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Chapter 3

Degradation of Polyurethanes for Cardiovascular Applications

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1. Introduction

Polyurethanes are a family of polymers used in a variety of biomedical applications but mainly in the cardiovascular field due to their good physicochemical and mechanical properties in addition to a good biocompatibility. Traditionally, segmented polyurethanes (SPUs), have been used in cardiovascular applications (Kuan et al., 2011) as permanent devices such as pacemaker leads and ventricular assisting devices; however, due to their great chemistry versatility, SPUs can also be tailored to render biodegradable systems for the tissue engineering of vascular grafts and heart valves. Therefore many research work have been focused on varying the chemical composition to enhance biostability or more recently to control the biodegradability of polyurethanes depending on specific applications in the cardiovascular field (Bernacca et al., 2002; Stachelek et al., 2006; Thomas et al., 2009; Wang et al., 2009; Hong et al., 2010; Arjun et al., 2012; Styan et al., 2012). In this way, polyurethanes for biomedical applications can be classified in two main types, according their relative stability in the human body as either biostables or biodegradables. In this chapter, general aspects of polyurethanes chemistry are presented first and then, the various types of degradations that can affect these polymers both *in vivo* and simulated *in vitro* conditions. Emphasis is also made on the mechanism of degradation under various conditions and the techniques used for following the changes in their properties.

2. Chemistry of polyurethanes

2.1. Synthesis of polyurethanes

Polyurethanes (PU's) properties depend both on the method of preparation and the monomers used. In general, PU's can be prepared in one shot process or more commonly by a two step method, especially for the case of segmented polyurethanes (SPU's). These materials are thermoplastic block copolymers of the (AB)n type consisting of alternating sections of hard segments, composed of a diisocyanate and a low molecular weight diol chain extender, and soft segments, generally composed of various types of polyols, also called macrodiols. In the two steps method for SPU synthesis, a prepolymer is first obtained and then chain extended as illustrated in Figure 1. In the first step, an excess of the diisocyanate reacts with the soft segment polyol to form the prepolymer. Here, the characteristic urethane linkages are formed through the reaction between the isocyanate groups and the hydroxyl-terminated end groups of the polyol. In the second step, the low molecular weight chain extender is used to link the prepolymer segments yielding a high molecular weight polymer. During this stage, additional urethane functional groups are formed when using a diol chain extender whereas ureas are produced when a diamine is used.

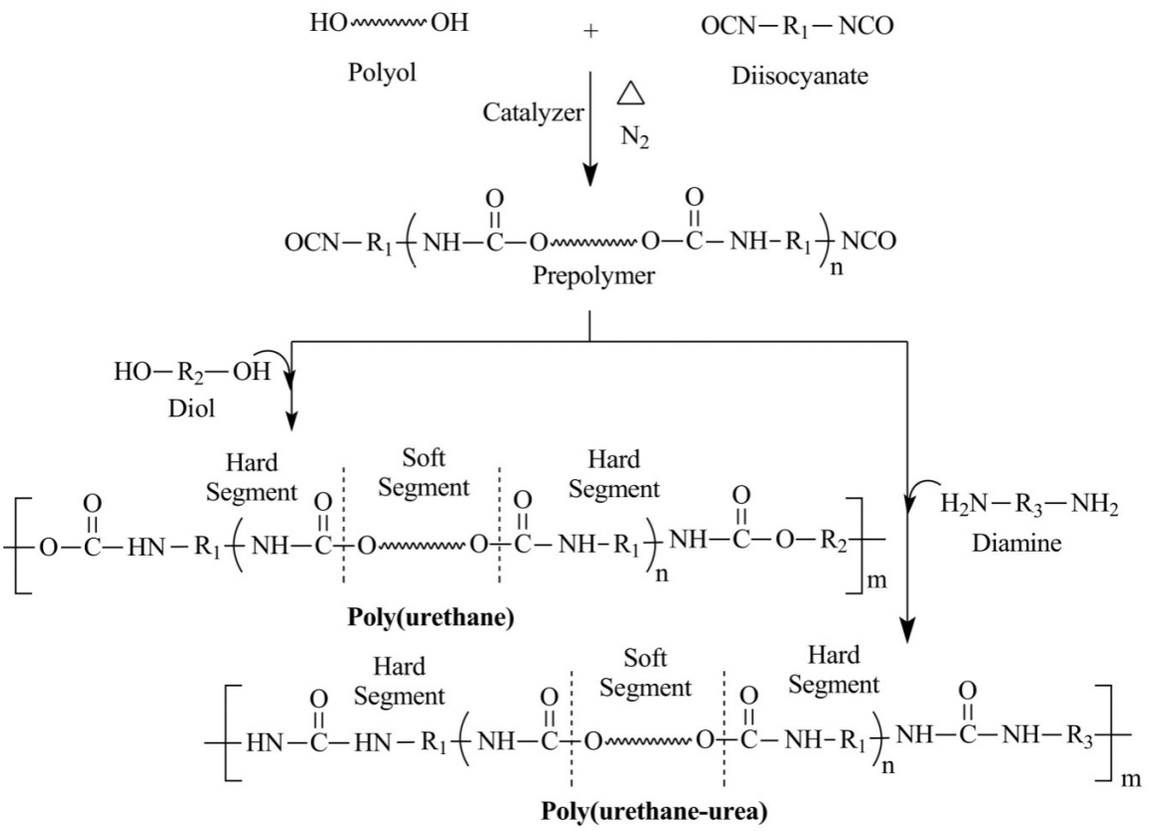

Figure 1. Standard two-step reaction to prepare segmented poly (urethane)s and poly(urethane-urea)s

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The properties of polyurethanes as those shown in Figure 1 depend on the various types of monomers that are used during their manufacturing (see Table 1). Historically, biostable polyurethanes were first developed by using polyether type of polyol and different aromatic diisocyanates. Further developments in this area were focused on the substitution of the polyether macrodiol by novel hydrocarbon, polycarbonate or siloxane macrodiols (Gunatillake et al., 2003) or a combination of these which in general are responsible for the flexibility of the SPUs (Król, 2007). In addition to the polyol chemical composition, their molecular weight and concentration have an important effect in the polyurethane behavior. They can be incorporated in various concentrations but up to 50-75% of the polyol is common.

Commercial and experimental polyurethanes have been synthesized by the combination of the aforementioned monomers. Poly(tetramethylene oxide) (PTMO) is the most common polyether in conventional medical formulations (Silvestri et al., 2011). Thus, for example, the Pellethane® 2363 80A and Elasthane™ 80A are poly(ether-urethane)s obtained by the reaction of PTMO, MDI and BD monomers; Tecoflex® by Thermedics is also a poly(ether-urethane) synthesised by the reaction of PTMO, HMDI and BD monomers while Biomer® is a poly(ether-urea-urethane) synthesized from PTMO, MDI and ethylenediamine. Bionate®, Myo Lynk™ and Chronoflex are polyurethanes prepared with polycarbonate diol. These commercial polyurethanes are typical examples of biostables polymers.

The use of vegetable raw materials containing hydroxyl groups such as starch, castor oil, vegetable oil, natural rubber, cellulose, etc, makes possible to obtain biodegradable polyurethanes (Krol, 2007; Aranguren et al. 2012). However, ester polyol commonly used to synthesize biodegradable polyurethanes are polycaprolactone, polylactic acid and adipate polyols. Polyethyleneglycol is a polyether which has been copolymerized with poly lactic acid and/or polycaprolactone because its higher hydrofilicity can accelerate the biodegradation when this is required (Guan et al., 2005b; Wang et al., 2011b).

The most frequently used diisocyanates in the synthesis of biodegradable polyurethanes for biomedical applications are aliphatic or cycloaliphatic as MDI and TDI which can release carcinogenic and mutagenic aromatic diamines (Heijkants *et. al.*, 2005). Aliphatic diisocyanates are less reactive than the aromatic counterparts but have a greater resistance to hydrolysis compared to aromatic diisocyanates, although this resistance frequently results in lower mechanical properties (Gogolewski, 1989).

In general, there are two types of compounds that are generally used as chain extenders, diols or diamines, which can either be aliphatic or aromatic, depending on the required properties in the synthesized polyurethanes. New chain extenders, including amino acids have been also used during polyurethane synthesis as isocyanates can react vigorously with amine, alcohol, and carboxylic acids (Thomson, 2005). These novel chain extenders have been used to synthesize biodegradable polyurethanes (Skarja et al., 1998; Marcos-Fernández et al., 2006; Sarkar et al., 2007).

Monomeric component	Type	Chemical compound	Type of polyurethanes
Polyol (macrodiols)	Polyethers	Poly(ethylene oxide) (PEO)	Biostables, Biodegradables (Sarkar et al., 2009; Lu et al., 2012)
		Poly(propylen oxide) (PPO)	Biostables, Biodegradables (Francolini et al., 2011)
		Poly(tetramethylene oxide) (PTMO)	Biostables (Silvestri et al., 2011; Jiang et al., 2012)
		Poly(caprolactone) (PCL)	Biodegradables (Sarkar et al., 2009; Lu et al., 2012)
		Poly(lactic acid) (PLA)	Biodegradable (Wang et al., 2011a)
		Poly hydroxyalkanoates (PHA)	Biodegradables (Li et al., 2009; Liu et al., 2009)
		Poly(ethylene adipate) (PEA)	Biodegradables (Macocinschi et al., 2009)
	Others	Poly(carbonate) (PCU)	Biostables (Spirkova et al., 2011)
		Polybutadiene (PBD)	Biostables (Thomas et al., 2009)
		Poly(dimethylsiloxane) (PDMS)	Biostables (Park et al., 1999; Madhavan et al., 2006)
Diisocyanate	Aromatic	Methylene diphenyl diisocyanate (MDI)	Biostables (Gunatillake et al., 1992; Styan et al., 2012)
		2,4-toluene diisocyanate (TDI)	Biostables (Labow et al., 1996; Basak et al., 2012)
	Aliphatic	4,4'-methylene bis(cyclohexyl isocyanate) (HMDI)	Biostables, Biodegradables (Thomas et al., 2009; Chan-Chan et al., 2010)
		1,6- hexamethylene diisocyanate (HDI)	Biostables, Biodegradables (Wang et al., 2011a; Baudis et al., 2012)
		1,4-butane diisocyanate (BDI)	Biostables, Biodegradables (Heijkants et al., 2005; Hong et al., 2010)
		Isophorone diisocyanate (IPDI)	Biostables, Biodegradables (Jiang et al., 2007; Ding et al., 2012; He et al., 2012)
		L-lysine ethyl ester diisocyanate (LDI)	Biodegradable (Abraham et al., 2006; Guelcher et al., 2008; Han et al., 2009; Wang et al., 2011b)
Chain Extender	Diols	Ethylene glycol (EG)	Biostables, Biodegradables (Król, 2007)
		Diethylenglycol	
		1,4-butanediol (BD)	
		1,6-hexanediol (HD)	
	Diamines	Aliphatic diamines	
		Aromatic diamines	
	Others	Amino acids	Biodegradables (Kartvelishvili et al., 1997; Skarja et al., 1998; Marcos-Fernández et al., 2006; Sarkar et al., 2007; Chan-Chan et al., 2012)

