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Chapter 1

Synthesis and Properties of Polyurethanes Based on Synthetic Polyhydroxybutyrate for Medical Application

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/60933

Abstract

Polyurethanes is a group of polymers whose unique properties make them useful in both the construction and the textile industry, and even in tissue engineering. One small, but very significant, urethane group connects specially selected macrochains to obtain a material with established properties.

The chapter is a literature review for research on the synthesis and properties of new degradable polyurethanes that contain soft segments synthesized with synthetic telechelic poly([R,S]-3-hydroxybutyrate) (R,S-PHB). Incorporation of oligomeric R,S-PHB (what was found degradable and biocompatible) into polyurethane structures gives them a chance of improving the properties important for medical applications. Aliphatic and aromatic polyurethanes with different soft segments were investigated due to their potential to be used in soft tissue regeneration.

Keywords: Polyurethanes, synthetic polyhydroxybutyrate, medical application

1. Introduction

Polyurethane (PUR) is a large and very diverse group of polymers, including elastomeric and thermoplastic materials (liquid, millable), foams, and ionomers in the aqueous dispersions [1–3]. The preparation of polyurethanes in such various forms has allowed their broad use in such industries as construction, engineering, automotive, textile, and medical. In medicine, their biocompatible, biostatic, and biodegradable properties are very desirable. The required

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properties can be achieved using appropriate monomers for polyurethane synthesis and for preparing their composites.

1.1. Polyurethanes in medicine

PURs' career in medicine has been going for almost 60 years since polyurethane foam for breast implants has been patented [4, 5]. According to studies of Jose Abel de la Pen˜a-Salcedo et al. [6] performed at the Institute for Plastic Surgery, polyurethane-covered implants are still the best option for breast reconstruction.

PURs are already used or investigated for utilization as membranes for wound dressing [7], as meniscal scaffold to treat partial meniscal loss [8], as drug nanocarriers for endovascular applications [9], as controlled release membrane system for delivery of ketoprofen [10], or as the biostable polyurethane/hydroxyapatite composites for bone replacement materials [11]. Whereas the shape memory PUR (based on PCL) used as wire in orthodontic appliance, could effectively align the teeth [12]. Waterborne polyurethane with chitosan as chain extender was also studied as antimicrobial agent for acrylic fabrics that could be used for the manufacture of blankets and carpets in hospitals [13].

One of the most important uses of PURs in medicine is the preparation of the implants for cardiovascular diseases, the use of which the specific properties of PUR (high mechanical strength, toughness and flexibility without the addition of modifiers, and good hemocompatibility resulting from occurring on the surface hydrophilic-hydrophobic balance) are very important.

1.2. Polyurethanes biostatic and biocidic

The very important danger during implantation is connected with bacterial and fungi contamination. Aside from antibiotics treatment after surgery, the use of biostatic implant is essential for the success implantation.

The bacterial adherence and encrustation was reduced after the immobilization on PUR (Tecoflex®) surface by polyvinylpyrrolidone-iodine (PVP-I) complex [14]. Modified films were much more hydrophilic than original films.

Surfaces coated with quaternized PUR possessed the antibacterial and antiviral properties [15]. For wound dressing application, the asymmetric PUR membrane, with diamino containing antibiotic sulphanilamide used as a chain extender could be utilized [16]. These antibiotic-conjugated PUR are enzymatic susceptible what fit them antibacterial activity. The antibacterial properties can also be achieved by using nanoparticles for polyurethane or its composites obtaining. The nanosilver nanoparticles are very often used [17].

1.3. Biodegradable polyurethanes

The first applications of polymers required their high resistance to environmental factors. They had to be stable (non-degradable) under the operating conditions throughout. This applies to the construction, packaging, textile, mechanical, medical, as well as other industries. However,

http://dx.doi.org/10.5772/60933

the growing environmental burden of polymer waste has caused plastics to be gradually replaced by degradable materials. In medicine, dynamically developing tissue engineering suggests many interesting solutions with biodegradable polymeric materials.

PURs were originally considered to be very resistant to environmental impacts and were used in the construction of the first "artificial hearts". So why not produce something biocompatible as polyurethane and simultaneously degradable for tissue reconstruction? Since the first time this question was formulated, a lot of really interesting investigations were conducted.

The use of monomers susceptible to environmental factors allows the production of biodegradable PURs potentially suitable to create scaffolds for the growth of living cells or as temporary implants. Hydrolysis-sensitive ester groups, mostly with oligomerols, are introduced into the PUR structure to build the soft segments.

Wang and co-workers [18] synthesized biodegradable polyurethanes with 11,11′-dithiodiundecanol employed as a soft segment. They concluded that the molecular weight of PURs substantially decreased and the surface morphology was significantly eroded after 8 days of incubation in SBF with reduced glutathione. Gisele Rodrigues da Silva et al. [19] observed that the biodegradable PURs based on PCL were able to release dexamethasone acetate for 371 days at almost constant rates.

1.4. Polyurethanes that are more biocompatible

Using of natural components (or their synthetic substitutes) for PURs synthesis is one of method for making them more biocompatible. Saralegi et al. used castor oil for soft segment building [20]. They obtained the shape memory thermoplastic PUR due to the addition of cellulose nanocrystals. L-arginine, glycine, and L-aspartic acid were used as chain extenders in poly(urea)urethanes synthesis by the Chan-Chan group [21]. The authors concluded that PURs containing L-arginine would be a potential candidate for cardiovascular applications and angiogenesis. Studies of Lin Jia and co-workers [22] showed the lack of cytotoxicity of PUR/collagen and PUR/gelatin nanofibrous scaffolds. The authors indicated on sufficient mechanical properties, supported SMC proliferation, and assisted in oriented morphological alignment of cells of PURs with L-arginine that make them the appropriate candidate for vascular tissue engineering.

