

Review Article

Amphiphilic Poly(3-hydroxy alkanoate)s: Potential Candidates for Medical Applications

Baki Hazer

Department of Chemistry, Zonguldak Karaelmas University, 67100 Zonguldak, Turkey

Correspondence should be addressed to Baki Hazer, bhazer2@yahoo.com

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Poly(3-hydroxy alkanoate)s, PHAs, have been very attractive as biomaterials due to their biodegradability and biocompatibility. These hydrophobic natural polyesters, PHAs, need to have hydrophilic character particularly for drug delivery systems. In this manner, poly(ethylene glycol) (PEG) and hydrophilic functional groups such as amine, hydroxyl, carboxyl, and sulfonic acid have been introduced into the PHAs in order to obtain amphiphilic polymers. This review involves in the synthesis and characterization of the amphiphilic PHAs.

1. Introduction

Biomaterials have been widely used in medical applications, such as drug delivery, tissue engineering, device-based therapies, and medical imaging [1, 2]. Synthetic and naturally occurring polymers have played important role in the treatment of disease and the improvement of health care. Among them, PHAs are promising materials for biomedical applications in tissue engineering and drug delivery system because they are natural, renewable, biodegradable, and biocompatible thermoplastics. PHAs have been used to develop devices, including sutures, nerve repair devices, repair patches, slings, cardiovascular patches, orthopedic pins, adhesion barriers, stents, guided tissue repair/regeneration devices, articular cartilage repair devices, nerve guides, tendon repair devices, bone-marrow scaffolds, tissue engineered cardiovascular devices, and wound dressing. However the direct use of these polyesters has been hampered by their hydrophobic character and some physical shortcomings [3]. The key to biocompatibility of biomedical implantable materials is to render their surface in a way that minimizes hydrophobic interaction with the surrounding tissue. Therefore, hydrophilic groups have been introduced into the PHAs in order to obtain amphiphilic polymer. This review has been focused on the chemically modified PHAs with enhanced

hydrophilic character as biomaterials for medical applications.

2. PHAs

PHAs are accumulated as intracellular granules as a result of a metabolic stress upon imbalanced growth due to a limited supply of an essential nutrient and the presence of an excess of a carbon source. These novel biopolymers have material properties ranging from rigid and highly crystalline to flexible, rather amorphous and elastomeric. There have been many studies reported on the modification reactions to enhance mechanical and thermal properties to prepare new biomaterials for the medical applications [4–13]. PHAs can be classified into three groups based on the number of carbon atoms in the monomer units: short-chain-length (*scl*PHA) containing 3–5 carbon atoms that are produced by *Ralstonia eutropha* (also referred *Watersia eutropha*, *A. Eutrophus*), medium-chain-length (*mcl*PHA) containing 6–14 carbon atoms, and long-chain-length (*lcl*PHAs), with more than 14 carbon atoms [14, 15]. *Pseudomonas oleovorans* is a very versatile microorganism for PHA production because it can produce medium chain length polyesters (*mcl*PHA) and long chain length polyesters (*lcl*PHA) from a wide variety of carbon substrates. These

TABLE 1: Classification of the bacterial polyesters.

Carbon source	Type	Poly(3-hydroxy alkanoate) (PHA)		Thermal and mechanical properties		
		Side chain (R)	Name*	T _g (°C)	T _m (°C)	Elongation (%)
Sugar, glucose, acetic acid	Short chain length	Methyl, ethyl	PHB PHV	15	170	5
Alkanoic acids, alkanes, and alkanols	Medium chain length	propyl, butyl, pentyl, hexyl, heptyl	PHHx PHHp PHO PHN PHD	-40	60	800
Plant oily acids	Long chain length	More than 14 carbon per repeating unit		-50	40	Soft, sticky

* B: butyrate, V: valerate, Hx: hexanoate, Hp: heptanoate, O: octanoate, N: nonanoate, D: decanoate, T_g and T_m are glass transition and melting temperatures, respectively.

types of the bacterial polyesters have been summarized in Table 1.

