

REVIEWS

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Thermoplastic Elastomers: Materials for Heart Assist Devices

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation;
D – writing the article; **E** – critical revision of the article; **F** – final approval of the article

Abstract

Heart assisting devices have become a standard element in clinical practice and provide support for the traditional methods of treating heart disease. Regardless of the construction of VAD (ventricular assist devices), there are crucial requirements that have to be met by the construction materials: high purity, desired physical, chemical and mechanical properties, easy fabrication and high stability and susceptibility to sterilization. They must not cause thrombosis, destroy cellular elements, alter plasma protein, destroy enzymes, deplete electrolytes, cause immune response and cancer, and must not produce toxic and allergic reactions, when they are applied in direct contact with biological tissues and fluids. This paper provides an overview of the polymeric materials as construction materials for cardiovascular support systems, focusing on the group of thermoplastic elastomers, mainly polyurethane and polyester based ones. It also highlights the advantages and disadvantages of currently used materials and the progress in the design of new materials with potential application in the biomedical field (**Polim. Med.** 2016, 46, 1, 79–87).

Key words: polymeric materials, polymer design, thermoplastic elastomers, blood contacting materials.

Cardiovascular diseases are responsible for over 17.5 mln deaths per year and are the main cause of death in the world [1]. Approximately 75% of these diseases are connected with the heart and bloodstream. Therefore, thousands of research groups, doctors, engineers and biotechnologists are working on different solutions for heart repair. In this review, we would like to present a specific group of polymeric materials – thermoplastic elastomers, most commonly used as construction materials for elements of heart assist devices – and the latest developments in this group of materials.

According to the directive 93/32/EEC, the classification of medical devices is based on the vulnerability

of the human body, taking into account the potential risk associated with the technical design and manufacture of the devices. In accordance with this directive, medical devices are divided into four classes and the invasive devices that are intended specifically to control, diagnose, monitor or correct a heart defect or the central circulatory system through direct contact with these parts of the body belong to class III, regardless of the contact time (temporary, short-term, long-term). Table 1 presents examples of different surgically implanted devices classified into class III, along with their use times.

Apart from the contact time, polymeric materials require high purity, desired physical, chemical and me-

Table 1. Selected examples of surgically invasive devices intended for different use time

Transient use (< 60 minutes)	Short-term use (> 60 minutes, < 30 days)	Long-term (> 30 days)
Angioplasty balloon catheters	cardiac output probes	prosthetic heart valves
Stent delivery catheters	temporary pacemaker leads	external ventricular assisting devices
Catheters containing or incorporating sealed radioisotopes	thoracic catheters intended to drain the heart, including the pericardium	vascular prosthesis and stents

chanical properties, easy fabrication and high stability and sterilizability. They must not cause thrombosis, destroy cellular and plasma elements, deplete electrolytes, cause excessive immune response or cancer, and must not induce toxic and allergic reactions, when they are in direct contact with biological tissues and fluids. All these requirements depend mainly on the synthesis and fabrication steps; therefore, using a less toxic catalyst and non-leaching additives (e.g. plasticizers, antioxidants, fillers) is highly desired for the polymerization of materials intended for biomedical application.

Segmented Polyurethane Thermoplastic Elastomers

Polyurethanes commercially used in specific medical applications belong to a group of segmented thermoplastic elastomers (TPE). Their characteristic feature is ease of processing by methods typically applied for thermoplastics, with the ability to maintain the high elasticity of cross-linked rubbers.

Polyurethanes (PU) were invented by Otto Bayer and his coworkers in the late 1930s; however, the thermoplastic elastomer polyurethanes (TPU) of biomedical significance (in particular for artificial heart application) were described and patented in 1958 by Schollenberger [2]. Distinctively, TPUs contain only some amount of urethane groups and others characteristic groups (such as ether, ester, carbonate etc.) in the polymer chains; they are more complex than common polyamides or polyesters. The structural diversity of TPUs is the result of three different monomers: a diisocyanate, a macroglycol (macrodiol), and a chain extender used to obtain these materials. The chemical and physical diversities of monomers lead to polymers with a microphase separated structure consisting of two incompatible hard and soft segments, as shown in Figure 1.