Very important for obtaining biocompatible material is the use for their synthesis substrates that are non-toxic and degraded into non-toxic compounds. In medical applications, 4,4'-methylene dicyclohexyl diisocyanate (H_{12}MDI) successfully replaced 4,4'-diphenylmethane diisocyanate (MDI), especially in the synthesis of biodegradable materials, thereby reducing the risk of creation of carcinogenic aromatic diamine as degradation product of PUR based on MDI.

Using natural components for polyurethanes building very often gives them a chance to be biocompatible and degradable simultaneously. The important groups of substrates useful for polyurethanes synthesis are polyhydroxyacids (PHA). Among them, polyhydroxybutyrate (PHB) is the most often used.

1.5. Biosynthesized polyhydroxybutyrate

As it was mentioned before, the most popular polyhydroxyacid is PHB. Since the 1920s when Lemoigne found the bacterial granules of supplementary material (later called polyhydroxybutyrate) in *Bacillus megaterium*, intensive researches on the biological and chemical obtaining of PHB, its properties, and application were conducted. The natural origin, biodegradability, and biocompatibility of polyhydroxybutyrate made it such interesting material for medical applications whereas its low water vapor permeability, which is close to that low-density polyethylene, promote it to food packaging applications [23].

PHB degrades into 3-hydroxybutyric acid, a common metabolite in human blood. 3-hydroxybutyric acid is produced in ketone bodies of mammals during the prolonged starvation [24]. 3-hydroxybutyric acid belongs to short-chain fatty acids and reveals antibacterial activity [25].

A lot of investigations suggest that PHB is non-genotoxic [26]. All this features promote PHB for medical applications. Lee and co-workers prepared a carrier system with targeting capability for imaging and drug delivery to cancer cells using catalytic characteristics of PHA synthase [27]. They found an attractive way of preparing functionalized nanoparticles by effective coupling between the hydrophobic surface of PHB nanoparticle and PHB chain grown from the fusion enzyme. Medvecký and co-workers [28] found that the addition of hydrophobic PHB microparticles into the calcium phosphate cement significantly improves the initial cement properties (the higher tensile and compressive strengths) and makes it a very promising material for bone substituting. Another way of PHB utilization in tissue reconstruction is by using it as the PHB–chitosan biopolymer scaffolds [29], PHB-calcium phosphate/chitosan barrier membrane [30], hydroxyapatite/PHB composites [31], or biodegradable stents [32]. The investigations of Shishatskaya at el. [33, 34] indicate that PHB is a good candidate for fabricating prolonged-action drugs as microparticles intended for intramuscular injection. Whereas Althuri and co-workers [35] concluded that folate functionalized PHB nanoparticles can be used as a polymer matrix to carry toxic drug compounds to targeted sites for treatment of life-threatening diseases such as cancer.

Nonetheless, the inherent brittleness and stiffness (connected to its semicrystalline nature) and inferior thermal stability, in addition to relative high cost, have blocked the popular use of PHB.

It is known that even the short exposure of PHB to temperatures near 180°C degrades it to olefinic and carboxylic acid compounds (e.g., crotonic acid) and various oligomers. Also, during storage, the degree of crystallization of polymer increases and causes the formation of irregular pores on its material surface and causes even higher stiffness. These disadvantages can be reduced by mixing of PHB with plasticizers, such as low molecular weight PHB [36], carboxyl-terminated butadiene acrylonitrile rubber, or biocompatible polyvinylpyrrolidone polymeric additives [37].

1.6. Chemically synthesized poly([R,S]-3-hydroxybutyrate)

The chemically synthesized substitute of natural PHB is synthetic poly([R,S]-3-hydroxybutyrate) (R,S-PHB). Synthetic R,S-PHB can be obtained by anionic ring-opening polymerization

http://dx.doi.org/10.5772/60933

of (R,S)-ß-butyrolactone. The supramolecular acid sodium salt complex of 3-hydroxybutyric acid ether 18-crown-6 can then be used as the initiator. The polymerization process is carried out in THF at room temperature. The resulting polymer could be reacted with 2-bromo- or 2-iodoethanol, finally causing PHB to be terminated with hydroxy groups on both sides [38–41].

