Journal of Polymers and the Environment
https://doi.org/10.1007/s10924-020-01946-x

REVIEW

Properties and Applications of Poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) Biocomposites

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Accepted: 21 October 2020

Abstract
Polyhydroxyalkanoates (PHAs) are biopolyesters accumulated by microorganisms as intracellular storage materials and they have attracted attention as "green plastic" alternatives to their petrochemical counterparts. Poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate), PHBV, is one of the most studied members of the PHAs family, with numerous applications. PHBV has three main features, biodegradability, biocompatibility and it is a biobased polymer (biosynthesis starting from renewable resources). These three features altogether qualify PHBV as a very promising polymer that has great potential to replace conventional non-degradable polymers, and to play a significant rule in the circular economy concept. However, PHBV has some prominent disadvantages that limit its wide utilization for commercial use, these drawbacks are mainly weak mechanical properties, low thermal stability, difficult processability and considerable hydrophobicity. In order to overcome the properties issues, to produce materials with more desirable features and to engineer purpose-specific PHBV-based systems, much research has been focused on improving its properties by forming composites and to utilize these produced composites for a wide spectrum of very promising applications. The purpose of the current work is to compile and classify the research accomplished in the field of PHBV biocomposites and their applications in different disciplines. It was found that many different types of nanofillers, natural fibers, agricultural waste, clay, silicate, wood and cellulose derived natural materials have been successfully incorporated into PHBV matrix. The resultant biocomposites were characterized, tested and found promising to be utilized in a wide spectrum of applications, namely packaging, tissue engineering and drug delivery systems. The potential benefits of PHBV-based biocomposites make a strong case for research into this area. Therefore, further research works need to be conducted in order to find new PHBV biocomposite materials for advanced applications.

Keywords Poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV) · Biocomposites · Drug-delivery · Tissue engineering · Thermal and mechanical properties

Introduction

Biopolymers are considered as very promising replacement for the conventional synthetic polymers that are derived from the petrochemicals industries. The key features of these biopolymers are their known biodegradability and biocompatibility [1] which qualify them to be utilized as environmentally friendly materials and for therapeutic applications in human bodies [2, 3].

Expanding the utilization and dependence on biodegradable polymers will definitely help protect the environment, respond to the planet threats and counteract against environmental challenges such as global warming and the accumulation of non-biodegradable plastic debris in oceans and elsewhere on the planet. Also, considering the well-known problem of toxic and carcinogenic monomers and tetramers leaching from the walls and surfaces of plastics in direct contact with humans, biocompatible polymers offer a key advantage to be used in commodities like toys, food cans, dishes, cups, other kitchen utensils, water and juice bottles in addition to all types of food packaging materials.

Biodegradable polymers could be classified as natural and synthetic based on their origin [1] (Fig. 1). Cellulose,

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Published online: 01 November 2020

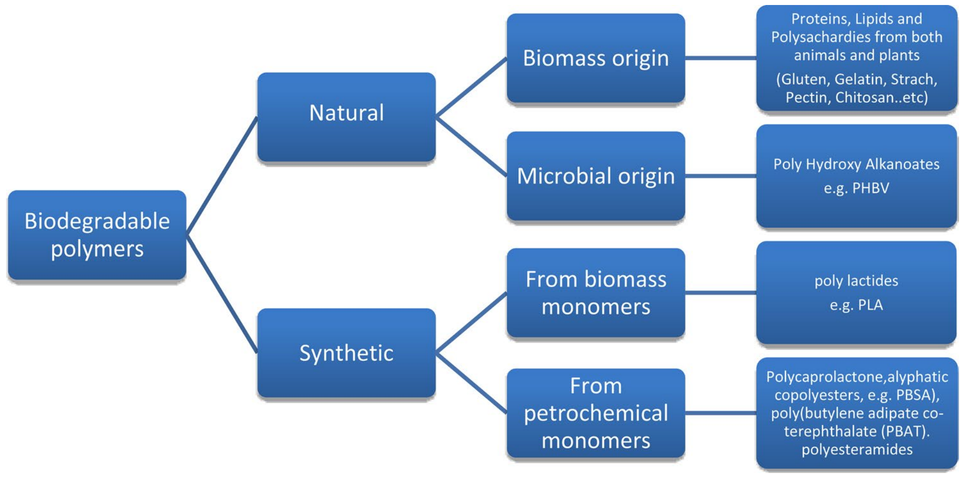


Fig. 1 Biodegradable polymers classification

chitosan, starch, collagen and gelatin are good examples of natural biodegradable polymers. Synthetic biodegradable polymers can be polyurethanes, poly amino acids, polyesters like polylactones and poly (α-hydroxyl acids) and many others. Microbial biodegradable polymers are mainly polyhydroxyalkanoates such as PHBV and poly (3-hydroxybutyrate) (PHB) in addition to poly (γ-glutamic acid).

Low carbon footprint, renewability and biodegradability are the driving forces to develop and expand the use of biobased materials, and to transform them into high-volume applications instead of limited niche markets. However, the narrow processing window, low heat deflection temperatures, poor barrier and many other properties are inherent drawbacks in many biobased plastics, those weaknesses limit the desired wide exploitation of such materials. Anyhow, such mentioned drawbacks and others can be overcome by forming biocomposites or blends [4].

Polyhydroxyalkanoate (PHA) are a very interesting family of biopolymers that are biosynthesized from different types of microorganisms, such microorganisms use different renewable carbon resources for the production process, and this makes it a good model for sustainable economy and environment. PHA's are intracellularly accumulated as carbon and energy reserves by several archaea and bacteria [5]. PHA's are biosynthesized as granules under stressed environmental conditions, mainly in the excess of carbon and deficient supplies of other essential growth nutrients like phosphate and nitrogen [5]. The recyclable biological process of PHAs is embedded into the closed carbon cycle of nature, which implies that their degradation does not cause an increase of the atmospheric CO_2 level; hence, PHA does not amplify or accelerate climate change [6] (Fig. 2).

Biosynthesized PHA was first reported in 1926 by Lemoigne [7], and that was the homopolyester PHB which is currently the most well-known member of the PHA family. PHB is a highly crystalline and hence a brittle polymer, and thermally unstable with a small window of thermal processing stability. PHA polymer is usually composed of 600 to 35,000 (R)-hydroxy fatty acid monomer blocks [8]. Each monomer unit contains usually a saturated side chain group but can also be a branched alkyl group, an unsaturated alkyl group and a substituted alkyl group, which are less frequent [9]. So far, there are more than 100 biosynthesized PHA types produced either by fermentation or genetic engineering [10], and there are more than 150 different PHA monomers identified [11].

By referring to the number of carbon atoms involved in their monomer structures, PHAs have been classified into three main categories [8]:

(A) Short chain PHAs; 3–5 carbon atoms.
(B) Medium chain PHAs; 6–14 carbon atoms.
(C) Long chain PHAs; 15 and more carbon atoms.

PHAs can also be classified as homopolymers and copolymers, homopolymers with only one single monomer as the building block (Fig. 3), and PHAs copolymers which are composed of two or more different building block monomers, examples include PHBV, poly(3-hydroxybutyrate-*co*-3-hydroxyhexanoate) (PHBHx), poly(hydroxybutyrate-*co*-hydroxyoctanoate) (PHBO), poly (3-hydroxybutyrate-*co*-3-hydroxyvalerate-*co*-3-hydroxyhexanoate) (P3HB3HV3HHx) [12, 13] and poly(3-hydroxybutyrate-*co*-4-hydroxybutyrate-*co*-3-hydroxyhexanoate) (P3HB4HB3HHx) [13, 14] poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate-*co*-4-hydroxybutyrate) (P3HB3HV4HB) [15].

