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USE OF POLYHYDROXYALKANOATE (PHA) AS A BIOMATERIAL: A REVIEW

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Abstract: The search for innovative biomaterials is intense in regenerative medicine and materials engineering. Polyhydroxyalkanoate (PHA) has stood out as a class of biodegradable polyesters produced by bacteria for energy storage. These polymers are highly valued for their biocompatible and biodegradable properties, making them ideal for medical devices, tissue engineering and controlled drug release. Applications include sutures, stents and scaffolds. The importance of PHAs as biomaterials lies in their sustainability and functionality, being an ecological alternative to synthetic polymers. Its biocompatibility and biodegradability avoid the need for additional surgeries to remove the implanted material and reduce the risk of rejection or chronic infection. PHAs have the potential to improve patients' quality of life and minimize environmental impacts.
Keywords: Polyhydroxyalkanoate, Biomaterial, Biodegradable, Sustainability.

INTRODUCTION

Biomaterials are substances designed to interact in a compatible way with biological systems, playing a crucial role in various medical applications, such as implants and dressings. Classified as metallic, polymeric, ceramic and composite, each type is optimized for specific functions, driven by advances in materials science and the demand for safer and more efficient medical solutions. Polymers stand out for their adaptability, with natural and synthetic variations, favoring regenerative medicine, such as polyhydroxyalkanoates (PHAs), which offer biodegradable alternatives to conventional plastics.

Continuous research and development in biomaterials is essential for advances in medicine, especially in the engineering of new medical devices and drug delivery systems. These materials must be meticulously designed to ensure biological compatibility and minimize adverse reactions, such as inflammation or rejection (FESTAS; RAMOS; DAVIM, 2020).

The evolution of biomaterials is crucial to meet the growing needs of modern medicine and improve the global quality of life by exploiting the composition and physical and mechanical properties of polymers to maximize their impact on health.

THEORETICAL REFERENCE

POLYMERS

Polymers are macromolecules formed by the repetition of simple structural units called, which are linked by covalent bonds, sharing electrons to achieve stability. Polymers can be classified as homopolymers, derived from a single type of monomer, or copolymers, composed of two or more types of monomers (Figure 1).

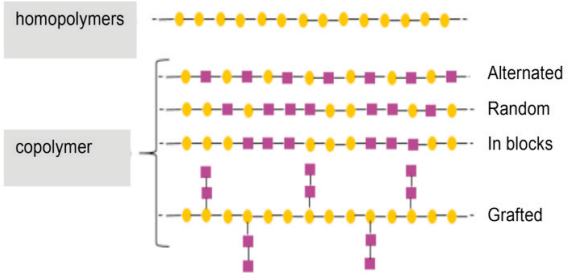

Figure 1: Polymeric Composition. Source: ANTUNES, 2013.

POLIHIDROXIALCANOATOS (PHA)

Polyhydroxyalkanoates (PHAs) are a family of polymers, normally found in biodegradable polyesters, produced naturally by microorganisms such as bacteria and algae, as an intracellular energy reserve, mainly in conditions of excess carbon and lack of oxygen and nitrogen. The composition of PHAs depends on the specific type of PHA and the producing microorganism.

PHAs can be classified into two main

groups based on the number of carbon atoms in their monomeric units. The first, known as short-chain polymers (Scl), includes molecules with 3 to 5 carbon atoms and the second, covers medium-chain polymers (Mcl), with 6 to 14 carbon atoms. PHAs with more than 14 carbon atoms are categorized as long-chain PHAs (Lcl-PHAs), which are very rare and less explored (GAHLAWAT, 2019).

To date, more than 150 distinct types of monomers have been described for the biosynthesis of PHAs, making them the broadest group of natural polyesters (SHARMA; SEHGAL; GUPTA, 2021; MAI et al., 2024).

PHAs degrade naturally under aerobic or anaerobic conditions and are highlighted by their properties of low affinity with water, high resistance to degradation by water and UV radiation, elasticity and water barrier (CHALAPUD; REALPE; GARCIA, 2022), in addition to biodegradability, biocompatibility and piezoelectricity. They are used in biomedical applications, comparable in performance to petroleum-derived polymers, making them biopolymers of global interest (DHANIA et al., 2022; BEHERA et al., 2022).

CHEMICAL COMPOSITION

The structure of PHA is particularized according to two precepts: The structure of the radicals linked to carbon atoms with R configuration in the skeleton of the polymer chain; the number and structure of monomers in the polymer chain.