Fig. 1. Schematic representation of hard (blue) and soft (red) segments

This incompatibility of hard and soft segments based on thermodynamic fundamentals is a common feature of polymeric multicomponent systems. Complete miscibility between two polymers or two-component block copolymers requires that the free energy of mixing (ΔG_m) is negative:

$$\Delta G_m = \Delta H_m - T\Delta S_m < 0 \quad (1)$$

where ΔH_m , ΔS_m , refer to enthalpy and entropy of mixing at temperature T , respectively. The entropy and enthalpy of mixing are given by following equations:

$$\Delta S_m = -k[n_1 \ln \phi_1 + n_2 \ln \phi_2] \quad (2)$$

$$\Delta H_m = k T \chi_{12} N \phi_1 \phi_2 \quad (3)$$

where ϕ_1 and ϕ_2 are the volume fractions of block 1 and 2, $N = n_1 + n_2$ is the overall degree of polymerization, and χ is the Flory-Huggins interaction parameter. Besides the Flory-Huggins parameter and degree of polymerization, steric hindrances (triblock, star block etc.) and overall volume fraction of components also strongly influence the susceptibility to microphase separation. Further, the dependence of the χ_{12} parameter on the temperature affects the enthalpic factor in free energy equation.

At the equilibrium state, macromolecules tend to reach the lowest free energy configuration. For A-B segmental system, some loss of translational and configurational entropy by local disordering, commonly known as *microphase separation* is observed. The specific microphase separated structure results in crystalline domain formation embedded in a soft, amorphous polymer matrix (Fig. 2). Hard segments form “physical crosslink” points, as a result of crystallization, amorphization or weak bond formation (ionic interaction, hydrogen bonds), while soft segments impart low modulus of elasticity, low glass transition temperature, and low cohesion energy between analogous segments.

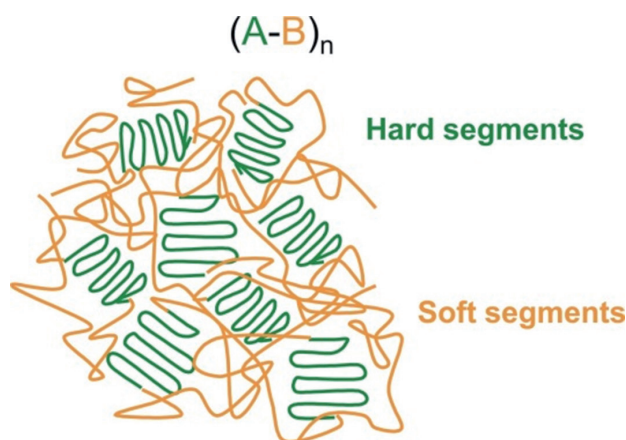


Fig. 2. Schematic representation of morphological structure of segmented polyurethanes

Polyurethanes are synthesized via polyaddition reaction in order to obtain $(A-B)_n$ multiblock copolymers with the urethane bond, as presented in Fig. 3.

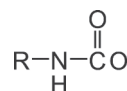


Fig. 3. Chemical structure of urethane bond

Regardless of the chemical composition of the copolymers, all of the commercial products consist of three major components (Fig. 4):

- polyether, polyester or polycarbonate diol;
- chain extender (low molecular diol, water);
- diisocyanate (linear, aromatic).