The homopolymer PHB is considered as the major member in the PHA family. Also, of the PHA family, the copolymer PHBV is a polyester with a more favorable properties compared to PHB like lower melting point and improved mechanical properties [16, 17]. Compared to PHB, the PHBV copolymer has shown a wider processing window by lower melting and glass transition points [18, 19], in addition

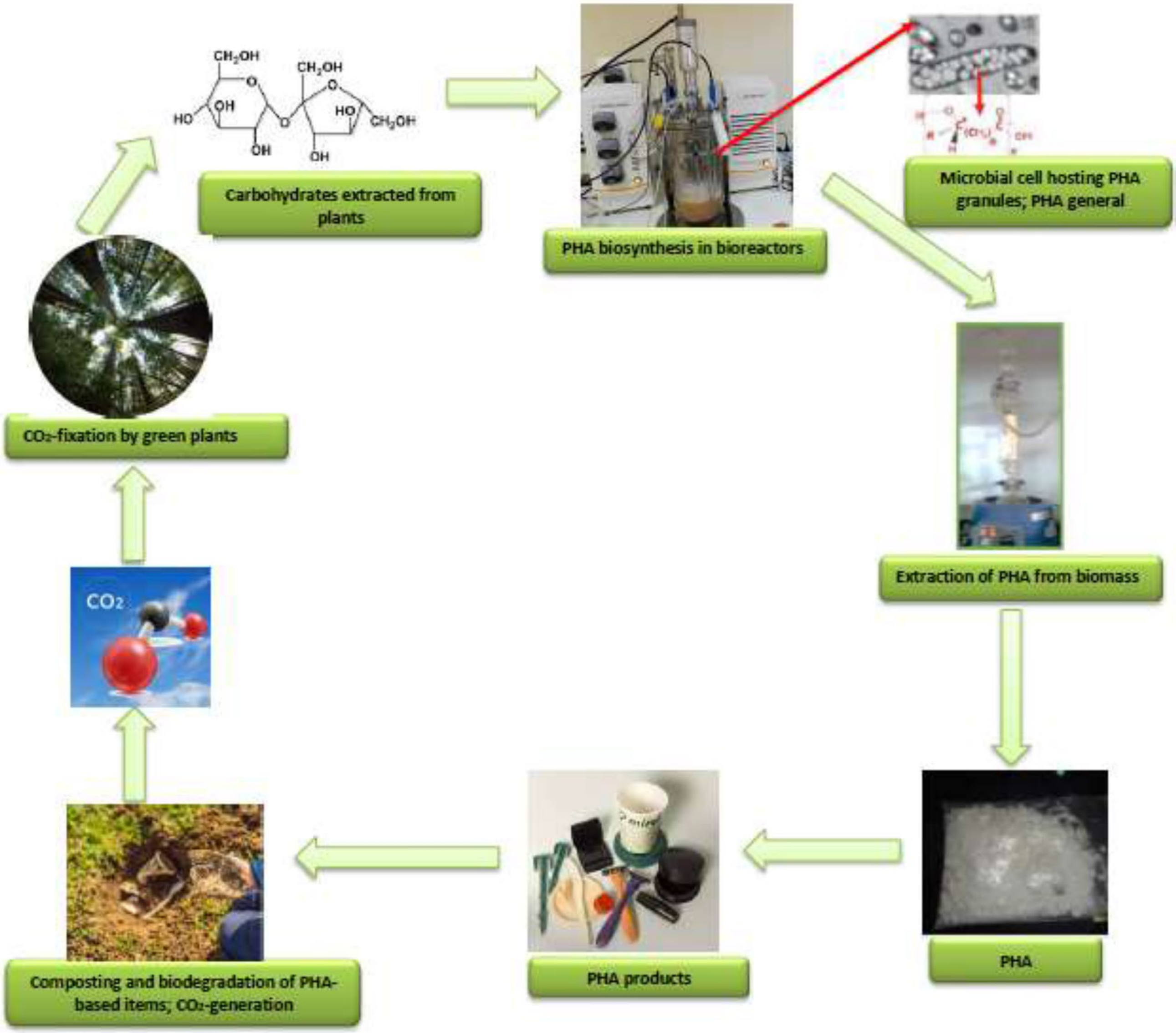


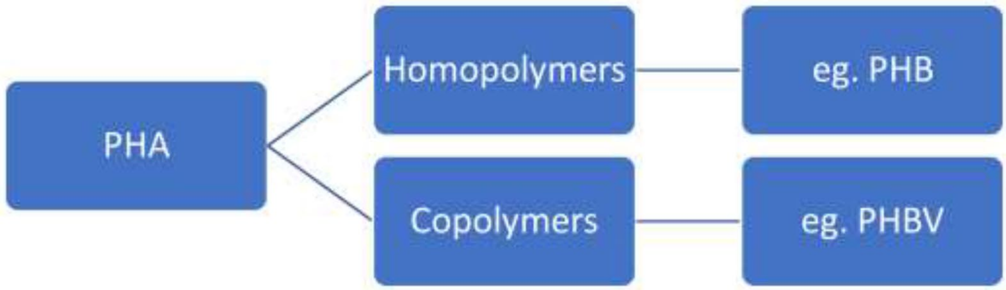
Fig. 2 Cyclic biological process of PHA

to lower crystallinity, less brittleness and more biodegradability as the valerate percentage increases [20, 21].

The PHBV is characterized by its biological origin, low cytotoxicity, piezoelectricity, thermoplasticity, biocompatibility with many types of cells, biodegradability, high absorption capacity, high degree of crystallinity, excellent oxygen barrier properties, high viscosity in a liquid state, chemical inactivity, ultraviolet radiation resistivity, solubility in chlorinated solvents, relatively low melting temperature, but it is still a rigid and relatively brittle polymer, it has low impact resistance, poor thermal stability, and considerable hydrophobicity [22–25].

Although PHB is considered as the major member in the PHA family, the PHBV copolymer-which was later discovered—has exhibited better biocompatibility, and this has made it extensively exploitable for the biomedical and pharmaceutical applications such as drug delivery systems, bone scaffolds, implant coatings and tissue engineering in general [26]. The current market of PHBV is very small compared to that of petroleum based plastic. The major factors that restrict the utilization of PHBV on a wider scale are the expensive highly pure substrates, the discontinuous production in batch or fed-batch; the need to add expensive precursors such as valerate and propionate, the use of toxic solvents throughout downstream clean-up and possible microbial contamination [27].