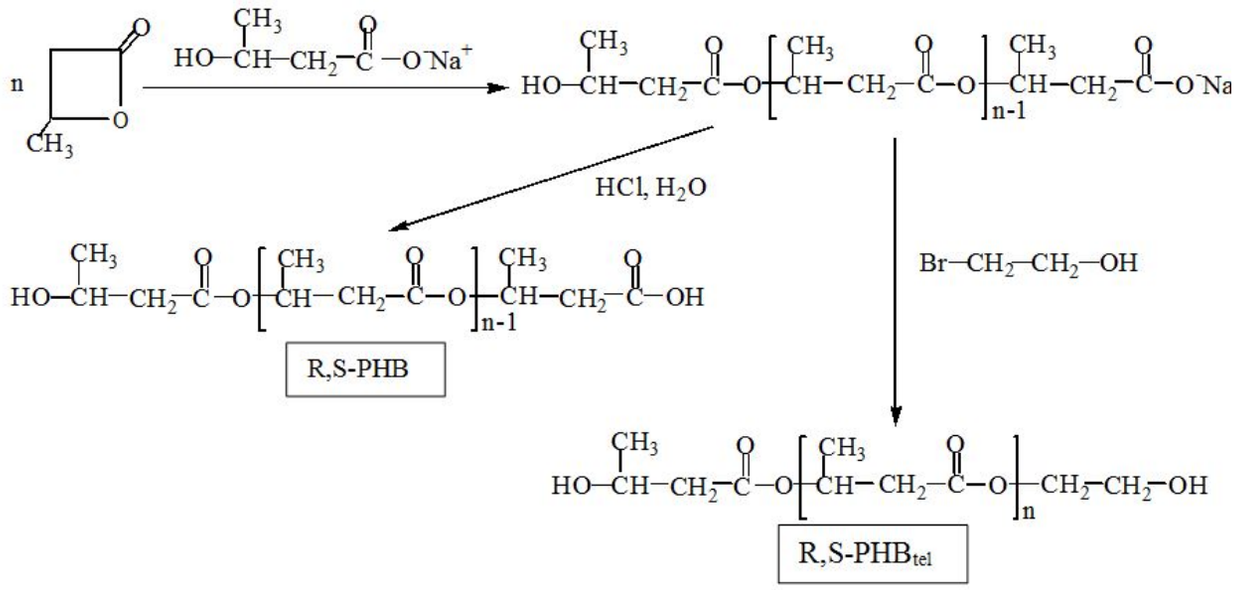

Figure 1. Scheme of how telechelic R,S-PHB (OH-terminated) and R,S-PHB (OH- and COOH-terminated) are obtained.

The literature indicated that materials obtained with synthetic R,S-PHB was biocompatible and biodegradable. The degradation products of the temporary patch made from PHB/R,S-PHB blends were metabolized and did not evoke inflammatory reactions [42]. Freier et al. [43] found that after 26 weeks of implantation of the patches (made with PHB/R,S-PHB blends) in the abdomen of rats, the loss of intestines of animals was almost completely restored and the introduced material had been substantially degraded.

Piddubnyak et al. [40] conducted a series of studies confirming the biocompatibility and non-toxicity of synthetic [R,S]-3-hydroxybutyrate oligomerols. The possibility of their formation into spherical particles of a diameter <1 micron, suggested that they could be used in obtaining nonsteroidal anti-inflammatory drugs. In the form of an aqueous dispersion, they could be introduced into the body through intravenous, intramuscular, or subcutaneous administration [44].

1.7. Marriage of PUR and PHB advantages in one product

Using for PUR synthesis, almost completely amorphous R,S-PHB that is close to its original state in the cell, ought to be utilized to obtain biocompatible and biodegradable material useful for medical application.

The work is a review of the research on the synthesis and properties of PURs containing synthetic poly([R,S]-3-hydroxybutyrate) and polycaprolactonediol or polyoxytetramethyle-

nediol in soft segments in the structure in terms of applications as medical devices. The properties of polyurethanes that could determine their usefulness for medical application (structure, morphology of surface, thermal and mechanical properties, water and oil sorption, density, degradability, spinnability, compatibility, and biostatic properties) were estimated.

Works with PURs based on natural and synthetic PHB are collected in Table 1.

Kind of PHB origin	Characteristic	Ref.
bacterial	Higher crystallinity than PURs without PHB.	[45]
bacterial (as copolymer P3/4HB)	High molecular weight and narrow molecular weight distribution.	[46]
bacterial (as copolymer P3/4HB)	Narrow distribution and suitable crystallinity to prepare films and pads. Non-toxic for cell growth and proliferation.	[47]
bacterial	Degradability with creation of 3-hydroxybutyric acid and crotonic acid as degradation products.	[48]
synthetic	Hydrolytic degradation of PURs based on PCL/HB increased with increasing of PHB fraction.	[49]
synthetic	The way of PURs based on R,S-PHB obtaining.	[50]
synthetic	Presence of R,S-PHB influenced on the structure of PURs.	[51]
synthetic	Degradability of PURs increased after using of R,S-PHB for their building.	[52]
synthetic	Electrospinning of PURs based on R,S-PHB.	[53]
synthetic	Degradability of PURs increased after using of R,S-PHB for their building.	[54]

Table 1. Polyurethanes based on PHB.

2. Experimental

2.1. Materials

Oligoesters, such as polycaprolactonediol (PCL) and polyhydroxybutyratediol (PHB), are used in the synthesis of polyesterurethanes. The oxidative-sensitive ether groups can be introduced into polyurethanes with polyoxytetramethylenediol (PTMG). 4,4'-diphenylmethane diisocyanate (MDI) and 4,4'-methylene dicyclohexyl diisocyanate (H_{12}MDI) are isocyanates that are often used for building of hard segments of polyurethanes.

Aromatic and aliphatic polyurethanes with synthetic poly([R,S]-3-hydroxybutyrate) incorporated into the soft segments structure were obtained and investigated.

2.1.1. Materials for polyurethanes synthesis

- Before the synthesis of polyurethanes, R,S-PHB (Mn~2000) (CMPW, PAN Zabrze), PCL (Mn~2000) (Aldrich), and PTMG (Mn~2000) (Aldrich) were dried by heating at 60°C–90°C for 3 h under reduced pressure;
- 4,4'-diphenylmethane diisocyanate MDI (Aldrich) was filtered and melted at temperature 40°C;

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- 4,4'-methylene dicyclohexyl diisocyanate (H_{12}MDI) (Alfa Aesar) (mixture of isomers) was purified via vacuum distillation;
- the chain extender 1,4-butanediol (1,4-BD) (Aldrich) was freed from moisture by an azeotropic distillation with benzene prior to use;
- the solvent dimethylformamide (DMF) (Labscan Ltd) was dehydrated over P_2O_5 and distilled under low pressure before synthesis; and
- catalysts dibutyltindilaurate (DBTDL) (Akra Chem) and stannous octoate (OSn) (Akra Chem) were used as received. Stannous octoate was approved by the US Food and Drug Administration as the catalyst for polyurethane synthesis [55].