The most common hydroxyalkanoate monomers are 3-hydroxybutyrate acid (3HB) and 3-hydroxyvalerate acid (3HV), 4-hydroxybutyrate acid (4HB), 3-hydroxyhexanoate acid (3HHx), and 3-hydroxyoctanoate acid (3HO), highlighting the diversity and adaptability of these polymers for different uses (Figure 2).

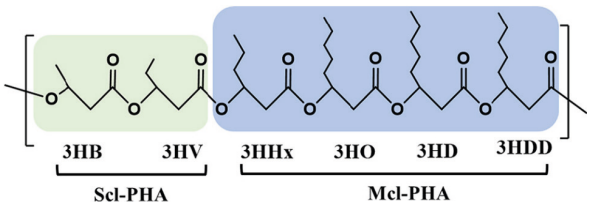

Figure 2: Monomers *Scl*-PHA and *Mcl*-PHA.
Source: Wang *et al*., 2022.

The scl-PHAs mainly consist of P3HB and PHB (BEHERA et al., 2022), which in turn can be copolymerized with different hydroxyalkanoate units to form various PHA copolymers, such as PHBV (poly-3-hydroxybutyrate-co -3-hydroxyvalerate) (Figure 3).

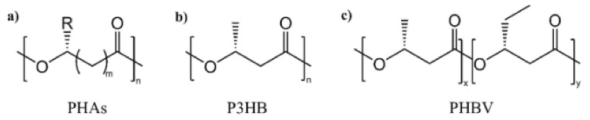

Figure 3: Structure of PHAs, P3HB and PHBV.
Source: Mai et al., 2024 based on Li and Loh, 2015.

The scl-PHA and its copolymers are semi-crystalline materials with high melting temperatures due to their high degree of crystallinity, while mcl-PHA, such as P(3HHx) (BEHERA et al., 2022), are known for their low melting temperatures, making them more suitable for medical applications due to their superior thermo-mechanical properties (CIESIELSKI; SŁAWOMIR et al., 2013). The proportion and sequence of these monomers in the polymer chain determine the physical and chemical properties of PHA, such as its crystallinity, mechanical resistance and degradation rate (WEI; FANG, 2022).

CRYSTALLINE STRUCTURE

The crystalline structure of polyhydroxyalkanoates (PHAs) varies depending on the specific type of PHA and the composition of the monomers that form it, as the author Liu et al. (2020) wrote that the thermal and mechanical properties of PHA can be regulated by controlling its monomeric composition.

PHAs are semi-crystalline polymers, which means they have ordered crystalline regions and disordered amorphous regions (WEI; FANG, 2022).

According to Mai et al. (2024), the crystal structures of the P3HB and P3HV polymers are orthorhombic in shape, also confirmed by Eesaee et al. (2022), presenting the lattice parameters: a = 5.76 Å, b = 13.20 Å, c = 5.96 Å for P3HB, and a = 9.32 Å, b = 10.02 Å, c = 5.56 Å for P3HV (Figure 4).

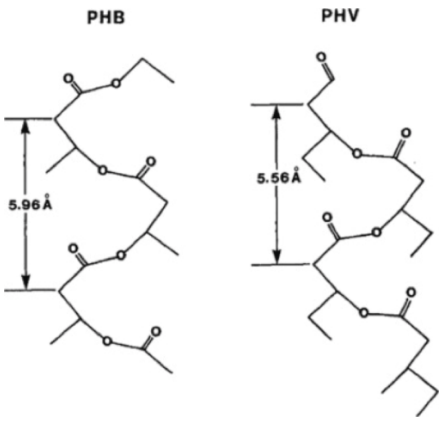

Figure 4: Crystalline Conformation of PHB and PHV. Source: Mai et al., 2024.

The structure of P3HB and P3HV molecules assumes a compact helix conformation (polymeric chains coil in a dense and organized manner, forming a spiral structure) and dextrorotatory 21 (helix rotates to the right along its axis when observed from a end), with a double helical axis and fiber repetition periods of 0.596 nm and 0.556 nm, respectively. The PHB or P3HB chains are organized into lamellar sheets, with the chains folded in a "zigzag" pattern and stacked on top of each other.

This crystalline structure gives PHB properties such as high crystallinity, rigidity and a relatively high melting temperature (around 180 °C) (WANG et al., 2022).

Other types of PHAs, such as the poly-3-hydroxybutyrate-co-3-hydroxyvalerate (PHBV) copolymer, have similar crystalline structures, but with some variations due to the presence of different monomers in the polymer chain. The addition of other monomers, such as 3-hydroxyhexanoate (3HHx) or 3-hydroxyoctanoate (3HO), can change the crystalline structure and, consequently, the physical properties of the polymer, making it more flexible and less crystalline.