The ideal and most feasible PHBV version would result from a cheap carbon source [28, 29] used as a substrate to feed highly efficient microbial strains that could produce the polymer with high efficiency [30] and with much reduced



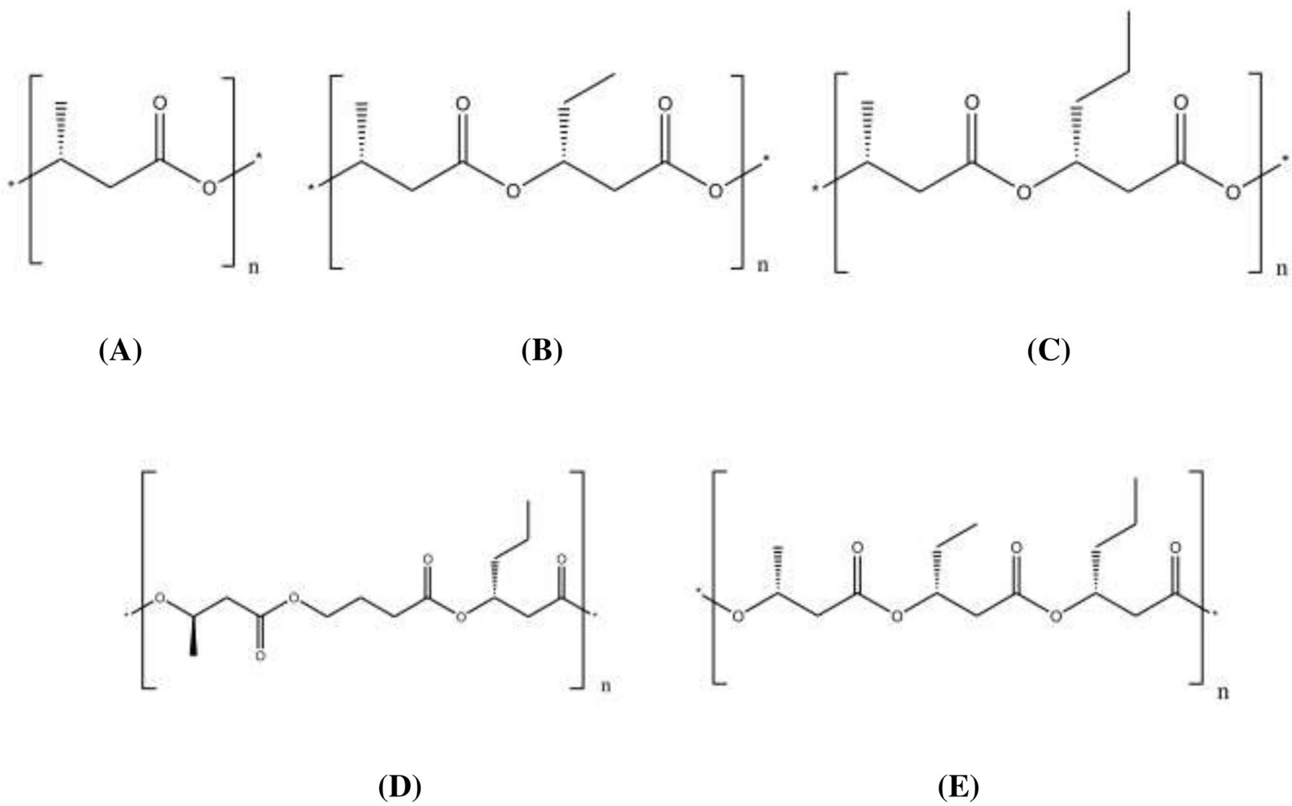


Fig. 3 **a** Poly(3-hydroxybutyrate) (PHB), **b** poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV), **c** poly(3-hydroxybutyrate-*co*-3-hydroxyhexanoate) (PHBHx), **d** poly(3-hydroxybutyrate-*co*-4-hydroxybutyrate-*co*-3-hydroxyhexanoate) (P3HB4HB3HHx), and **e** poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate-*co*-3-hydroxyhexanoate) (P3HB3HV3HHx)

cost in the downstream processing and extraction of the polymer [31]. In fact, these are the major three disciplines of current intensive research to commercialize PHBV on a wide scale.

Imperial Chemical Industries (ICM) was the first to commercialize PHBV in 1990, it has been commercialized in production as shampoo bottles (trademarked as Biopol®) that were available in supermarkets in Europe, but later the patents were sold to Monsanto and further to Metabolix [32].

Regardless of the previously mentioned concerns on PHBV properties and process costs [33], PHBV has been investigated to be exploited in a wide range of very promising applications. In order to overcome the properties issues, much research works have been focused on forming biocomposites where fillers have enhanced or even totally introduced new features [34]. Most of the applications were oriented towards packaging, reinforced materials and biomedical applications including drug delivery, tissue engineering and a few others (Fig. 4).

There have been many reported works to review the scientific progress achieved in the field of PHA family applications and biocomposites, such as their applications in

Fig. 4 PHBV various applications

therapeutics field [35, 36], in tissue engineering and bone scaffolds [37, 38], their copolymers [39] and many others [16, 40, 41]. On the other hand, and despite of the very promising features and huge amount of published research on PHBV biocomposites and their applications, there have been very limited published works compiling, organizing and classifying these achievements and scientific progress in different arenas [34, 42].

PHBV Composites for Packaging Applications

PHBV has been used extensively in packaging applications [43–45]. The well-known antimicrobial properties of zinc oxide (ZnO) and silver nanoparticles (AgNPs) have been introduced into PHBV for food packaging applications [38–48]. For example, zinc oxide has been used with reduced graphene oxide and introduced onto glycerol-plasticized PHBV in different percentages to form hybrid nanocomposites that were melt-extruded for food packaging purposes [49]. Also, zinc oxide alone was used with different sizes (micro and nanoparticle sizes) and different morphologies to reinforce PHBV films. The results showed that in addition to the expected antimicrobial properties of the filler which qualifies it to be used in food packaging, the incorporation of the zinc oxide nanoparticles enhanced the thermal and optical properties of the nanocomposite films [47]. Composite films of PHBV and ZnO nanoparticles were prepared by solvent casting, the optimum percentage of added ZnO was found to be 4 wt%, This ratio showed the highest crystallinity, the best barrier properties in addition to the maximum tensile strength and Young's and storage moduli. The antibacterial tests were also good as expected. The extreme compatibility between the particles and the matrix and the high enhancement on the properties can be attributed to the formed hydrogen bonding [50]. For the purpose of enhancing the antimicrobial and mechanical properties and with the lowest immigration rate to improve the shelf life of poultry items, the leaf extract of *Thymus vulgaris* was used for the fabrication of zinc oxide–silver nanocomposites which were incorporated into PHBV-chitosan. These have shown great antimicrobial activity that suggest them as replacement for the traditional petrochemical-based polymers which are currently in use for food packaging of poultry items [51].

Stabilized silver nanoparticles 0.04 wt% have been incorporated into PHBV to result in a nanocomposite with 56% reduced oxygen permeability compared to neat PHBV, and the produced films had a prolonged—up to 7 months—antimicrobial activity against the prominent food borne pathogens, *Salmonella enterica* and *Listeria monocytogenes*. The outcome results have shown very promising biodegradable composites that could be potential films and coatings in the field of active food packaging [46].

Another study has investigated ternary composites with nanohybrids of silver and cellulose nanocrystals incorporated in PHBV via solution casting, higher silver nanoparticles percentage was associated with better mechanical, overall migration, barrier and antibacterial properties, in addition to better thermal stability. The results of biocompatibility, barrier properties, lower migration levels and the high antibacterial effect of 99.9% suggest that these composites can be promising in food packaging [52].

A nanohybrid combination of cellulose nanocrystals and zinc oxide has been composited in PHBV matrix by simple solution casting, the produced nanocomposites showed excellent antibacterial ratio of 95.2–100% for both bacteria *Escherichia coli* and *Staphylococcus aureus* and exhibited degradation of 9–15% after 1 week. The incorporation of cellulose nanocrystals and zinc oxide showed enhanced hydrophilicity and barrier properties. The nanocomposite of 10 wt% fillers have improved Young's modulus (183.1%), tensile strength (140.2%) and enhanced thermal stability by increasing the maximum decomposition temperature (T_{max}) value by 26.1 °C. The composites have also been investigated in terms of in vitro degradation [53].

Recently, green nanocomposites based on PHBV with cellulose nanocrystals have shown better physical and mechanical properties [54]. Also, biodegradable films of PHBV with cellulose nanocrystals have been prepared by solvent casting method, the nanocomposites with 4 wt% of cellulose nanocrystals showed enhanced barrier properties against oxygen and water vapor suggesting the possible utilization of these nanocomposite films in packaging applications [55].

