Poly(hydroxy alkanoate)s in Medical Applications

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This review summarizes the state-of-the-art knowledge of the usage of poly(hydroxy alkanoate)s in medical and sanitary applications. Depending on the monomers incorporated into the polymers and copolymers, this class of polymers exhibits a broad range of (thermo-)plastic properties, enabling their processing by, e.g., solution casting or melt extrusion. In this review, strategies for the polymer analogous modification of these materials and their surfaces are highlighted and correlated with the potential applications of the corresponding materials and blends. While the commercial availability of purified PHAs is addressed in brief, special focus is put on the (bio-)degradability of these polymers and ways to influence the degradation mechanism and/or the duration of degradation.

Key words

poly(hydroxy alkanoate), polymer analogous modification, polymer processing, biodegradation, medical application

Introduction

In the past decades, mankind has produced more plastics than ever before, while simultaneously, due to the stagnation in oil production and the general demand for "greener" products, plastics from renewable resources have become more and more important[1,2]. Such materials often face significant challenges when compared to petrochemical plastics, particularly in terms of higher production costs and availability of the source materials[3,4]. Whilst competitive costs are still a very important factor for the commercial usage of polymers from renewable resources, advanced medical applications, such as tissue repair, polymer-based depots for controlled drug release or implants, have paved the way for biodegradable as well as biocompatible materials. Petroleum-derived products commonly cannot meet the requirements inherent to those applications. In the past years, polyurethanes and derivatives from poly(ethylene glycol) (PEG), which used to be the "golden standard" for polymers in medical applications, have been continuously replaced by different polymers and blends from natural resources due to their superior biocompatibility and biodegradability. Poly(hydroxy alkanoate)s (PHAs) (Fig. 1) are one of the new materials that have received a lot of attention since their discovery in 1926 by Lemoigne[5].

Short chain length (*scl*) PHAs (Table 1) with 3–5 carbon atoms per repetition unit, and medium chain length (*mcl*) with 6–14 carbon atoms per repetition unit are the two main representatives of the PHA congeners. These two types of PHAs differ tremendously in their mechanical behavior. Glass transition temperatures of *scl*-PHAs like PHB range around 5–10 °C and can be drastically lowered by copolymerization with PHV or P4HB (yielding the copolymers P(HB-HV) and P(HB-4HB), while *mcl*-PHAs have their glass-transition points at lower temperatures[6,7]. While *scl*-PHAs are brittle and tend to have high crystallinity, *mcl*-PHAs are more flexible, but exhibit a comparably low mechanical strength. Especially the brittle behavior of the *scl*-PHAs has limited its usage in industrial production.

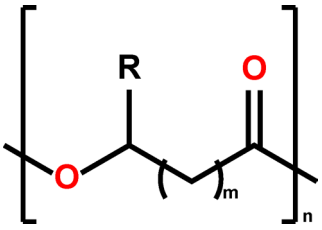

Fig. 1 – *Generic structural formula of PHAs. The integer m typically has the value of 1 (with the exception of 4-hydroxyalkanoates such as 4-hydroxybutyrate), the integer n quantifies the degree of polymerization.*

Blends and copolymers of PHAs have evolved into a desired strategy to overcome these shortcomings; this new material class is still under intense investigation[4]. The monomers most commonly considered in research are listed in Table 1. Apart from the investigation of new blends and copolymers, the

