



Insights into the application of polyhydroxyalkanoates derivatives from the combination of experimental and simulation approaches

Maykel González Torres ^{a, c, *, 1}, Eduardo Villareal ^b, María de los Angeles Moyaho Bernal ^c, Marco Álvarez ^b, José González-Valdez ^d, Janet Alejandra Gutiérrez Uribe ^a, Gerardo Leyva Gómez ^e, Jorge Raúl Cerna Cortez ^{c, **, 1}

^a Instituto Tecnológico y de Estudios Superiores de Monterrey, Campus Puebla, 72453, Mexico

^b Facultad de Odontología, Universidad Nacional Autónoma de México, 04510, Mexico

^c Benemérita Universidad Autónoma de Puebla (BUAP), Puebla, 72000, Mexico

^d Instituto Tecnológico y de Estudios Superiores de Monterrey, Campus Monterrey, 64849, Mexico

^e Facultad de Química, Universidad Nacional Autónoma de México, Ciudad de México, 04510, Mexico

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ABSTRACT

The combination of spectroscopy studies with simulation models can be a useful tool to predict the applications of macromolecules. However, it is currently unknown if applications of polyhydroxyalkanoate (PHA) derivatives can be determined with this methodology. Here, we used a new nuclear magnetic resonance (NMR) technique to structurally characterize poly (3-hydroxybutyrate) grafted with 2-aminoethyl methacrylate and combined the experimental results with those of molecular dynamic simulations. The NMR results show the possible grafting mechanism and final structure of the grafted polymer. Quantum and molecular dynamic simulations of the proposed structures were carried out to determine the reactive sites, hydrogen bonds, and physical movements of atoms. Using the information gathered, the application of the polymer as a scaffold for cell growth was discussed. It was concluded that this approach would be advantageous to achieve considerable savings in cost and time while developing potential applications of these bio-derived polyesters.

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1. Introduction

Poly (3-hydroxybutyrate), also known as P (3HB) (first member of PHA family), is an important biopolymer that can be obtained from renewable resources [1]. Several reports have shown that P (3HB) is an excellent candidate for use in tissue engineering [2], due to its good biocompatibility and biodegradability [3]. It has also been used during the synthesis of carriers for novel drug-delivery systems [4]. Its extensive range of applications has increasingly attracted the attention of researchers, which has led to the development of models regarding the fermentative production of this biopolymer [5]. For instance, mathematical modeling related to the

bivariate population balance has been developed to describe the dynamic evolution of P (3HB) [6]. Simulation is a powerful tool for the kinetic modeling of polymerization [7] and for the designing of genetic networks, which it can be used throughout the development of novel structures, from theoretical design to a practical approach for commercial usage [8]. However, the simulation of P (3HB) grafted structures has barely been studied, although good miscibility prediction of P (3HB) blends has been achieved using association mathematical models [9].

Simulations also deal with the tribological properties of materials [10,11]. For instance, computational research using a coarse-grained model has been used to study the scratch resistance of high-density polyethylene, which has similar physical properties to that of P (3HB) [11]. Furthermore, molecular dynamics (MD) of polymer viscoelasticity has arisen as a useful tool to understand the mechanical properties of polymers [12,13]. The objective of MD simulations is to attain information that is inaccessible experimentally, or to compare to results of experiments that are previously or subsequently performed [11]. Usually, the simulation of

* Corresponding author. Instituto Tecnológico y de Estudios Superiores de Monterrey, Campus Puebla, 72453, Mexico.

** Corresponding author.

E-mail addresses: maykel.gonzalez@itesm.mx (M. González Torres), jorge.cerna@correo.buap.mx (J.R.C. Cortez).

¹ These authors contributed equally to this work.

tribology involves the investigation of crystalline or semi-crystalline materials. This work represents an approach to understand the chemical properties of semi-crystalline polyesters by providing information on the hydrogen-mediated electrostatic attraction [14], [15].

Hydrogen bonding has been found to affect the P (3HB) crystallization behavior [16]. Hydrogen bonding interactions can alter the PHAs degree of crystallinity, miscibility, structure, and morphology, which are closely related to the polymer's applicability [17]. It is of note that most studies found in the literature are focused on the PHA hydrogen bonding interaction in blends [18], [19]. Additionally, with attention to the hydrogen bonds, the quantum-chemical calculation studies of infrared and Raman spectroscopy of P (3HB) and its copolymers have been reviewed before [15]. Nowadays, increasing attention has been directed to the hydrogen bonding interaction of polymers blends to understand the tacticity effect in their miscibility [20]. In general terms, MD has also been demonstrated to be a suitable tool for the prediction of organic molecule spectra, chain length, and conformation [21], [22].

In an earlier investigation, we carried out an experimental synthesis of 2-aminoethyl methacrylate hydrochloride (AEMA) grafted onto P (3HB), and studied the degree of crystallinity using vibrational spectroscopy [23]. Recently, P (3HB-g-AEMA) was structurally characterized by solid-state ^{13}C -CPMAS-NMR, thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC), swelling experiments, tensile testing and scratch resistance (tribology) [24]. The purpose of the current research is to combine these preliminary exploratory results with simulation tools to determine the possible bioengineering applications of the graft copolymer, as an example of the usefulness of these materials.