2.1.2. Polyurethane synthesis and sample preparation

The synthesis of polyurethanes was carried out in a two-step reaction at the vacuum reactor, as previously described [56].

First, the prepolymer was prepared from oligomerols and H_{12}MDI or MDI, at 60°C–90°C in a presence of a catalyst at reduced pressure according to the appropriate required molar ratio of NCO:OH groups for 2–3 h. Oligomerols used in synthesis: a mixture of PCL and R,S-PHB or a mixture of PTMG and R,S-PHB. For comparison, PURs based only on PCL or PTMG without R,S-PHB were also obtained. The synthesis of prepolymer was carried on mass but next the prepolymer was dissolved in DMF to solid mass concentration of 40%. The chain extender (1,4-BD) was added to obtain equimolar ratio NCO:OH groups. The propagation reaction of prepolymer was carried on for 2–3 h at 60°C.

PUR	Molar ratio of OH groups of reagents used in PURs synthesis				Molar ratio of NCO/OH in prepolymer (diisocyanate)
	PCL	R,S-PHB	PTMG	1.4-BD	
PUR-2A-1	-	0.23	0.77	2.7	3.7 (MDI)
PUR-2A-2	-	-	1	2.7	3.7 (MDI)
PUR-2A-3	0.77	0.23	-	2.7	3.7 (MDI)
PUR-2A-4	1	-	-	2.7	3.7 (MDI)
PUR-3A-1	-	0.23	0.77	2.7	3.7 (H_{12}MDI)
PUR-3A-2	-	-	1	2.7	3.7 (H_{12}MDI)
PUR-3A-3	0.77	0.23	-	2.7	3.7 (H_{12}MDI)
PUR-3A-4	1	-	-	2.7	3.7 (H_{12}MDI)

Table 2. Composition of the obtained polyurethanes.

After the extension of prepolymer chains, the solution of polyurethane was poured on Teflon plates and heated for solvent evaporating (2 h/80°C). Next, the foils were heated in a vacuum dryer for reaction completing (5 h/105°C). Before the estimation of polyurethanes properties, the foils were conditioned at room temperature at least 2 weeks.

The obtained and investigated PURs differed in soft and hard segment structures and in their ratio (Table 2).

2.2. Methods of investigations, obtained results, and discussion

2.2.1. The structure of obtained polyurethanes

The structures of obtained aromatic and aliphatic PURs were investigated using FT-IR and ^{1}HNMR methods (results presented in [51]).

The value of vibration absorption of the carbonyl group in the ester moiety at 1,740 cm^{-1} is indicative of the presence of the amorphous phase of polyhydroxybutyrate (the presence of the crystal phase of stretching vibration of C=O would be observed at 1,725 cm^{-1}) [56, 57]. These differences in the frequencies corresponding to the vibrations of the carbonyl bond were explained by Wu and co-workers [58] by the decrease in oxygen dipole moment under the influence of hydrogen from a neighboring chain. The interaction is stronger when the oxygen is closer to the hydrogen atom. Amorphousness of R,S-PHB used in the synthesis of polyurethane, was also confirmed by the presence of bands of CH_3 at 2,985 cm^{-1} and C-O-C stretching vibration band at 1,186 cm^{-1} [57, 59]. It is known that asymmetric stretching vibration of CH_3 at 3,009 cm^{-1}, 2,995 cm^{-1}, 2,974 cm^{-1}, and 2,967 cm^{-1} in the natural polyhydroxybutyrate indicate its crystallinity [57].