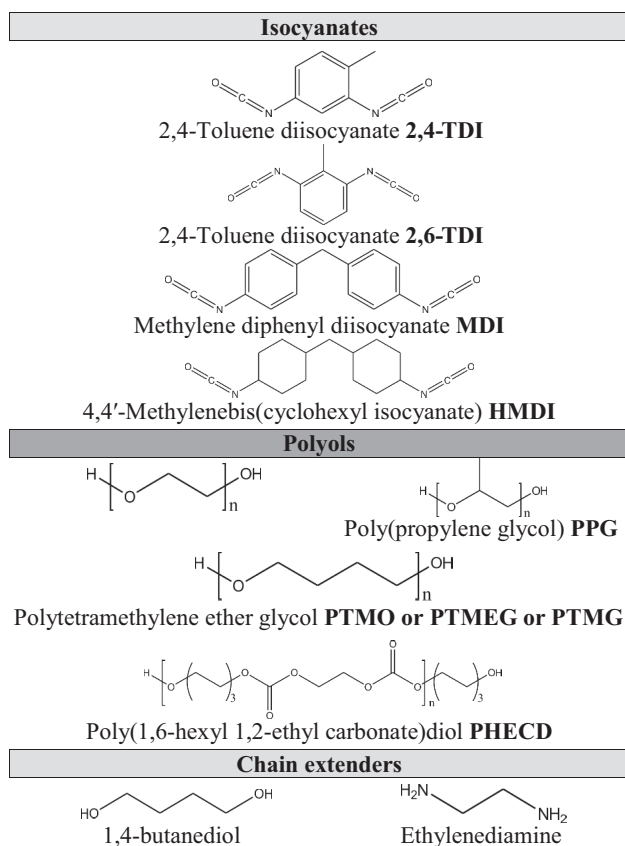


Fig. 4. Monomers typically used for PU synthesis

As mentioned above, the polyaddition reaction between all three of these substrates results in the phase separated structure of the polyurethane multiblock copolymers. In a polymer chain, we can distinguish two incompatible segments: hard segments that are formed by the reaction of the isocyanate with a chain extender, and soft segments that are responsible for their excellent mechanical properties (high strength and flexibility). The chemical structure of the hard and soft segments and their weight ratio also determines the susceptibility of the polyurethane materials to oxidative and enzymatic degradation, as well as microbial colonization. In the next paragraphs, we will discuss the influence of the chemical composition of medical grade polyurethanes on selected properties.

It is already known that the segmented (multiblock) structure of the thermoplastic polyurethane elastomers has a strong influence on the thermal, mechanical and the functional properties of the product. The weight ratio between the hard and soft segments, as well as their chemical composition, has a major effect on the phase separation of TPUs.

Due to the fact that TPUs are processed by traditional melt-processing methods (e.g. injection molding or extrusion), in most cases, the determination of the thermal properties is necessary to avoid thermal degradation and to match proper process parameters.

The most common method used to examine the thermal properties is differential scanning calorimetry (DSC). The melting (T_m), crystallization (T_c), and glass transition temperature (T_g) are analyzed during the heating – cooling – 2nd heating stages. It is already known that melting and crystallization process characterize the crystalline phase, whereas the glass transition temperature is mainly influenced by the amorphous phase. For TPU, thermal stability is determined as a function of: diisocyanate chemical structure, hard segments fraction and type of chain extender, and length of polydiol segments.

Korley et al. [3] investigated the influence of soft segment length on the TPU phase separation. Crystallizable soft segments composed of poly(ethylene oxide) (PEO) or poly(ethylene oxide)-poly(propylene oxide) (PEO-PPO-PEO) were reacted with HDI-BDO hard segments. In this TPU system, the PEO-PPO-PEO macrodiol did not exhibit crystallinity, whereas the PEO remained semicrystalline. Additionally, the higher molecular weight of PEO increased the incompatibility between the hard and soft segments.

Li et al. [4] analyzed the thermodynamic behavior of two different diisocyanates, HDI and MDI, as hard segments in copolymers with polycaprolactone (PCL) as soft segments (Fig. 5). The main consequence of the different chemical structures of these diisocyanates was chain mobility, the most important parameter inducing phase separation or phase mixing at thermodynamic equilibrium state. MDI, as an aromatic compound, favors phase separation, due to the lower mobility and higher solubility parameter ($10.6 \text{ cal}^{1/2} \text{ cm}^{-3/2}$), as compared to HDI ($9.3 \text{ cal}^{1/2} \text{ cm}^{-3/2}$).

Miller et al. [5] reported that the synthesis method strongly influences the hard segment length and, thereby, the phase mixing. For materials prepared by one-step polymerization, they observed higher crystallinity and a lower degree of phase mixing as compared to corresponding materials synthesized by a multistep process. Additionally, they noticed that the annealing temperature increases the crystallinity degree, providing