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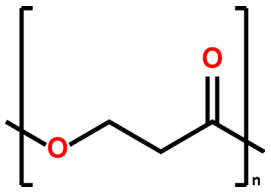
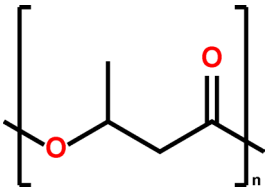
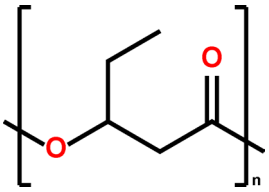
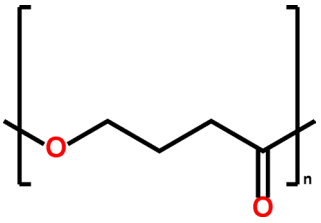
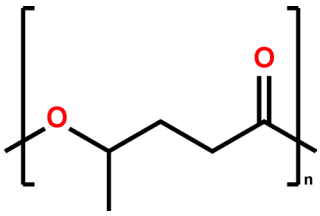
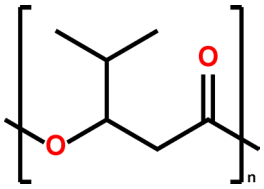
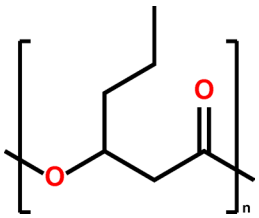
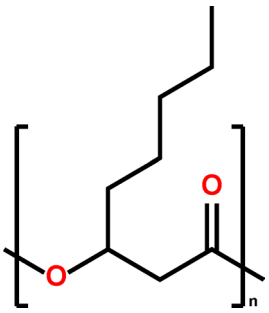
Table 1 – *Representative repetition units in scl-PHAs and mcl-PHAs*

scl-PHAs	 Poly(3-hydroxy propionate) PHP	 Poly(3-hydroxy butyrate) PHB (P3HB)	 Poly(3-hydroxy valerate) PHV (P3HV)
		 Poly(4-hydroxy butyrate) PHB (P4HB)	 Poly(4-hydroxy valerate) PHV (P4HV)
mcl-PHAs	 Poly(3-hydroxy methyl-valerate) PHMV (P3MHV)	 Poly(3-hydroxy hexanoate) PHHx (P3HHx)	 Poly(3-hydroxy octanoate) PHO (P3HO)

investigations of new approaches for the functionalization of existing saturated and unsaturated PHAs is still a very hot topic[8–15]. The development of PHAs with tailor-made material qualities for direct usage in a broad spectrum of applications has become easier to achieve than ever before.

Production

In nature, PHAs are synthesized by a variety of different *Gram-positive* and *Gram-negative* bacteria. More than 300 different microorganisms that are able to synthesize and accumulate PHA intracellularly are known today[16]. The list includes wild type bacteria, such as *Cupriavidus necator, Azotobacter species*, *Pseudomonas species*, and *Methylobacterium species* as well as engineered strains of, e.g., *Escherichia coli* and *Cupriavidus necator*[17–19]. These types of bacteria synthesize PHA polymers or copolymers and store them in the form of granules in the cytoplasm. The ability for the cells to grow to high cell densities on the one hand, and to accumulate a high (total cell mass) percentage of PHA on the other, is the key criterion to look for in potential production strains. Hence, despite the fact that a high number of microorganisms capable of producing PHAs have been identified, only very few bacteria from this list are suited for industrial scale production.

Bacteria produce PHAs as storage polymers for carbon and energy under metabolism-limited conditions if carbon and energy sources are present, but one or more growth-essential nutrients, such as phosphate, nitrogen or oxygen are deficient. The biosynthesis of PHAs usually occurs with purified sugars or edible oils as feedstock, but alternative carbon sources, such as whey[20], palm oil[21], sunflower meal[22], and different waste materials[23–25] have been reported as well. In addition, strategies for the production from sugar molasses are under thorough investigation[3,26,27]. The main reason for the on-going search for cheap substrates as feedstock originates from the challenge to produce PHAs within the same range of costs like polyethylene (PE) or polypropylene (PP). Alternative carbon sources, more

efficient processing and improved production strains are fields of active research to overcome this challenge[28].

Cavalheiro *et al.* showed the possibility of PHB production by *Cupriavidus necator* using waste glycerol from the biodiesel industry[29]. They observed that the specific growth rate peaks with a glycerol feed in the range of 20–40 g L^{-1} due to the amounts of sodium still present in the feedstock are due to the precedent transesterfication processes.