3. Amphiphilic PHAs

Amphiphilic polymers can be synthesized by introducing hydrophilic groups such as hydroxyl, carboxyl, amine, glycol, and hydrophilic polymers such as PEG, poly(vinyl alcohol), polyacryl amide, poly acrylic acids, hydroxy ethyl methacrylate, poly vinyl pyridine, and poly vinyl pyrrolidone to a hydrophobic moiety. Because of their ability to form micelles, amphiphilic block copolymers are strong candidates for potential applications as emulsifiers, dispersants, foamers, thickeners, rinse aids, and compatibilizers [16, 17]. Similarly, amphiphilic PHAs can also be synthesized by introducing hydrophilic groups such as hydroxyl, carboxyl, amine, sulfonic acid, ethylene glycol, and PEG. PEG is a polyether that is known for its exceptional blood and tissue compatibility. It is used extensively as biomaterial in a variety of drug delivery vehicles and is also under investigation as surface coating for biomedical implants. PEG, when dissolved in water, has a low interfacial free energy and exhibits rapid chain motion, and its large excluded volume leads to steric repulsion of approaching molecules [18]. These properties make PEG excellent biocompatible material. Hydroxylation of the PHAs can be carried out by using both biosynthetic and chemical modification. The biosynthetic hydroxylation of the PHAs has successfully been reviewed by Foster, recently [19]. Chemical modifications of the PHAs have been extensively studied [6, 9, 15, 20–24]. In this review, selective chemical modification reactions in order to obtain amphiphilic PHAs will be discussed.

4. Synthesis of Amphiphilic PHAs

Selective chemical modification of the PHAs involves functionalization and grafting reactions of the PHAs. Hydrophilic

groups such as hydroxyl, carboxyl, amine, glycol and sulfonic acid can be introduced into the PHAs by means of functionalization. In grafting reactions, some hydrophilic groups have been attached in the PHA chain to obtain amphiphilic polymer.

4.1. Transesterification. Some ester group(s) of the PHA is exchanged with an alcohol in transesterification process. Transesterification is carried out in melt or in solution. Hydroxylation of the PHBs via chemical modification is usually achieved by the transesterification reactions to obtain diol ended PHB. Transesterification reactions in the melt between poly(ethylene glycol), mPEG, and PHB yield diblock amphiphilic copolymer with a dramatic decrease in molecular weight [25]. Catalyzed transesterification in the melt is used to produce diblock copolymers of poly([R]-3-hydroxybutyric acid), PHB, and monomethoxy poly(ethylene glycol), mPEG, in the presence of a catalyst, in a one-step process. The formation of diblocks is accomplished by the nucleophilic attack from the hydroxyl end-group of the mPEG catalyzed by bis(2-ethylhexanoate) tin.

When the transesterification reaction between PHB and ethylene glycol in diglyme as a solvent is carried out, the telechelic PHB with MW at around 2000 Dalton is obtained [26]. Stannous octanoate as a transesterification catalyst causes the reaction of carboxylic end group and diol, quantitatively. Basically, short chain diol or polyol moiety can rarely renders a hydrophilic character to the longer hydrophobic PHA. Therefore amphiphilic character of the telechelic PHAs and PEGylated PHAs have been stood poor.

Telechelic PHB obtained by this way can be used in the preparation of the polyester urethanes via diisocyanate chain extension reaction with synthetic aliphatic polyester as soft segment [27, 28]. PHB-g-Poly(ϵ -caprolactone) (PCL) graft copolyester urethane samples exhibited the elongation at break up to 900%.

