically sensitive groups on the polymer backbone [144].

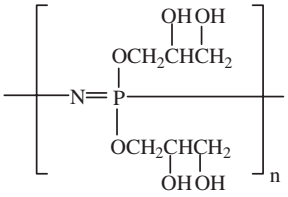


(II)



(III)

Alkoxy-substituted polyphosphazenes are also shown to be hydrolytically unstable. Examples include, glyceryl-substituted polyphosphazene (III) [152], glucosyl and methyl amino-cosubstituted polyphosphazene [153] as well as esters of glycolic or LA-substituted polyphosphazenes [154].



(VI)

Glycerol-substituted polyphosphazenes (VI) can be cross-linked by reacting with cross-linking agents such as adipoyl chloride and hexamethylenediisocyanate. The glycolic or lactic acid-substituted polymers hydrolyze much faster than the homopolymers PLA and PGA.

Although many studies have focused on investigating the effect of various substituents on hydrolytic stability, thermal and other properties, there is hardly any information on mechanical properties of biodegradable polyphosphazenes reported in the literature. The most widely investigated area of application is controlled drug release, and readers are referred to a recent review article for details [155].

Numerous degradation studies carried out have shown that hydrolysis of polyphosphazenes leads to compound(s) derived from the pendant groups, and phosphate and ammonia due to backbone degradation. The rate of degradation as well as the physico-chemical properties of these polymers can be tuned by incorporation of appropriate ratios of different pendant group. By careful controlling the nature and composition of side group substituents, it is possible to control the rate of degradation of polyphosphazenes over periods of hours, days, months or years. The influence of different amine

groups on the hydrolytic degradation of polyphosphazenes was extensively studied by Allcock *et al*. [156]. Majority of the aminated polymers undergo faster degradation in acidic pH compared to physiological or basic pH.

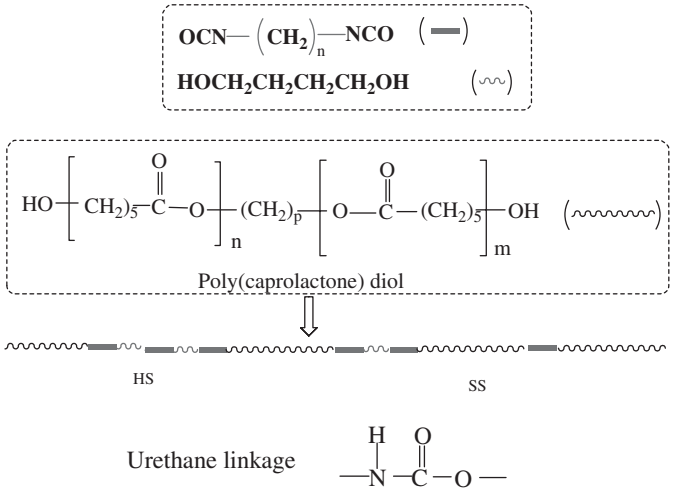
Biocompatibility and biodegradation: Laurencin *et al.* [157] have investigated methylphenoxy and either imidazolyl or ethylglycinate-substituted polyphosphazenes for skeletal tissue regeneration. Both materials supported the growth of MC3T3-E1, an osteogenic cell line. Increase in imidazolyl side groups resulted in a reduction in cell attachment and growth on the polymer surface and an increase in the rate of degradation of the polymer. In contrast, substitution with ethylglycinato group favored increased cell adhesion and growth accompanied with an increase in the rate of degradation.

In another study, Laurencin *et al.* [158] reported that porous matrices of poly[(50% ethylglycinato) (50% *p*-methylphenoxy) phosphazene] with pore sizes of 150–250 μm are good substrates for osteoblast-like cell attachment and growth.

Polyurethanes

Synthesis and properties: Thermoplastic polyurethanes (TPUs) represent a major class of synthetic polymers that have been evaluated for a variety of biomedical applications. Conventional TPUs are prepared from three monomers, a diisocyanate, a diol or diamine chain extender and a long-chain diol. These monomers react to form linear, segmented copolymers consisting of alternating hard and soft segments, which are characteristic structural features of conventional TPUs. The hard segment (HS) is composed of the alternating diisocyanate and chain extender molecule, whereas the soft segment (SS) is formed from the long-chain linear diol. Scheme 1 illustrates the general structure of TPU. Owing to thermodynamic incompatibility of hard and soft segments, TPUs exhibit two-phase morphology. The HSs aggregate to form microdomains resulting in structure consisting of glassy or semicrystalline domains and rubbery SSs aggregate to form soft domains, which are mostly amorphous. TPU can also be prepared by reacting equi-molar amounts of a linear diol and a diisocyanate, and this strategy has been used in designing biodegradable polyurethanes. By choosing two SS polyols with glass transitions above and below ambient temperature, TPU elastomers with good mechanical strength can also be prepared using this approach.

The interest in polyurethanes for biomedical applications is due to their excellent mechanical properties, good biocompatibility and structural versatility achievable to tailor polymer structure to meet the needs of a wide variety of medical implant applications. Polyurethanes are currently used in applications such as cardiac pace makers and vascular grafts. Most of the research on biomedical polyurethanes was focused on improving biocompatibility and stability as well as designing low modulus elastomers for applications such as synthetic heart valves. These research efforts have resulted



Scheme I. Example of an aliphatic TPU.

in the development of siloxane-based polyurethanes (Elast-Eon^{TM}), which have greater *in vivo* stability than conventional polyetherurethanes such as those based on poly(tetramethylene oxide) (PTMO) [159].