Table 1. Common monomers used in the synthesis of biostable and biodegradable polyurethanes

During polyurethane synthesis, several side reactions may occur leading to branching, crosslinking, or changes in the stoichiometry of reactants. For example, undesirable branching and crosslinking may occur at elevated temperatures between isocyanates and urethanes (Allophanate formation) and isocyanates and ureas (Biuret reactions). Furthermore, the

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presence of water causes isocyanate groups to form unstable carbamic acids, which subsequently decompose to amines with the liberation of CO_2 gas (see Figure 2). These newly formed amines react with isocyanates to form ureas, thus changing reactant stoichiometry and leading to lower molecular weight polymers. Additives are sometime used for improving specific properties of the polyurethane, for example Vitamin E and Santowhite®, two hindered phenolic antioxidants, prevents oxidative chain scission and crosslinking of poly(ether urethane) by capturing oxygen radicals (Schubert et al., 1997; Christenson et al., 2006). Di-tert-butylphenol and bisphosphonates have been incorporated to promote bromoalkylation of urethane nitrogens in prepolimerized polyurethanes to inhibit the oxidation or calcification (Alferiev et al., 2001; Stachelek et al., 2007). Other compounds as fluorocarbon or polydimethylsiloxane end groups have been attached to the surface of polyurethanes in order to enhance their biostability and hemocompatibility (Ward et al., 2007; Xie et al., 2009; Jiang et al., 2012).

In general, monomer type and stoichiometry, type and concentration of catalyzer, temperature and moisture, and the use of additives are important in parameters for controlling the properties of these polymers.

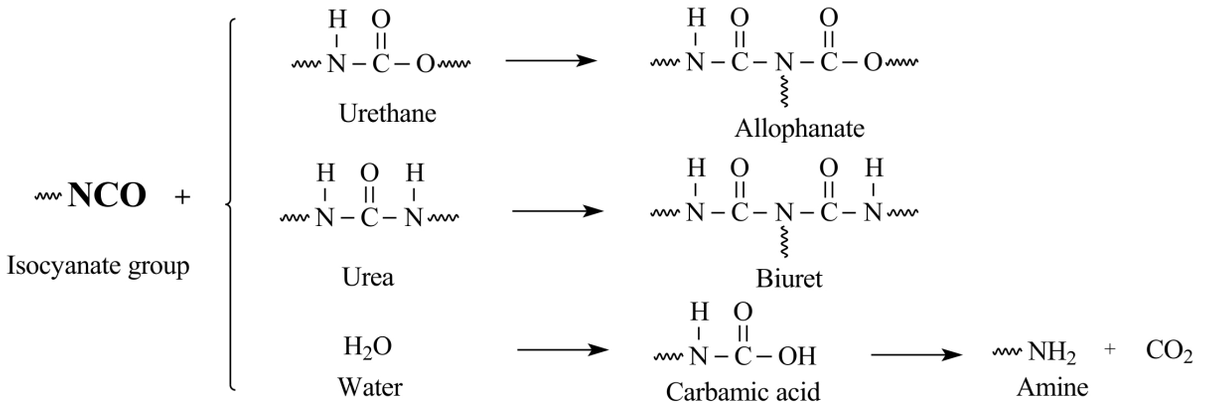

Figure 2. Secondary reactions involved during polyurethane synthesis

3. *In vivo* degradation

SPU´s traditionally has been used in medical devices due to their excellent mechanical properties and an acceptable hemocompatibility. However, in the long term they suffer from poor biostability (Santerre et al., 2005). The main reason of this behavior is that living tissues are a very aggressive environment and even when the degradation of these polymers can be simulated by *in vitro* experiments, after *in vivo* usage they can be severally degraded. The *in vivo* failure of polymeric cardiovascular devices has been attributed to a combination of hydrolysis, oxidation, environmental stress cracking and calcification. However, depending on the composition of the polymer one of these predominate over the other.

Polymer degradation in the biological environment results from the synergistic effects of the enzymes present in biological fluids, oxidizing agents and mechanical loads. For example, α-2-macroglobulin, cholesteryl esterase, A2 fosfolipase, K protease and B Cathepsin are enzymes that are known to degrade polyurethanes (Zhao et al., 1993; Dumitriu, 2002). Even when some enzymes require very specific biological substrates, some of them seem to recognise and act over non biological substrates such as polymers (Santerre et al., 2005). White blood cells play also an important role in the *in vivo* degradation. Some experiments conducted using implanted metallic cages have shown that neutrophiles, monocytes, monocyte derived macrophages (MDM) attach to polymer surfaces, leading to the presence of multinucleated giant cells and foreign body reaction. It is generally accepted that one of the immediate immune responses by the body is the release of reactive oxygen species (ROS). In addition, neutrophils and monocytes release hypochlorous acid (HClO) and lysosomal hydrolases as part of their reaction to foreign surfaces. It has been also reported that activated MDM release ROS leading to the formation of hydrogen peroxide (Christenson et al., 2006; McBane et al., 2007). In addition, during the inflammatory reaction macrophages are able to lower the local pH up to 4. This condition can be simulated by following the ISO 10993 section 5.

Suntherland et al. (Sutherland et al., 1993) suggested that poly(ether urethanes) (PEU) cannot be significantly degraded by preformed products of phagocytic cells (such as cationic proteins and proteases) or by activated oxygen species such as superoxide and hydrogen peroxide. In view of the chemically stable nature of PEU, they hypothesized that the *in vivo* degradation of these materials might involve attack by chlorine-based and/or nitric oxide (NO)-derived oxidants, major oxidative products of activated phagocytes. Therefore, they exposed Pellethane to polymorphonuclear neutrophils (PMN) isolated from heparinized venous blood drawn from normal adult donors. The results reported support the idea that PMN-generated chlorine compounds are likely responsible for initial damage to PEU after brief implantation and in addition to macrophage-derived NO and/or peroxynitrite (ONOO-).

Van Minen et al. (van Minnen et al., 2008) studied the *in vivo* (26 weeks of subcutaneous implantation in rats and 2.5 years in rabbits) degradation of porous aliphatic SPU based on butanediisocyanate, DL-lactide-co-caprolactone soft segments and extended with BD-BDI-BD block urethane. After 1 week macrophages were observed along with giant cells and after 4 week phagocytosis was observed. The number of these cells was reduced with time but after 3 years fragments of the polymer remained. Furthermore, few macrophages were observed in the lymph nodes suggesting their local degradation.

Adhikari et al. (Adhikari et al., 2008) studied the *in vivo* degradation of two-part injectable biodegradable polyurethane prepolymer systems (prepolymer A and B) consisting of lactic acid and glycolic acid based polyester star polyols, pentaerythritol (PE) and ethyl lysine diisocyanate (ELDI) using sheep femoral cortical defect model. No adverse acute or chronic inflammatory tissue response was noted in the interface tissues of the precured polymer implants. By 6 weeks, there was direct apposition of new bone to the polymers. New bone and fibrovascular tissue was also observed within the porous

spaces of the precured polymers by 6 weeks, and fluorochrome analysis suggested that this bone had started to be laid down at between 4 and 5 weeks. The polymer without β-tricalcium phosphate (TCP) showed histological evidence of some degradation by 6 weeks with progressive increase in polymer loss by 12 and 24 weeks. The polymer with β-TCP showed no evidence of degradation at 6 weeks and only minimal loss at 12 weeks. By 12 weeks, there had been considerable degradation of the polymers and at week 24, polymer was completely degraded.

The *in vivo* degradation of segmented poly(urethane urea)s (SPUUs) with hard segments derived only from methyl 2,6-diisocyantohexanoate (LDI) and PCL, PTMC (polytrimethylene carbonate), P(TMC-co-CL), P(CL-co-DLLA), or P(TMC-co-DLLA) as soft segment was conducted by Asplund et al. (Asplund et al., 2008). The *in vivo* study of SPUU-PCL using male Sprague-Dawley rats displayed the typical foreign body response seen with most inert polymeric implant materials. The reaction at 1 week thus displayed an infiltration of ED1 positive macrophages closest to the implant surface, an outside layer of fibroblasts and some collagen formation. At 6 weeks, the foreign body capsule had matured, displaying lower numbers of interfacial macrophages and an increased amount of collagen in the fibrotic capsule. The thickness of the foreign body capsule was similar to the controls. These observations seemed also to be reflected in the number of ED1 positive macrophages, as well as in the total number of cells throughout the reactive capsule.

Hafeman et al. (Hafeman et al., 2008) synthesized polyurethane scaffolds by one-shot reactive liquid molding of hexamethylene diisocyanate trimer (HDIt) or lysine triisocyanate (LTI) and a polyol as hardener. Trifunctional polyester polyols of 900-Da and 1,800-Da molecular weight were prepared from a glycerol starter and 60% ε-caprolactone, 30% glycolide, and 10% D,L-lactide monomers, and stannous octoate catalyst. Tissue response was evaluated by subcutaneous implantation in male Sprague-Dawley rats for up to 21 days. During this time, initial infiltration of plasma progressed to the formation of dense granulation tissue. All of the implants showed progressive invasion of granulation tissue with little evidence of an overt inflammatory response or cytotoxicity. Fibroplasia and angiogenesis appeared to be equivalent among the different formulations. Extracellular matrix with dense collagen fibers progressively replaced the characteristic, early cellular response. The LTI scaffolds exhibited a greater extent of degradation at 21 days, although the incorporation of PEG into the HDIt scaffold accelerated its degradation significantly. Degradation rates were much higher *in vivo*. With time, each of the materials showed signs of fragmentation and engulfment by a transient, giant cell, foreign body response. After the remnant material was resorbed, giant cells were no longer evident.