In summary, the crystalline structure of PHAs is influenced by the composition of the monomers and can vary between different types of PHAs, affecting their mechanical and thermal properties.

MECHANICAL AND THERMAL PROPERTIES OF PHAS

The development of copolymeric materials such as PHBV, P3HB, P4HB and PHBHHx, with high comonomer contents, aims to disrupt the crystalline structure of 3HB and reduce the overall crystallinity of the polymer until the pseudoeutectic point is reached, generally between 45% and 55% of comonomer content, increasing flexibility and toughness, but decreasing strength and stiffness (WANG et al., 2001).

P3HB and its copolymer P(3HB-co-3HV) with low hydroxyvalerate (HV) content are known for their rigidity and low impact resistance due to high crystallinity (LAYCOCK et al., 2013).

The degradation of PHBV is faster than that of PHB (MIU; EREMIA; MOSCOVICI, 2022). P3HB tends to secondarily crystallize during storage, resulting in greater fragility (WANG et al., 2022).

Methods to improve PHB toughness include plasticizers and nucleating agents (PERRET et al., 2019). The melting temperature (Tm) determines the processing range of the polymer and a greater difference between Tm and the decomposition temperature (Td) will provide a wider processing range.

The P3HB has high mechanical strength

and hardness, but is brittle and has low elongation at break (WANG et al., 2022). The addition of comonomers can decrease the melting temperature and glass transition temperature, increasing the segmental mobility of the chains (BLUHM et al., 1986).

Molecular weight also plays a crucial role, with microbial PHAs having molecular weights between 200 and 3000 kDa, being ideal for thermoplastic applications above 600 kDa (MAI et al., 2024).

PHA PROCESSING

CHEMICAL EXTRACTION

According to Samrot et al. (2021), polyhydroxyalkanoates (PHAs) are synthesized within cells in the form of granules surrounded by proteins, and it is necessary to extract these granules to isolate them in their pure form, which involves breaking down the cellular matrix (NISHA et al., 2012). In industrial environments, this is done using enzymes that degrade proteins and cell walls. A common extraction method is the use of solvents containing chlorine and oxygen, or enzymes that selectively digest cellular materials other than PHAs (JIANG et al., 2018; RAMSAY et al., 1994).

Several renewable resources, such as organic and agricultural residues, vegetable oils and animal fats, have also been used for this purpose (SATHYA et al., 2018; BEHERA et al., 2022), although this technique faces scalability limitations due to the complexity of enzymes and chemicals used (VANDI, 2018). Solvent extraction dissolves the PHA from biomass in an organic solvent, such as chloroform, methyl ether or methylene chloride, among others JIANG et al., 2018; JACQUEL et al., 2008).

BIOLOGICAL EXTRACTION

Currently, there are two main methods for producing polyhydroxyalkanoates (PHAs) from bacteria (GRIGORE et al., 2019). The first is pure culture, widely adopted in industry for large-scale production, in which genetically modified or pure strain bacteria are used to synthesize PHA. These biogenic polyester compounds generally range from 0.2 μm to 0.5 μm in diameter and are stored as insoluble inclusion bodies in the cytoplasm (OBRUCA et al., 2020; BEHERA et al., 2022). However, pure culture requires stringent, sterile environmental conditions and highly purified carbon substrates, resulting in considerable production costs that negatively impact PHA's economic competitiveness compared to conventional petrochemical plastics (SABAPATHY et al., 2020).

The second method uses mixed microbial communities (MMCs) as a biological vehicle for PHA production (WEI; FANG, 2022). This process involves three main steps: anaerobic fermentation, where complex bio-waste is converted into volatile fatty acids (VFAs); enrichment of MMCs, where cultures with good PHA synthesis capacity are selected and maximized under conditions of nutritional imbalance, generally in two stages; and proliferation of the MMCs under unrestricted conditions until they reach a significant concentration. The properties of PHA copolymers vary depending on the type of carbon raw material and the specific metabolic pathways, in addition to the activities and substrate specificities of the enzymes involved (LU; TAPPEL; NOMURA, 2009). Although biological methods are more common due to the biocompatibility, biodegradability and lower environmental impact of PHAs, chemical methods can offer advantages in terms of controlling polymer properties and industrial scalability.