Khosravi-Darani *et al.* reported the microbial production of PHB from C_1 carbon sources such as methanol, methane or CO_2[30]. Although commercial PHB production from these carbon sources has not yet been established by many companies[31], the consideration of using such cheap substrates would be very favorable. Mozejko recently showed that saponified waste palm oil can be used as an attractive renewable resource for *mcl*-PHA synthesis[32]. With a polymer productivity of 57.8 mg L^{-1} h^{-1} and a mass fraction of PHA in cell dry mass of 43 % of cell dry mass CDW after 17 h of fermentation, this method proved to be an efficient approach. Muhr *et al.* reported the usage of fractions of waste lipids from animal processing as a feedstock for PHA production[24], showing that *Pseudomonas citronellolis* as well as *Pseudomonas chlororaphis*[33] are prospective candidates for large-scale production of PHA. Tanadchangsaeng *et al.* reported the biosynthesis of a statistical copolymer of P(HB-HMV) with up to 38 mol-% of PHMV[34]. *Cupriavidus necator* expressing the PHA synthase from *Pseudomonas species* was fed with structural analogs that served as HMV precursors.

Engineered strains

Apart from the wild type strains of microorganisms such as *Cupriavidus necator*, there is an on-going trend to engineer suitable microorganisms to produce PHA[35]. In recent years, a number of strains were engineered for PHA accumulation rates of up to 90 wt.-% of CDW[36]. Jeon *et al.* produced engineered recombinant *Ralstonia eutropha* strains in a manner that the bacteria produced PHAs such as statistical P(HB-HHx) copolymers in quantities up to 40 wt.-%[19]. Notably, unrelated carbon sources such as glucose, fructose and gluconate were used as feedstock. Mifune *et al.* showed that engineered strains of *Cupriavidus necator* for the production of statistical P(HB-HHx) copolymers were able to reach over 80 wt.-% of PHA accumulation, using soy bean oil as carbon source[18]. Saika and coworkers recently published results concerning a recombinant *E. coli* for the production of statistical P(HB-HMV) copolymers from leucine by expressing leucine metabolism-related enzymes derived from *Clostridium difficile*[17]. Tripathi *et al.* reported a β-oxidation weakened *Pseudomonas putida* KT2442, able to produce a diblock copolymer of the composition PHB-*block*-PHHx[37]. The utilized recombinant strain of *Pseudomonas putida* consists of *pha* operon and therefore is able to produce *mcl*-PHA.

Mixed culture approaches

Purified and single strain cultures are by definition more expensive than the mixed culture approach, which can also provide the ability to use cheaper substrates[3]. Especially the cheap carbon sources of this approach make it an interesting possibility for an environmentally sustainable PHA production system. Fradinho *et al.* showed that a PHA production from individual and mixed volatile fatty acids (acetate, propionate, butyrate, lactate, malate and citrate) can be achieved[38]. Only acetate and butyrate led to PHB formation, propionate induced the synthesis of statistical P(HB-HV) copolymers. It was postulated that acetate is likely to act as a co-substrate for butyrate and propionate uptake, since uptake rates of both carbon sources were increased in the presence of acetate. Johnson *et al.* worked on the enrichment of a mixed bacterial culture with a high PHA storage capacity in order to compete with genetically engineered bacteria producing PHA from pure substrates like sugars[39]. These optimized processes led to high contents of PHA in the cell dry mass and high production rates, but expensive substrates, equipment, and high energy input were required. Within this study, a maximum PHB content of 89 wt.-% within 7.6 h under continuous feeding with acetate was achieved. Anterrieu *et al.* showed the integration of biopolymer production with process water treatment at a sugar factory[40]. The challenges in these studies were to find a way to combine nitrogen removal with PHA production.