Khouw et al. (Khouw et al., *2000*) reported that the foreign body response to degradable materials differs between rats and mice. van Minnen et al., (van Minnen et al., 2008) also suggested that it is possible that the response between rats and rabbits differs as well, due to the faster degradation in the rabbit. This may be related to differences at the enzymatic or cellular level, but also to the highly mobile and well vascularized skin of the rabbit, as compared to the rat.

3.1. Calcification

Mineralization or calcification (formation of various types of calcium phosphates such as apatite) is a well documented event in various medical devices, especially in those used in the cardiovascular field. Calcification is in fact, the most common macroscopic cause of failure in heart valves including those made of polyurethanes (Santerre et al., 2005). Even when calcification has been identified in heart valves, *in vitro* experiments on SPU showed little mineralization and associated exclusively to failure regions, indicating that the SPU´s have a lower intrinsic capacity for calcification compared to bovine bioprosthesis (Bernacca et al., 1997).

3.2. Thrombosis

Plasma protein adsorption is well accepted as one of the first events to occur when blood is in contacts with a biomaterial. These adsorbed proteins mediate the subsequent interactions of cells and platelets with the surface and may induce thrombus formation, which remains one of the major problems associated with the long-term use of blood-contacting medical devices. The surface properties of the implanted materials are determinant in protein adsorption and biological interactions with the material. The effects of various physicochemical properties such as surface hydrophilicity/hydrophobicity balance, surface charge density, ability to form hydrogen bonds, and chemical composition of biomaterials on protein adsorption as well as subsequent blood platelet adhesion have been investigated (Xu et al., 2010).

Antithrombogenicity is one of the essential requirements for a vascular graft, but it is very difficult to achieve. There are two common approaches employed to attain this goal. One is to develop biomaterials with inherent antithrombogenicity or to use surface modified biomaterials with an anticoagulant. The other approach is to quickly and completely endothelialize the inner surface of the tubular scaffolds, thereby, reducing thrombogenicity (Yan et al., 2007).

Thrombosis is a leading cause of vascular graft failure in small-diameter prostheses, where it leads to decreased flow or occlusion. In addition to inducing acute or subacute failure of grafts, it may be a cause of late failure owing to thrombosis superimposed on stenosis due to other causes of vessel narrowing, such as intimal hyperplasia. Methods to improve vascular grafts (e.g., antithrombotic therapy) have been shown to be beneficial in decreasing graft occlusion after surgery. Agents known to inhibit thrombogenesis or promote anticoagulation (e.g., heparin, prostaglandin E1, hirudin, dipyridamole, tissue factor pathway inhibitor and aspirin) have also been bound to the lumen of the synthetic vessels (Wang et al., 2007; Lu et al., 2012).

3.3. Environmental stress cracking and metal ion oxidation

Traditionally, SPUs have been used as permanent devices such as pacemaker leads insulation and ventricular assisting devices. When used as pacemaker lead insulators, they substitute silicone rubbers and have been used as biostable polymer for outer or inner insulated

coating of coaxial bipolar pacemakers. Unfortunately, decades of experience showed that they were degraded by environmental stress cracking (ESC) or metal ion oxidation (MIO) or even autooxidation (AO) within a period of 28 and 34 months.

Environmental stress cracking includes crack formation and propagation on the surface of the polyurethane (Santerre et al., 2005). However, this type of degradation is a combination of the *in vivo* chemical degradation with the presence of mechanical stresses. In other words, polymer chain scission caused by the chemical degradation, create microscopic defects that are augmented by the presence of mechanical loads, leading to the formation of cracks on the surface (Wiggins et al., 2003). ESC it is also enhanced by the presence of residual stresses in the polymeric surface introduced during manufacturing and not eliminated during polymer annealing (Santerre et al., 2005).

The generally accepted *in vivo* degradation MIO mechanism involves the presence of hydrogen peroxide (H_2O_2) produced by a variety of inflammatory cells (McBane et al., 2007; Chandy et al., 2009) and divalent metal ion such as Co^{2+} released from the lead. This reaction is known as the Haber-Weiss reaction and yields hydroxyl radicals that can attack α-methylene groups in the polyether (PTMO based polyurethanes) to render hydroperoxydes with decompose in the presence of divalent cations rendering carbonyl groups that can accelerate (catalyse) further this decomposition (Kehrer, 2000; Wiggins et al., 2001). Polyether diol based polyurethanes are prone to oxidation and environmental stress cracking (ESC) (Król, 2007). However, polycarbonate based-polyurethanes (PCNUs) have been proven superior to polyether and polyester PUs, especially in terms of reduced ESC and metal ion oxidation (MIO), although they are still susceptible to hydrolysis (McBane et al., 2007).

Environmental stress cracking, calcification and thrombosis only became evident after a sufficiently long-term implantation of several years. For biodegradable PUs, which are designed to degrade in a relative short period (several months), the effective degradation mechanisms are hydrolysis with or without the assistance of enzymatic catalysis (Chen et al., 2012).

4. *In vitro* degradation to simulate *in vivo* degradation

In vivo experimentation using an animal model is not always available for elucidating the degradation mechanism of polyurethanes. Instead, various *in vitro* experiments have been designed to simulate their *in vivo* degradation. Among these tests, hydrolytic degradation has been conducted using distilled water (at elevated temperature), strong acids and alkalies, and sometimes physiological conditions using Phosphate Buffer Saline (PBS) as degradating media.

4.1. Hydrolytic degradation

Degradation of segmented polyurethanes through hydrolysis depends strongly not only on the chemical composition of the soft segment, when is the major component, but also on the

rigid segment chemistry. It is generally accepted that water absorption is a necessary condition for hydrolytic degradation of materials. Therefore, in a typical hydrolytic degradation test the rate of water absorption (or sample weight gain) can be correlated with sample weight loss (Mondal et al., 2012).

The presence of labile ester linkages in PCL containing polyurethanes makes them susceptible to degradation in the presence of water (Gunatillake et al., 1992; Nakajima-Kambe et al., 1999; Kannan et al., 2006). This type of reactions is catalysed by the presence of acids or alkaline compounds. In some cases, the acid is produced by the degradation of the soft segment; caproic acid in the case of PCL or lactic acid in the case of PLA. Polyester urethanes are more prone to hydrolytic degradation although they are more resistant to oxidative environments as can be observed in Table 2, where PCL based polyurethanes (BSPU1 and BSPU2) and a commercial polyether polyurethane (Tecoflex) are compared (Chan-Chan et al., 2010).

	H_2O	NaOH 5M	HCl 2N	H_2O_2 30 wt.%
BSPU1*	1.46 ± 0.08	63.42 ± 7.63	82.70 ± 2.60	13.08 ± 3.35
BSPU2*	6.15 ± 1.35	87.23 ± 4.76	52.65 ± 13.26	19.07 ± 7.01
Tecoflex	0.63 ± 0.3	1.66 ± 0.66	1.48 ± 1.62	2.16 ± 1.47

* BSPU's were prepared with PCL, HMDI and either butanediol (BSPU1) or dithioerythritol (BSPU2) as chain extenders.

Table 2. Polyurethane mass loss (%) after degradation under hydrolytic and oxidative accelerated conditions

Because of the susceptibility of the ester groups to hydrolysis, biodegradable poly(ester urethanes) degrade *in vitro* through bulk erosion via chain scission. During hydrolysis, new carboxylic acid groups are formed that auto-catalyze the degradation, leading to faster degradation in the bulk than at the surface. Thus, a decrease in molecular weight preceding the loss of mechanical properties and weight loss is typical for such degradation. In addition, an increase in crystallinity is observed, if the soft segment contains a crystalline fraction. Polyesters in the soft segment will, therefore, increase the effect of hydrolysis compared with polyether or polycarbonates (Ma et al., 2012).

Tanzi et al. (Tanzi et al., 1991) degraded various commercial polyurethanes used in the cardiovascular field among them Cardiothane 51, Pellethane 2363 80A, Estane 5714 Fl, Estane 58810 and Biomer. The degradation was conducted in water or alkaline borate buffer (pH 10) at 37°C, 60°C and 85°C from 96 h to 168 h. They found that after hydrolytic degradation in distilled water at 85°C for 96 h, borate buffer during 96 h at 60°C and borate buffer during 168 h at 37°C there were no changes in tensile properties although a reduction in molecular weight was reported.

Polyester urethanes based on methylene-bis(4-phenylisocyanate) (MDI), BD and polyadipate diol were prepared by Pretsch (Pretsch et al., 2009) and accelerated degradation studied in distilled water at 80°C where the degradation process was followed by DSC. It was found that the intensities of the melting peaks and therefore the crystallinity of the soft segments

increase after one day. Then, two main degradation scenarios were proposed: first, a hydrolytic scission of polymer chains in the molten soft segments take place, which is accelerated by the ''high'' immersion temperature; second, and on top of it, there is an annealing effect. For example, the domains of segmented polyurethane elastomers may become unstable at high temperatures and mixing of hard and soft segments is enforced.

Wang et al. (Wang et al., 2011a) prepared segmented polyurethanes based on poly(D,L-lactic acid)diol, hexamethylene diisocyanate (HDI) and with either peperazine (SPU-P), 1,4-butanediol (SPU-O) or 1,4-butanediamine (SPU-A) as chain extenders. The degradation process was conducted in double distilled water at 37°C and 50 rpm. For these SPUs, acidic groups from the degradation of PDLLA and BD could reduce the pH value of medium, while the dissolution of the hard segment (amide group and carbamide) could alkalize the medium; after 12 weeks, the pH values of SPU-O, SPU-A and SPU-P were 2.57, 3.87 and 3.71, respectively. These results suggest that the chain extender can play a main role in the degradation mechanism as using an alkaline chain extender can neutralize the acidity, the hydrophilicity and hydrolysis sensitivity of these bonds.