The variety of chemical functionality that can be built into the polymer chain allows the design of polyurethanes that are degradable in the biological environment. In designing biodegradable polyurethanes, the chemical structure of the diisocyanate and polyol play a pivotal role. By the appropriate choice of these compounds and relative proportions, polyurethanes with a range of mechanical properties as well as biodegradation characteristics to suit different applications can be formulated. Figure 5 shows a few examples of diisocyanates useful in formulating biodegradable polyurethanes. Although diisocyanates are toxic compounds, once incorporated into a polyurethane, the resulting polyurethane after hydrolytic degradation does not release the diisocyanate, but the corresponding diamine. Accordingly, the choice of the diisocyanate is largely governed by the toxicity of the corresponding diamine. Diisocyanates such as 4,4′-methylene diphenyl diisocyanate (MDI) and toluene diisocyanate (TDI), commonly used in many industrial polyurethane formulations, are not used in formulating biodegradable polyurethanes because of the high toxicity of the corresponding diamines. Aliphatic diisocyanates such as ethyl lysine diisocyanate (ELDI), methyl lysine diisocyanate (MLDI), hexamethylene diisocyanate (HDI) and 1,4-butanediisocyanate (BDI) are among the most suited in formulating biodegradable polyurethanes.

Polyester polyols are the preferred choice for obvious reasons. The ester linkages are susceptible to hydrolytic degradation and certain enzymes also can render ester linkages to degrade. The SS diols used in biodegradable

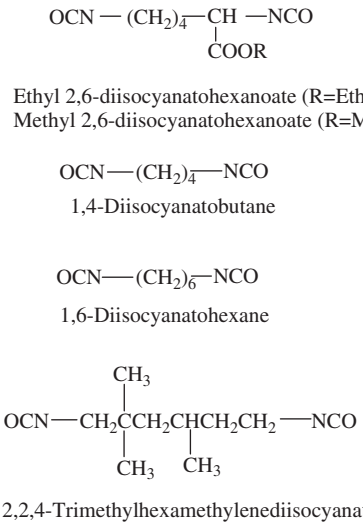


Fig. 5. Diisocyanates used in biodegradable polyurethane formulations.

polyurethanes are polyesters, and the exceptions are Pluronics, as these polyether polyols are used as copolyols to increase hydrophilicity.

In this review, properties of biodegradable polyurethanes are provided based on the type of diisocyanate used on the polyurethane formulation.

1,6-Hexamethylenediisocyanate-based polyurethanes: HDI is the most widely investigated diisocyanate in formulating biodegradable polyurethanes. The choice of this diisocyanate is largely due to the relative non-toxic nature [160] of the corresponding diamine 1,6-hexanediamine. The symmetrical molecular structure also leads to strong intermolecular attractions through hydrogen bonding resulting in elastomers with high strength. Elastomers with ultimate tensile strength over 60 MPa and elongation of 580% have been reported for HDI-based polyurethanes [161,162]. HDI-based TPUs display a tendency to cold draw and fibers with high strength can be drawn from HDI-based polyurethanes.

Structure property relationship of HDI-based polyurethanes with a range of linear polyester diols has been reported, and among these polycaprolactone is the most widely investigated SS diol. Gorona *et al*. [163] synthesized a series of polymers based on poly(ε-caprolactone)diol (ε-PCL) with molecular weight in the range 1,080–5,800. HDI was used as a chain extender in preparing these polymers, but elastomers with good mechanical strength (UTS 30 MPa) and elongation at break (980%) were obtained by this approach.

Many researchers have investigated the effect of incorporating mixtures of SS polyols, in most cases two polyols, to achieve different mechanical properties and to improve biocompatibility as well as to alter degradation behavior of polyurethanes. Saad *et al.* [164] have prepared a series of

copolymers containing PCL and poly(*R*-3-hydroxybutyrate)diols which are linked by HDI. These copolymers differ from the conventional segmented polyurethanes in that the diisocyanate is used as a linker without a chain extender. In these copolymers, PHB due to its crystalline nature plays a role of the HS, and copolymers containing 20 wt% PHB have shown tensile strength up to 27 MPa and elongation at break 890%. Increasing the PHB content decreased the strength of the copolymer. A similar study reported by Cohn *et al.* [165] investigated triblock copolymers prepared by chain extending linear triblock copolymer diol ε-PCL-PEO-ε-PCL with HDI. The water uptake as well as the rate of degradation increased with the increase in PEO content in the polyurethane and its molecular weight.

Gorona *et al.* [163,166,167] have investigated the effect of incorporating hydrophilic polyols poly(ethylene oxide) (PEO), poly(ethylene–propylene–ethylene)oxide (PEO-PPO-PEO) diol and hydrophobic ε-PCL on properties of biodegradable polyurethanes. The HSs in these polyurethanes were 1,6-hexamethylenediisocyanate chain extended with either 1,4-butanediol or 2-amino-1-butanol. Increasing the PEO content resulted in higher water absorption; a polyurethane based on a 50/50 mixture of PEO (MW 2,000) and ε-PCL (MW 530) absorbed 212% water, compared with 2% water absorption for PCL-based polymer. The amount of PEO, and its molecular weight significantly affected the mechanical properties, water absorption, calcification and hydrolytic degradation.

Linear diols of triblock copolymers based on LA and ethylene glycol, chain extended with HDI produce poly(ether-ester) urethanes with different degradation rates [168]. Polyurethane based on copolymer diol with a higher PLA content was more hydrophobic, degraded slowly in *in vitro*, compared to the copolymer with high PEG content. Kylmä *et al.* [169] have employed a melt processing method to prepare polyester urethane blends to investigate the effect of blending poly(lactic acid-*co*-ε-caprolactone-urethane) [P(LA-*co*-CL)] on properties and morphology of lactic acid-based amorphous poly(ester-urethane)s. The copolymer polyols with different ratios of LA and CL were used as the rubber to modify the properties of more rigid PLA-based polyurethane. The polyester urethanes were prepared by chain extending the corresponding linear diols with HDI. The incorporation of the rubbery polyurethane, resulted in toughening of the more brittle PLA-based polyurethanes, and polyurethane based on a linear copolymer diol of LA and CL (70/30) with 20% loading in the blend produced a polymer with elongation approaching 100%. However, the strength of the materials was significantly compromised.

Gorona *et al.* [170] have investigated the effect of PCL molecular weight (530–2,000 range), catalyst and chain extender on properties of polyurethanes based on HDI and isophorone diisocyanates. The highest strength (63 MPa tensile strength) was observed for polyurethane based on PCL with a molecular weight of 530. The type of catalyst, chain extender and PCL

molecular weight had a significant effect on mechanical properties of the polyurethane.