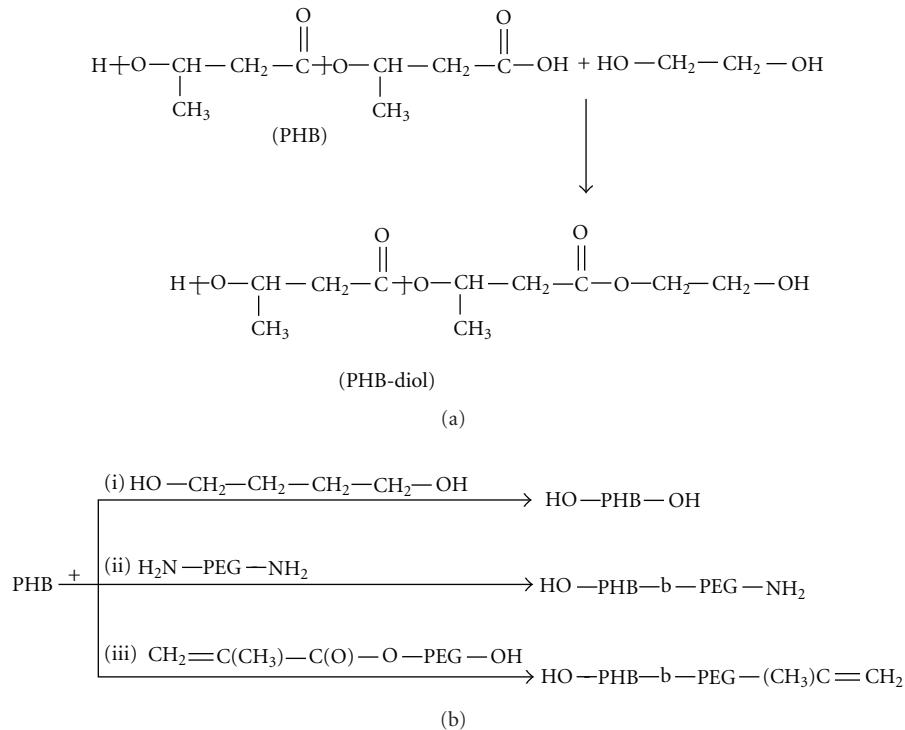


FIGURE 1: (a) Formation of the diol ended PHB via transesterification in the presence of ethylene glycol. (b) Transesterification reactions of PHB with (i) butane diol, (ii) transamidation with bisaminopropyl ended PEG, and (iii) transesterification reactions of PHB with methacryloyl oxy ethylene glycol in solution.

Two segmented biodegradable poly(ester-urethane) series, based on bacterial PHB as the hard segments, and either PCL or PBA as the soft segments, were easily synthesized by one-step solution polymerizations. Transesterification reaction of PHB with methacryloyl oxy poly(ethylene glycol) (MW: 526), poly(ethylene glycol) bis (2-aminopropyl ether) with MW 1000 and 2000 was achieved to obtain PHB-b-PEG telechelic diblock copolymers [29]. Similarly, telechelic PHB can also be obtained by transesterification with 1,4-butane diol in 1,2-dichloro benzene under reflux conditions. The transesterification reactions can be designed in Figure 1.

4.2. Carboxylation and Hydroxylation of the Pendant Double Bonds. Most used unsaturated PHAs are mclPHAs obtained from unsaturated edible oils and synthetic olefinic substrates. When *Pseudomonas oleovorans* is grown on unsaturated carbon source such as soybean oily acids, 7-octenoic acid and 10-undecenoic acid, unsaturated PHAs are obtained [30–33]. Figure 2 shows the synthesis of the unsaturated PHAs.

Microbial polyesters containing unsaturated side chains are open the way for chemical modification reactions to prepare PHA derivatives. Pendant double bonds of the poly(3-hydroxy octanoate-co-10-undecenoate), PHOU, can be oxidized to the diol (PHOU-diol) and carboxylic acid (PHOU-COOH). KMnO₄ is used as an oxidizing agent. In mild conditions PHOU-diol is obtained [34]. While PHOU was insoluble in a polar solvent, PHOU-diol was soluble

in methanol, acetone/water (80/20, v/v), and DMSO, even with 40%–60% of double bonds unconverted, but it was insoluble in nonpolar solvents such as chloroform, THF, acetone. Figure 3 shows the PHOU-diol. The use of NaHCO₃ even in hot solution (55°C) resulted mainly in diol groups, not carboxylic groups, while the same reaction at room temperature using KHCO₃, led to the conversion of the pendant unsaturated groups to the carboxyl groups [35]. Figure 4 shows the PHOU with pendant carboxyl groups.