4.2. Oxidative degradation

Polyether urethanes (PEU) are readily degraded by oxidative conditions (Stachelek et al., 2006). Furthermore, the presence of metallic ions such as cobalt accelerates this process (Gunatillake et al., 1992; Dumitriu, 2002; Santerre et al., 2005). The MIO mechanism was reproduced *in vitro* by immersing a lead into a hydrogen peroxide solution. In a different *in vitro* test, a sealed PEU tube containing cobalt metal in the center was immersed into a 3% hydrogen peroxide solution and MIO was observed on the inner surface of the tube. The cobalt ion and hydrogen peroxide react to form hydroxyl radicals, simulating the oxidative radicals present at the material-macrophage interface.

Takahara et al. (Takahara et al., 1991) degraded SPU´s based on MDI, BD (50% rigid segment content) and various polyols using 0.1 M $AgNO_3$ oxidative solution. They found a reduction in mechanical strength of those SPU´s based on PTMO due to surface cracking related to ether scission upon oxidation.

Suntherland et al. (Sutherland et al., 1993) degraded Pellethane 2363 80A using 10 mM HClO in phosphate buffer (PB) at 25°C. In addition, peroxynitrite (ONOO-) degradation was achieved via the oxidation of hydroxylamine in an oxygen atmosphere at elevated pH. They observed a significant reduction in molecular weight, increase in polydispersity index and an increasing content of oxygenated species on the polymer surface.

Tanzi et al. (Tanzi et al., 2000) studied the oxidative degradation of polyether (Pellethane 2363 80A) and polycarbonate (Corethane 80A, Bionate 80A and Chronoflex AL 80A) urethanes in 0.5 N nitric acid (acidic) and sodium hypochlorite (4% Cl_2, alkaline) up to 14 days at 50°C and under constant strain (100%). It was found that PEU were more degraded under alkaline oxidation (HClO) mainly in the absence of applied strain while PCU was more affected by HNO_3.

Our own work using Tecoflex as model PEU degraded in H_2O_2 did not show significant changes in FTIR absorptions and only small differences in the bands located at 3330 cm^{-1} and 1660 cm^{-1} were observed (see Figure 3), although this was clear when the polyol was tested alone. However, TGA revealed that their degradation temperature were lowered and the amorphous content determined by XRD only exhibited a little changes (Chan-Chan et al., 2010).

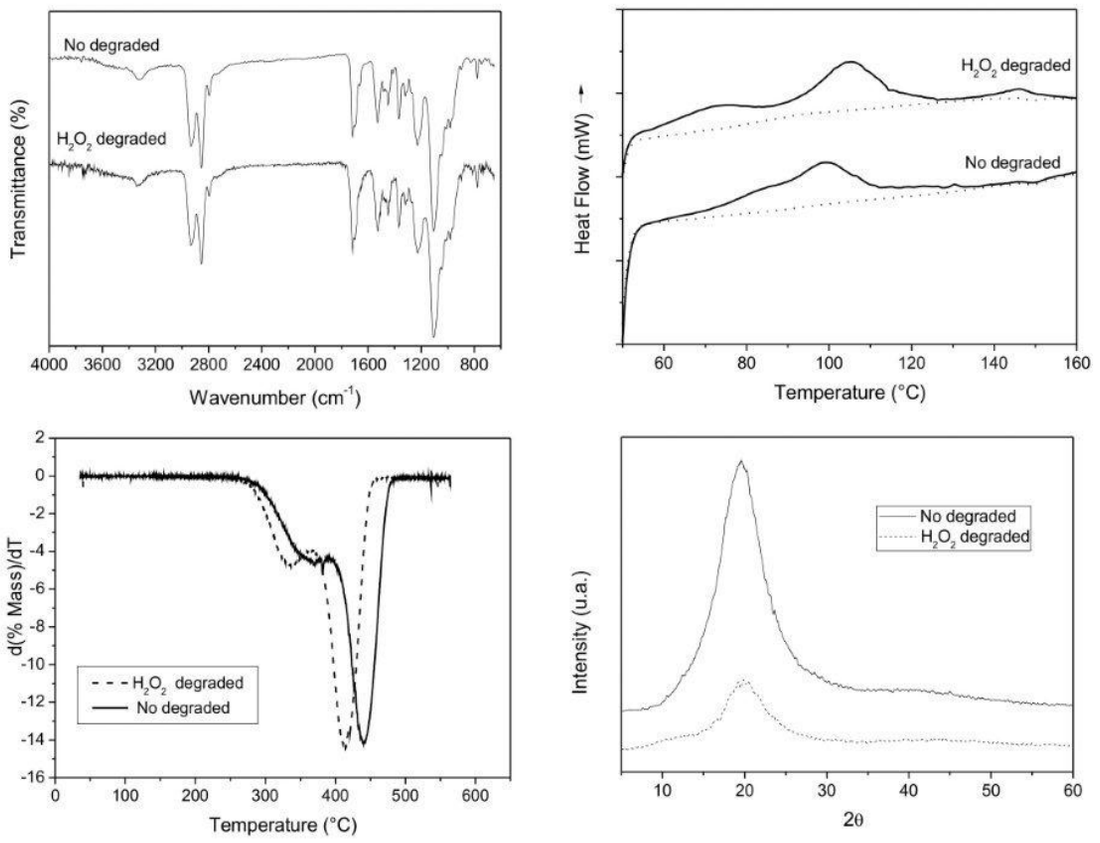

Figure 3. Chemical and structural changes in Tecoflex after degradation under oxidative conditions

4.3. Degradation in physiological media

Poly(ester urethane)urea (PEUU) and poly(ether ester urethane)urea (PEEUU) from polycaprolactone, polycaprolactone-b-polyethylene glycol-b-polycaprolactone, BDI and putrescine were prepared by Guan et al. (Guan et al., 2005a) and degraded in phosphate buffered saline (PBS, pH=7.4) at 37°C; scaffold degradation was related to the porosity and polymer hydrophilicity. The scaffolds exhibited progressive mass loss over the 8-week period ranging from 13.3% to 20.7% for PEUU scaffolds and from 25.4% to 47.3% for PEEUU scaffolds. In this study, the polymer films and scaffolds did not show evidence of an autocatalytic effect during the monitored degradation process. Furthermore, the presence of BDI and 1,4-butanediamine in the hard segment of PU yielded putrescine as degradation product, which

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is already present in the body and has been implicated as an important mediator of cellular growth and differentiation in response to growth factors.

Two gelatin based poly(ester urethane) were prepared by Sarkar et al. (Sarkar et al., 2006) using polyethylene lactate ester diol as a soft segment, and degraded in phosphate buffer saline solution (pH 7.4) at 37°C in a Biochemical Oxygen Demand (BOD) incubator shaker. It was found that the weight loss (up to 45.7% in 30 days) occurred due to the hydrolytic degradation of the gelatin based polyester urethane scaffold by PBS solution and it was proportional to the gelatin content.

Sarkar et al. (Sarkar et al., 2008) prepared segmented polyurethanes using polyethylene glycol (PEG) or poly caprolactone diol (PCL) as the soft segment while hexamethylene diisocyanate (HDI) or dicyclohexylmethane 4,4-diisocyanate (HMDI) were used with desaminotyrosyl tyrosine hexyl ester (DTH) as the chain extender in the rigid component. For degradation in PBS (0.1M, pH 7.4 containing 200 mg of sodium azide) samples were incubated at 37°C. It was found that PEG-based polyurethanes degrade at a faster rate compared with PCL-based polyurethanes due to their hidrophillicity and that this effect was marked when using high molecular weight PEG. It was also found that more amorphous SPU (i.e. exhibiting more phase mixing and therefore more urethane linkages H-bonded with the soft segment), such as those prepared with HMDI, degrade faster as they absorb more water.

Knight et al. (Knight et al., 2008) studied new hybrid thermoplastic polyurethane (TPU) system that incorporates an organic, biodegradable poly(D,L-lactide) soft block with a hard block bearing the inorganic polyhedral oligosilsesquioxane (POSS) moiety and degraded them in PBS buffer at 37 °C over a 2 months period. They found that less than 4% of the original mass elutes from the sample after a month in the buffer, most likely from chain ends on the surface of the sample undergoing hydrolysis. Although only a small mass loss was observed, the molecular weight of the samples dropped dramatically after only one week to 40% of the initial molecular weight.

Biodegradable ionic polyurethanes (PUs) were synthesized from methylene di-p-phenyl-diisocyanate (MDI), polycaprolactone diol (PCL-diol) and N,N-bis (2-hydroxyethyl)-2-aminoethane-sulfonic acid (BES) by Zhang et al. (Zhang et al., 2008). *In vitro* degradation of the PUs was evaluated by recording the samples' weight loss, molecular weight changes, and mechanical properties changes over time in PBS buffer solution at 67°C to accelerate degradation. Although there was a 20% molecular weight reduction, degradation rate was lower in those PUs containing sulfonic acid compared to PU´s without this chain extender. This was explained in terms of their higher phase separation.

Segmented polyurethane based on poly(ε-caprolactone), ethyl lysine diisocyanate or hexamethylene diisocyanate in combination with ethylene glycol or ester from ethylene glycol and lactic acid (2-hydroxyethyl 2-hydroxypropanoate) were degraded *in vitro* (0.1 M phosphate buffered saline at 37°C in a shaken incubator set at 50 rpm (ASTM F 1635)) over a 1 year period (Zhang et al., 2008). It was found that all polyurethanes exhibited considerable molecular weight decrease over the test period and ester chain extender polyurethanes showed

the highest mass loss and that it was directly proportional to hard segment not to the PCL used as soft segment.

Guelcher et al. (Guelcher et al., 2008) prepared injectable polyurethanes by two-component reactive liquid molding of low-viscosity quasi-prepolymers derived from lysine polyisocyanates and poly(3-caprolactone-co-DL-lactide-co-glycolide) triols and degraded porous discs by incubation in PBS at 37°C and 5% CO_2 for 2, 4, 6, and 8 months. They found that these polymers degrade by hydrolysis of ester linkages to yield α-hydroxy acids and soluble urethane fragments. Furthermore, the materials prepared from PCL triol exhibit minimal (e.g., <5%) degradation after 8 months. However, materials prepared from P6C3G1L (triol synthesized from a glycerol starter and a mixture of monomers comprising 60% caprolactone, 30% glycolide, and 10% DL-lactide) exhibit 15-27% mass loss after 8 months.