1,4-Butanediisocyanate-based polyurethanes: Similar to HDI, BDI due to its symmetrical molecular structure produce polyurethanes with good mechanical properties. Furthermore, the degradation product 1,4-butanediamine (putrescine) is a naturally occurring non-toxic compound. Guan *et al.* [171] synthesized a family of polyester urethaneureas from poly(caprolactone) diol, BDI, lysine ethyl ester or putrescine as chain extender. Flexible elastomers with elongation at break of 660–895% and tensile strength from 9 to 29 were produced and lysine chain extended polyurethaneureas were generally weaker materials compared with those based on putrescine. Spaans *et al.* [172] synthesized high tensile strength (35 MPa) polyurethanes from BDI and ε-PCL. De Groot *et al.* [173] prepared polyurethanes based on BDI and copoly(L-lactide/ε-caprolactone) using prepolymer method. Chain extension of isocyanate-terminated prepolymer with butanediamine was not possible due to the susceptibility of lactide bonds to aminolysis. Chain extension with 1,4-butanediol produced polyurethanes with poor mechanical properties, presumably due to trans-esterification. This problem was avoided by chain extending the copolymer diol with an isocyanate-terminated block, and polyurethane with tensile strength of 45 MPa was obtained.

Lysine diisocyanate-based polyurethanes: Lysine diisocyanate (LDI) is another diisocyanate that has received recent attention from researchers for developing biodegradable polyurethanes. Polyurethanes based on LDI when degraded release lysine, a non-toxic amino acid presents in proteins such as collagen, as one of the main degradation products.

Lysine diisocyanate is not commercially available (being developed by Kyowa Hakko Kogyo Co., Ltd.) but can be prepared from L-lysine monohydrochloride [174,175]. Both ELDI and MLDI can be prepared. Storey *et al.* [176] have prepared poly(ester urethane) networks from LDI and a series of polyester triols based on DL-lactide, γ-caprolactone and their copolymers. Networks based on poly(DL-lactide) were rigid ($T_g = 60^{\circ}C$) with ultimate tensile strengths of ~40–70 MPa, whereas those based on caprolactone triols were low modulus elastomers with tensile strengths of 1–4 MPa. Networks based on copolymers were more elastomeric (elongation up to 600%) with compressive strengths between 3 and 25 MPa. Hydrolytic degradation under simulated physiological conditions were dependent on the type of triol and DL-lactide-based networks were the most resistant with no degradation observed for 60 days, caprolactone-based triol networks were resistant up to 40 days, whereas the high lactide-based copolymer networks were the least resistant and substantial degradation observed in about 3 days.

Bruin *et al.* [174] have reported on the synthesis of degradable polyurethane networks based on star-shaped polyester prepolymers. The star prepolymers were prepared from myoinisitol, a pentahydroxy sugar molecule by ring-opening copolymerization of L-lactide or glycolide with caprolactone.

The prepolymers were cross-linked using 2,6-diisocyanatohexanoate. The degradation products of these PU networks are considered non-toxic. The resulting network polymers were elastomeric with elongation in the range 300–500% and tensile strengths varying between 8 and 40 MPa depending on the branch length etc. Preliminary experiments in guinea pigs have shown that the polyurethanes biodegrade when implanted subcutaneously.

Zang *et al.* [177] have developed a peptide-based polyurethane scaffold for tissue engineering. LDI was reacted first with glycerol to form a prepolymer, which upon reaction with water produced a cross-linked porous sponge due to liberation of carbon dioxide. Initial cell growth studies with rabbit bone marrow stromal cells (MSC) have shown that the polymer matrix supported cell growth and was phenotypically similar to those grown on tissue culture polystyrene.

Hirt *et al.* [178] and De Groot *et al.* [179] reported on the synthesis and properties of degradable polyurethanes based on LDI, 2,2,4-triethylhexamethylene diisocyanate and a number of polyester and copolyester polyols such as Diorez®, caprolactone, ethylene glycol copolymers, and polyhydroxy butyrate and valerate copolymers. The polyurethanes ranged from elastomers with elongations at break as high as 780%, but with low tensile strengths (5.8–8.1 MPa). Saad *et al.* [180] reported on the cell and tissue interaction of four such polymers prepared from 2,2,4-trimethylhexamethylene diisocyanate and 2,6-diisocyanato methyl caproate, and polyols, α,ω-dihydroxy-poly(*R*-3-hydroxybutyrate-*co*-(*R*)-3-hydroxyvalerate)-block-ethylene glycol and two commercial diols, Diorez® and PCL-diol. *In vitro* studies indicated that these polyesterurethanes did not activate macrophages and showed good level of cell adhesion and growth, which were also confirmed by *in vivo* results.

The incorporation of a chain extender with a hydrolytically labile linkage has been investigated to increase the degradation rates of polyurethanes as well as to modify the properties. Skarja and Woodhouse [181,182] have investigated the effect of an amino acid (phenylalanine)-based chain extender on polyurethanes prepared from methyl lysine diisocyanate (MLDI), polycaprolactone and PEO. Their results showed that PEO-based polyurethanes were generally weaker but PCL-based materials were relatively strong. However, no results were reported on the degradation of these polyurethanes. Gunatillake *et al.* [183,184] have prepared a series of diol chain extenders based on α-hydroxy acids and ethylene glycol. Polyurethanes based on these chain extenders degraded faster than those based on conventional chain extenders such as 1,4-butanediol and ethylene glycol. Dahiyal *et al.* [185] have incorporated chain extender with phosphate ester linkages. Examples include bis(2-hydroxyethyl)phosphate and bis(2-hydroxyhexyl)phosphate. One advantage claimed for this polyurethane is the ability to covalently attach drugs as pendent to the polymer chain via the phosphorous.

Gogolewsky and Pennings [186,187] have reported on a design of an artificial skin composed of polylactide/polyurethane mixtures where the PU was non-degradable. *In vivo* studies with guinea pigs showed that the artificial skin adhered to wound well, and protected from fluid loss and infections up to 40 days exhibiting potential as a skin substitute.