PHBV reinforced with PHBV-grafted multi-walled carbon nanotubes (PHBV-*g*-MWCNTs) were prepared through a simple solution casting method, the films were transparent in the visible light, and have shown improved thermal stability and mechanical, barrier, and migration properties for the food packaging application [56].

Copper oxide nanoparticles and PHBV were used to form bilayer–structure nanocomposite, the first bottom layer was PHBV with 3% mol of 3-hydroxyvalerate (3 HV) that was compression molded, it was then coated with an electrospun nanofibrous composite mat which is composed of PHBV (18% mol 3 HV) and copper oxide nanoparticles. In this study, considerable virucidal and bactericidal performance was reported against the food-borne pathogens murine norovirus, *S. enterica* and *L. monocytogenes* with low copper oxide loading. The composites were also biodegradable [57].

Paper is considered as the most environmental friendly and economical material for food packaging. Because of the inadequacies in the nature of paper, oil-based polymers have been extensively used as paper coating materials. However, the produced coated paper loses the biodegradability and recyclability properties [58]. Nanocomposites of PHBV were prepared with a commercial montmorillonite Cloisite® 30B (CS30B) and a novel modified clay to be coated on paper, for food packing application. Also the water vapor transmission rates (WVTRs) of the PHBV/nanocomposite-coated papers were measured. Overall, PHBV and its composites coating treatments lowered the WVTR values by up to 118 times. Due to an improved moisture barrier, the resulting coated paper is considered as a promising green-based food packaging material [58]. A similar study has been reported later on (PHBV) where solution intercalation process was applied using two types of organomodified clay minerals. Ring opening polymerization of polyhydroxybutyrate in the presence of Cloisite®30B was applied to synthesize intercalated clay mineral (PHB-C30B), the effect of the intercalated mineral and Cloisite®30B on PHBV films in terms of wettability and moisture absorption was investigated, and expressed as contact angle and water vapor transmission rate (WVTR) of the composites [59].

The modified clay vinyl triethoxy silane grafted Sepiolite has been used to prepare a nanocomposite with PHBV by solvent casting method. Thermal and mechanical properties were improved, and hence the authors suggested that the clay polymer nanocomposite films could be used in the packaging field [60]. Also, nanocomposite films based on PHBV and chemically modified Sepiolite have been developed by solution casting method. Water-barrier properties in addition to thermal and biodegradation tests suggested the possible utilization of these biocomposites in the field of food packaging [61].

Purified alfa micro-cellulose fibers were used as filler to form PHBV biocomposite with enhanced barrier properties for packaging and membrane applications [62]. Another biocomposite was prepared using bamboo fibers by injection molding following extrusion compounding, The tensile modulus of the prepared biocomposites at 40 wt% fiber ratio was improved by 175% compared to neat PHBV [63].

Agricultural by-products of wheat straw, corn straw and soy stalk were composited with PHBV (total of 30 wt% ratio) to improve the tensile and storage modulus of PHBV by maximum of 256% and 308% when it is reinforced with of the agro-residues. Also, for equal amounts of the three biomass fibers (10 wt% ratio each, total 30 wt% ratio), and compared to the corresponding poly propylene composites, the tensile and flexural behavior of PHBV composites showed much higher values. In addition, the impact strength and strain at break have been enhanced by around 35% through alkali treatment of wheat straw fibers [64]. Another study has investigated a composite of wheat straw alone with PHBV for food packaging materials to respiring fresh products [65].

Coconut fibers that are impregnated with oregano essential oil were used to reinforce PHBV and form green composite sheets by compression molding. The biocomposite exhibited bacteriostatic effect against *S. aureus* with even low fibers content 3 wt%. The results suggest that these can be used as vehicles entrapping extracts or compounds and could be applied in the field of shelf life extension by packaging [66].

Lignocellulosic fibers from three different types of agricultural residues have been used as fillers within PHBV to investigate their potential use in packaging, brewing spent grains and olive mills in addition to wheat straw were tested. The results showed that all composites have degraded mechanical properties. The authors concluded that PHBV/wheat straw fibers composites could be promising to reach the requirements of respiring food products, whereas PHBV/olive mills composites would be more suitable for water sensitive products [67].

Natural rubber has also been used to prepare a biocomposite with PHBV by melt blending and found to enhance toughness and flexibility but with a decreased tensile strength, so trimethylolpropane triacrylate (TMPTA) coagent and peroxide were both used to synergistically optimize the mechanical properties. The optimum blend had a notched impact strength of 27.5 J/m, tensile strength of 28.1 MPa, flexural modulus (1% secant modulus) of 8679 MPa and was comparable to polypropylene in terms of sealability and water vapor permeability, in addition it was claimed to be safe for food-contact applications [68].

PHBV Composites for Drug Delivery Applications

PHBV and all PHB copolymers have been widely investigated in the field of drug delivery [69].

In addition to its well established biodegradability and biocompatibility, many other properties have qualified PHBV to be a superior candidate for drug delivery applications, it has more amorphous structure compared to PHB, and that is considered more convenient for drug release because drugs can diffuse easily through the chains of a polymeric amorphous area. Also, as long as PHBV can be highly and easily dissolved in chloroform and dichloromethane while it has poor solubility in other solvents, it can readily form nanoparticles through the emulsification-solvent evaporation method [70]. In addition, PHBV biodegradation is relatively slow and this makes it a potential long term drug release candidate [71]. Very recently, a research work review was published on the utilization of PHBV in the specific field of antitumor applications [42].

Superparamagnetic iron oxide (magnetite) has been encapsulated into PHBV nanoparticles for the purpose of biomedical applications. The results showed that these can be potential nanocarriers for site-specific delivery of drugs and as contrast agents for magnetic resonance imaging, also promoting hyperthermia [72]. In a similar research, iron oxide has been used to prepare PHBV nanocomposite particles that are biodegradable and superparamagnetic for the purpose of magnetically-guided drug delivery systems [73].

Cerium oxide nanoparticles were incorporated into electrospun PHBV membrane for healing applications of diabetic wound. This study has shown that membranes of PHBV with incorporated cerium oxide nanoparticles have great potential to be utilized as wound dressings that enhance cell proliferation and vascularization in addition to promoting the diabetic wounds healing [74].

In another study, bioactive wollastonite and PHBV were prepared as composite microspheres where gentamicin drug was encapsulated into them by the absorption method. This has resulted in microsphere composites with controlled drug release behavior, which could be used as bone filling implantations for bone repair [75].

Hydroxyapatite particles (HA) have been incorporated into microspheres of PHBV and loaded with the osteoporosis preventing drug alendronate. This composite with controlled release behavior can well support the proliferation of mesenchymal stem cells and is a potential candidate for bone repair applications [76].

Using the selective laser sintering technique, the biomolecule bovine serum albumin was loaded into nanocomposite microspheres based on calcium phosphate and PHBV (Ca-P)/PHBV scaffolds. It was suggested that these nanocomposite scaffolds with controlled architecture obtained through selective laser sintering could be incorporated with biomolecules which empowers them with more functions for the purpose of bone tissue engineering application or to qualify them to be used for drugs localized delivery [77].

A composite based on the flavonoid Icariin and PHBV was fabricated and applied onto an anodic oxidized titanium plate as a biodegradable coating for drug delivery. The conclusion is that icariin/PHBV coating can enhance the bioactivity of titanium based orthopedic implants [78, 79].