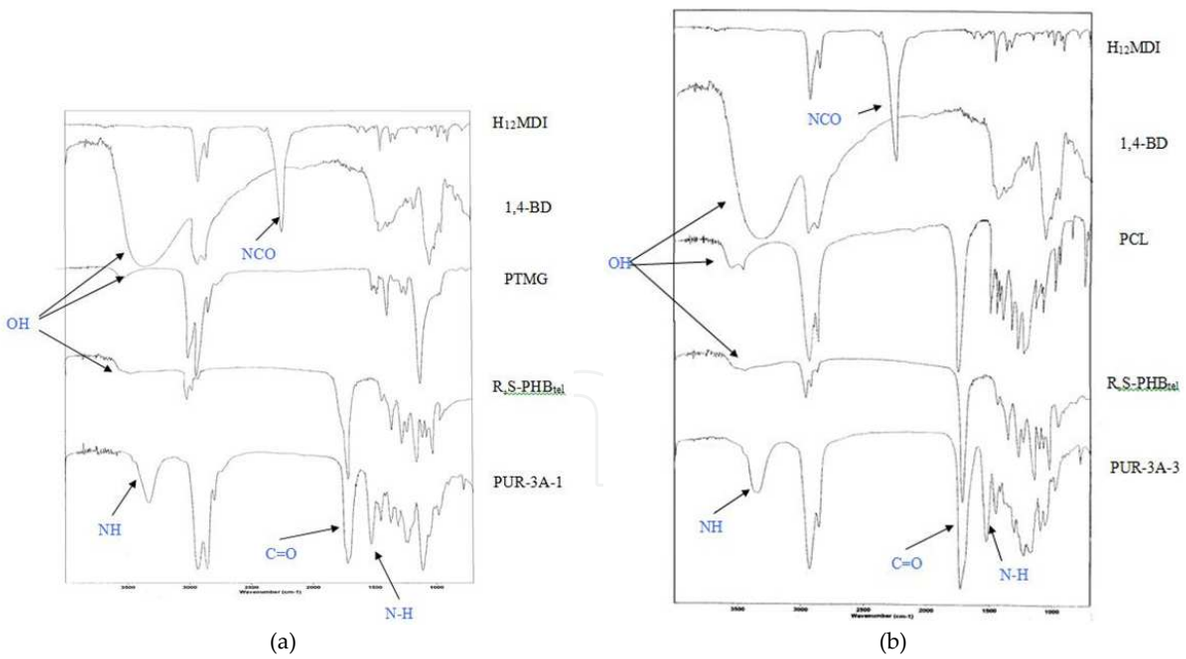

Figure 2. FT-IR spectra of substrates and PUR-3A-1 (a) and substrates and PUR-3A-3 (b).

FT-IR spectra supported the formation of urethane groups during polyaddition reaction of OH groups of oligomerols (R,S-PHB, PCL, and PTMG) and NCO groups of diisocyanates (MDI and H_{12}MDI).

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In the spectra of PUR-2 and PUR-3 series with PTMG in soft segments (PUR-2A-2, PUR-2B-2, PUR-3A-2 and PUR-3B-2), a single band (without shoulder) at around 3,330 cm^{-1} corresponded to the NH stretching vibration of urethane groups. The absence of any bands above 3,500 cm^{-1} indicated that all group -NH were involved in the formation of hydrogen bonds.

Simultaneously, in an area corresponding to the stretching vibration of C=O groups of the urethane two bands (at 1,720 cm^{-1}/1,705 cm^{-1} for PUR-3 and at around 1,732 cm^{-1}/1,703 cm^{-1} for PUR-2) were observed. The intensities of these bands were comparable for PUR-3A-2. The literature indicated that the first band corresponded to vibration of free groups C=O and the other for associated groups [60]. The presence of free groups C=O suggested that not all -NH were involved in the formation of hydrogen bonds within the urethane groups, but some of them could be associated with the oxygen moiety of ether. The intensity of the absorption bands of the C=O hydrogen bonded clearly decreased after the introduction of R,S-PHB into the soft segments. On spectra PUR-3A-1 at 1,740 cm^{-1} appeared the band of stretching vibration characteristic for non-hydrogen bonded C=O of ester groups.

In the spectra of all polyurethanes with PCL in their structure, there were clear bands of stretching vibration characteristic for associated -NH. For polymers PUR-2 they were at 3,334 cm^{-1} and at about 3,360 cm^{-1} for PUR-3. At frequencies a bit lower, the presence of broad bands with low intensity was also observed. It indicates the existence of two types of hydrogen bonds, between the -NH groups and the carbonyl group of urethane and between -NH and ester group. On the other hand, the intensity of the bands of stretching, hydrogen-bonded C=O of urethane (amide I band) and ester groups on PUR-2A-3 and PUR-2A-4 spectra (at 1,702 cm^{-1} and 1,705 cm^{-1}) was small.

Thus, the FT-IR spectra of the polyurethanes indicated that urethane groups (partly hydrogen bonded) were formed and the end groups of substrates were completely converted.

On ^{1}HNMR spectra of aliphatic PURs, peaks due to the NH group were observed in the region of 6.6–7.1 ppm [51], whereas on the spectra of aromatic PUR they were located at 9.2–9.5 ppm. The NH groups coming from urethane groups were forming hydrogen bonds with carbonyl groups of ester and urethane groups and the hydrogen bonds with ether groups. It was also concluded that the greater NCO:OH ratio, the more urethane-urethane hydrogen bonds were formed [51]. An addition, R,S-PHB caused the slight increase in number of urethane-urethane hydrogen bonds. The presence of an allophanate structures was observed at 8.5 ppm (for aromatic PURs) and as a very small peak at 9.65 ppm (for aliphatic polyurethanes based on PTMG).

2.2.2. Thermal properties

The presence of the synthetic R,S-PHB (with a lateral methyl group) in soft segments caused a disturbance in the phase separation and increase the glass transition temperature (estimated by DSC at a heating rate of 20°/min, at a temperature ranging from - 80°C to + 200°C) of the aromatic and aliphatic PURs in comparison to PURs without R,S-PHB [61,62].

sample	T_g [°C]	Tm1 [°C]	ΔH_1 [J/g]	T_{m2} [°C]	ΔH_2 [J/g]
PTMG	-70.8	47.8	129.6	-	-
PCL	-60.8	68.3	84.5	-	-
R,S-PHB	-12.3	56.3	4.3	-	-
PUR-2A-1	-67.6	-	-	174.1	1.3
PUR-2A-2	-73.3	35.0	2.0	177.0	12.6
PUR-2A-3	-28.5	44.0	1.4	175.2	7.3
PUR-2A-4	-38.5	51.3	2.8	179.1	5.7
PUR-3A-1	-55.3; -10.5	37.8	0.7	107.4; 135.9; 157.5	2.5; 4.0; 2.2
PUR-3A-2	-55.3	39.8	0.8	164.5	17.0
PUR-3A-3	-32.4	50.7	3.6	90.2; 138.1	4.7; 9.1
PUR-3A-4	-49.1	50.2	19.5	107.7; 131.6; 143.0	5.0; 5.1; 2.9

Table 3. Thermal properties of oligomerols and polyurethanes (results presented in [61, 62]).