Micro-porous polyurethane amide and polyurethane–urea scaffolds have been evaluated by Spaans *et al.* [188] for repair and replacement of knee-joint meniscus. The SSs in these polyurethanes were based on 50/50 l-lactide/PCL and chain extenders were adipic acid and water, the reaction of latter with BDI provided carbon dioxide to produce porous scaffolds. Salt crystals were also added to produce porous structure, and the addition of surfactants combined with ultrasonic waves regulated the pore structure. Porous scaffolds with porosity of 70 to 80% were achieved by this technique. These scaffolds exhibited tearing problems during suturing [189], which was partly circumvented by using a different suturing system. A meniscal replica implanted contained only fibro-cartilage after 18 weeks and decreased the degradation of the articular cartilage.

Gunatillake *et al.* [190–192] have developed polyurethane prepolymers that can be cross-linked to form both rigid and elastomeric compositions useful in a range of biomedical applications including scaffolds in tissue engineering. The differential reactivity of the isocyanate functional groups in diisocyanates, such as LDI, is used to prepare prepolymers that are liquid at and above ambient temperatures by reacting with multi-hydroxy functional core molecules, such as pentaerythritol. Under controlled reaction conditions, star/hyperbranched polyols with isocyanate end-functional groups can be prepared. Reaction of prepolymer with an appropriate hydroxyl compounds, biodegradable polyurethane networks can be prepared. With the appropriate choice of precursors, polyurethane with high mechanical properties can be prepared.

Polyurethanes based on other diisocyanates: TDI, 2,2,4-trimethylhexamethylene diisocyanate, 1,1′-methylene-bis(4-isocyanatocyclohexane) (HMDI) and isoporone diisocyanate are among the other diisocyanates investigated, although to a lesser extent, in formulating biodegradable polyurethanes.

Storey *et al.* [193] have prepared a series of polyurethane networks by cross-linking D,L-lactide, glycolide, ε-caprolactone and trimethylene carbonate copolyester triols with TDI. Amorphous networks with tensile strength approaching 50 MPa were obtained with ε-PCL as SS polyol. Glycolide containing PU networks showed the fastest degradation rate. Bogdanov *et al.* [194] investigated the effect of ε-PCL molecular weight (2,000, 4,000 and 7,300) on properties of HMDI-based polyurethanes, and showed that strain-induced crystallization occurred when stretched above 100%. In another study, Lee *et al.* [195] prepared a series of polyurethanes based on HMDI and a mixture of poly(butylenes succinate) (PBS) and poly(ethylene glycol) SS polyols. Elastomers with elongation at break in the range 160–230% and tensile strength 2.0–2.4 kg/mm^2 were observed and DSC results showed that

PBS segments formed crystalline domains. Incorporation of PEG increased the degradation rate.

Biocompatibility and biodegradation: Both *in vitro* and *in vivo* studies have indicated that the biocompatibility of biodegradable polyurethanes is generally very favorable. Animal studies have demonstrated rapid cell in-growth with no adverse tissue reactions. However, the mechanism(s) of degradation, effect of degradation product, their toxicity and how those products are removed from the body are not clearly understood.

Tissue in-growth and degradation of two biodegradable polyurethanes based on ε-PCL/L-LA (MW 2,000), BDI and chain extender 1,4-butanediol (BDO) were investigated by subcutaneous implantation in rats [196]. The polymers were fabricated as foams with different porosities using the salt leaching method. In the foam with high porosity, complete tissue in-growth was observed, before polymer degradation, whereas the foam with lower macroporosity, the polymer degraded before complete tissue in-growth. Authors have indicated that fewer interconnected pores in the latter as the primary reason for low tissue in-growth. In another study [197], similar polyurethanes foams were implanted in the avascular region of canine lateral menisci. The study demonstrated that the polymer implants did not inhibit the healing process, and the scaffold became intensively integrated with the host meniscal tissue.

Polyurethane networks based on LDI and poly(glycolide-*co*-γ-caprolactone) macrodiol was evaluated by Bruin *et al.* [198] as two-layer artificial skin. The degradation of the skin *in vivo* was faster than that in *in vitro*. Subcutaneous implantation in guinea pigs showed that the porous polyurethane networks allowed rapid cell in-growth, degraded almost completely 4–8 weeks after implantation and evoked no adverse tissue reactions. Grad *et al.* [163,199] have studied the chondrocyte attachment, growth and maintenance on biodegradable aliphatic polyurethanes based on ε-PCL and pluronics [163] *in vitro* for 42 days. The results demonstrated that porous scaffolds supported chondrocyte attachment and production of extracellular matrix proteins. However, with prolonged time in culture, the diffusion of large amount of matrix molecules into the culture medium and the cell dedifferentiation were noticed. In another study [198], the degradation of these polyurethanes was demonstrated by *in vitro* hydrolytic experiments (37°C, pH 7.4 buffer). At 42 weeks in buffer, 2% weight loss and molecular weight reduction of 15–80% were observed and the extent of degradation was largely dependent on the polymer composition and the hydrophilic segment (Pluronic) content.

In vitro degradation studies [200] of a family of poly(ester urethane)s (Degrapol^{TM}) have shown that (PBS buffer at 37°C and 70°C) the rate of degradation is predominantly controlled by the number of easily hydrolyzable linkages. Degrapol block copolymers are built from HSs of poly [3-*R*-hydroxybutyrate)-*co*-(3-*R*-hydroxyvalerate)] (PHBV) and copolyester SSs ethylene glycol, poly(glycolic acid)diol and ε-PCL. The study concluded

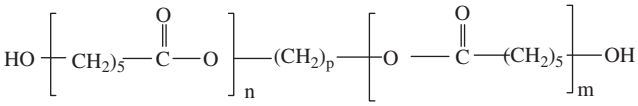
that the degradation rate is determined by the quantity and distribution of weak links in Degrapol; high glycolate-containing polymers degraded rapidly. Borkenhagen *et al*. [201] investigated a series of Degrapol polyester urethanes as nerve guidance channels (NGC). Nerve regeneration along an 8-mm gap transected in the sciatic nerve of rats was demonstrated with NGC fabricated from Degrapol. Over a 24-week period weight losses of 33–88% were observed for polymer with different amounts of PHBV. Inflammatory reactions associated with polymer degradation did not interfere with nerve regeneration.