Processing

The development of new techniques in production processing has been a highly active research field in recent years[41–45]. Based on their mechanical properties and their (commercial) availability (see above), *scl*-PHAs (homopolymers as well as copolymers) are focused on. Due to the melting points of PHP (77 °C) and PHB (175 °C)[46], as well as PHV (105 °C)[47], *scl*-PHAs and derived copolymers can be processed by injection molding, extrusion, extrusion bubbles into films and hollow bodies, and fibre spinning. While polymer degradation of *scl*-PHAs starts from temperatures only slightly above their melting temperatures, namely from approx. 180 °C, the processing parameters have to be fine-tuned with high precision. For a better understanding of the degradation process and potential bottlenecks of

the PHA class, several studies were made in the last decade[32,33]. Recently, Hufenus *et al.* reported the fiber melt-spinning of PLA and statistical copolymers of the composition P(HB-HV) for the production of new materials for biomedical purposes[50]. They were able to produce fibers with suitable mechanical properties, e.g. tensile strength and Young's modulus to construct a textile fabric (Fig. 2).

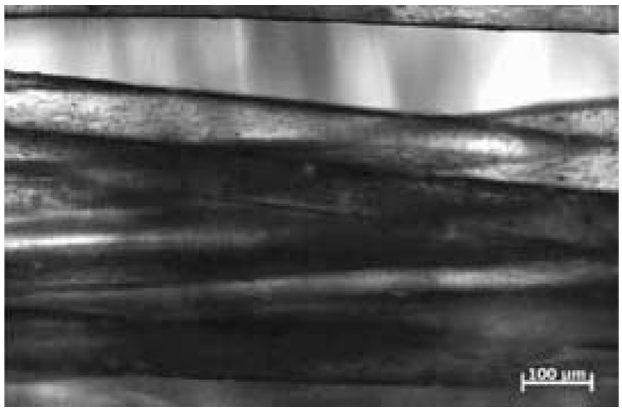


Fig. 2 – *Overlay of light and fluorescence micrographs showing cell adhesion on fibers composed of a PLA core and a coating of statistical copolymers of P(HB-HV). Reprinted from reference[50] with permission from John Wiley and Sons.*

Prior to any processing, PHAs have to be purified in order to remove bacterial components present in the crude polymers – for biomedical applications, in particular, the bacterial endotoxins have to be removed[51]. Sevastianov *et al.* reported the importance of proper endotoxin removal for *in-vivo* applications[52]. Notably, PHAs are most commonly soluble in dichloromethane, chloroform, and dichloroethane, although other solvents like ethyl acetate or methyl *tert*-butyl ether have recently been investigated as well[53,54]. Koller *et al.* reported the usage of the "anti-solvent" acetone for the purification of *scl*-PHAs in a novel closed system combining components for extraction, filtration and product work-up, compared to already established repeated dissolution-precipitation strategies[55,56]. By designing a new apparatus and optimizing the operating temperature and pressure control, a method was developed that can also be applied to *mcl*-PHAs.

Modification

The most common homopolymer PHB, and the most common statistical copolymer P(HB-HV), have significant shortcomings in terms of brittleness and high degree of crystallinity[57]. P4HB and copolymers containing 4HB are under investigation for their mechanical properties for further surgical applications[58,59]. The tensile strength of P4HB is close to ultrahigh molecular weight PE and is a very flexible material of high strength. However, PHB and the statistical copolymer P(HB-HV) are the only PHAs currently available in large scale. Post-synthetic and polymer analogous strategies were developed in order to overcome the shortcomings of the pristine PHAs.

Combining PHAs with other polymers in the form of a blend enables new substance classes with modified and tailor-made characteristics, such as brittleness, crystallinity, and degradation rates[60,61]. The *scl*-PHAs, due to their crystallinity, are more resistant to biodegradation than *mcl*-PHAs. By blending a different polymer, such as a *mcl*-PHA into the matrix of a *scl*-PHA, higher degradation rates can be achieved while having similar polymer properties. Martelli *et al.* reported the characterization of *mcl*-PHA-based blends, focusing on blends of the statistical copolymer P(HB-HV) and a *mcl*-PHA composed of PHO, poly(hydroxy decanoate), and poly(hydroxy dodecanoate)[62]. The addition of 5 wt.-% of the *mcl*-PHA resulted in an increased strain at break of 50 %, compared to non-modified statistical copolymers of P(HB-HV).