In the present work, Heteronuclear Multiple Quantum Coherence (HMQC) of P (3HB-g-AEMA) was carried out to detect the long-range coupling between the carbon and hydrogen atoms of the grafted polymer, to help elucidate the mechanism of the graft reaction, and to propose a structure for simulation. Afterwards, quantum chemical and molecular dynamics calculations were combined to simulate the behavior of the macro-molecules in a virtual biological system, which supports the possibility of predicting appropriate substrate interfaces, – e.g., (scaffolds/cell lines).

2. Experimental

2.1. Materials

P (3HB), AEMA, ethanol, and acetone (Sigma Aldrich, Germany) were used as received without further purification.

2.2. Methods

2.2.1. Synthesis

The experimental synthesis of P (3HB-g-AEMA) was carried out through simultaneous irradiation, where both the polymer (P (3HB)) and monomer (AEMA) are subjected to high-energy radiation [25]. P (3HB) and AEMA were subjected to the same source of ^{60}Co - γ -radiation in air (Gamma Beam 651 PT, Nordion International), with a dose of 11.85 kGy and a dose rate of approximately 1.9 kGy/h (measured with a Fricke dosimeter). The glass ampoules were adequately sealed for synthesis. The polymerization was conducted by adding 100 mg of monomer to 400 mg of P (3HB) and mixing with 2 ml of ethanol. The product was purified by Soxhlet extraction with acetone. The purified graft copolymer was dried until it reached a constant weight.

2.2.2. Nuclear magnetic resonance

The heteronuclear multiple quantum coherence (HMQC) technique was used for the detection of long-range coupling between the proton and carbon atoms in the graft copolymer P (3HB-g-AEMA). The NMR spectroscopy was carried out using the Mercury 400 BB equipment with a resonance frequency of 400 MHz. The grafted P (3HB) was dissolved in hot deuterated chloroform.

2.2.3. Quantum chemical calculations of P(3HB) reactivity

Theoretical calculations of the P (3HB) molecule were carried out to determine the reactive sites. Quantum chemical calculations were performed according to the density functional theory (DFT) using the DMol3 code. The potential functional employed during the analysis was GGA-B3LYP, used without any parameter optimization. The calculations were treated by a double-numeric-quality basis set with d-polarization functions. The calculations were all done with a convergence criterion of 10^{-6} au on the energy and electron density.

2.2.4. Molecular dynamics simulations of P(3HB) and the graft copolymer

All-atom MD simulations of P (3HB) and P (3HB-g-AEMA) were carried out as follows: GROMACS version 4.5.3 [26] and GROMOS54a7 force field [27] supplemented with P (3HB) and P (3HB-g-AEMA) parameters taken from Automated Topology Builder version 2.1 [28], [29]. The polymers were modeled using the ChemDraw program. MD simulations were performed under periodic boundary conditions in cubic boxes of two sizes; the first with an edge of 3 nm, and the second with an edge of 5 nm. The difference between the virtual box sizes was due to the number of monomers inside each box. The systems were solvated using the simple point charge (SPC) water model, and steepest descent minimization was performed on all P (3HB) and P (3HB-g-AEMA) models subjected to MD simulations. A *v*-rescale thermostat [30] and a Parrinello–Rahman barostat [31] were used to control the temperature and pressure; temperature coupling was employed at 300 K, and isotropic pressure coupling was scaled at 1 bar pressure. The LINCS algorithm was applied to constrain bond lengths; Lennard-Jones interaction was employed a 1.0 nm cut-off, and electrostatic treatment for the long-range interactions was performed using the particle mesh Ewald sum method. All systems were simulated for 10 ns.

3. Results and discussion

3.1. Heteronuclear multiple quantum coherence (HMQC) nuclear magnetic resonance study

Fig. 1 shows the Heteronuclear Multiple Quantum Coherence (HMQC) Nuclear Magnetic Resonance spectra of P (3HB-g-AEMA). From the ^1H NMR spectra (HMQC), the signals at $\delta = 1.34$ ppm, $\delta = 2.73$ – 2.80 ppm, and $\delta = 5.41$ ppm correspond to the CH_3 , CH_2 and CH protons of P (3HB), respectively. Whereas, the new signals at $\delta = 1.70$ ppm and $\delta = 2.24$ ppm are attributed to the CH_3 and CH_2 protons of the grafted polymer. The analysis of the graft copolymer shows that novel interactions are obtained in the fingerprint zone compared with that for P (3HB) in our previous studies [32]. The signal of the coupling of $\text{CH}_3^*-\text{C}^*\text{H}_3$ at $\delta = 1.7$ ppm and $\delta = 7.3$ ppm was unusual; the signal was very small and could not be observed clearly because of the HMQC scale, but the induced fingerprint signal could be clearly observed. Furthermore, coupling of $\text{CH}_2^*-\text{C}^*=\text{O}$ ($\delta = 2.24$ ppm; $\delta = 180$ ppm) and $\text{CH}^*-\text{C}^*\text{H}_3$ ($\delta = 5.4$ ppm; $\delta = 17.6$ ppm) was observed. The latter coupling is a consequence of the appearance of a new signal in the ^{13}C NMR spectra ($\delta = 180$ ppm; poly (2-aminoethyl methacrylate) (PAEMA) carbonyl group). The rest of the signals were assigned to CH_3

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