Multi-block poly(ether ester urethane)s consisting of poly[(R)-3-hydroxybutyrate] (PHB), poly(propylene glycol) (PPG), and poly(ethylene glycol) (PEG) were prepared by Loh et al. (Loh et al., 2007). The poly(PEG/PPG/PHB urethane) copolymer hydrogels were hydrolytically degraded in phosphate buffer at pH 7.4 and 37°C for a period of up to 6 months. The degradation products in the buffer were characterized by GPC, ^{1}H NMR, MALDI-TOF, and TGA. The results showed that the ester backbone bonds of the PHB segments were broken by random chain scission, resulting in a decrease in the molecular weight. In addition, the constituents of degradation products were found to be 3-hydroxybutyric acid monomer and oligomers of various lengths (n= 1–5).

Multiblock poly(ether ester urethane)s comprising of poly(lactic acid) (PLA), poly(ethylene glycol) (PEG), and poly(propylene glycol) (PPG) segments and hexamethylene diisocyanate were synthesized by Loh et al. (Loh et al., 2008). Their degradation process in pH 7.4 buffer solution (8.0 g of NaCl, 0.2 g of KCl, 1.44 g of Na_2HPO_4, and 0.24 g of $K_2H_2PO_4$ in 1 L of solution) was studied over a period of 3 months. Multi-modal GPC profiles of these polymers suggested that the polymer degrades in fragments with molecular weight of about 2000, 4000, 6000 and 8000 g/mol. These gels degraded at a much faster rate than the previously reported PEG-PPG-PHB poly(ester urethane) thermogels, which were reported to degrade over a period of 6 months.

Degradation of segmented poly(urethane urea)s (SPUUs) with hard segments derived only from methyl 2,6-diisocyanatehexanoate (LDI) and PCL, PTMC, P(TMC-co-CL), P(CL-co-DLLA) or P(TMC-co-DLLA) as soft segment was conducted by Asplund et al. (Asplund et al., 2008). For the hydrolysis study, sterile and nonsterile samples were placed in 40 mL PBS buffer solution (pH 7.4) and put in an oven at 37°C. Degradation was studied after 5, 10, 15, and 20 weeks and analyses performed in triplicate for each sample. The effect of sterilization was studied after 10 weeks of hydrolysis. Physical ageing was studied after 5 and 15 weeks at 50°C. They found that the degradation rate was dependant on the soft segment structure, with a higher rate of degradation for the polyester-dominating PUUs exhibiting a substantial reduction in intrinsic viscosity. A tendency of reduction of tensile strength and strain hardening was seen for all samples. Also, loss in elongation at break was detected, for PUU-P(CL-DLLA) it went from 1600% to 830% in 10 weeks. Gamma radiation caused an initial

loss in inherent viscosity and induced more rapid hydrolysis compared with nonsterilized samples, except for PUU-PTMC.

Yeganeh et al. (Yeganeh et al., 2007) prepared epoxy terminated polyurethanes from glycidol and isocyanate-terminated polyurethanes made from poly(ε-caprolactone) (PCL) or poly(ethylene glycol) (PEG) and 1,6-hexamethylene diisocyanate. Degradation studies were performed using tris buffered saline solutions (TBS; 0.05, 0.1molL^{-1} NaCl, pH 7.4) and incubated at 37°C up to 6 months. They observed that degradation rates correspond to their water-absorbing ability, with faster degradation in the more absorbent polymers while the weight loss, due to hydrolytic degradation, increased as the amount of PEG content increased. A possible explanation is that following dissolution of some PEG segments, there will be an increase in the porosity of the blends, leading to a greater surface area for water to access the ester bonds of hydrophobic PCL, which dominates the degradation rate. Other possible explanations include an increase in the hydrophilicity of the surface, which accelerates degradation, or an increase in the mobility of the PCL molecules, which could also facilitate hydrolytic degradation. Also the rate of hydrolysis was raised with increasing time, which might result from the augmentation content of hydrophilic hydroxyl, amine, and carboxylic groups generated at the surface during degradation.

Wang et al. (Wang et al., 2008) prepared novel biodegradable and biocompatible poly(ester-urethane)s by *in situ* homogeneous solution polymerization of poly(3-caprolactone) diol, dimethylolpropionic acid (DMPA), and methylene diphenyl diisocyanate in acetone followed by solvent exchange with water. The hydrolytic degradation test was conducted on buffer solution (pH=7.4) at 37°C up to 12 weeks and showed that the degradation rate was little affected by the DMPA content in the range investigated, but was observed to be influenced by the hard segment content.

Hong et al. (Hong et al., 2010) synthesized poly(ester carbonate)urethane ureas (PECUUs) using a blended soft segment of poly(caprolactone) (PCL) and poly(1,6-hexamethylene carbonate) (PHC), 1,4- butane diisocyanate and putrescine as chain extender. They found that degradation of PECUUs in aqueous buffer (PBS at 37°C) and subcutaneous implantation in rats (Adult female Lewis rats) was slower than poly(ester urethane)urea but faster than poly(carbonate urethane)urea (PCUU). Over a period of 56 days, poly(ether urethane)ureas (PEUU) exhibited a 9% mass loss in addition to a reduction in inherent viscosity, while all of the PECUUs and PCUU did not show detectable loss of mass. *In vivo* it was observed that the majority of the PEUU scaffold was degraded, and loose connective tissue occupied the implant area with few observed putative macrophages. For the PECUU 50/50 scaffolds, more remnant material was seen with darker violet staining of the putative infiltrating macrophages and fibroblasts.

Chan-Chan et al. (Chan-Chan, et al. 2012) synthesized new polyester poly(urethane-urea)s and their molecular weight changes during PBS degradation were monitored by gel permeation cromatography (GPC) (see Figure 4). Significant weight loss was not observed at six months but bulk degradation was corroborated by this analytical technique.

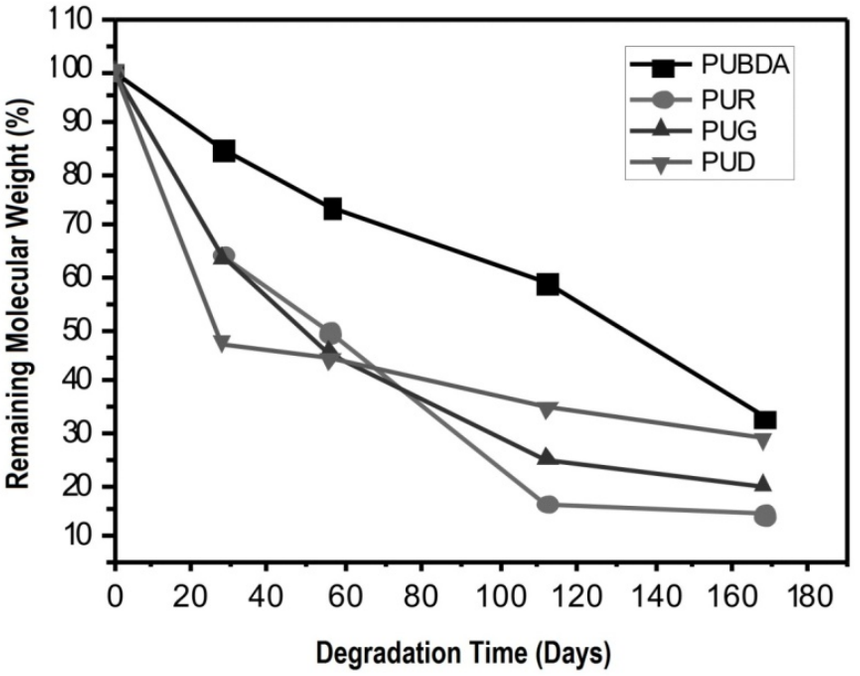

Figure 4. Molecular weight reduction in polyurethanes based on butanediamine (PUBDA), arginine (PUR), glycine (PUG) and aspartic acid (PUD).

4.4. Enzymatic degradation

Huang et al. (Huang et al., 1979) reported that a low molecular weight poly(ester-urea), poly(L-phenyl alanine/ethylene glycol/1,6-hexane diisocyanate), and a model diesterdiurea, dimethyl diphenyl alanine hexamethylene urea, were hydrolyzed by chymotrypsin at pH 8. They also observed degradation with papain latex (pH 6.5, PBS) of the model diesterdiurea.

Takahara et al. (Takahara et al., 1992) degraded SPU´s based on MDI, BD and various polyols using papain (80 U/mL) and papain activating solution (0.05 M cysteine, 0.02 EDTA, pH=6.5) in sodium acetate buffer solution. In this study it was found that PEO based polyurethanes exhibited the larger mass loss from all the SPU´s studied in addition to a reduction in Young´s modulus and tensile strength due to a reduction in molecular weight.

Labow et al. (Labow et al., 1996) degraded in elastase (from human neutrophils or pancreatic porcine) a poly(ester-urea-urethane) containing [^{14}C]toluene diisocyanate (TDI), poly(caprolactone) and ethylenediamine as well as a poly(ether-urea-urethane) containing [^{14}C]TDI, poly(tetramethylene oxide) and ethylenediamine (ED). They used neutrophils, which contain elastolytic activity, as they are present during the inflammatory response. Ten-fold more radioactive carbon was released when porcine pancreatic elastase was incubated with [^{14}C]TDI/PCL/ED than when human neutrophil elastase was used. Ten-fold less radioactive carbon was released when [^{14}C]TDI/PTMO/ED was incubated with porcine pancreatic elastase (PPE) as compared to [^{14}C]TDI/PCL/ED. Radioactive carbon release data for [^{14}C]TDI/PCL/ED polymer incubated with trypsin, a possible contaminant in pancreatic por-

cine elastase showed no significant release of radioactive carbon by the same number of units of trypsin which would be present in the commercial PPE preparation used in the biodegradation experiments.

Skarja and Woodhouse (Skarja et al., 2001) studied degradable segmented polyurethanes containing a phenylalanine diester chain extender and degraded them in buffer chymotrypsin and trypsin solutions for up to 28 days. In this study it was found that the presence of phenylalanine resulted in an increased susceptibility to enzyme-mediated while the magnitude of degradation and erosion was highly variable and was dependent on soft segment type (PCL or PEO) and molecular weight (500-2000 g/mol).