Wu and colleagues developed a simple and safe nanoparticle system by coating P(HB-HHx) (statistical copolymers) nanoparticles with poly(ethylene imine) for application in *in-vitro* and *ex-vivo* cellular manipulation. The particles were produced from Rhodamine-B-loaded P(HB-HHx) nanoparticles with a diameter of 154 ± 71 nm, which were subsequently coated with poly(ethylene imine) in order to facilitate the binding to and uptake by cells[63]. A similar strategy for the coating of nanoparticles of statistical copolymers of P(HB-HV) by poly(vinyl alcohol) was published by Masood *et al.*[64] The particles contained the anti-cancer drug Ellipticine. Boyandin *et al.* reported blends composed of different tropical soils and their influence on the biodegradation of PHA homopolymers and blends[65]. Various factors such as differences in soil and climatic conditions were found to play a crucial role in the degradation. The major degraders of PHA could be identified as bacteria of the genera *Burkholderia, Bacillus, Cupriavidus, Streptomyces, Nocardiopsis* and *Mycobacterium,* as well as the fungi *Gongronella butleri, Penicillium species, Acremonium recifei, Purpureocillium lilacinus,* and *Trichoderma pseudokoningii*.

Polymer-analogous reactions have particularly focused on adding functionality to unsaturated PHAs involving the highly reactive double bond of the PHA's side-chains. Reports comprise the carboxylation[9], hydroxylation[10], introduction of amine groups[11], and combination with other (hydrophilic) polymers like PEG[12]. The polymer-analogous cross-

linking of polymer chains is another strategy aiming at the increase of the mechanical strength of PHAs[13]. Rupp *et al.* reported the UV-induced crosslinking of a *scl*-PHA copolymer, namely films of P(HB-HV), with a bisazide capable of absorbing UV light[14]. By addition of up to 3 wt.-% of the bisazide (BA) to P(HB-HV), crosslinking degrees of more than 90 % could be achieved within irradiation times of less than 1 minute. This process was successfully employed in photolithographic processes that produced images with 50 μm resolution (Fig. 3).

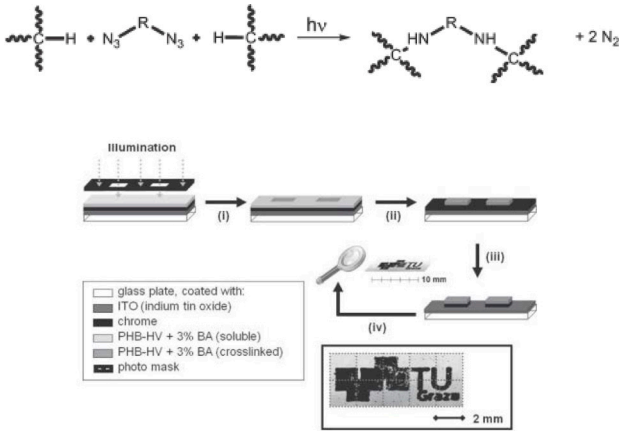


Fig. 3 – *Top: Crosslinking of polymer chains with a bisazide (BA) under UV irradiation. Bottom: Multi-step photolithographic processes based on P(HB-HV). Reproduced in part from reference[14] with permission of The Royal Society of Chemistry.*

The thermally induced crosslinking of biopolyesters (comprising PHAs) by telechelic poly(ethylene glycol)-bisazides was summarized in a patent[15], potentially overcoming the long degradation rates of pristine PHAs. Recent work by Wu *et al.* focused on the characterization of PHA composites that were either chemically crosslinked with cellulose acetate or blended with chestnut shell fibers, the latter for enhanced biodegradation[66,67]. The compounds produced were characterized, among others, by biodegradation rates, adhesion of cells, hydrophilicity and mechanical properties (Fig. 4). The results confirm the strategy, since the mechanical properties, especially the tensile strength, of both composites increased. The biodegradation rate was also higher in both composites compared to pure PHA, maintaining biocompatibility.