Carboxylation of PHOU using OsO₄ as oxidant can be performed with the small decrease in MW after the reaction [36]. The quantitative hydroxylation of pendant vinyl groups of poly(3-hydroxy-10-undecenoate) (PHU) with the use of either the borobicyclononane or the borane-tetrahydrofuran complex is also achieved in high yield [37, 38]. After hydroxylation, the thermal stability and the molecular weight of the hydroxylated PHU showed small decreases; however, full solubility in methanol and almost full solubility in water are achieved [37, 38].

Water wettability of saturated PHAs, poly(3-hydroxy butyrate) (PHB) and poly(3-hydroxy butyrate-co-3-hydroxy hexanoate) (PHBHHx) can also be improved by carboxyl ion implantation. Ion implantation is performed at energy of 150 keV with fluences ranging from 5×10^{12} to 1×10^{15} ions/cm². Contact angle measurements are confirmed that the ion implantation improves the water wettability [39].

Epoxidation of the unsaturated polyester with m-chloroperbenzoic acid, as a chemical reagent, yields to

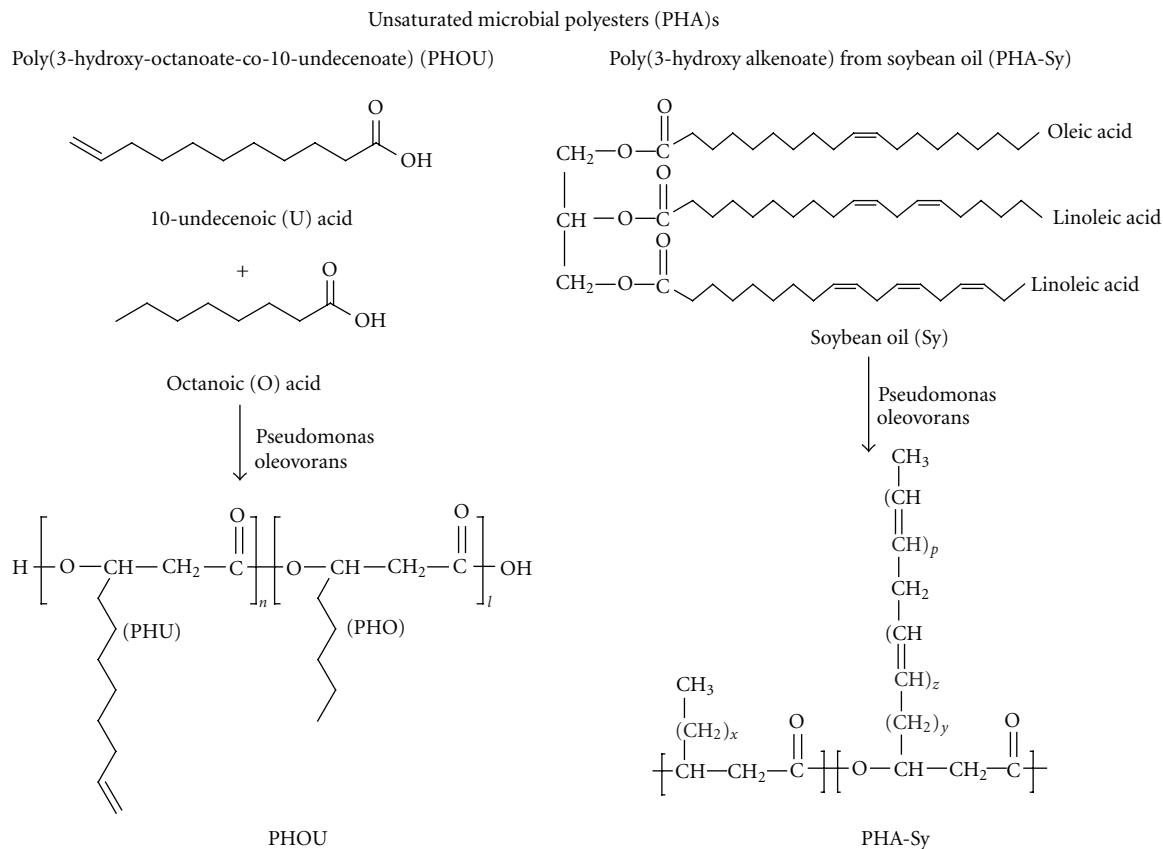


FIGURE 2: Synthesis of two types of unsaturated PHAs from *Pseudomonas oleovorans* (i) grown on soybean (PHA-Sy) and (ii) 10-undecenoic acid and octanoic acid (PHOU).

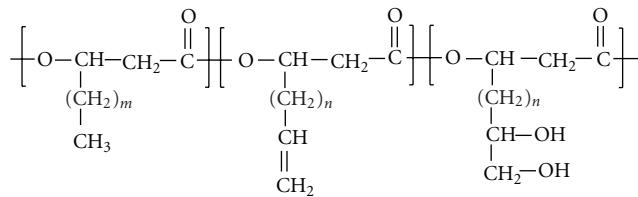