Highly porous scaffolds of 45S5 Bioglass®-based glass–ceramic were coated with drug loaded solution of PHBV and vancomycin. The coated material enhanced the mechanical properties, the drug releasing profile and other results suggested that the fabricated loaded drug biocomposites represent potential scaffolds candidates for application in bone tissue engineering [80]. In a very similar study by the same author, the PHBV was coated onto the porous 45S5 as microspheres where vancomycin drug was successfully encapsulated, the resultant bioactive composites showed good sustainable prolonged drug-releasing profile [81].

Utilizing matrix assisted pulsed laser evaporation, biodegradable coatings of the silk fibroin and PHBV biocompatible composite were grown on titanium substrates for biomedical uses. The results showed that increasing PHBV content on the expense of silk fibroin leads to slower degradation, slightly lower hydrophilicity and a more stable behavior of the coatings, the authors also infer that the prepared coatings can be potential systems for localized drug delivery where a prolonged delivery profile can be achieved by larger PHBV content [82].

3D fibrous composite scaffolds have been produced via co-electrospinning system of PHBV/poly (ε-caprolactone), diatom shell incorporated pullulan, also, the antibiotic cefuroxime axetil was loaded and its controlled release was investigated. The co-electrospun scaffold showed better osteocompatibility, cell distribution and cell spreading. The authors suggest that these can be promising for bone tissue engineering [83].

PHBV composites membranes reinforced by functionalized cellulose nanocrystal-poly[2-(dimethylamino)ethyl methacrylate] have been processed by electrospinning to form a double stimuli-responsive drug delivery system. The incorporated particles enhanced crystallization, hydrophilic and thermal properties of PHBV and resulted in an intelligent and long sustained drug release system [84].

Nanoprecipitation method was used to prepare drug-loaded PEGylated PHBV and PHB nanoparticles as drug delivery systems with epirubicin as the model drug, a longer sustained release profile of 8 days was found at pH 4 compared to pH 7. The tests showed that the antibacterial properties against *E. coli*, *Pseudomonas aeruginosa* and *S. aureus* bacteria were significant compared to the free drug of equivalent amount [85].

In an attempt to overcome the undesirable and adverse systemic toxic effects of the lung anticancer drug sunitinib, it has been loaded on PHBV nanoparticles, and the tests showed that it kept its pharmacological activity. The authors conclude that this formulated inhalable powder could represent a potential biocomposite of local therapy medication for lung cancer [86].

In order to accomplish a dual drug delivery carrier as a novel composite hydrogel, PHBV microparticles encapsulating mupirocin and ketoprofen were prepared and embedded in a physically crosslinked (κ-carrageenan/locust bean gum) hydrogel. The composite has also been tested in terms of biocompatibility, and the overall results qualify this hydrogel to be a potential biomaterial composite for dual drug delivery, mostly for applications of wound healing [87].

In another attempt to develop a double drug delivery system for cancer therapy, nanoparticles of PHBV/lactic-*co*-glycolic acid were loaded with both 5-fluorouracil and oxaliplatin to achieve co-delivery of both drugs. It was shown that the co-loaded nanoparticles exhibited much higher antitumor efficiency in comparison to the free drugs together [88].

A double-emulsion high-speed technique was used to obtain PHBV nanoparticles loaded with the anti-inflammatory, antimicrobial and antiviral quercetin, the encapsulation efficiency was found to be 51%, the nanoparticles showed biocompatibility with fast release of the drug (most of the drug released in 5 h) when immersed in water [89].

Nano diamond and nano hydroxyapatite particles were used in PHBV to prepare biocomposites loaded with vancomycin drug by injection molding. The nanofillers enhanced the flexural elastic modulus by 34% that became similar to natural bone, and the composites showed a prolonged sustained release of the vancomycin. In addition, in vitro assays exhibited a good adhesion and growth of cells expressing good biocompatibility and bioactivity, these results show the potential of these composites to be used as bone defect filling material [90].

Hydrocortisone was encapsulated in PHBV nanoparticles that were prepared by emulsification–solvent evaporation, and the resultant drug delivery system was suggested for topical ophthalmic administration. The ocular toxicity profile showed that new system is neither irritating nor producing any alteration in the permeability and in the transparency of the cornea. Additionally, no cytotoxicity on bovine keratocytes has been reported. The results suggest that this drug delivery system could be a good option for topical ophthalmic administration of drugs [91].

The anticancer drug docetaxel has been loaded into drug delivery systems of polymeric nanoparticles based on PHBV and vitamin E polyethylene glycol succinate (PHBV–TPGS), and these have been prepared by a modified emulsification solvent evaporation method. The in vitro cytotoxicity tests and other results suggested that these systems are effective in enveloping and chaperoning to the site of action, they have also exhibited sustained and controlled release of the drug and hence reducing drug dose and toxicity [92].

PHBV Composites for Tissue Engineering and Other Biomedical Applications

PHBV has shown great potential in many biomedical applications including biodegradable implants, biosensors, tissue patches, cartilage repair scaffolds, porous scaffolds for bone repair and engineering purposes [93–95], absorbable surgical sutures, medical packaging [96] and cardiovascular stents [97] and others.

Tissue Engineering

A research has been conducted on PHBV with different valerate molar percentages (0, 8, 12 and 24%) where hydroxyapatite nanoparticles were used as nanofillers in the polymer matrix. Clearly, one of the resultant composites, namely the P(HB-*co*-8% HV)/HA (30% w/w) has shown mechanical strength in compression of 62 MPa, which is about the same of several human bones and so it is promising as a biomaterial for use in fixing some bone fractures. Moreover, this composition has shown the highest modulus among other different composites [98]. In order to enhance the tissue compatibility of the PHBV/HA composites for application in tissue engineering, collagen was immobilized on the surface of the porous scaffolds [99]. In another study PHBV was blended with poly lactic acid (PLA) and the blend was 3D-printed as a potential candidate for biocompatible material applications. Also, the 3D printed specimens have exhibited good biocompatibility with human embryonic kidney 293 (HEK293) cells, indicating real promise as biological scaffolds for tissue engineering [100].

A comparison have been accomplished between single and multi-walled carbon nanotubes in a composite with PHBV; (SWCNTs)/PHBV and (MWCNTs)/PHBV composites for biocompatibility and osteoinductivity. The composites were implanted in bone defects of rat femoral. The results showed that there were no observed differences between MWCNTs and SWCNTs in PHBV reinforcement, though MWCNTs/PHBV composites exhibited better biocompatibility and osteoinductivity both in vivo and in vitro [101].

Nanocomposites of hydroxyapatite nanoparticles and PHBV were fabricated with controlled pore architectures and high porosity. The authors suggest that these nanocomposite scaffolds may serve as a promising 3D substrates for bone tissue engineering [102]. Another more recent research paper reported the fabrication of nanofibrous scaffolds based on PHBV and hydroxyapatite nanoparticles. The produced composites were tested for bioactivity and biocompatibility and suggested accordingly to be used for bone tissue engineering [103]. In another study, biocomposites coatings of PHBV, calcium phosphate, β-tricalcium phosphate and hydroxyapatite were synthesized by matrix assisted pulsed laser evaporation. The purpose was to investigate the prepared biocomposites for bone tissue engineering applications. The wettability and interaction with mesenchymal cells confirmed the suitability of some of the prepared composites for biomedical applications [104].

Another composite was fabricated for the purpose of bone tissue engineering, and this time it was based on integrating β-Ca_2SiO_4 nanoparticles with PHBV to produce scaffolds with high porosity and interconnected porous structure. The results of cells adhesion and proliferation indicated that the synthesized materials could be potential composites for application in bone tissue engineering [105].