Applications

Certain microorganisms with the ability to produce PHA depolymerases can promote the biodegradation of PHA. Under aerobic conditions, they are degraded into water and carbon dioxide and, under

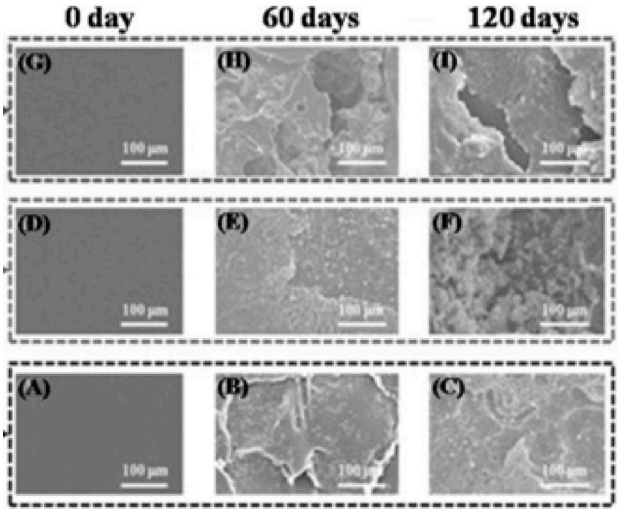


Fig. 4 – *SEM images of the morphology of PHA composites after 0, 60, and 120 days of degradation. A-C: pristine PHA, D-F: PHA crosslinked with cellulose actetate, G-I: PHA grafted on acrylic acid/cellulose acetate. Biodegradation by Acetobacter pasteurianus can be monitored by the erosion in the films. Reprinted from reference[66] with permission from Elsevier.*

anaerobic conditions, into methane and water[68]. The biodegradability and biocompatibility of PHAs makes them the ideal candidate for a broad spectrum of applications. However, the rates of degradation are not always suited to the purpose, and depend highly on the microbial environment of the PHA product[69–73]. Corresponding applications of PHAs include improved forms of food packaging[74], waste bags, or agricultural plastics. Sudesh and colleagues reported about the synthesis of PHA from palm oil and new applications thereof[21]. In their approach, they investigated PHA as a potential facial oil blotting material as well as a potential dye remover from wastewater.

Recent work from Sridewi *et al.* showed that (blended) PHB-TiO_2 electrospun nanocomposite fibers and films (Fig. 5) can be used for the removal of dyes, such as malachite green via decolorization, degradation, and detoxification[75]. Materials derived from the fiber melt-spinning of PLA and P(HB-HV) (reported by Hufenus *et al.*, see above)[50], were sub-

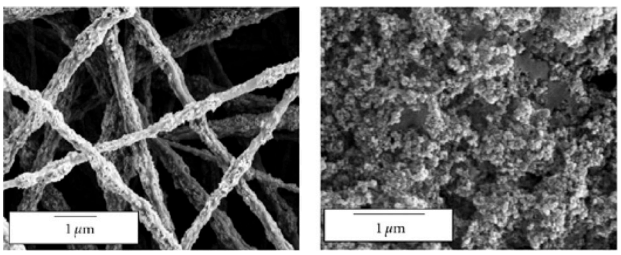


Fig. 5 – *SEM micrographs showing the morphological features of electrospun fibers (left) and spincast films (right) of PHB blended with TiO_2. Reprinted from reference[75] with permission from Hindawi Publishing Corporation.*

jected to biodegradability studies on human fibroblasts that revealed no toxicity of the fibers and cells proliferated well under the condition provided by these new materials. Additionally, the molecular weight loss caused by biodegradation of the fibers reduced the tensile strength up to 33 % after 4 weeks of incubation, further proving the promise of this new material in medical applications.