FIGURE 3: PHOU with pendant hydroxyl groups (PHOU-OH).

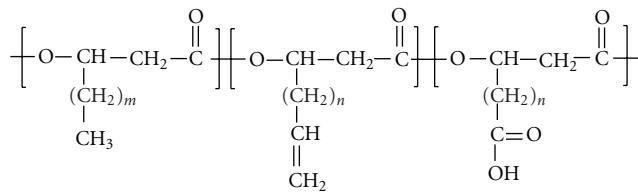


FIGURE 4: PHOU with pendant carboxylic acids (PHOU-COOH).

quantitative conversions of the unsaturated groups into epoxy groups [40]. Primary and secondary amines can be reacted with epoxide groups to yield hydrophilic compounds. Reaction between hexamethylene diamine with epoxidized PHOU provides cross-linked polyester [41].

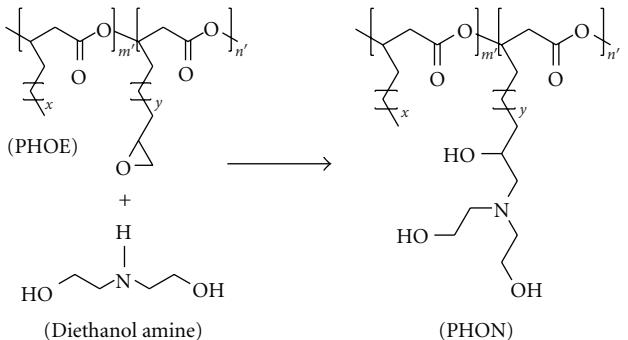


FIGURE 5: The conversion reaction of epoxidized-PHOU (PHOE) to hydroxylated PHOU in the presence of diethanol amine (PHON).

Enhanced hydrophilicity of the PHOU has recently been achieved by the reaction between epoxidized PHOU and diethanol amine to give highly hydrophilic polyester, PHON [42]. The first reaction involved the transformation of the vinyl-terminated side chains of PHOU to epoxide groups (PHOE). Figure 5 shows the conversion reaction of epoxidized PHOU (PHOE) to hydroxylated PHOU in the presence of diethanol amine.

The successful side chain conversion was further substantiated by the change in solubility when converting PHOU to PHOE to PHON. As the functionalized side chains became more polar, the polymer became soluble in more polar solvents. In this aspect, PHON was soluble in water.