It is well-known that the segmented poly(urethane ureas) prepared from 4,4-diphenylmethane diisocyanate, oligotetramethylene glycol, and diamines are not easily hydrolyzed by enzymes. This was further extended by Thomas and Jayabalan (Thomas et al., 2001) who reported that completely aliphatic poly(urethane urea) based on 4,4-methylene bis-cyclohexyl isocyanate/hydroxy terminated polybutadiene/1,6-hexamethylene diamine did not degrade in papain after 30 days at 37°C.

Labow et al. reported that cholesterol esterase cleaved polyetherurethanes at the most probable site susceptible to hydrolytic cleavage, which is the urethane bonds, resulting in the release of free amine (Labow et al., 2002). Santerre's group has also reported the degradation of polycarbonate polyurethanes with cholesterol esterase (Tang et al., 2002). Both the carbonate and urethane bonds were cleaved, resulting in many products ranging in molecular weight from 150 to 850 g/mol, as identified by GC–MS.

Yamamoto et al. (Yamamoto et al., 2007) degraded with different thiol proteases (papain, bromelain, and ficin) and Protease K and chymotrypsin, lysine diisocyanate (LDI) based poly(urethanes) and segmented poly(urethane ureas). For this, 1 mg of enzyme was added into the test tube coated with the polymer at 37°C and the total organic carbon (TOC) measured. From ^{1}H NMR results, it was evident that the pendant methyl ester group in LDI was rapidly hydrolyzed, followed by slow hydrolysis of urethane bonds in the backbone chain while the susceptibility of urea bonds to papain was very low. Before 50 h almost 30% of the PU has been degraded, with ethylene glycol exhibiting the highest rate of degradation; thiol proteases were most effective for all SPUUs. LDI/PTMO (Mw=2000 g/mol)/1,3-propylendiamine (PDA) (2/1/1), which does not contain degradable soft segments (caprolactone block), showed degradation by various proteases. This fact strongly suggests that the cleavage of the hard segment (urethane and/or urea) by these proteases occurred. For the SPUU the expected water-soluble degradation products are diamine, α-hydroxy caproic acid, and its low molecular oligomers, in addition to lysine derivatives.

Hafeman et al. (Hafeman et al., 2011) investigate the effects of esterolytic and oxidative conditions on scaffold degradation by incubating in 1 U/mL cholesterol esterase (CE), 1 U/mL carboxyl esterase (CXE), and 10 U/mL lipase (L) hydrogen peroxide (20 wt% hydrogen peroxide (H_2O_2) in 0.1 M cobalt chloride ($CoCl_2$), and buffer alone (0.5 M monobasic sodium phosphate buffer with 0.2% w/w sodium azide) and measured the mass loss for 10 weeks at 37°C. Polyurethane scaffolds were prepared by one-shot reactive liquid molding of hexam-

ethylene diisocyanate trimer (HDIt) or lysine triisocyanate (LTI) and a polyol as hardener. Trifunctional polyester polyols of 900-Da molecular weight were prepared from a glycerol starter and 60% ε-caprolactone, 30% glycolide, and 10% D,L-lactide monomers (6C), ($t_{1/2}$ = 20 days) and 70% caprolactone, 20% glycolide, and 10% lactide (7C) ($t_{1/2}$ = 225 days) and stannous octoate catalyst. Incubation with esterases slightly accelerated degradation relative to PBS. Differences in degradation between the three candidate enzymes at any given time point were not significant. In contrast, incubation with medium that created an oxidative microenvironment had a more significant effect on the polyurethane degradation rate, especially for the LTI-based materials, except the 6C/HDIt (hexamethylene diisocyanate trimer) + PEG, which interestingly degraded faster in the presence of cholesterol and carboxyl esterase than in oxidative medium.

A new family of water borne polyurethanes (WBPU) were synthesized by Jiang et al. (Jiang et al., 2007) using isophorone diisocyanate (IPDI), polycaprolactone (PCL), polyethylene glycol (PEG) and BD:Lysine (1:1) as the chain extender. The polyurethane was then enzymatically degraded in PBS (pH = 7.4) with a solution mixture including PBS 60.0 ml, 0.1% $MgC1_2$ 15.0 ml and Lipase AK (10 mg/ml) 15.0 ml and then incubated with shaking for certain time at 55°C, which was the optimum temperature for enzyme activities of Lipase AK. An increased degradation was observed as decreasing of the amount of PEG in soft segments of WBPU, as judged from the change of tensile properties with time, owing to Lipase AK only interacting with PCL soft segments in these polymers structures. This result reveals that the degradation rate is proportional to the PCL content, and inverse proportion to the PEG content in the WBPUs. Depending on the PCL content, degradation started even at 6 h in the presence of Lipase AK.

A polyurethane was synthesized with LDI, PCL, and BD in the presence of dilaurate as catalyst by Han et al. (Han et al., 2009) and then degraded in PBS with a solution mixture including 4.0 mL PBS, 1.0 mL 0.1 wt.% $MgCl_2$ and 1.0 mL Lipase AK (10 mg/mL) in water at 50°C. It was found that loss mass decreased with increasing the PCL soft segment content in hydrolytic degradation in PBS. Because PCL is hydrophobic in comparison with the polar hard segment, increasing its content would decrease water uptake of PU films, and then decrease mass loss. In contrast, in the presence of Lipase AK the mass loss was observed to be increased with increasing the PCL soft segment content.

Biodegradable polyurethanes were prepared by Wang et al., using PLA-PEG-PLA as soft segment, and L-lysine ethyl ester diisocyanate (LDI) and 1,4-butanediol (BD) as rigid segment (Wang et al., 2011b). These polymers were degraded in PBS (0.1 M PBS with 0.9% NaCl and 0.02% NaN_3, pH 7.4, 6 and 5) and enzymatic (0.1mg/ml lipase from porcine pancreas in 0.1 M PBS with 0.9% NaCl and 0.02% NaN_3, pH 7.4) solutions at 37 °C to simulate *in vivo* dynamic tissue environment. PU samples demonstrated rapid degradation in 96 h (more than 90%) which might be attributed to hydrophilicity of PEG segments, low number-average molecular weight and microphase separation degree of these polyurethanes and enzyme functions. The enzymatic degradation rate was higher than hydrolytic degradation rate, verifying that Lipase from porcine pancreas can accelerate hydrolysis on these polyurethanes.

A series of pH-sensitive biodegradable polyurethanes (pHPUs) were designed and synthesized using pH-sensitive macrodiol (poly(ε-caprolactone)-hydrazone-poly-(ethylene glycol)-hydrazone-poly(ε-caprolactone) diol (PCL-Hyd-PEG-Hyd-PCL)), L-lysine ethyl ester diisocyanate (LDI) and L-lysine derivative tripeptide as chain extender by Zhou et al. (Zhou et al., 2011). The polyurethanes could be cleaved in acidic media (pH ~ 4-6) as well as degraded in PBS (100 mM, and pH 7.4) overnight at room temperature and enzymatic solution (Lipase AK (10 mg/mL, 2 mL) in PBS buffer solution with 0.1 wt % $MgCl_2$ (2 mL) and then incubated with cyclic shaking at 52.5°C). It was found that the hydrolysis rates of the two samples observed in Lipase AK PBS are higher than that in PBS i.e. 31.1% and 35.9% of weight loss are detected after hydrolytic and enzymatic degradation for 144 h of pHPU4 (pHPU prepared with LDI/macrodiol/tripeptide 3.15/2/1), respectively. The results indicate that the pHPUs are also facile to degrade in enzymatic solution, which is in agreement with reported literatures that Lipase AK is able to accelerate the PCL-based polymers biodegradation. Polymers with more pH sensitive macrodiol and lower crystallinity degraded even faster. The importance of studying these materials (pH-sensitive biodegradable polyurethanes) lies in the fact that they been used for intracellular multifunctional antitumor drug delivery (Zhou et al. 2012).

Elliott et al. (Elliott et al., 2002) determined mechanism of enzymatic degradation by HPLC/MS. Prior to product separation and identification, residual enzyme (chymotrypsin) was removed from the incubation solution samples. This process was necessary since the chymotrypsin could interfere with the accurate detection of the degradation products in the high performance liquid chromatography (HPLC) columns, and because proteins have a tendency to aggregate and then later precipitate during the gradient run, thereby causing additional difficulties in data acquisition. The results of the tandem mass spectrometry (MS/MS) analysis indicated that chymotrypsin may act to cleave urea bonds adjacent to L-phenylalanine residues. This is a significant finding since it confirms that the polyurethanes are susceptible to selective enzymatic degradation in the hard segment. Traditionally, this domain of the polyurethane has been considered a relatively stable group. The materials used in this study, however, were especially developed to encourage degradation of the hard segment rather than relying solely on degradation of the soft segment. Hence, the results of this study confirm that this goal was achieved. The cleavage of urea bonds by chymotrypsin is an important finding as it contradicts results of a previous study with similar chemistry that found that urea bonds adjacent to L-phenylalanine residues were not cleaved. However, since the level of chymotrypsin activity was not stated in the other study, it may be possible that the right conditions were not presented in order to degrade the urea bond (Elliott et al., 2002).

4.5. Lipid degradation

Lipid absorption has been reported to occur in many medical devices such as heart valves made of silicon, leading to their calcification. In addition, fatigue properties of SPU have been reduced by lipid absorption.

Takahara et al. (Takahara et al., 1992) degraded SPU´s based on MDI, BD and various polyols using 0.25 % phophatidyl choline and 0.1% M cholesterol liposome solution during 28 days at 37°C. They found that SPU based on PDMS disintegrated under these conditions while PTMO based SPUs exhibited a severe reduction in tensile strength and elongation. These results were not related to the presence of a specific chemical group in the soft segment as PEO based SPU´s were not affected.

4.6. Compost biodegradation

Synthetic poly(ester urethanes) are known to be degraded by microbes mainly due to the presence of ester linkages, being more susceptible those containing long chains rather than short polyester chains. Lactic acid based polyester urethanes have been degraded with compost inoculum (thermophilic-stage household waste compost was added to 100 ml of ASTM solution and the CO_2 evolved was followed by Hiltunen et al. (Hiltunen et al., 1997). The data showed that poly(ester-urethanes) did not biodegrade at 25°C but when the temperature was raised, biodegradation was accelerated. At 37°C the stereo structure of polymer chains had a strong effect on biodegradation. This temperature was below the glass transition temperature of poly(ester-urethanes) but about the same as the glass transition temperature of prepolymer chains. The lower the glass transition temperature of prepolymer, the faster the biodegradation. Urethane bonds probably break first, and after that the properties of lactic acid prepolymer chains determine the biodegradation behavior. All poly(ester-urethane) samples biodegraded well at 55°C, and the percentage of biodegradation varied between 45 and 77% in 55 days. At 60°C the poly(ester-urethanes) biodegraded well and they reached even higher levels of biodegradation than Biopac™ and lactic acid. The biodegradation varied from 45 to 77% in 55 days.