Castro-Mayorga *et al.* showed the stabilization of antimicrobial silver nanoparticles (preventing their agglomeration) by a PHA obtained from mixed bacterial culture[74]. The study demonstrated that unpurified statistical copolymers of P(HB-HV) can be used as capping agent that helps prevent agglomeration.

The area most considered for possible application of PHAs and PHA blends is the area of medical applications[1,8,58,76–84]. The usage as a system for drug delivery is perhaps the longest investigated application in this area, but still a highly active field[85,86]. Naveen *et al.* synthesized nanofibers mats of PHB by electrospinning and loaded them with Kanamycin sulphate to test against *Staphylococcus aureus*. The drug release of the antibiotic showed more than 95 % release within 8 hours[84]. Xiong and colleagues prepared nanoparticles of PHB, statistical copolymers of P(HB-HHx) and PLA and loaded them with lipid-soluble colorant rhodamine B isothiocyanate as a model compound[87]. Due to their size, nanoparticles can penetrate deeply into tissue material and are more efficiently taken up by cells. They achieved a high loading efficiency of around 75 % with the PHB homo- and P(HB-HHx) statistical copolymers, and a drug release over a period of at least 20 days, while reference PLA nanoparticles only lasted 15 days. Chaturvedi *et al.* used blends of PHB with cellulose acetate phthalate (CAP) in different compositions for drug loading with 5-fluorouracil, an anticancer drug, and investigated the simulated colon delivery of the said drug[88]. The pH-sensitive property of the blend caused a higher *in vitro* release at alkaline pH than at acidic pH, suggesting its potential for colon delivery.

Tissue repair has become one of the major fields when combining PHA with medical applications[77,81,83,89]. The high biocompatibility of PHB, which is not surprising when considering the natural occurrence of 3HB in the blood stream[1], makes it an ideal candidate for scaffolds, which can later be used for the repair of tissue damage. Results of animal testing clearly showed the high biocompatibility of implants of PHB and P(HB-HV) statistical copolymers. Shishatskaya *et al.* and Volova *et al.* investigated the physiological and biochemical characteristics of Wistar rats implanted with PHA sutures. Long-term (1 year) observations showed that the animals with PHB or P(HB-HV) threads were active and healthy throughout the experiment, and suggested that the implanted polymer threads did not affect the organism in a negative way[56,90]. For biodegradable implants, the high crystallinity is indeed a problem, rendering the attack of degrading enzymes more difficult[91]. Various blends of different PHAs, such as P(HB-HV), are therefore under investigation, combining the excellent biocompatibility of PHB with a lower degree of crystallinity provided by the incorporated PHV[89].

Basnett *et al.* reported novel blends composed of PHO and PHB for medical applications. In their study, blends with various ratios of PHB and PHO in various ratios were created, and degradation as well as biocompatibility tests were carried out[92]. The degradation found in these blends occurred via surface erosion and not bulk degradation, which would lead to a more controlled degradation, while still maintaining the core structure. Combined with an increased biocompatibility with HMEC-1 cells, these blends showed a very promising perspective for the development of biodegradable materials.

Another strategy for tissue repair was reported by Ellis and colleagues who produced laser-perforated biodegradable PHA scaffold films[93]. The pores of the films of statistical copolymers of P(HB-HV) exhibited micrometer dimensions. Hence, once the cells were seeded onto the film surface, they could attach and proliferate on the upper surface as well as through the pores and into the region of the damaged tissue. In their study, they achieved an increased surface amorphicity at the pore edges, which may facilitate cell adhesion and could promote growth and migration of cells for regenerative medicine.

Sutures of PHB and P(HB-HV), respectively, were found to exhibit the mechanical strength required for use in muscle-facial wounds, and, hence, they were tested on animals intramuscularly[90]. The environmental tissue reacted to the PHAs by a transient post-traumatic inflammation, as well as in the formation of fibrous capsules with a thickness of up to 200 μm, which thinned upon prolonged exposure. If the sutures were implanted for periods of up to one year, they stimulated no suppurative inflammation or necrosis.