Incorporation of oligomerols into PUR structures generally increased their glass temperatures. Moreover, using R,S-PHB for soft segment building increased the Tg of soft segments.

Obtained PURs were amorphous with the low value of crystalline phase. The introduction of R,S-PHB into PUR structures generally reduced crystallinity of soft segments (lower melting enthalpy was observed) [53]. In particular, it caused the reduced susceptibility of PCL to crystallization, which was the result of partial miscibility of both oligoestroles [62].

Temperatures in the range 90°C–179°C indicated the presence of long-range order of hard segments. A few melting endotherms on DSC thermograms (in the mentioned range) of aliphatic PURs (series PUR-3) were probably the result of using nonlinear diisocyanate for hard segment building. H_{12}MDI was a mixture of stereoisomers that may be formed into crystallites with different construction and size, and polymorphism.

The low degree of crystallinity suggested that investigated PURs could be degradable under the conditions of a living body.

2.2.3. Microscopic observation

The surfaces of the samples and surfaces revealed after breaking of obtained PUR samples in liquid nitrogen (cryogenically broken samples), they were tested by Transmission Electron Microscopy (TEM) using a two-step replica.

Studies of electron microscopy of PUR samples showed that they were characterized by varying degrees of homogeneity of the physical (morphological), depending on the chemical composition of the polymers. For samples with reported crystallization of soft segments, crystalline elements were usually in the form of spherulites.

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The surface of aromatic polyurethane PUR-2A series samples was smooth or only slightly rough. The cryogenically fractured surface of these samples were homogeneous in the micrometer scale, which indicated that the cracking (during the preparation of the samples) occurred between the crystalline areas, and thus in the weaker points of the polymers. The observed morphology was characteristic of non-crosslinked polymers. It was called un-radial or "mount-depression" morphology [63].

The aliphatic PUR surfaces and their cryogenically fractured surfaces were a bit rougher than the aromatic ones and that could influence their degradability. The surface morphology was comparable for all investigated samples.

There were no significant differences in the morphology of the samples of PUR based on PTMG or PCL. It was found, however, that the introduction of poly([R,S]-3-hydroxybutyrate) into the soft segment structures resulted in a slight decrease in the roughness of the surface of test samples and that could favorably influence the adhesion of blood elements in the study of the effects on blood parameters of polymers [64].

2.2.4. Mechanical properties

The mechanical properties determined for the obtained PUR materials included hardness (in degrees Shore A), tensile strength (Rr), and elongation at break (εr).

PUR	Hardness [°Shore A]	R_r [MPa]	$R_{r\,ster.}$ [MPa]	εr [%]	$\varepsilon_{rster.}$ [%]
PUR-2A-1	82	3.5±0.1	4.6±0.3	110±10	127±6
PUR-2A-2	85	24.6±0.5	20.2±1.8	492±11	734±67
PUR-2A-3	81	9.8±0.3	7.8±0.8	532±40	537±18
PUR-2A-4	82	15.4±0.6	11.1±1.8	616±53	685±139
PUR-3A-1	80	6.9±1.9	12.0±1.2	183±81	403±74
PUR-3A-2	76	7.9±0.5	5.7±0.8	383±37	143±74
PUR-3A-3	86	8.3±1.5	9.4±1.5	361±80	287±99
PUR-3A-4	84	9.0±0.5	8.2±2.3	30±11	29±6

Table 4. The hardness and tensile strength (±standard deviation) before and after the sterilization of PURs (results partially presented in [61,62]).

It was concluded that incorporation of R,S-PHB into aromatic and aliphatic PUR structures slightly reduced their tensile strength and elongation. The hardness of polyurethanes was in the range of commercial polyurethane elastomers used in medicine [61, 62].

The tensile strength of PURs obtained with the participation of the aliphatic diisocyanate (H_{12}MDI) was generally lower than PURs containing asymmetric and aromatic MDI. Investigations of model PURs (constructed only with H_{12}MDI and PTMG, without chain extenders),

indicated that in these polymers disordered hydrogen bonding were formed, making the phase separation of soft and hard segments difficult what reduced the mechanical strength of the materials [60].

The influence of sample sterilization on their mechanical properties was estimated. Gas plasma technology (dihydrogen peroxide) was used for sterilization. In some cases, tensile strength ($Rr_{ster.}$) and elongation at the break ($\varepsilon r_{ster.}$) of samples increased after the sterilization process. During the plasma sterilization, the free radicals were generated that could lead to slight cross-linking chains, thereby increasing the elasticity and tensile strength of the obtained PURs [61, 62].

2.2.5. Density

Easy penetration of water and degrading factors into the material is an important factor in the degradation of polymers. The density of the material is one of the parameters that determine the sorption of water.

PUR	Density ±SD [g/cm^3]	PUR	Density ±SD [g/cm^3]
PUR-2A-1	1.098±0.024	**PUR-3A-1**	1.081±0.002
PUR-2A-2	1.089±0.004	**PUR-3A-2**	1.051±0.004
PUR-2A-3	1.189±0.007	**PUR-3A-3**	1.152±0.008
PUR-2A-4	1.177±0.008	**PUR-3A-4**	1.135±0.003

Table 5. Density of polyurethanes (results partially presented in [54, 61, 62, 65]).