4.3. Quaternization and Sulfonation of the PHAs. Halogenation of the polymers is a versatile method to open the way for further functionalization [29, 43, 44]. Addition of the chlorine and bromine into the double bond is quantitative and halogenated PHAs can be easily obtained by this way [29]. Chlorination is performed by either the addition to double bonds of the unsaturated PHA obtained from soybean oil (PHA-Sy) or substitution reactions with saturated hydrocarbon groups [43, 44]. Chlorination of the sticky, soft PHA-Sy with double bond provides polyester with hard, brittle, and crystalline physical properties depending on the chlorine content. By this way, it is possible to introduce 35 wt% chlorine to the PHA. In case of the chlorinated PHO, glass transition temperature has been shifted to +2°C from -40°C [44]. For further functionalization, quaternization reactions of the chlorinated PHA with triethylamine (or triethanol amine) can be performed. Additionally, aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ can be reacted with solution of chlorinated PHA (PHA-Cl) in acetone to give sulfonate derivative of the PHO [44].

4.4. Grafting Reactions of the PHAs

4.4.1. Chitosan Grafting. Chemical modifications of chitosan by grafting method are important to prepare multifunctional materials in different fields of application and to improve its chemical, physical, and mechanical properties [45, 46]. Chitosan-g-Poly(3-hydroxy butyrate-co-3-hydroxy valerate) (PHBV) graft copolymer was synthesized and grafting of linoleic acid on chitosan were performed by condensation reaction under vacuum at 90–95°C. Chitosan-g-PHBV graft copolymers exhibit different solubility behavior such as solubility, insolubility, or swelling in 2 wt% acetic acid and in water as a function of degree of substitution of NH_2 while pure chitosan does not swell in water. Chitosan-g-PHBV graft copolymer is shown in Figure 6.

4.4.2. Sugar Grafting. Glycopolymers are emerging as a novel class of neoglycoconjugates useful for biological studies and they are prepared either by copolymerization or grafting methods [47]. Since it has been shown that thiosugars are potent tools in glycobiology, 1-thiomaltose derivatives have been grafted onto PHAs in two ways [48]; the thiol sugar is added to the double bond and the reaction between thiol sugar and bromo end groups of polyester biosynthesized from 11-bromoundecanoic acid [49]. These new grafted polymers are insoluble in dichloromethane and chloroform, but very soluble in *N,N*-dimethylformamide and dimethyl sulfoxide, as opposed to their parent PHAs. As expected, modified PHAs are more hydrophilic than their parent compounds.

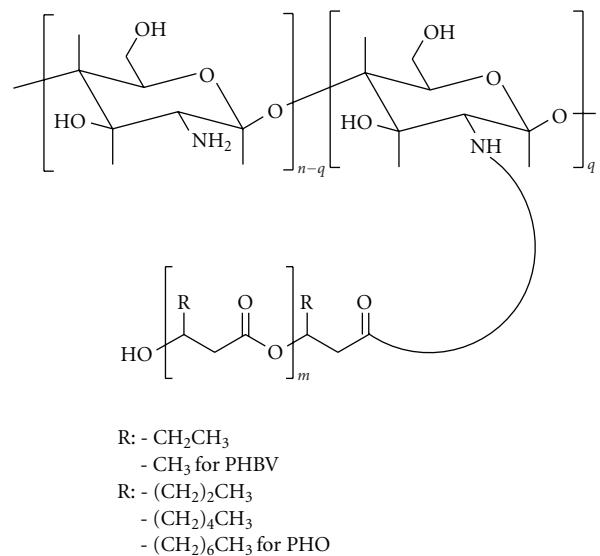


FIGURE 6: Chitosan-g-PHBV graft copolymer.