Guan *et al*. [171] have synthesized a family of polyesterurethaneureas from poly(caprolactone) diol, BDI, lysine ethyl ester or putrescine as chain extender, and investigated the toxic effects of their *in vitro* degradation products. The polymers degraded with $>50\%$ mass loss in buffer, and endothelial cells cultured for 4 days with medium containing degradation products showed no toxic effects; surface modification with RGD peptide further enhanced cell adhesion.

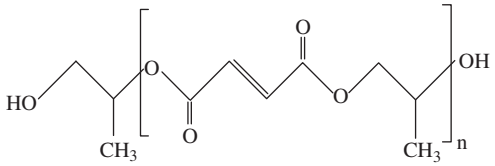
Biodegradable polyurethanes exhibit good biocompatibility as demonstrated in a number of studies summarized above. Numerous *in vitro* degradation studies have demonstrated the degradation of these materials. In most polyurethane compositions, the nature of the SS forming polyol governs the degradation rates, although the diisocyanate structure and relative proportions of soft and hard segments also influence the degradation rates. What is lacking are detailed studies to understand the exact nature of the degradation products, and how those products are resorbed/released from the body.

Injectable biodegradable polymers

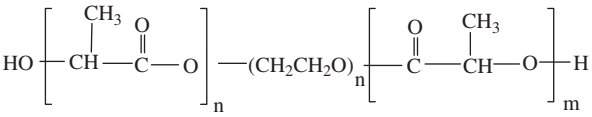
The design of synthetic polymer systems as injectable liquids, gels or pastes has received considerable research interests because of the potential opportunities to develop advanced therapies and products for repairing damaged tissues or organs. These injectable polymer systems have the advantage of employing minimally invasive procedures such as arthroscopic delivery to provide support while the damaged tissues are regenerated. Additionally they may also be useful for delivering cells, growth factors or other promoters to accelerate the tissue regeneration process. The biodegradable synthetic polymers described previously in this review have been experimented for use as prefabricated scaffolds with some success for tissue engineering application, but they have many limitations to adopt as injectable polymer systems that cure *in situ* or by an external trigger. Precursors developed based on the monomers used in many synthetic biodegradable polymers have the potential to be developed as injectable polymers. Figure 6 illustrates few examples of such precursors reported in the literature. This section reviews some of the recently reported synthetic injectable polymer systems with potential for use in advanced medical implants and tissue engineering technologies.



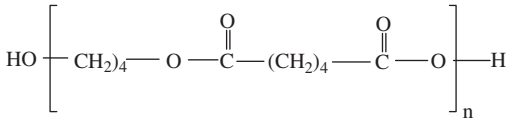
Poly(caprolactone) diol (p = 2, 4 etc)



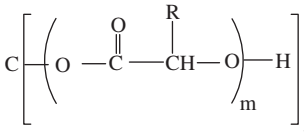
Poly(propylenefumarate) diol



Poly(ethyleneglycol-co-lactic acid) diol



Poly(tetramethyleneadipate) diol

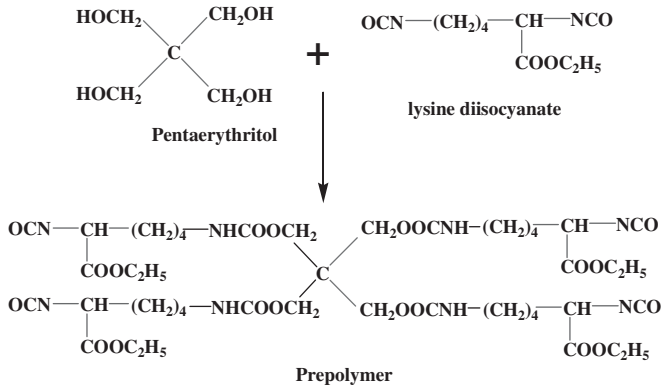


Star polyols of glycolides (R=H) and lactides (R=CH_3)

Fig. 6. Examples of polyols used in biodegradable polyurethanes.

Urethane-based injectable polymers

Synthesis and properties: Gunatillake *et al.* [190–192,202–204] have developed polyurethane prepolymers that can be cross-linked to form both rigid and elastomeric materials (NovoSorb^{TM}) useful in a range of biomedical applications including scaffolds for tissue engineering. The differential reactivity of the isocyanate functional groups in diisocyanates, such as LDI, is used to prepare prepolymers that are liquids at and above ambient temperatures by reacting with multi-hydroxy functional core molecules, such as pentaerythritol. Under controlled reaction conditions, star/hyperbranched prepolymer with isocyanate end-functional groups can be prepared (Scheme 2). For example, reacting a diisocyanate with a core molecule, such as pentaerythritol,



Scheme II. Synthetic route to prepare isocyanate end-functional prepolymer (A).

glucose or glycerol produces isocyanate end-functional prepolymers. A typical example of a prepolymer (Prepolymer A) is shown in Scheme 2. The second component (Prepolymer B) is usually a polyester polyol and suitable polyols include polycaprolactone, poly(ortho esters), poly(glycolic acid), polylactic acid and their copolymers (Fig. 6). The polyol component may be modified by adding a second polyol to alter hydrophilic/hydrophobic characteristics. Reaction of prepolymer A with B (along with other additives if needed) in appropriate proportions produces a cross-linked polymer network. Reaction of prepolymer with an appropriate hydroxyl compounds, biodegradable polyurethane networks can be prepared. With the appropriate choice of precursors, polyurethane with high mechanical strength can be prepared. For example, materials with compressive strength of 260 MPa and compressive modulus over 2 GPa have been reported [192]. These degradable polymers were developed as two-part systems with options to incorporate cells or other biological components to promote cell growth and to polymerize *in situ*. Porous solid polymers can be obtained by reacting with a cross-linker such as water, which generates carbon dioxide during curing. The polymer compositions can be formulated to cure with temperature rise controlled not to exceed body temperature [192].

Both *in vitro* and *in vivo* studies have demonstrated the biocompatibility and degradability of these polymers [205,206].