In another interesting study, fibrous scaffolds of silk fibroin, PHBV and reinforced with hydroxyapatite nanoparticles were prepared by electrospinning method to mimic bone tissue structure. The fibrous nanocomposite membranes supported bone-like apatite crystal growth after 28 days, and also supported cell attachment, hence proving their bioactivity and biocompatibility, respectively [106]. In another later research, PHBV nanofiber mats have been modified by silk fibroin and plasma treatment. The treated PHBV-silk fibroin mats showed high hydrophilicity, cell proliferation and cell viability which support their utilization in the field of bone tissue engineering [107].

Bredigite ($Ca_7MgSi_4O_{16}$), hydroxyapatite and mixture of both nanoparticles have been prepared by sol–gel method, and then used to reinforce PHBV fibers in an electrospinning process. The research concluded that incorporating 10% of mixture nanoparticles into the PHBV nanofibers has led to enhance the mechanical properties with high ability for apatite formation, and thus producing a promising candidate material for bone regeneration application [108]. In another study, bredigite nanoparticles were used alone to reinforce PHBV and produce nanofibers through electrospinning technique. The composite scaffolds had improved Young's modulus and tensile strength compared to PHBV alone, they have also shown good bioactivity and biocompatibility, the results altogether suggest that these scaffolds can be potential materials candidates for bone tissue engineering [109].

For the purpose of application in bone repairing, pearl powder was mixed with PHBV and the resultant composites have been processed by electrospinning. The naturally nontoxic pearl powder acted as crystal nucleus for the deposition of HA particles. Cells activity and biocompatibility have been enhanced by introducing pearl powder, and the resultant material was considered as a potential osteoconductive composite [110].

In a simple solution blending method, tungsten disulphide inorganic nanotubes were composited with PHBV.

The composites had better thermal stability than that of PHBV, and a highly efficient nucleating effect for tungsten disulphide inorganic nanotubes was observed. The authors claim that the results qualify these composites for applications in packaging and biomedical fields like bone tissue engineering [111].

Electrospun nanofibrous scaffolds based on different compositions of PHBV, chitosan and hydroxyapatite were produced with different fibers diameters, the researchers concluded that chitosan and hydroxyapatite played a synergistic effect that promoted the regeneration of bone tissue, and hence making these scaffolds as potential biomaterials for the proposed application [112].

3D-printed scaffolds of PHBV/calcium sulfate hemihydrate were fabricated by fused deposition modelling and coated with chitosan hydrogel. In vivo investigation of the scaffolds suggested that these materials can effectively promote new bone formation and hence proposing them as potential products for bone defects repair [113].

For the purpose of engineering new biomaterials that can be used in orthopedic devices in the field of joint replacement, collagen immobilized PHBV film loaded with bovine serum albumin capped silver nanoparticles has been formulated, the target was to promote or retain cell viability and still inhibit bacterial growth. The antimicrobial tests showed that the film has a wide effect against *S. aureus*, *E. coli* and *P. aeruginosa* with low concentration compared to sulfamethoxazole trimethoprim and gentamicin, and still the released silver containing particles have no impact on cells viability [114, 115].

Another biodegradable and biocompatible composite based on PHBV, strontium carbonate nanoparticles and platelet-rich plasma was fabricated for the purpose of bone tissue engineering. The preliminary results indicated that the fabricated electrospun biocomposite scaffold could be used for bone regeneration [116].

PEGylated and acetylated cellulose nanocrystals have been incorporated into PHBV with 3 wt% ratio to furnish super hydrophilic scaffolds with improved water uptake and compressive modulus qualifying them for tissue engineering applications [117].

Nano diamond and nano hydroxyapatite particles were used in PHBV to prepare biocomposites loaded with vancomycin drug by injection molding. The nanofillers enhanced the flexural elastic modulus by 34% that became similar to natural bone, and the composites showed a prolonged sustained release of the vancomycin. In addition, in vitro assays exhibited a good adhesion and growth of cells expressing good biocompatibility and bioactivity, these results show the potential of these composites to be used as bone defect filling material [90].

Matrices of PHBV were produced to create a cartilage by tissue engineering. The authors showed that PHBV matrices had good healing response, which was effective in cartilage regeneration and hence have great potential to be used in the repair of joint cartilage defects [118].

PHBV nanofibrous coatings were obtained by electrospinning onto sintered 45S5 Bioglass®-based glass–ceramic pellets, the coatings can be used to tailor the surface topography of bioactive glass–ceramics for applications such as scaffolds in tissue engineering [119]. In addition, highly porous scaffolds of 45S5 Bioglass® -based glass–ceramic were coated with drug loaded solution of PHBV and vancomycin. The PHBV coating enhanced the mechanical properties, also the drug releasing profile and other results suggested that the fabricated loaded drug biocomposites represent potential scaffolds candidates for application in bone tissue engineering [80].

For the purpose of application in cartilage tissue engineering, PHBV was composited with calcium silicate and tested through in vitro experiments of scaffold-cell interactions and observation of in vivo cartilage formation. The results suggested that PHBV/calcium silicate scaffolds can be more applicable for cartilage tissue engineering than neat PHBV scaffolds [120]. Also, PHBV with silicate containing hydroxyapatite have been electrospun to produce promising scaffolds for bone tissue engineering [121].

In the field of nucleus pulposus tissue engineering, PHBV, chitosan and chondroitin sulfate nanoparticles were prepared in a composite hydrogel for which the water uptake ability and viscoelastic properties were similar to native tissue. After testing the material in terms of mechanical and bioactivity properties, the authors concluded that these composites represent great potential for the targeted application [122].

Utilizing selective laser sintering, three-dimensional nanocomposite scaffolds based on calcium phosphate/PHBV were successfully fabricated. The in vitro studies have revealed that human osteoblast-like cell line (SaOS-2) had normal morphology and phenotype in addition to high cell viability after 3 and 7 days culture. Also, a significant improvement on alkaline phosphatase activity and cell proliferation was observed. Similarly, the biomolecule bovine serum albumin was loaded into nanocomposite microspheres using selective laser sintering technology. It was suggested that these nanocomposite scaffolds could be incorporated with biomolecules which empower them with more functions for the purpose of bone tissue engineering application or to qualify them to be used for drugs localized delivery [77, 123].

3D fibrous composite scaffolds have been produced via co-electrospinning system of PHBV/poly (ε-caprolactone) and diatom shell incorporated pullulan. Also the antibiotic cefuroxime axetil was loaded on the system and its controlled release was investigated. The co-electrospun scaffold showed better osteocompatibility, cell distribution and cell spreading. The authors suggest that these can be promising for bone tissue engineering [83].

Nanodiamond particles were embedded into molybdenum disulfide nanosheets, then the constructed co-dispersion nanostructures were incorporated into PHBV bone scaffolds, which were fabricated by selective laser sintering. Compared to pure PHBV, the resultant scaffold exhibited 52% enhancement on compressive strength and 94% on tensile strength, also good positive viability for cell proliferation, cytocompatibility for cell adhesion, spreading and growth were observed [124].

Other Biomedical Application

PHBV has also been grafted with maleic anhydride (PHA-*g*-MA) and then carboxylated multi-walled carbon nanotubes (MWCNTs-COOH) were dispersed to form a composite with enhanced thermal and mechanical properties. The study has shown considerable enhancements in the mechanical and thermal properties of the PHA-*g*-MA/MWCNTs-COOH composites compared with PHBV, the authors have explained this through the formation of ester carbonyl groups through the reaction between MWCNTs-COOH and the MA groups of PHA-*g*-MA [125]. The same authors have also done the same grafted copolymer but with hyaluronic (H) instead of MWCNTs, and they have investigated the produced films for biocompatibility, the conclusion was that PHBV/H or PHA-*g*-MA/H can form potential membranes for biomedical applications [126].