4.4.3. PEG Grafting. Diazo linkaged PEG, a polyazoester synthesized by the reaction of PEG and 4,4'-azobis(4-cyanopentanoyl chloride) creates PEG macroradicals which is easily attack to the double bonds of the unsaturated PHA to obtain the PHA-g-PEG cross-linked graft copolymers [50]. PHAs containing double bonds in the side chain (PHA-DB) were obtained by cofeeding *Pseudomonas oleovorans* with a mixture of nonanoic acid and anchovy (hamci) oily acid (in weight ratios of 50/50 and 70/30). PHA-DB was thermally grafted with a [50].

Graft copolymers of the saturated mclPHAs can be synthesized by using macroradicals via H-abstraction from the tertiary carbon of the polyester [51, 52]. Similarly, macroradicals onto the PHAs are induced by the UV irradiation via H-abstraction in the presence of a PEG-macromonomer to prepare PEG-g-PHO graft copolymers [53, 54]. Homogeneous solutions of poly(3-hydroxyoctanoate) (PHO) and the monoacrylate-poly(ethylene glycol) (PEGMA) monomer in chloroform were irradiated with UV light to obtain PEGMA-grafted PHO (PEGMA-g-PHO) copolymers. The results of the protein adsorption and platelet adhesion tests show that the blood compatibility was also enhanced by grafting the PEGMA chains. The adsorption of proteins and platelets was increasingly suppressed, as the grafting degree of PEGMA onto PHO increased. Glycerol 1,3-diglycerol diacrylate-grafted poly(3-hydroxyoctanoate) copolymers are also prepared by heating homogeneous solutions of PHO, diacrylate monomer, and benzoyl peroxide initiator [55]. The resulting copolymers have enhanced thermal properties and mechanical strengths. The surfaces and the bulk of the graft copolymers became more hydrophilic as the diglycerol diacrylate grafting density in the copolymer increased. Many studies have reported that hydrophilic surfaces, such as those of hydro gels and PEG-grafted polymers, suppress protein adsorption and platelet adhesion. The surfaces of this graft copolymers become more hydrophilic with grafted

TABLE 2: Methods for the synthesis of the amphiphilic PHAs.

PHA	Synthesis	Product	Reference
PHB	Transesterification with mPEG2000 (in melt)	PHB-b-PEG	[25]
PHB	Transesterification with PEG2000 (in solution)	PHB-g-PEG	[29]
PHB	Transesterification with Diethylene glycol (in melt)	PHB-diol	[26]
PHO	UV-irradiation with methacrylated-PEG	PHO-g-PEG	[53]
PHU	UV-irradiation with methacrylated-PEG	PHO-g-PEG	[54]
PHO	Free radical polymerization with acrylate	PHO-g-Poly-glycerol diacrylate	[55]
PHA-un-	Free radical polymerization with saturated polyazoester based on PEG	PHA-g-PEG	[50]
PHOU	Epoxidation and reaction with diethanol amine	PHA with pendant amine side groups	[42]
PHOU	Epoxidation and reaction with hexamethylene diamine	Cross-linked PHOU	[41]
PHB	Condensation with chitosan	PHB-g-chitosan	[45]
PHO	Condensation with chitosan	PHO-chitosan	[46]
PHOU	Hydroxylation of the double bonds	PHOU with pendant-OH	[34, 37, 38]
PHOU	Carboxylation of the double bonds	PHOU with pendant-COOH	[35, 36]
PHB	Urethane formation of PHB and PCL containing dihydroxyl ends	PHB-g-PCL	[27, 28]
PHOU	Thiol addition of thio-maltose to double bonds	PHOU-g-sugar	[48]
PHOU	Esterification of carboxylated PHOU with PEG	PHOU-g- PEG	[56]

diglycerol groups. These surface characteristics make this graft copolymer to prevent protein adsorption and platelet adhesion very effectively. Domenek et al. achieved the amphiphilic copolymer based on PHOU and PEG [56]. Carboxylic acid terminal groups in the side chains are reacted with PEG in the presence of dicyclohexyl carbamate at room temperature. Amphiphilic graft copolymer obtained is soluble in the mixture of H₂O/acetone (80/20) whereas precursor PHOU is not soluble.