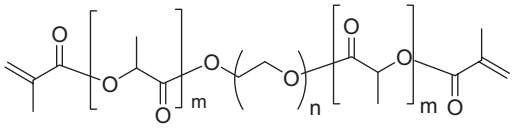
Free radically polymerizable injectable polymers

Synthetic polymers: Free radically polymerizable synthetic polymers have found diverse applications in medicine ranging from simple externally applied scaffolds to internally placed bone cements. Most potential synthetic biomaterials developed for use in this area have injectable consistency, with or without cellular material and cured in a fraction of a second by free radical

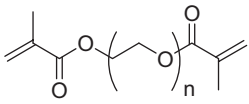
polymerization. The macromer or prepolymers are designed to either cure with photo or redox initiation. The focus of this section will be on free radically cross-linkable biodegradable material that can be resorbed by the body over a period of time. Some have the potential of inclusion of biological material including laboratory-cultured cells that have the necessary phenotype to generate the required tissue. The reader is directed to brief review articles covering literature up to 2001 by Mikos *et al.* on ''Photoinitiated polymerization of biomaterial'' [207] and on ''New directions in photopolymerizable biomaterials'' by Anseth *et al.* [208].

Our group, initially at the Commonwealth Scientific and Industrial Research Organisation (CSIRO) and now at Polynovo Biomaterials, have been interested in the development of an *in-situ* curing polymer that a surgeon could quite rapidly and easily inject to a defective site by arthroscopic means, shaped to fit irregular defectives sites before photo cured to a hard material when desired. We have called the method ''cure on demand'' and patented recently [209]. The core of these multi-arm polymers is designed to be low molecular weight lactic/glycolic homo or copolymers and the terminal ends functionalized with free radically cross-linkable groups. They can be tailored to degrade from very fast to very slow by changing the composition of the polymer chains and depending on the application at hand. Curing is achieved with visible or UV light, is very rapid and typically takes 20–60 s to obtain solid material. The attractions of cure on demand system are the injectability of polymers, making way to surgeons to perform minimally invasive procedures, the ability to cure under physiological conditions (wet environment and 37°C) and when desired, leaving ample time for the surgeon to repair irregular sites and cure when desired with minimal heat generation.

More recently, we have synthesized a variety of different polymers and polymer types, tested *in vitro* and *in vivo* and formulated a library of polymers that are suitable for a variety of applications. These applications vary from orthopedic, cartilage, scaffolds, to matrices for the delivery of biological materials. While initially the main aim was to formulate the material to have an injectable consistency, these prepolymers can be made to putty-like material that cures on demand, to prefabricated films with thickness as low as 100 μm, 3D structures for tissue engineering, etc.



PEG-LA-DMA



PEGDMA

Delivery of chondrocytes for cartilage repair is reported to be successful with PEG-based macromonomers. A group led by Kristi Anseth is a

significant contributor to this area and have investigated the suitability of PEG-based materials for chondrocyte delivery [210]. A blend of linear PEG, chain extended with LA units and end capped with methacrylate groups with poly(ethylene glycol) dimethacrylate (PEGDMA) were used in this investigation. The chondrocytes are encapsulated in a 10–15% mixture of this blend in PBS, photo cross-linked to a hydrogel upon delivery. While the LA links in the polymer are introduced to enhance the degradability of the matrix, the latter dimethacrylate gives the strength by increased cross-link density and hence the mechanical strength, the cross-link density and the rate of degradation is controlled by the relative proportions of the two-blended materials. Chondrocytes encapsulated in these gels were shown to be viable for 6 weeks and produce cartilaginous tissue rich in glycosaminoglycans and collagen. The degradation of the blend with 15% PEGDMA was shown to match closely with the rate at which the cartilaginous tissue in growth.

They have also examined the effect of many other factors that dictate survival of cells in the encapsulant. In one study [211] cross-link density of the blend is varied to investigate the effect of and correlate the rate of degradation of the encapsulant to the evolution of the extracellular matrix components. The degree of cross-linking also affects the mechanical strength of the scaffold material and influence the morphology of the chondrocytes encapsulated in an implant under compressive strain. The study highlights the importance of the optimization of the cross-link density to achieve ideal non-cell deformations and heterogeneity in designing encapsulant materials. Another study [212] has shown that an increase in the thickness of the scaffold material from 2 to 8 mm, a typical defect size in a cartilage, does not compromise the biochemical content of the cellular matrix produced. Cell studies have been conducted using these PEG hydrogels [213–216].

Mallapragada *et al.* [217] have synthesized and characterized copolymers of poly(ethylene glycol) methylether methacrylate (PEGMEM) and 2-(diethylamino)ethyl metacrylate (DEAEM) for biomedical applications including gene delivery. At a ratio of 30:70, PEGMEM:DEAEM, the copolymer is claimed to be water soluble and potentially injectable to the defect site. The cell viability studies carried out have shown the copolymer to be less toxic than the homopolymer of DEAEM.

Cross-linked PVA derivatives (Fig. 7) have been used as hydrogels for cell delivery in many tissue-engineering studies. Preparation of PVA-based hydrogels are generally achieved by functionalization of the many pendant

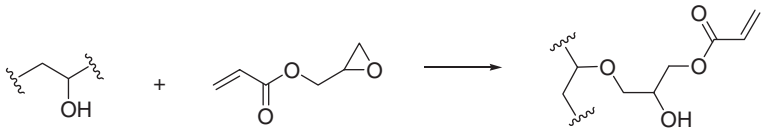


Fig. 7. Acrylate functionalization of PVA.

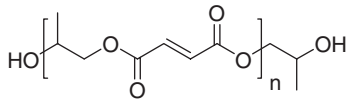
hydroxyl groups with glycidyl methacrylate (West) or methacrylamidoacetaldehyde dimethylacetal (Anseth). The final cross-link density required to give the needed mechanical strength is adjusted by varying the degree of functionalization of the backbone of the PVA polymer. The efficiency by which these polymers can be cross-linked with the photo initiators and characterization of the final hydrogels are well documented in the literature.

West *et al.* [218] have seeded PVA hydrogels with human dermal fibroblasts, cultured, and evaluated for cell viability, proliferation and extracellular matrix production. Viability of cells for 2 weeks with homogeneous cell proliferation and the production of extracellular matrix proteins were observed. Modified with RGD peptides these cross-linkable polymers were found to support increased attachment and proliferation of fibroblasts in a dose-dependent manner. West *et al* has reviewed the advantages of photo polymerizable hydrogels, the photo initiators and the materials in current use.