Polyurethanes based on MDI and PCL with different molecular weights were prepared by Watanabe et al. (Watanabe et al., 2009) and degraded by soil burial test at 28°C. It was found that biodegradation rate of the polyurethanes increased as the number of average molecular weight (Mn) of poly(caprolactone) diol used increased from 500 to 1000 (urethane content 11.9 to 7.6 wt % respectively), whereas it decreased as the Mn of poly(caprolactone) diol increased from 1200 to 2000 (4.2 wt % of urethane content). Furthermore, when 2000 PCL triol was used led to a high degradation ratio.

4.7. Thermal degradation of polyurethanes

Although the thermal degradation of both polyurethanes (PU) and segmented polyurethanes (SPU) has been extensively investigated due to their wide range of applications, studies on thermal decomposition of polyurethanes used specifically in biomedical field such as catheters, heart valves, vascular prostheses, etc., are less common as generally these materials are not subjected to high temperatures during their *in vivo* performance [Cervantes-Uc et al. 2009]. In some cases, these studies are used to investigate the composition and stability of the remaining material after the chemical hydrolysis and oxidation of SPU [Chan-Chan et al. 2010] as well as to determine the soft and hard segment ratio of polyurethanes.

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The thermal degradation of polyurethanes allows determination of the proper conditions for manipulating and processing them and for obtaining high-performance products that are stable and free of undesirable by-products; if not processed properly, commonly by extrusion or by injection moulding, the PU's would generate toxic products to the human body, which is very critical in biomedical applications [Gomes Lage et al. 2001].

It is well known that polyurethanes are not thermal stable polymers and that the onset degradation temperature of the urethane bond depends on the type of isocyanate and alcohol used. It is a general rule that the more easily formed polyurethanes are less stable, i.e. more easily dissociated when compared with more difficulty formed ones [Petrovic et al. 1994]. Petrovic reported that the degradation temperature for these materials ranged from 120°C to 250°C depending on their structure [Petrovic et al. 1994]; however, literature reports processing temperatures closer to 180°C [Guignot 2002].

Polyurethanes are thermally degraded through three basic mechanisms. First, by urethane bond dissociation into its starting components (isocyanate and alcohol); secondly, by breaking the urethane bond with formation of primary amines, carbon dioxide and olefins; and finally, splitting the urethane bond into secondary amine and carbon dioxide [Petrovic et al. 1994; Cervantes-Uc et al. 2009].

5. Degradation mechanism

The nature of PU chemistry is central to understand why some PUs undergo faster degradation than others (Santerre et al., 2005). However, the degradation mechanism of polyurethanes depends on not only the PU chemistry structure but also the degradation environment, i.e. in the presence of water, acidic, alkaline or oxidative conditions, or in the presence of enzymes. Generally, the characterization of the by-products during the degradation of the polyurethane is the key to understand the mechanisms of degradation. Identification of degradation products is an important issue but of equal interest is the eventual toxicity of the degradation products. If the biomaterial degrades, either spontaneously or due to biological activity, components can leach into surrounding tissues and cause an inflammatory response if not easily metabolized by natural pathways. Therefore, it is compulsory to identify the major species produced at different stages of degradation and the kinetics of their formation (Azevedo et al., 2005).

Accelerated degradation has been used to determinate stability of non degradable polyurethanes (Gunatillake, 1992) but it can be used to provide valuable information about degradation mechanism of resorbable polyurethanes. In this context, both soluble products and solid residues can be studied with different analytical techniques and tests to determine their composition.

The main techniques used to evaluate the degradation of biomaterials can be divided into surface analysis (infrared spectroscopy, X-ray photoelectron spectroscopy, contact angle measurements), which are more appropriated to monitor the changes occurring in the first

stages of degradation, and bulk analysis (determination of changes in molecular weight, weight loss, temperature transitions, mechanical properties) for characterizing the later stage of degradation (Azevedo et al., 2005).

In general, polyesterurethanes are susceptible to hydrolytic degradation because of ester groups in the soft segments while polyetherurethanes are susceptible to oxidative degradation. Furthermore, it has been observed that ester linkages hydrolyze about a magnitude faster than urethane linkages, and it has been shown that urea linkages hydrolyze faster than urethane, although at slightly acidic conditions. Figure 5 shows the possible mechanism of hydrolytic degradation of various functional groups present in polyurethanes.

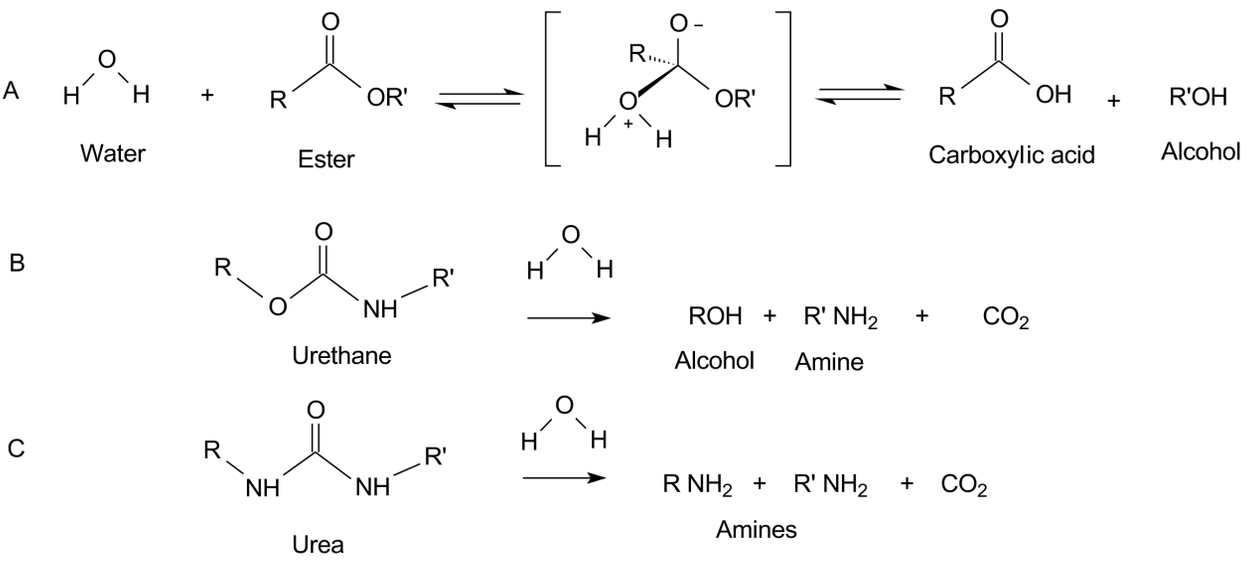

Figure 5. Hydrolytic degradation mechanism of polyesters (A), poly(urethane) (B) and poly(ureas) (C).

In spite of this, the degradation rate of the poly(ester urethane) based on PCL was found to be slow (i.e., 15% weight loss in 11 weeks (Wang et al., 2008). Furthermore, IR spectra for the degradation products of the LDI/PCL and LDI (lysine methyl ester diisocyanate)/P6C3G1L (triol synthesized from a glycerol starter and a mixture of monomers comprising 60% caprolactone, 30% glycolide, and 10% DL-lactide) materials after 2 and 8 months in PBS (Guelcher et al., 2008) shows an absorption band at approximately 1070-1050 cm^{-1}, which is assigned to C-O stretching vibrations in alcohols and carboxylic acids. This observation implies that the polyurethanes degrade by hydrolysis of ester linkages to yield α-hydroxy acids and is further supported by the appearance of the strong peaks at 1675-1650 cm^{-1}, which correspond to the COO asymmetric stretching vibration associated with carboxylic acid salts. Therefore, it is possible under these conditions that phosphate salts of carboxylic acids will form in the PBS solution due to the reaction of carboxylic acids with the basic phosphate salts present in PBS. Hydrolysis of LDI/PCL containing poyurethanes networks in sodium hydroxide solutions has been reported to yield L-lysine as a degradation product; however, the presence of L-lysine in the degradation products under physiological conditions was not confirmed.

Other studies reported the presence of lysine in the degradation products from lysine-derived polyurethanes networks.

Segmented polyurethane based on poly(ε-caprolactone), ethyl lysine diisocyanate or hexamethylene diisocyanate in combination with ethylene glycol or ester from ethylene glycol and lactic acid (2-hydroxyethyl 2-hydroxypropanoate) with greater hard segment content (HS) liberate higher amine concentrations during their degradation (Tatai et al., 2007). Amine concentration was determined using a spectrophotometer by acquiring the A_{570} (absorbance at 570 nm) of the test sample and by quantifying the detected concentration with use of the standard curve. This being expected, on the assumptions that PUs with higher HS contained more urethane bonds. To detect amine groups using this technique, a degradation product must undergo hydrolysis at its respective urethane linkage. Since this process is somewhat slower than that of ester bond hydrolysis, it seems that part of the degradation product may still contain urethane segments.