A solvent casting method was used to prepare a ternary composite of PHBV, nano magnesium calcium phosphate and zein. The produced ternary composites showed enhanced hydrophilicity, bioactivity and in vitro degradability that qualify them to the next level for biomedical applications [127].

PHBV functionalized graphite oxide was fabricated via freeze drying method, and then Fe_3O_4 nanoparticles have been loaded to form thermally and mechanically stable, bioimaging Fe_3O_4/graphite oxide-grafted-PHBV composites films. The composite films were found to exhibit more efficiency against gram-negative bacteria strains than to gram-positive strains. Also, the tests of adhesion and proliferation of the cells suggested their biocompatibility [128].

In a comparative study, carbon nanofibers and graphene oxide nano sheets have been used in PHBV in order to qualify the effects of these fillers on PHBV in terms of mechanical, thermal, bioactivity, and biocompatibility properties for the purpose of accelerating these materials in biomedical applications. Though both composites have shown promising results to be utilized in biomedical application, it is the composite containing graphene oxide nano sheets that showed higher cell adhesion, proliferative activity against time and antibacterial activity [129].

Curcumin loaded PHBV nanofibers have also been fabricated and suggested in wound-healing applications [130].

Fish scales have been utilized to prepare composites both in PHBV and maleic anhydride grafted PHBV. Cytocompatibility, antimicrobial and antioxidant properties of the two composites demonstrate their potential to be used in biomedical applications [131].

A composite multilayer scaffold based on PHBV and other materials was fabricated and tested on rabbits as a meniscal scaffold that has shown histological and biomechanical results which were comparable to polyurethane scaffolds [132].

Sheet-like cellulose nanocrystal–ZnO nanohybrid was developed by one-step hydrothermal method. The nanohybrids—being antibacterial agents and UV absorbers—were introduced into PHBV by electrospinning. The incorporation of the nanohybrids greatly enhanced PHBV crystallization ability, thermal stability, excellent antimicrobial ratios of *S. aureus* and *E. coli*. Also, nanofiberous composites with 9 wt% cellulose nanocrystal–ZnO have blocked out most of the UV irradiations for both UVA (99.72%) and UVB (99.95%) with high ultraviolet protection factor (UPF) value of 1674.9. The fibrous composites have shown potential to be applied in wound dressings and other functional biomaterials [133].

Magnetic PHBV microspheres of less than 1 μm size have been prepared by incorporating superparamagnetic iron oxide nanoparticle in PHBV via emulsion–solvent extraction/evaporation method. The tests results suggest the suitability of the fabricated microspheres for biomedical applications [134, 135].

Silver nanoparticles have been loaded onto PHBV nanofibers to study in vitro cell compatibility and in vitro antibacterial activity. The PHBV nano fibrous scaffolds with nanoparticles less than 1.0 wt% showed not only good in vitro cell compatibility but also good antibacterial activity. The research suggested that PHBV nano fibrous scaffolds with silver nanoparticles of less than 1.0 wt% have a potential to be used in joint arthroplasty [136].

Also, and for the purpose of wound covering mats, electrospinning process was used to fabricate nanofibrous scaffolds of PHBV with embedded graphene oxide and collagen. Graphene oxide was shown to increase the antibacterial activity against *S. aureus* and *E. coli*, decrease the pore size and hydrophilicity and enhance mechanical strength. On the other side, collagen addition enhanced hydrophilicity and cell proliferation but without affecting porosity and mechanical strength significantly [137].

Acid treated MWCNTs were also used in PHBV to produce composites with the crystallization temperature, heat of crystallization, and thermal stability of the composites increase. Consequently, the mechanical properties of the composites have been substantially improved. The composites become hydrophilic and have no obvious toxicity to the murine fibroblast L929 cells when the content of A-MWCNTs is below 1.5 wt% [138]. Table 1 summarizes the applications of different PHBV-based composites with desired properties.

Reinforced Materials of PHBV-Based Composites

High-performance materials and biocomposites made of, or reinforced with natural sources are increasing worldwide [139].

Table 1 Applications of PHBV-based composites with desired properties

PHBV composites	Type of fibers/fillers	Desired properties	Applications	References
PHBV/ZnO	Inorganic	Antibacterial, thermal and optical properties	Packaging	[47]
PHBV/silver and cellulose nanocrystals	Nanohybrids	Biocompatibility, biodegradability, lower immigration rate, high barrier properties	Packaging	[52]
PHBV-grafted multi-walled carbon nanotubes	Natural	Thermal stability and mechanical, optical transparency or opacity barrier, and migration properties	Food packaging	[56]
PHBV/clay vinyl triethoxy silane grafted Sepiolite	Inorganic	Thermal and mechanical properties	Food packaging	[60]
PHBV/wheat straw, corn straw and soy stalk	Natural	Mechanical properties (tensile and storage modulus)		[64]
PHBV/natural rubber	Natural	Mechanical properties (toughness and flexibility)	Food packaging	[68]
PHBV/superparamagnetic iron oxide	Inorganic	Biodegradability, magnetically-guided drug delivery and biocompatibility	Drug delivery	[72, 73]
PHBV/flavonoid Icariin	Natural	Enhance the bioactivity of orthopedic implants	Drug delivery	[78, 79]
PHBV/cellulose nanocrystal-poly[2-(dimethylamino)ethyl methacrylate]	Natural	Crystallization, hydrophilic and thermal properties	Drug delivery	[77]
PHBV/cerium oxide nanoparticles	Inorganic	Enhance cell proliferation and vascularization	Healing of diabetic wound	[67]
PHBV/hydroxyapatite particles	Inorganic	Proliferation of mesenchymal stem cells	Bone repair	[76]
PHBV/nano diamond and hydroxyapatite	Nanohybrids	Biocompatibility and bioactivity	Bone filling material	[90]
PHBV/hydroxyapatite nanoparticles	Inorganic	Biodegradability, biocompatibility mechanical strength	Tissue engineering	[98, 99, 102–104]
PHBV/ multi- walled carbon nanotubes	Natural	Biocompatibility and osteoinductivity	Tissue engineering	[101]
PHBV/β-Ca_2SiO_4	Inorganic	Porosity, cells adhesion and proliferation	Tissue engineering	[105]
PHBV/silk fibroin	Nanohybrids	High hydrophilicity, cell proliferation and cell viability	Tissue engineering	[107]
PHBV/bredigite	Inorganic	Biocompatibility, bioactivity and mechanical properties	Tissue engineering	[108, 109]
PHBV/bovine serum albumin and silver nanoparticles	Nanohybrids	Antibacterial	Joint replacement	[114, 115]
PHBV/PEGylated and acetylated cellulose	Natural	Water uptake and compressive modulus	Tissue engineering	[117]
PHBV/chitosan and chondroitin sulfate	Natural	Mechanical properties and bioactivity	Tissue engineering	[122]
PHBV/poly (ε-caprolactone) and diatom shell incorporated pullulan	Nanohybrids	Osteocompatibility, cell distribution and cell spreading	Tissue engineering	[83]

Reinforcement with Natural Fibers

PHBV has been successfully compounded with natural fibers of *Posidonia oceanica* to form biocomposites for which processability by extrusion, mechanical properties and potential biodegradability have been assessed in a natural marine environment. The produced composite with 30 wt% of the natural fibers has shown enhanced mechanical properties and excellent biodegradation profile within less than six months, so the authors suggested that the developed composites can be suitable to manufacture items to be used in marine environments, for example, in natural engineering interventions [140, 141].

Agave fibers were another type of natural materials which were utilized to prepare composites with PHBV, the resultant biocomposites have shown positive results on modulie reinforcements and toughening of this relatively brittle polymer [142]. PHBV was also prepared in a composite with abaca fibers and they have enhanced its biodegradability when evaluated through the soil-burial test [143].