As a summary, Table 2 indicates the sum of the chemical modification reactions to obtain amphiphilic PHAs.

5. Conclusion

Microbial polyesters are biocompatible and biodegradable hydrophobic natural thermoplastics. Amphiphilic PHAs from swollen in water to soluble in water are much more desirable in the drug delivery system and tissue engineering. In most attempts to synthesize amphiphilic PHAs, degradation of the polyester chain has been unavoidable. To obtain new amphiphilic PHAs with high molecular weight and their medical applications have been attractive for scientists.

Acronyms

PHA:	Poly(3-hydroxy alkanoate)
PEG:	Poly(ethylene glycol)
sclPHA:	Short-chain-length PHA
mclPHA:	Medium-chain-length PHA
lclPHA:	long-chain-length PHA
PHB:	Poly([R]-3-hydroxybutyric acid)
mPEG:	Monomethoxy poly(ethylene glycol)
PHOU:	Poly(3-hydroxy octanoate-co-10-undecenoate)
PHU:	Poly(3-hydroxy-10-undecenoate)
PHBhx:	Poly(3-hydroxy butyrate-co-3-hydroxy hexanoate)
PHON:	Diethanol amine derivative of PHOU
PHOE:	Epoxide derivative of PHOU
PHA-Sy:	PHA obtained from soybean oil
PHA-Cl:	Chlorinated PHA
PHA-DB:	Poly(3-hydroxyalkanoate)s containing double bonds in the side chain
PEGMA:	Monoacrylate-poly(ethylene glycol)
PHBV:	Poly(3-hydroxy butyrate-co-3-hydroxy valerate)

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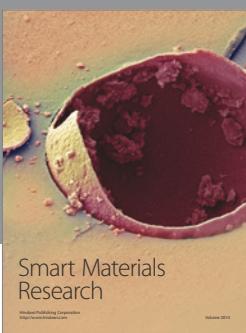
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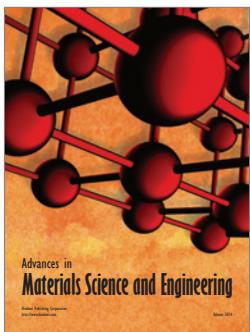
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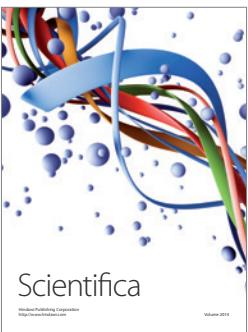
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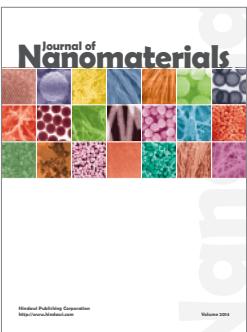
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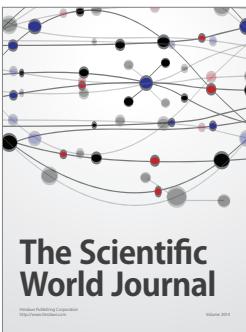
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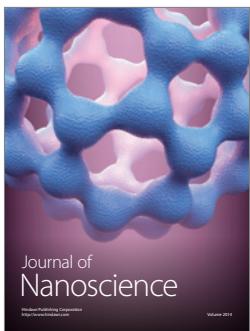
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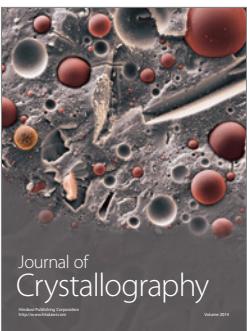
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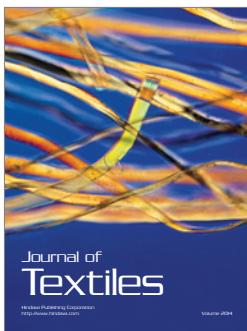
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