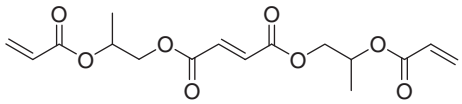
Anseth *et al.* [219] have led a study to design a PVA-based polymeric carrier for chondrocytes in cartilage repair. The key components of the investigated carrier were methacrylate functionalized PVA and chondroitin sulfate, cross-linked by UV light. Both the ingredients were tested individually and in a number of combinations to produce interpenetrating network structures and found to have various swelling and compressive strengths depending on the cross-link densities of the two components. While the cross-linked homopolymer chondroitin sulfate degraded completely in 20 h in the presence of chondroitinase ABC, the 50:50 blend with PVA-MA gave only a mass loss of 25% during the same period. Cell encapsulation work attempted with the same polymers in the presence of a cross-linkable RGD sequence demonstrated cell viability for 3 days. Detailed evaluation of the characterization [220] and degradation behavior of these types of hydrogels have been evaluated and compared to theoretical approaches. Results demonstrate that the theoretical predictions correlated well with mass loss data obtained and with increased cross-link density the complete degradation of the hydrogels increased. The experimental data were later compared to a bulk degradation mathematical model [221].

The group led by Kristi Anseth [222] has developed scaffolds having high porosity (~80%) for bone tissue engineering. In this study [223], a few of cured linear oligomers of LA with ethylene glycol as the core, functionalized with terminal acrylate groups have been evaluated for bone formation. The porous scaffolds were fabricated using a particulate leaching technique with sodium chloride as the porogen. The scaffolds *in vitro* in PBS at 37°C degraded with a 30–60% mass loss in 8 weeks. An *in vivo* rat model [222] based on these polymers to study bone formation in a critical-sized cranial defect with or without adsorbed osteoinductive growth factors has revealed the polymers to degrade in approximately 8 months. While more bone in growth was observed when growth factors were included in the implants compared to

untreated sites, while those that did not have growth factors (only polymer) were primarily filled with fibrous tissue with mild inflammation after 9 weeks.



poly(propylene fumarate)



poly(propylene fumarate) diacrylate

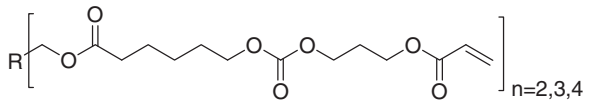
Free radically cross-linkable poly(propylene fumarate)-based networks [224–230] have been extensively investigated for *in vitro* biocompatibility, degradability and cell viability [231,232]. These materials are evaluated as potential matrices to deliver cells in orthopedic applications. Developed as a blend that can be injected, the formulation is composed of a linear macromonomer, a diacrylate functionalized oligomer that is cured with a free radical UV initiator, bis(2,4,6-trimethyl benzoyl) phosphine oxide, at 365 nm. The linear macromonomer is an alternating copolymers of fumaric acid and propylene glycol having number average molecular weight set at 1,700 and 2,600 g/mol while the free radically cross-linkable oligomer is composed of the same fumarate core, end capped with two polypropylene glycol and two terminal acrylate units. The network structures are produced by free radical polymerization of the unsaturated groups within the repeating fumarate units and the terminal acrylate functions. The mechanical properties of the cross-linked polymers, curing profiles, their solution viscosities and heat generation during curing have been separately evaluated [233,234].

Inclusion of cross-linkers in the blend in varied proportions is used to control the cross-link density of the network and is shown to have an influence on cell viability/attachment. Fibroblast attachment is observed to be greatest to networks with the highest double bond conversions and increases with the increase of the acrylate-based cross-linker. This highlights the fact that the central fumarate double bond is less reactive than the acrylate group and participates in a lesser extent in the network formation. While the leachables from the non-cross-linked polymer mixtures were found to be cytotoxic, the accelerated degradation products (1 N NaOH, 60°C) and each of the components of the oligomers, fumaric acid, acrylic acid, etc. separately was found to be non-cytotoxic at low concentrations.

Two other cross-linking agents *N*-vinyl pyrrolidone (NVP), PEG-diacrylate (PEG-DA), have been studied earlier by the same group [235,236]. The latter cross-linker is used to formulate an injectable biodegradable hydrogel, together with oligo[poly(ethylene glycol)fumarate] (OPF), which has been evaluated for cell viability using MSC from rats [237]. The cells are shown to be viable after 2 and 24 h with 80% viable in 24 h for less than 25% (w/v) concentration of OPF oligomer. Although high viability is achieved at these

OPF levels, the general trend is decreased viability with increased fumarate oligomer in the blend. Of the two PEG-DA used, Mn 575 and 3,400, significant increased cell viability is observed for the higher molecular weight PEG-DA. The effect of leachables from the hydrogels have separately been tested for cell viability and once cross-linked these leachable products have been shown to have minimal adverse effects on the viability of MSC with 90% cell viability. The redox free radical initiator system [238] used for these experiments is also shown to have minimal interference with cells, and each component, tested separately, is shown to be non-cytotoxic.

Recently, novel biodegradable amino acid containing anhydride polymers have been developed for orthopedic applications [239]. These oligomers are based on methacrylated aminocarproyl maleamic acid, methacrylated alanyl maleamic acid, triethylene glycol dimethacrylate, etc. to afford novel blends. The compressive strengths for these blends varied from 31 to 114 MPa. The changes in mechanical strength during degradation have also been evaluated.



poly(CL/TMC) diacrylate

Liquid acrylate-endcapped biodegradable copolymers have been prepared by Matsuda *et al.* [240]. The copolymers of ε-caprolactone and TMC are prepared by ring-opening polymerization in the presence of tin(II)2-ethyl hexanoate as catalyst in toluene and the resulting copolymer purified by precipitation. Trimethylene glycol and di, tri and tetra functional PEG derivatives are used as initiators. The hydroxyl-terminated copolymers are subsequently functionalized with acryloyl chloride to afford the cross-linkable prepolymers. Matsuda *et al.* in their investigation have shown that these copolymers cured with the radical initiator camphorquinone (and dimethylaminoethyl methacrylate as sensitizer) preferentially degrade by surface erosion except when PEG is used as the core initiator molecule. In this event the polymer absorb water due to the hydrophilic nature, swells and undergoes surface as well as bulk erosion as expected. Fabrication of sterolithographic microstructured architectures through rapid liquid to solid transformations using a moving UV-light pen and a computer-aided design program has been demonstrated in a subsequent communication [241]. *In vivo* subcutaneous implants in rats and micro-needle-structured surfaces loaded with anti-inflammatory drugs have confirmed the earlier observation of the degradation to be by surface erosion when the core was triethylene glycol.