Method	Chemical	Conditions	Purity and recovery
Extraction by solvent	chloroform	Mix continuously at 25 degrees Celsius for 12 hours	Purity: 94-96,% ; Recovery: 65-70%
	methylene chloride	Mix continuously at 25 degrees Celsius for 12 hours	Purity: 95-98,% ; Recovery: 24-25%
	1.2 - Dichloroethane	Mix continuously at 25 degrees Celsius for 12 hours	Purity: 93-98,% ; Recovery: 66-70%
	Acetone	Mixing continues at 120 degrees C bar for 20 minutes under anaerobic conditions, followed by filtering the hot solution and cooling to 4 degrees Celsius to precipitate the polymer.	Purity: 98,4% ; Recovery: 96,8%
	Medium chain alcohols	In continuous stirred tank reactors, a multistage extraction technique is used. Cool the extract to recover the polymer after removing cellular	Purity: > 98,0% ; Recovery: 95,0%
Hypochlorite digestion	Sodium hypochlorite	Biomass concentration: 10-40 g/L; pH: 8-13.6; temperature: 0-25 C, digestion time: 10 minutes – 6 h; hypochlorite concentration: 1-10.5% weight/volume (plv)	Purity: 90 – 98.0%; Recovery: 90-95%
	Sodium hypochlorite and chloroform	Biomass concentration: 1% (plv), temperature: 30 C, digestion time: 1 hour, hypochlorite concentration: 3-20% (vlv)	Purity: 86.0%; Recovery: NG; Purity: 93.0%: NG
Enzymatic digestion	Trypsin, bromelain, pancreatin	Digestion with 2% trypsin (50 C, ph 9.01h) or 2% bromelain (50 C, ph 4.75, 10 h) or 2% pancreatin (50 C, ph 8.08, 8h), followed by centrifugation and washing with 0.85% solution	Purity: 87.7 – 90.3%; Recovery: NG

Table 1: Chemical Methods for Extracting PHAs. Source: adapted from MIU; EREMIA; MOSCOVICI (2022).

Microorganism	Carbon Source	PHA Yield (%w/v)	Solvent	PHA	Extraction Method
Cupriavidus necator,	Vegetable oil	95	Cyclohexanone	PHB	Solvent extraction
Pseudomonas aeruginosa	Castor oil and euphorbia oil	20–30	Chloroform	PHA	Solvent extraction
E. coli BL21	Glucose	20	Lysozyme and proteinase K	PHB	Enzyme extraction
Sinorhizobium meliloti	Sucrose	50	Triton X-100-EDTA	PHA	Surfactant–Chelate
Bacillus cereus	Glucose	9	Chloroform	PHB	Solvent extraction
Pseudomonas oleovorans	Octanoic acid	34	Chloroform	PH0-DEG	Solvent extraction
Caulobacter crescentus	Caulobacter medium, glucose	18	Chloroform	PHB	Solvent extraction
Halomonas boliviensis	Starch hydolysate, maltose, maltotetraose and maltohexaose	56	Chloroform	PHB	Solvent extraction
Legionella pneumophila	Nutrient broth		Chloroform	PHB	Solvent extraction
Spirulina platensis	Carbon dioxide	10	Methanol	PHB	Solvent extraction
Rhodopseudomonas palustris SP5212	Acetate, malate, fumarate, succinate, propionate, malonate, gluconate, butyrate, glycerol, citrate	7.7	Chloroform	PHB, PHBV	Solvent extraction
Rhodopseudomonas palustris SP5212	Hydroxybutyrate, valerat	49.06, 30	Chloroform	PHB, PHBV	Solvent extraction
Aeromonas hydrophila	Lauric acid, oleic acid	28	Hexane	PHA	Solvent extraction
Agrobacterium tumefaciens SU-11	Glucose	43	Chloroform and sodium hypochlorite solution	PHA	Solvent extraction
Bacillus sp.	Sucrose	11–41		PHB	Solvent extraction
Escherichia coli	Glycerol	5.2	Chloroform	PHA	Solvent extraction
Serratia sp.	Xylose	37.50	Methanol	PHB	Solvent extraction
Enterobacter sp. SU16	Glucose	40		PHA	Non solvent Precipitation

Table 2: Synthesis of PHA from various microorganisms. Source: SAMROT et al., 2021.

BIOMATERIALS

The National Institutes of Health (NIH) has provided a widely accepted definition of biomaterials, describing them as substances or combinations of substances, natural or synthetic (except drugs), that can be used for any period of time. These materials have the ability to improve or replace, totally or partially, any tissue, organ or bodily function, aiming to preserve or improve a person's quality of life (WILLIAMS, 1999) and are biocompatible with the human body. Biocompatibility is defined by Williams (2019) as the ability of a material to interact with the host's body in a specific application without causing inflammatory, allergic, toxic, mutagenic or carcinogenic reactions. Materials used in biomedical applications must be safe, effective and of high quality, possessing fundamental characteristics, among which biocompatibility is the most crucial.