On the topic of nerve injury repair, a new strategy provided by Wang *et al.* described the usage of PHA as scaffolds for human bone marrow stromal cells[94]. A statistical terpolyester of the composition P(HB-HV-HHx) was compared with poly(lactic acid) and P(HB-HHx) for their function in differentiating the human bone marrow stromal cells into nerve cells. It could be shown that the terpolyester had stronger cell adhesion, proliferation and differentiation than the other two polymers. Three-dimensional scaffolds of a composite composed of

P(HB-HHx) and mesoporous bioactive glass (in different mass ratios) were printed with a 3D bioplotter by the group of Zhao *et al.*, aiming at the delivery of materials for enhanced bone regeneration[95]. These highly porous, yet robust scaffolds showed good bioactivity, stimulated human bone marrow stromal cells adhesion and stimulated bone regeneration in *in-vivo* experiments (Fig. 6).

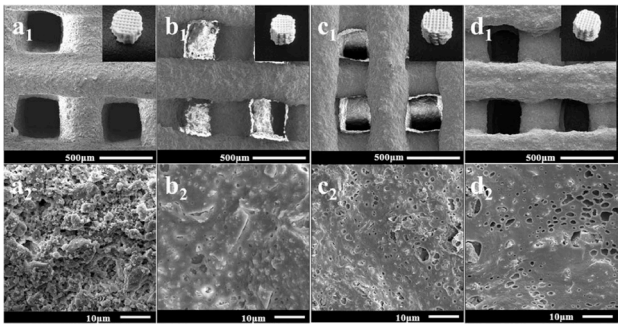


Fig. 6 – *SEM images of composite scaffolds of P(HB-HHx) and mesoporous bioactive glass (MBG) at different magnifications (top and bottom). A: reference material poly(vinyl alcohol):MBG = 1:7; B: P(HB-HHx):MBG = 1:7; C: P(HB-HHx):MBG = 1:5; D: P(HB-HHx):MBG = 1:3. Reproduced in part from reference[95] with permission of The Royal Society of Chemistry.*

Conclusions and outlook

New technologies and evolution of production modes (batch, feed batch, continuous) methods have allowed PHAs to become a recognizable player in the field of biodegradable polymers. Research in biotechnology and strain engineering has enabled the production of PHAs from cheap substrates, inline with existing processing facilities such as waste treatment and easier-to-handle microorganisms compared to the wild type production strains reported in the past. Continuous improvements of PHA contents within the cells and growth rates are reported on a regular basis.

PHAs are still far from joining the competitive level of production costs compared to petroleum-based polymers such as PP or PE. Hence, currently, PHAs can be only considered for advanced applications, in which they cannot be replaced by petroleum-based polymers. Correspondingly, PHAs are well-suited for any application that requires biocompatibility and/or biodegradability of the polymer. Notably, purity requirements are high for such applications, and the removal of impurities, such as endotoxins, further increases the production costs. For medical applications, in particular the homopolymers PHB and PHV as well as the statistical copolymer PHB-stat-PHV have been investigated. These so-called scl-PHAs can be processed by melt processes as they are thermoplasts, or by solution processes due to their solubility in (a limited number of) organic solvents.

In order to adapt the polymers' properties to the specific application details and requirements, several techniques can be applied to PHAs, not to mention the blending with other (biodegradable and biocompatible) polymers, and polymer-analogous modification by, e.g., crosslinking as prominent examples. Using these techniques, a broad spectrum of tailor-made mechanical and physical properties can be realized. In the area of medical applications, in particular tissue engineering could benefit from these recent developments and improvements. PHA blends as scaffolds for tissue repair are a highly active research area that has produced a lot of very promising results from in-vivo tests in recent years.

PHAs, quo vadis? Facing the need for advanced and/or alternative medical devices for tissue engineering, drug delivery, and implants in their broadest sense on the one hand, and the promising research results in recent years, the applicability of PHAs in those medical areas is more than plausible in the near future.

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