An initiator is a key component in a free radically cross-linkable formulation. The initiator molecule by interaction with photons in the case of

photo initiation or chemically with the interaction of two species (redox initiators) provides the initially radicals for the terminal double bonds to cross-link together. A wide range of initiators are commercially available for the curing of acrylate type formulations, often developed for coating applications, however, their use in biomedical applications is limited due to uncertainties on how high energy radicals would interact with cellular membranes. Several groups have initiated these studies to demonstrate that some initiators have no adverse effect on cell populations and cause minimal oxidative damage and subsequent cell death. Elisseeff and co-workers [242] have investigated the varied cytocompatibility of a number of free radical initiators on six cell lines. Cellular proliferation rates, growth kinetics and detailed comparison of available photo initiators are described. In another publication, Anseth and associates [243] have investigated the cytocompatibility of UV and visible light photo-initiating systems on NIH/3T3 fibroblasts. Both studies have concluded that the commercial UV initiator Irgacure 2959 is well tolerated by many cell types and is suited to biomedical corrective therapies.

Chemically modified natural polymers: HA is known to be involved in developmental events in the morphogenesis of many embryonic organs such as in cell proliferation in limb development, tendon regeneration and fetal wound repair. It is also known to be a major component of the cardiac jelly during the development of the heart, is non-thrombogenic and non-immunogenic [244]. Combined with these known facts, its relative abundance from natural resources and ease with which it can be modified to a useful biological material, modified HA is regarded to be one of the key chemically modified natural candidate polymers that have found use in the area of biomedical implants.

HA is a polysaccharide, composed of repeating units of *N*-acetyl glucosamine, with many un-functionalized hydroxyl groups. Hence, modification of naturally occurring HA is mostly achieved by functionalizing the hydroxyl groups with the (meth) acrylate group. Many different methods are used to achieve this, but the most common ones being the use of methacrylic acid or methacrylic anhydride in the presence of a base. Following the reaction the methacrylated HA (MA-HA) is often washed, precipitated and dialyzed before use.

Applications that have used modified HA vary from implantable bone, cartilage substitutes, scaffolds for would healing to HA gels being used as matrices for tissue engineering of heart valves. In one of the recent studies carried out by Anseth and co-workers [244] investigated the use of modified HA hydrogel scaffolds as a biological carrier for valvular interstitial cells (VIC). VICs are said to resemble myofibroblasts, which are reported to play and important role in tissue remodeling. In this study, various molecular weights of HA were tested and the degradation products of HA hydrogel and the starting macromers were observed to significantly increase VIC proliferation, the lower molecular

weights exhibiting the greatest stimulation compared to the controls. Addition of low molecular weight HA degradation products to VIC cultures were observed to increase by four- and two-fold in matrix and elastin production, respectively. In addition it was shown that VICs encapsulated with HA hydrogels remained viable with significant elastin production in 6 weeks making way to better understanding of the relationship between HA and VICs.

A new class of biodegradable hydrogels composed of a blend of functionalized poly(D,L)-lactic acid and hydrophilic dextran segments has been synthesized [245]. The unsaturated vinyl groups are separately introduced to the poly(D,L-lactic acid) (PDLLA) segments and dextran by acrolylation in the presence of a base. The mixture is cross-linked in DMSO using a free radical initiator, 5% w/w 2,2-dimethoxy 2-phenyl acetophenone. Many blends with different weight ratios have been prepared, cross-linked and characterized. The swelling ratios for the cross-linked blends have been evaluated and the various blended hydrogels are claimed to have a wide range of water absorption difficult to achieve with pure hydrophilic gels.

HA is known to participate in the differentiation, proliferation and migration of cells during wound healing and hence the attraction in its use in applications in simple and superficial wound applications. The relative abundance of HA from natural resources and the ease with which it can be modified to materials that are of value has made modified HA one of the very attractive implantable biomaterials.

Concluding remarks

Among the many families of synthetic biodegradable polymers explored for various biomedical applications polyglycolides, polylactides and their copolymers remain the most widely investigated. Several products based on these polymers are in clinical use currently. The biodegradability of these polymers as well as the bioresorption of degradation products remains as the main attraction to this family of polymers for further exploitation for use in emerging technologies in the biomedical field. Research efforts over the last two decades have focused on various copolymerization approaches to overcome some of the disadvantages of these polymers. Incorporation of hydrophilic segments to alter mechanical properties as well as to tailor degradation time to suit different applications have produced polymer systems for drug delivery applications and some tissue engineering technologies.

Among other classes of biodegradable polymers, biodegradable polyurethanes offer many advantages, which include inherent good biocompatibility, processing versatility and combinations of structure variations to tailor properties ranging from soft elastomers to rigid materials. These features provide many opportunities to tailor materials to meet the needs of many emerging technologies. Polyphosphazenes and polyanhydrides are two other classes of polymers with useful properties for drug delivery applications.

The development of synthetic injectable polymers systems with capabilities to deliver cell and biological molecules still remains a major area of challenge for biomaterials researchers. Recent developments in urethane-based systems and free radically polymerizable precursors based on polyesters and urethanes have shown very promising results and these two systems have the greatest potential to overcome the many challenges in the delivery of cells and biological molecules, such as growth factors. These polymer systems offer the combination of versatility in tailoring structure to meet mechanical property specifications and degradation times as well as the options to cure *in situ* or on demand for flexibility in delivery employing minimally invasive surgical procedures.

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