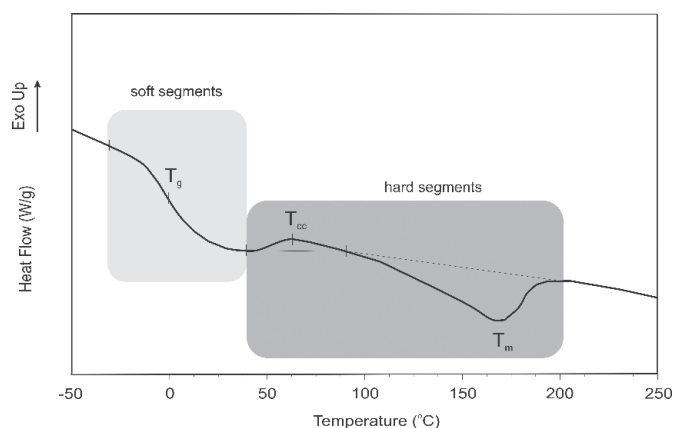


Fig. 5. Second heating scan of polycarbonate polyurethane

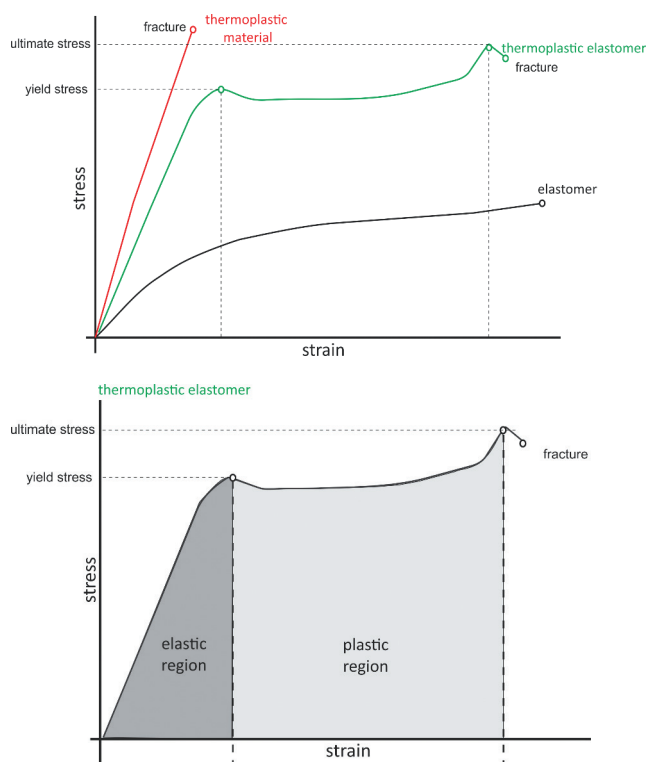


Fig. 6. Mechanical characteristic of a) different groups of polymeric materials, b) thermoplastic elastomers

that hard segments are long enough to crystallize. In any other case, they remain dissolved in the soft phase.

The degree of phase separation does not only strongly affect the thermal properties. The other consequence is a broad range of mechanical properties of TPU. As with all thermoplastic elastomers, TPU exhibit mechanical characteristics between those of thermoplastic and rubber materials. Figure 6 shows stress-strain curves of the different materials.

Why Are Polyurethanes Attractive for Medical Applications?

The segmented structure of TPU determines not only the thermo-mechanical properties, but is also responsible for their high compatibility with the living tissues, e.g. muscles or blood. It is already known that the TPU microphase separation is principally thermodynamically driven by the adverse interactions between polar urethane (hard segments) and nonpolar macrodiol units (soft segments), thus preferentially leading to the regulation of proteins absorption on polymer surface and preventing platelets from activating, and, in consequence, fibrin formation (Fig. 7). Additionally, those interactions are disturbed at the surface, the nanoscale atomic layer, where the polymer comes in contact with the gas or liquid environment. When the polymer is exposed to the hydrophobic atmosphere (polyurethane-air), the nonpolar soft segments segregate preferably on

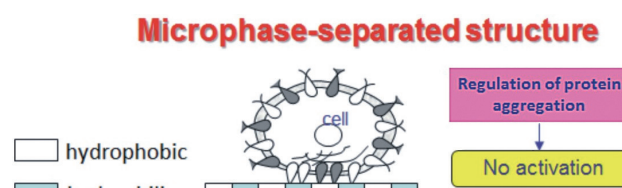


Fig. 7. Regulation of proteins on microphase-separated surface of segmented polyurethanes

the polymer surface. Conversely, when polymer surface comes in contact with the hydrophilic environment, e.g., blood, polar hard domains organize at the interface. The ability of such specific rearrangement is possible due to the relatively high mobility of soft segments at body temperature (T_g significantly lower than body temperature). This phenomenon is strongly influenced by the hard/soft segment ratio, their chemical composition, the soft segment average molecular weight, and the degree of crosslinking (number of hydrogen bonds between macromolecules).