Hafeman et al. (Hafeman et al., 2011) investigate the effects of esterolytic and oxidative conditions on scaffold degradation by incubating in 1 U/mL cholesterol esterase (CE), 1 U/mL carboxyl esterase (CXE), and 10 U/mL lipase (L) hydrogen peroxide (20 wt% hydrogen peroxide (H_2O_2) in 0.1 M cobalt chloride ($CoCl_2$), and buffer alone (0.5 M monobasic sodium phosphate buffer with 0.2% w/w sodium azide) and analysed the degradation products by HPCL. Hydrolysis of ester bonds was anticipated to yield α-hydroxy acids (e.g., hydroxycaproic, lactic, and glycolic acids), which was confirmed by HPLC. The lysine triisocyanate (LTI) scaffolds produced more α-hydroxy acids than trimer of hexamethylene diisocyanate (HDIt) scaffolds. The 7C/LTI (triol synthesized from a glycerol starter and a mixture of monomers comprising 70% caprolactone, 30% glycolide and 10% lactide) formulation, which degraded more slowly due to the longer polyester half-life, yielded lower concentrations of α-hydroxy acids than the 6C/LTI (60% caprolactone, 30% glycolide and 10% lactide) formulation. Inclusion of polyethylene glycol (PEG) in the 6C/HDIt scaffold reduced the amount of α-hydroxy acids in the degradation medium due to the replacement of 50% of the polyester with PEG. Several unidentified peaks appeared in the HPLC spectra, which are conjectured to be adducts of α-hydroxy acids and either lysine or ethanolamine connected by urethane or urea bonds. Oxidation of urethane and urea bonds was predicted to yield lysine and ethanolamine from LTI scaffolds, and cyanuric acid from HDIt scaffolds. Both lysine and ethanolamine were detected in the degradation products from LTI scaffolds when incubated in PBS; however, cyanuric acid was not detected in the degradation products from HDIt scaffolds. The amount of lysine recovered from 6C/LTI scaffolds was significantly greater than that from 7C/LTI scaffolds after 14 weeks, which is consistent with the faster *in vitro* degradation of the 6C/LTI materials. At 36 weeks, 18% of the lysine incorporated in the 6C/LTI scaffolds was recovered, while 100% of the original mass had degraded to soluble degradation products. This suggests that the majority of the lysine was incorporated in soluble urethane and urea adducts with α-hydroxy adducts. The recovery of ethanolamine arises from the hydrolysis of the ester group in LTI and a urethane bond. Ethanolamine was not detected (<0.001 μg/mg polyurethane) until 14 weeks, and at later time points the etha-

nolamine concentration increased with time. The recovery of ethanolamine upon complete dissolution of the 6C/LTI scaffold at 36 weeks was 9%.

Suntherland et al. (Sutherland et al., 1993) degraded Pellethane 2363 80A with either HClO or ONOO. An oxidative reaction involving the ether or ester moieties of PEU would be reflected by a decrement in the urethane-aliphatic ester and/or aliphatic ether stretching peaks on ATR/FTIR analysis. Indeed, a substantial decrement in the aliphatic ether stretching at 1105-1110 cm^{-1} relative to the urethane-aliphatic ester peak at 1075 cm^{-1} has been observed in implanted material. In fact, the intensity of both aliphatic ether and urethane-aliphatic ester peaks decreases after long-term implantation, suggesting that both groups are oxidized *in vivo*. PEU previously exposed to HClO exhibited a decrement in the signal from the urethane-aliphatic ester.

FTIR has been used to determine the composition of residues after degradation. In this sense, hydrolytic degradation of polyester urethanes affects carbonyl bands at 1730 cm^{-1}. Soluble products of the ester scission are carboxyl acids and alcohols that can be observed between 2500 and 3500 cm^{-1}. Pérez et al. (Pérez et al., 2006) studies showed that urea bonds derived from amino acids can be hydrolyzed in basic conditions but after more prolonged period than ester groups, this degradation was monitored by capillary electrophoresis-ion trap-mass.

Oxidative degradation has been generally associated with poly(ether-urethane)s, since many studies have determined that these polymers degrade by mean alpha-hydrogen abstraction adjacent to oxygen in polyethers and polycarbonates (Christenson et al., 2004; Xie et al., 2009). In contrast, few works related to oxidative degradations on polyester polyurethanes has been done, and even less has studied the mechanism of degradation of polyurethane ureas. However recent studies about oxidative degradations of PCL and polyester poly(urethane urea)s PCL based have showed ester, urethane and urea groups are susceptible to oxidative degradation (Sabino, 2007; Sarkar et al., 2007; Hafeman et al., 2011). This mechanism is illustrated in Figure 6.

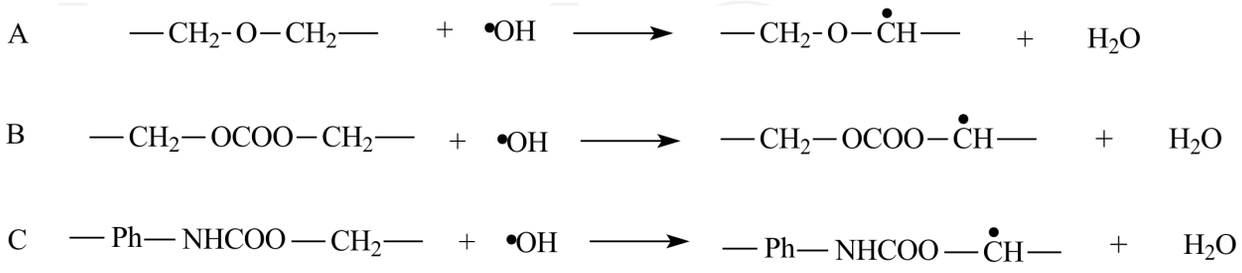

Figure 6. Mechanism of oxidative degradation by H_2O_2 in poly(ether urethanes) (A), poly(carbonate urethanes) (B) and aromatic polyurethanes (C).

Oxidative degradation using HClO is less commonly pursued but it may be clinically more relevant as hipochlorous anions can be produced by neutrophils. These conditions can be simulated *in vitro* and the suggested mechanisms of the polyurethane degradation can be depicted in Figure 7.

http://dx.doi.org/10.5772/53681

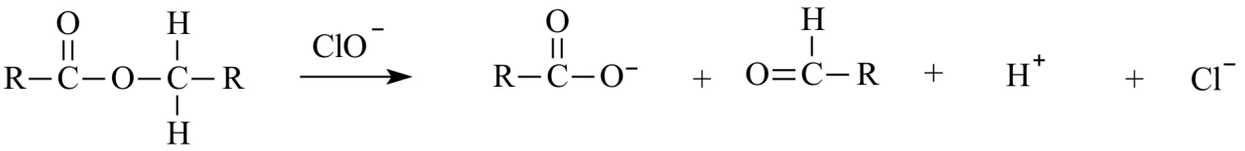

Figure 7. Mechanism of oxidative degradation in polyurethanes by means of HClO

Degradation of polyurethanes with H_2O_2 (30% v/v) does not seem to affect ester bonds but affect urea bonds as observed by FTIR. The wide band of 3650-3400 cm^{-1} and a small peak in 930 cm^{-1} corresponding to carboxylic acid confirm scission of urea groups as shown in Figure 8. Other bands such as those at 1298 cm^{-1} show some crosslinking by C-N bonds and an increase in PCL crystallinity, as the 1143 y 1189 cm^{-1} bands, corresponding to amorphous and crystalline PCL, changed (Chan-Chan, 2012).

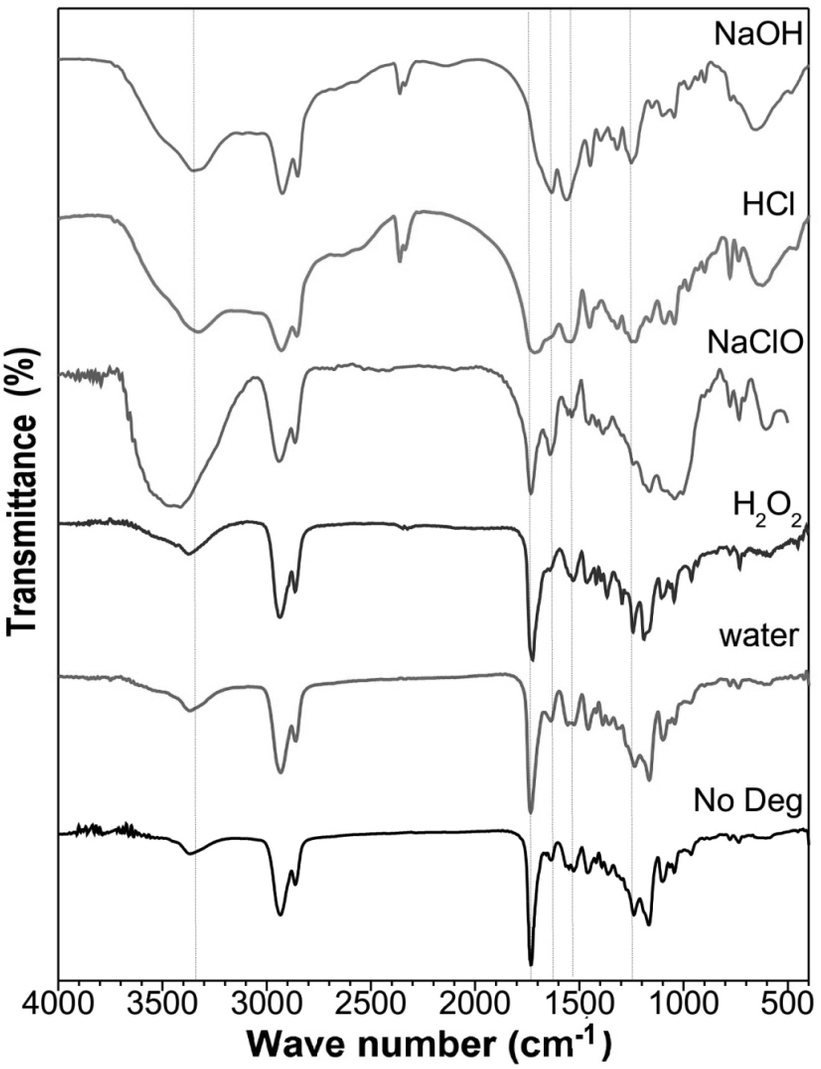

Figure 8. FTIR spectra of poly(urethane ureas) degraded in various media.

6. Conclusions

Polyurethanes are very versatile polymers that found application in the biomedical field, especially in cardiovascular applications. In spite of their good physicochemical and mechanical properties and acceptable biocompatibility they are prone to degradation under different conditions. These conditions range from hydrolysis, oxidation, metal induced oxidation, environmental stress cracking, enzyme-assisted degradation, etc. which can be found *in vivo* during the useful life of the device. In order to simulate these, *in vitro* approaches has been followed. Thanks to this information today it is well accepted that polyurethanes are no longer inert materials placed within the body. However, this disadvantage can be used to modulate their degradation to a rate that can be controlled mainly by their composition, and be used in the design of tissue engineering scaffolds.

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