2.2.6. The oil and water sorption

The implanted material, immersed into a living body is affected by surrounding solutions. Physiological body fluids are constituted of water and floating inorganic and organic compounds, such as lipids. The tendency of water and lipids sorption by polymer is important for its stability in natural conditions. Water plays a key role in the process of hydrolysis whereas lipids accelerate calcification and environmental stress cracking of PUR surfaces. Moreover, the tendency for oil sorption could predispose polymer to albumin sorption. Albumin is peptide absorbable on implant surface what makes the natural junction with natural environment.

The sunflower oil and water sorption by PUR samples were performed at the physiologic temperature of the human body (37°C).

It was stated that the oil sorption by PUR samples based on PTMG and R,S-PHB was much higher than for PURs with PCL and R,S-PHB in soft segments [65, 66].

As it was expected, aliphatic PURs (based on asymmetric diisocyanate) absorbed more oil than aromatic ones. The oil sorption by aliphatic and aromatic PURs were significantly reduced after the introduction of R,S-PHB into soft segments based on PTMG [61, 62]. It could suggest

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an increase the hydrophility of PURs after R,S-PHB incorporation into their structure. Moreover, it indicated that PURs based on PTMG could be more biocompatible (according to their affinity to lipids) than PURs with PCL.

PUR	Oil sorption ±SD [%]	Water sorption		PUR	Oil sorption ±SD [%]	Water sorption	
		after 24h [%]	after 2 weeks [%]			after 24h [%]	after 2 weeks [%]
PUR-2A-1	4.0±0.16	1.8	3.9	**PUR-3A-1**	6.9±0.28	1.3	1.5
PUR-2A-2	10.1±0.97	1.5	1.3	**PUR-3A-2**	13.4±0.27	2.0	1.5
PUR-2A-3	0.7±0.05	1.1	0.9	**PUR-3A-3**	0.7±0.01	1.1	1.1
PUR-2A-4	1.4±0.32	0.8	0.7	**PUR-3A-4**	0.6±0.22	0.9	1.1

Table 6. The weight changes of PUR samples after incubation in sunflower oil (results partially presented in [61, 62, 65]).

Estimated wetting angle (57°C–71°C) suggested that PURs were hydrophilic [64]. But they absorbed a very low amount of water and only a bit higher in the case of using of PTMG for soft segments building. As mentioned before, the glass temperature of soft segments of polyetherurethanes and polyether-esterurethanes (Table 3) was lower than Tg of polyesterurethanes (PURs with PCL and PCL+R,S-PHB). Lower glass temperature was connected to them being less stiff than polyesterurethanes [67]. In case when the chains were stiff, their mobility was reduced so water could not penetrate easy between them. Higher water absorption by PURs based on PTMG could suggest their higher susceptibility to degradation in aqueous medium. In a PUR network, the particles (such as free radicals and enzymes) that could facilitate its degradation may penetrate with the water.

The presence of R,S-PHB in soft segments increased the water sorption of aromatic PURs [61].

2.2.7. Bacteriostatic properties

The influence of polyurethane PUR-3A-3 on microorganisms (*Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*) was investigated using disk methods [68, 69]. The *Staphylococcus aureus* growth around PUR samples was the most inhibited. The bacterial growth was inhibited for 6 mm around a circle sample (diameter of the sample was 8 mm). Knowing that 3-hydroxybutyrate belonging to fatty acids revealed antibacterial activity, it was concluded that R,S-PHB was responsible for the decreasing microorganism growth [68]. But the determined number of survival *Staphylococcus aureus* bacteria directly contacted with PUR sample PUR-3A-3 in a tube method showed only slight decrease of bacteria quantity in comparison to control probe [69]. It suggested its bacteriostatic but no bactericidal properties.

2.2.8. Hemocompatibility

Hemocompatibility of obtained PURs was estimated by observations of changes in morphology and coagulation parameters of whole blood after 4 h of direct contact with polymer samples using flow cytometry and photooptical methods [64, 65].

Parameter [unit]	PUR-2A-3	PUR-3A-1	PUR-3A-3	Blood sample without PUR	Reference value
WBC [*10^3/μl]	6.0	5.9	6.1	6.1	4.0-10.0
RBC [*10^6/ μl]	4.4	4.4	4.4	4.3	4.0-5.0
HGB [g/dl]	12.6	12.7	12.6	12.2	12.0-16.0
HCT [%]	38.1	38.8	37.9	38.0	37.0-47.0
MCV [fl]	87.6	88.0	87.4	87.2	80.0-96.0
MCH [pg]	28.8	28.8	28.8	28.8	27.0-32.0
MCHC [g/dl]	32.9	32.7	33.0	33.0	31.0-36.0
RDW [%]	13.7	13.8	13.9	13.7	11.5-14.5
PLT [*10^3/μl]	255.5	253.4	246.8	247	140.0-400.0
MPV [fl]	9.5	11.3	10.7	9.4	7.0-12.0
APTT [RATIO]	31.3	36.5	29.4	29.8	26.0-37.0
FIBR [g/l]	3.2	1.2	3.5	3.4	1.5-4.5

Table 7. Blood parameters after direct contact with PUR samples and those without contact.

The values of hematologic parameters before and after the incubation of PUR samples in blood were in reference ranges. Differences in comparison to the control probe were not observed that suggests the lack of hemolysis activated by polyurethane presence. Insignificant changes in platelet and fibrinogen concentration and in APPT during direct contact of blood with polymer samples suggested that polyurethanes based on synthetic poly([R,S]-3-hydroxybutyrate) could be atrombogenic [65].