Thermoplastic Polyether Polyurethane (PEU)

The first use of segmented polyurethanes in a ventricular assist pump was noticed by Boretos and Pierce in 1967 [6]. This polymer had been developed by DuPont and then was licensed to Ethicon Inc., with the trade name Biomer® – polymer for biomedical applications. At present, Biomer® is no longer commercially available, but there are several types of polyether polyurethanes on the market e.g. Elasthane™ by DSM, Pellethane® by Lubrizol, and ChronoThane® by AdvanSource Biomaterials. Figure 8 illustrates one of the typical structures of polyether polyurethanes.

All PEU are segmented polymers with a methylene di(*p*-phenyl isocyanate) (MDI) hard segments, poly(tetramethylene oxide) (PTMO) soft segments, and 1,4-butanediol (BD) as chain extender. Commercially available products are usually classified according to their hardness, usually in the range from 53 Shore D to 80 Shore A. Although possessing a broad range of different chemical and physical properties [7, 8] and excellent biocompatibility, PEU have one major disadvantage: susceptibility to environmental stress cracking (ESC). This term was originally used by Stoke [9] in 1984 and this effect is mainly attributed to the presence of ether bonds in polymer chain, which were susceptible to oxidation catalyzed by stress. Much research was devoted to understanding and preventing this process. At this moment, it is known that this degradation process is not only affected by the high stress level applied to the polymer, but also as a consequence of the presence of many biological agents, like macrophages and foreign body giant cells [10, 11]. Their presence at the polymer sur-

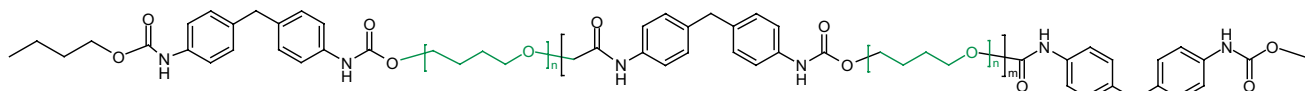


Fig. 8. An example of polyether polyurethane composed of MDI units (hard segments) and PTMO block (soft segments)

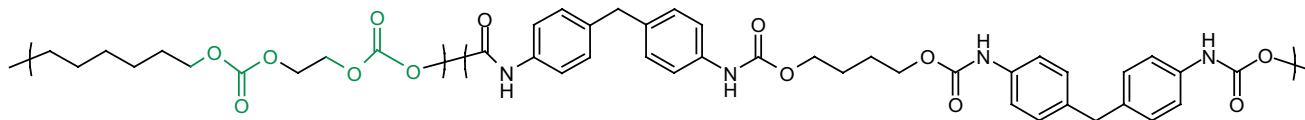


Fig. 9. Schematic structure of polyurethane copolymers with polycarbonate polyol

face accelerates surface erosion that propagates later to the bulk, leading to the loss of mechanical stability of the polymeric implant [10]. In order to reduce the oxidation of polyether soft segments, different antioxidants have been used, e.g. Methacrol, Santowhite or natural antioxidant, vitamin E [12, 13]. Compared to synthetic antioxidants, Methacrol was immiscible in the polymer matrix and its leaching was responsible for pitting the polymer surface. On the other hand, Santowhite was less efficient in preventing oxidation in comparison to vitamin E, probably due to different inhibition mechanisms of the oxidation process. Another method to restrain or even eliminate the oxidation process is to incorporate fluoropolymer into some of isocyanate polymer end groups, forming new end groups. After two years of study *in vivo*, it was determined that Elasthane™80A with 4 to 6% fluoro-end groups exhibits no bulk degradation and significantly lower amount of surface cracks, as compared to unmodified polymer [14].

Thermoplastic Polycarbonate Polyurethane (PCU)

Polycarbonate polyurethanes represent a new generation of polymeric materials for medical application, especially for blood contacting devices. A schematic structure of these materials is presented in Figure 9.