DISCUSSION

According to Paul et al. (2024), PHA is a biodegradable polymer widely used in various applications due to its biocompatibility and sustainability. Hu et al. (2018) and Eesaee et al. (2022) also highlight that, due to their biocompatibility and non-toxicity, PHAs are excellent options for applications in packaging, as well as in the medical and pharmaceutical areas. Products such as sutures, stents, heart valves, orthopedic pins, articular cartilage, tendon, bone marrow scaffolds and bandages are manufactured with improved PHAs (MIU; EREMIA; MOSCOVICI, 2022; SCHMIDT; STOCK; HOERSTRUP, 2007).

Polyesters such as poly 3-hydroxybutyrate (PHB), polyhydroxyvalerate (PHV), and poly(3-hydroxybutyrate 3-hydroxyvalerate) (PHBV) have been widely studied for orthopedic applications, allowing the formation of new bone tissue without inducing a chronic inflammatory response (MIU; EREMIA; MOSCOVICI, 2022).

The first commercial product approved by the FDA in 2007 was TephaFLEX from Tepha Medical Devices, a linear thermoplastic polyester produced through fermentation of recombinant gram-negative bacteria E. coli. The absorbable biopolymer P4HB offers sutures that are up to 35% stronger than synthetic polydioxanone and 19% stronger than polypropylene, and can be transformed into other absorbable medical devices, including sutures, grafts and textiles such as surgical mesh (MIU; EREMIA; MOSCOVICI, 2022; WU; WANG; CHEN, 2009). Phasix™ mesh, made from P4HB, can be a treatment option for hernias due to its mechanical resistance (MOLINA et al., 2021; VAN ROOIJEN et al., 2018). Furthermore, the P4HB biopolymer has been effectively used in tissue engineering. Commercial PHB and PHBV products are sold under names such as Biopol® (Monsanto), Nodax® (Procter & Gamble), PHBH® (Kaneka Corporation), Eamat® (Tianan), and Biomer P® (Biomer) (VROMAN; TIGHZERT, 2009), in addition to GalaFLEX® (Galatea-Tepha) (MIU; EREMIA; MOSCOVICI, 2022). Products such as Phantom™ fiber, MonoMax® suture, BioFiber™ scaffold and GalaFLEX® mesh are examples of commercial applications of these biomaterials (MIU; EREMIA; MOSCOVICI, 2022; MANAVITEHRANI, 2016).

Li; Yang; Loh (2016) investigated water-soluble polymers, showing that PHAs functionalized with polar groups or copolymerized with hydrophilic components result in smart biomaterials with remarkable properties. Although PHA has several properties that make it ideal for the development of high-value-added polymeric products, such as packaging and medical devices, its large-scale production and commercialization are limited by the high cost compared to conventional polymers

(GOVIL et al., 2020). To reduce these costs, it is crucial to establish profitable processes with high PHA yields, and a promising alternative is the use of lignocellulosic biomass (RAZA; ABID; BANAT, 2018).

Strategies to modify PHAs, particularly scl-PHAs, involve combining them with other materials or polymers and adding additives or reinforcements to create composites, including nanocomposites (EESAEE et al., 2022). Reinforcements such as natural fibers, polysaccharide nanocrystals and inorganic fillers can be used to improve the thermal, mechanical, physical and barrier properties of PHAs.

Among the members of the PHA family, mcl-PHAs are ideal for medical devices and tissue engineering, such as cardiovascular sutures and drug delivery systems (CONSTANTINIDES et al., 2018; MIHAELA et al., 2017). The biomedical sector's need for flexible and elastomeric materials makes mcl-PHAs, such as P(3HO), ideal for skin tissue engineering, cardiovascular implants, heart valves and wound healing (GRIGORE et al., 2019; LUKASIEWICZ et al ., 2018; URBINA et al., 2018).

CONCLUSION

Polyhydroxyalkanoates (PHAs) are biodegradable and biocompatible polymers, produced naturally by bacteria via fermentation using renewable substrates, standing out as ecological alternatives to synthetic polymers derived from petroleum. They are safe for use in various medical applications, such as implants and controlled drug release devices, due to their compatibility with biological tissues and their biodegradability allows them to break down naturally in the body, reducing the need for surgical interventions for removal and minimizing associated risks. to waste. However, challenges such as variability in their mechanical and thermal properties and melting temperatures close to degradation require adjustments to maximize their applicability. With continued research and development to optimize their properties, PHAs have significant potential to advance regenerative medicine and other biomedical areas, contributing to safer, more effective and environmentally responsible medical solutions.

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