2.2.9. Degradability

The influence of the surrounding environment on implanted material can be simulated using hydrolytic and oxidative solutions. Also, simulated body fluids (SBF) and Ringer solutions included ions that could be found in natural fluids are often used for estimation of biomaterials degradability.

Deionized water or phosphate buffer solution (PBS) is generally used for obtaining hydrolytic conditions in investigations of polymers degradation. According to Christenson et al. [70], the degradation of PURs in a solution of $CoCl_2/H_2O_2$ effectively reflected the oxidation occurring in the living body. The similar changes in the structure of the polymers after one year implantation in the body of rats and after 24-day action of the oxidation mixture were observed. It has been found that the arrangement of $CoCl_2/H_2O_2$ degraded the soft segments of the polyetherurethanes 17 times faster and the polycarbonate urethanes - 14 times [70]. Aliphatic PUR were also degraded in SBF and Ringer solution.

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PUR	The weight changes ±SD [%]			
	36 weeks of incubation in PBS	16 weeks of incubation in $CoCl_2/H_2O_2$	36 weeks of incubation in SBF	36 weeks of incubation in Ringer
PUR-2A-1	-1.4±0.1	-22.4±0.9	not estimated	
PUR-2A-2	0.4±0.3	-34.3±0.5		
PUR-2A-3	-3.2±0.1	-30.2±3.3		
PUR-2A-4	0.9±0.2	-7.5±0.7		
PUR-3A-1	-60.3±13.2	-70.9±1.7	disintegration	-16.1±3.5
PUR-3A-2	-55.2±2.3	-29.7±4.3	10.0±2.5	-0.8±0.1
PUR-3A-3	-5.2±0.1	-11.2±0.4	-36.6±1.8	-13.6±0.1
PUR-3A-4	1.4±0.1	-8.2±0.1	6.2±1.0	-1.2±0.3

Table 8. The weight changes of PUR samples after incubation (at 37°C) in phosphate buffer solution (PBS), oxidative solution ($CoCl_2/H_2O_2$), simulated body fluids (SBF), and Ringer solution (Ringer) (results partially presented in [52, 54, 71]).

The susceptibility to hydrolytic and oxidative degradation of obtained PUR with synthetic poly([R,S]-3-hydroxybutyrate) indicated that these materials were more sensitive to the oxidative than hydrolytic conditions. Using an aliphatic diisocyanate in the synthesis (instead of aromatic) increased the susceptibility of PURs to degradation, especially in hydrolytic environments. More susceptible to degradation processes were PUR with PTMG than PCL in soft segment [71].

Introduction of R,S-PHB into the soft segments increased the rate of degradation in all investigated solutions. Aliphatic PURs based on R,S-PHB and PTMG appeared as the most sensitive to conditions of all degradative solutions (higher sample mass loss and molecular weight reduction were noticed) [54].

In some cases, after 36 weeks of incubation the sample mass did not change significantly or even increased. The observed molecular weight reduction after incubation of PURs based on PCL in phosphate buffer indicated that ester linkages were hydrolyzed but because of the insolubility of PCL products, they were not rinsed polymer bulk [54]. Mondal et al. [55] suggested that the degradation products could be retained in bulk films by hydrogen bonding, van der Waals force, polar interaction, etc.

Meanwhile, increasing of sample mass of PUR-3A-2 and PUR-3A-4 after incubation in SBF was probably the result of salts molecules trapping between the macrochains of the polymer network what influenced on the samples mass [52]. Moreover, according to microscope observations of polymer samples presented earlier presence of R,S-PHB in soft segments of PURs protected them against the salt sediments.

Degradability of PURs with R,S-PHB in soft segments could be also controlled by their mixing with PLA [66]. The presence of PLA in polyurethane blends accelerated their degradation in hydrolytic, trypsin, and lipase solutions. The significant reduction of molecular weight of polymer samples after incubation in phosphate buffer and the lack of mass changes after incubation in enzyme solutions suggested that polyurethanes and their blends were degraded via chemical hydrolysis. The investigations of morphology of the surface structure, which was changed after the incubation in both enzymes indicated that the enzymatic hydrolysis had been already initiated [66].

2.2.10. Electrospinning

DSC and WAXS results indicated that similar PURs (with molar ratio of NCO:OH=2:1 in prepolymer) containing PCL in soft segments had higher ability for crystallization than those having PTMG in soft segments [53]. It was the reason why PURs containing PTMG and R,S-PHB in soft segments was chosen for electrospinning. Polymer appeared as spinnable in an electric field, with thermal stability (no phase transitions) in the temperature range up to 95°C. Electrospinning of polyether-esterurethane from hexafluoro-2-propanole solution resulted in the formation of fibers with an average diameter ca. 2 μm. [53].

3. Conclusion

It could be stated that PURs based on synthetic poly([R,S]-3-hydroxybutyrate) displayed the properties appropriate for further investigations for medical applications such as degradable scaffolds. Properties of presented polyester- and polyester-etherurethanes suggest that they could be biocompatible, biostatic, and biodegradable under conditions of living body environment. It suggests also that aromatic diisocyanate may be successfully replaced by an aliphatic one. Incorporation of synthetic polyhydroxybutyrate into soft segments of PURs decreased their degree of crystallinity and increased degradability.

Using polycaprolactonediol for PUR synthesis is appropriate for the design of material undergoing slow and gradual degradation in living body. Higher oil sorption and faster rate of degradation of aliphatic PURs based on polyoxytetramethylenediol promote it for being used as biodegradable scaffolds with hydrophobic active substance.

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