The main known trademarks of those materials are: Bionate® (DSM), Carbothane® (Lubrizol), and Chrono-Flex® (AdvanSource Biomaterials). Similar to PEU, the microphase separated structure of PCU is responsible for the excellent mechanical properties and influences protein absorption and platelet adhesion, for materials with hardness ranging from 75 Shore A to 75 Shore D. As described in the literature [15, 16], the carbonate linkage (-O-CO-O-) is believed to be more stable than the ether one (-C-O-C-), when exposed to aggressive physiological environment.

Segmented Polyester Thermoplastic Elastomers

Polyester (aliphatic-aromatic) multiblock copolymers are an alternative group to polyurethane thermoplastic elastomers. These materials are also classified as thermoplastic elastomers, due to their microphase-separated structure, as a consequence of the coexistence of hard and soft segments in polymer structure. A schematic chemical structure of these materials is presented in Fig. 10.

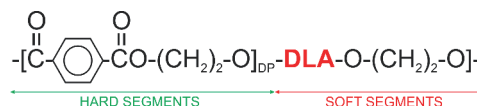


Fig. 10. Chemical structure of polyester multiblock copolymer; DP – degree of polycondensation from 1.4 to 29.6 depending from the hard/soft segments ratio. DLA refers to unsaturated dilinoleic acid (dimer of linoleic acid)

A new group of polyester thermoplastic elastomers was developed by the Polish Artificial Heart Program, coordinated by the Foundation for Cardiac Surgery Development in Zabrze. As illustrated in Figure 10, poly(ethylene terephthalate-ethylene dilinoleate) copolymers are synthesized by two stage melt polymerization, typical for polyester or poly(ester-ether) copolymers [17, 18]. The first step of this process is the transesterification of dimethyl terephthalate (DMT) and ethylene glycol (GE), carried out at normal pressure and at a temperature of 200°C and in the presence of zinc acetate as catalyst, resulting in the formation of oligomers of ethylene terephthalate as in PET. After the removal of methanol (95% from stoichiometry) as the by-product, dilinoleic acid (DLA) (product of dimerization of linoleic acid) is added. The polycondensation step is carried out under low pressure and at a temperature of about 265°C until the power consumption of stirrer motor reaches the highest value. Such controllable synthesis method allows one to specify and repeat the synthesis conditions in order to obtain materials with reproducible properties – one of the most important requirements for polymeric materials

produced on a large scale. Since the 1960s [19, 20], the PET homopolymer is a commonly applied polymeric material in different blood contacting applications, including surgical sutures, meshes, and vascular grafts. Due to the high crystallinity and hydrophobic aromatic rings in the polymer chain structure, this material is resistant to hydrolysis and is biostable. PET copolymerization with hydrophobic, a long chain fatty acid dimer, results in materials with tunable properties, depending on the hard/soft segment ratio. As presented in earlier work [21], by changing the weight ratio between soft and hard segments, it is possible to obtain materials with diverse mechanical, thermal and structural properties.

The comparison between the thermal properties of PET-DLA copolymer (50 wt.% of hard segments) and PCU is presented in Figure 11. The microphase-separated structure of both materials results in comparable second heating scans. The glass transition temperature, characteristic for soft segments, is slightly lower for PET-DLA copolymer, due to the longer aliphatic chain of the monomer, and unrestricted motion of the chains, whereas the PCU structure is stabilized by the hydrogen bonds. The endothermic peak corresponds to melting transition and, due to the higher crystallinity of PET domains, PET-DLA copolymer possess higher melting temperature and enthalpy compared to PCU.

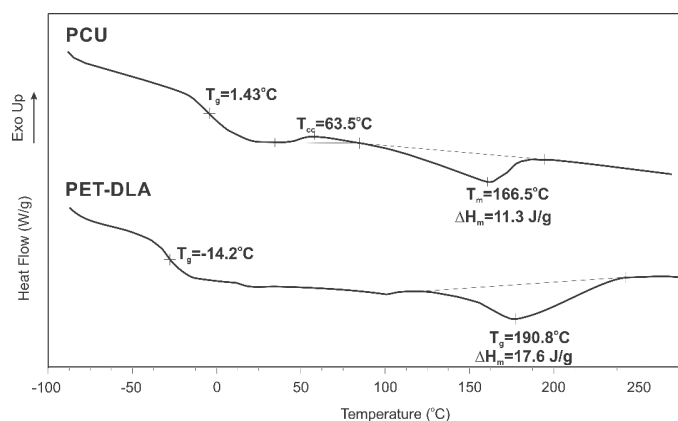


Fig. 11. DSC thermograms of 2nd heating of PCU and PET-DLA copolymer; T_g – glass transition temperature, T_{cc} – cold crystallization temperature, T_m – melting temperature, ΔH_m – melting enthalpy

As a result of their thermoplastic character, the presented materials can be processed by traditional methods like injection molding or extrusion. Examples of elements obtained from PET-DLA copolymer (50 wt.%) by injection molding technique, as well as raw polymeric granules, are presented in Figure 12.

The difference in hard-soft segment interactions between polyester and polyurethane materials also results in their thermo-mechanical stability. As presented in Figure 13a, both materials show a similar de-



Fig. 12. Polymeric granules, injection molded samples for mechanical testing (type 5A, ISO 527) and pneumatic elements of the pump obtained from 50-50 PET-DLA copolymer

crease of Young's modulus measured during the static tensile test. This fact is associated with their structure: both possess comparable hard/soft segment ratios, so the mechanical response to applied stress is in the same range.

A notable difference between PET-DLA and PCU was observed for another parameter: the secant modulus @ 50% elongation. For polyester copolymer, the secant modulus at a higher temperature decreased by only 15%, while for PCU a significantly higher decrease was observed (Fig. 13b). The main explanation of this phenomenon is imperfect microphase separation characteristic for all PUs. It is commonly known that the coexisting microphases are not pure, but consist

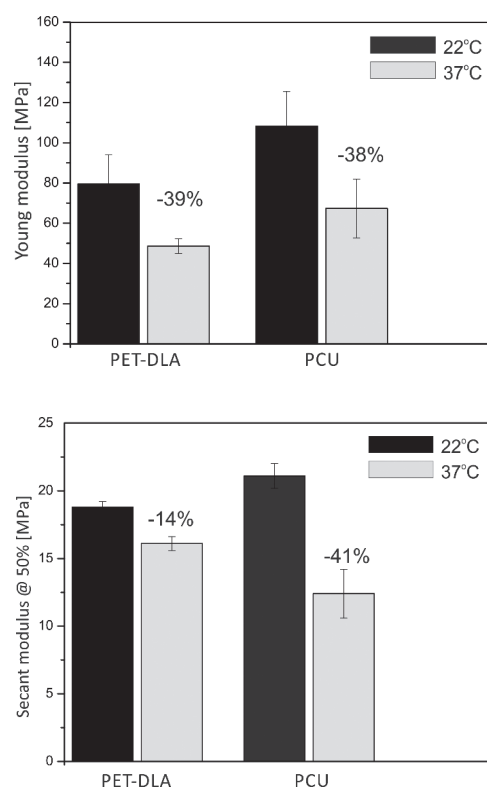


Fig. 13. PET-DLA vs. PCU mechanical properties: a) Young modulus, b) secant modulus @ 50% elongation

of mixed hard and soft segment units. The presence of intersegmental mixing within the microphases affects both morphology and mechanical properties of the materials.

For PET-DLA material, the crystallinity of hard segments is significantly higher, resulting in more ordered microstructure, and thus higher mechanical stability.

In order to explore the potential of PET-DLA copolymers for their application as blood contacting materials, indirect hemolytic testing was carried out, according to ISO 10993-4 standard. Figure 14 presents selected blood parameters, free hemoglobin and red blood cells number, for blood contacted with polymeric extracts. The control values represent the selected parameters of blood incubated in the same conditions but without contact with polymeric extracts. These preliminary results indicate non-hemolytic properties of PET-DLA material.

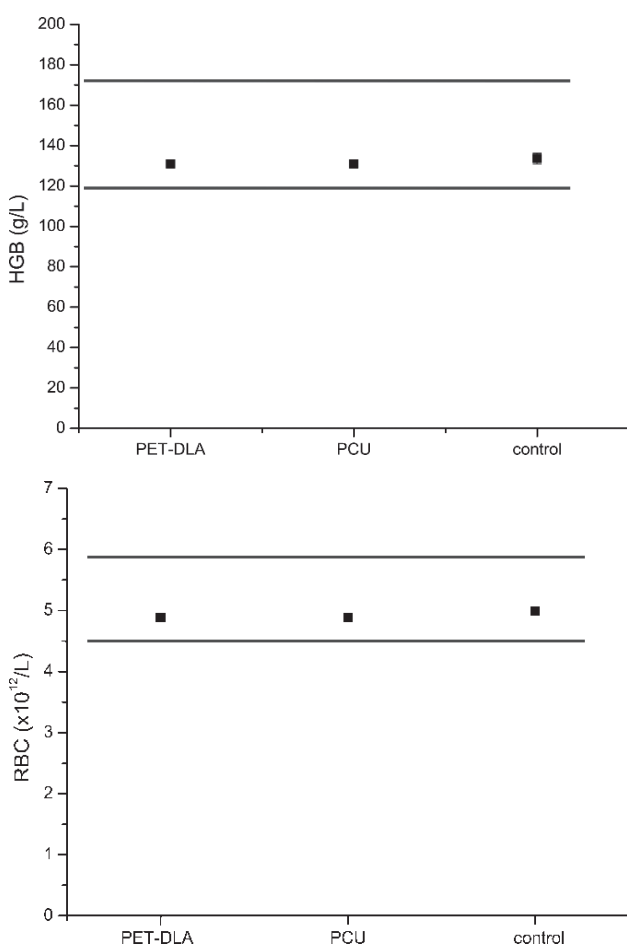


Fig. 14. Blood parameters after contacting with polymeric extracts (HGB – free hemoglobin concentration, RGB – red blood cells concentration). Lines represent reference values

Other Polymeric Materials

In the case of vascular grafts, two synthetic materials are in use for over fifty years, namely poly(ethylene terephthalate) (PET) and expanded poly(tetrafluoroethylene) (ePTFE). Textiles based on these two polymers can be in woven or knitted forms, in the shape of tubes with a diameter greater than 8 mm. Although both materials are currently in use as vascular implants, there are two major problems related to these polymers: inflammatory reaction and thrombosis [22]. Therefore, surface modification is applied in order to enhance blood compatibility and increase the endothelial and smooth muscle ingrowth. The first step is usually the activation of polymer surface by plasma treatment in order to achieve covalent bonding of active compounds [23–25], as listed in Table 2.

Table 2. Reagents to modify PET and ePTFE surface

Reagent	Reference
Vascular endothelium growth factor	[26–28]
RGD ((Arg–Gly–Asp) tripeptide)	[29,30]
Heparin	[24,31–33]
Phospholipids	[34–36]

For the heart-lung machine, all elements have to be of the highest quality, especially in parts that come in contact with the blood. They are mainly located in the first module [38] and these are: reservoir, pump head, and an oxygenator provided with a heat exchanger or an arterial filter. Therefore, the tubing, where the blood is circulated, is crucial for such a device. Tubing needs to be elastomeric, it needs to be fatigue resistant during cyclic deformations, biocompatible with the blood and also transparent. Several polymers exhibit these major properties, e.g. silicone, Santoprene™ thermoplastic vulcanizates (mixture of *in situ* crosslinking EPDM and polypropylene), PVC, and polyurethanes. Unfortunately, they have some disadvantages, such as low molecular products, e.g. di-(2-ethylhexyl) phthalate, used as plasticizer in PVC production [39], and also their surfaces can be prone to microbial biofilm formation, causing nosocomial infections. Several approaches are proposed in order to eliminate these type of infections: incorporating antibiotics on polymer surfaces [40] or coating with poly(vinyl alcohol) films containing nanosilver particles. Since heparin is the most effective anticoagulant substance, there have been trials to produce PVC–heparin complexes, with addition of dextran and iron (III) by electrostatic interaction. Such multilayer coating drastically reduced platelets and protein absorption and increase significantly hydrophilicity of PVC surface [41], yielding materials with improved blood compatibility, especially for medical devices used in extracorporeal circulation circuit.

Summary

PUs are a major group of polymeric materials occupying the biomaterials market, specifically for manufacturing heart assist devices and other blood contacting systems. Over sixty years of continuous research on these materials has provided much data, including both their advantages and disadvantages, and ultimately

ly resulted in obtaining medical grade status from the regulatory bodies. However, one should note that PUs were not intentionally designed for blood contacting materials, they were simply accommodated by the medical market to occupy a certain niche. Therefore, there remains a need to develop new formulations using macromolecular engineering in order to tailor specific material properties for specific applications.

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