Both mercerization (i.e., alkali-treatment) and silane-treatment, separately and together, were performed on the coir fibers. This pretreatment has been performed for the purpose of enhancing the interfacial adhesion between the coir fiber and the PHBV polymer matrix and hence increasing the effectiveness of coir fibers as reinforcement. The composites were prepared by microcellular and conventional injection-molding processes. The addition of coir fibers has improved mechanical properties such as strain-at-break and specific toughness. Also, PHBV treated fibers composites showed high degree of crystallinity compared to the untreated fibers composites [144].Utilizing twin-screw extrusion and injection process, PHBV has been reinforced with varying amounts of curauá fibers, the composites had slightly enhanced mechanical properties though there was poor adhesion between the matrix and fiber [145]. Unidirectional Alfa fibers were investigated as mechanical reinforcements to PHBV. The modeling study was performed to compare real life mechanical properties to that expected by modeling [146].

Sisal fibers and clay particles were used in composites with PHBV for the purpose of enhancing mechanical and thermal properties which were slightly enhanced for some selected compositions [147]. Green biocomposites based on flax fibers treated with alginic acid and PHBV were investigated for biodegradability under composting conditions as per ASTM D5338. The study concludes that introducing flax fibers (treated and untreated) into PHBV offers enhanced biodegradation to the green composites [148].

In another study PHBV was reinforced with natural fiber textile, and the mechanical properties in addition to creep behavior have been studied. The study also showed that the reinforced bio-based composites under investigation have similar mechanical properties to many conventional construction materials [149]. Biodegradable films based on acetylated chitin nanocrystals and PHBV matrix were evaluated in terms of mechanical and thermal properties.

Both Young's modulus and tensile strength have improved by 67 and 44%, respectively, when 5% of the acetylated nanocrystals were incorporated into the PHBV matrix [150].

Reinforcement with Agricultural Waste

For the purpose of producing biocomposites of PHBV with improved biodegradability, and to utilize agricultural waste materials, different types of olive pomace have been used as fillers to form biocomposites that were investigated for biodegradability compared to neat PHBV. All types of the pomace have contributed positively to enhance the biodegradation of the PHBV. In fact, less than 90 days were sufficient for all types of the prepared composites to completely biodegrade in a standardized soil environment, while it took neat PHBV 123 days to achieve 91% degradation under the same conditions [151]. Also, biocomposites with added value were fabricated from PHBV using three types of agricultural fibers which are considered as regionally significant food crop residues, namely solid stem wheat, hollow stem wheat and barley [152]. Extruded composites based on PHBV, oil palm empty fruit bunch and a fertilizer were prepared as biodegradable plastic fertilizer with slow release [153]. Spent coffee bean powder was also used as filler in PHBV matrix to form green biocomposites by simple solution casting, the authors claim that those had comparable tensile and thermal properties like polypropylene and polyethylene and hence they are suggesting these composites as a better alternative due to their biodegradability and sustainability [154]. Olive husk flour (20 wt%) has been used after being surface-modified by trimethoxyoctadecylsilane to be incorporated into PHBV to form biocomposites that show higher thermal stability, crystalline index and better tensile properties [155].

Reinforcement with Wood-Derived Materials

Green composites fabricated from maple wood fiber and PHBV by extrusion–injection molding process have shown enhanced tensile and flexural modulus compared to neat PHBV. The heat deflection temperature was increased while coefficient of linear thermal expansion was reduced [156]. In another extrusion injection molding process, a natural composite was fabricated based on the lignocellulosic filler oak wood flour and PHBV. The fiber–matrix compatibilization techniques have been investigated [157]. For the purpose of developing knowledge on the linkage between mechanical properties and the micro scale structure, and to understand the long-term indoor stability and material properties of the biocomposite, composites of pine wood flour and PHBV modified by boron nitride (BN), and an inorganic filler, talc, were prepared [158]. Also, composites that are composed of wood and PHBV have been fabricated with different extrusion processing parameters and conditions in order to investigate the effect of processing conditions on the tensile strength and mechanical performance of the prepared composite [159, 160]. In another research, hybrid composite of PHBV with natural wood fibers and talc were fabricated via the extrusion–injection molding, improvement on mechanical and thermal properties were noticed in a synergistic fashion [161].

Reinforcement with Cellulose-Derived Materials

PHBV was compounded with man-made cellulose, jute and abaca fibers, the incorporation of fibers increased the tensile stiffness and strength significantly; enhancements in impact and tensile strength by the man-made cellulose fibers have been achieved [162]. Cellulose nanowhiskers were aligned in PHBV matrix utilizing an external electric field. The aligned composites showed substantial mechanical anisotropy [163]. PHBV has been grafted onto cellulose nanocrystals using toluene isocyanate as a coupling agent. Compared to neat PHBV, the decomposition temperature increased by 48.5 °C and the crystallinity has slightly decreased, also compared to cellulose nanocrystals contact angle of 30°, the formed graft has a contact angle of 58° indicating the expected decreased hydrophilicity [164]. While greater thermal degradation and inhibition of the foaming behavior have resulted from the incorporation of nanofibrillated cellulose fiber into the PHBV, the tensile modulus of the nanocomposite almost doubled and the storage modulus above the glass transition temperature has increased [165]. PHBV has also used in a ternary composite with PLA and cellulose in order to have 100% biodegradability, the effect of ball-milling the cellulose pulp fibers was investigated [166]. Recently, nanocomposites of PHBV with cellulose nanocrystals (CNCs) have been prepared and processed in different methodologies. The tensile strength improvement (by 13%) was observed only in the case of the peroxide-aided extrusion [167].

In a recent research, cellulose nanocrystals and cellulose nanofibers were both used as hybrid fillers in PHBV and prepared by melt compounding, different mixtures have been prepared and investigated in terms of thermal, mechanical and crystallization properties [168].

Reinforcement with Clay and Silicate Minerals

PHBV has been prepared in a composite with organoclays nanoparticles by twin-screw extrusion, then the mixture was processed by a continuous extrusion process that was assisted by continuous supercritical carbon dioxide (sc-CO_2). This has resulted in nanobiocomposite foams with higher porosity up to 50% and better homogeneity [169].

Nanocomposite of organophilic montmorillonite with PHBV was synthesized and found to have reduced PHBV crystallinity, melting point and biodegradability, while increased the processing temperature as the organophilic montmorillonite increased [170].

Utilizing twin screw extrusion process, hydrophilic fumed silica nanoparticles has been composited with PHBV in order to enhance its thermal properties. Introducing silica nanoparticles into the PHBV with 5% ratio has increased the onset and inflection temperature of its thermal degradation while it has either minimal or negative influence on the mechanical properties [171].

Natural and organosilanes-modified halloysite nanotube fillers were used with 3 wt% to fabricate nanocomposites with PHBV by melt processing in a twin screw co-rotating extruder. Lower viscosity and lower degradation temperatures of the biopolymer have resulted in the presence of aminosilane-modified halloysite nanotube [172].

Another two types of nanoparticles were used to synthesize composites of PHBV, these are tubular like clay, halloysite (HNT), and organomodified montmorillonite cloisite 30B (C-30B), that resulted in an increase in Young's modulus, a higher melting point only in case of halloysite, and a decrease of impact strength and strain at break in the case of montmorillonite and cloisite 30B [173, 174]. In another study, morphology, thermal and barrier properties of PHBV-organomodified montmorillonite prepared by melt intercalation were investigated [175]. In another very similar study the clays montmorillonite and halloysite nanoparticles were modified with (3-aminopropyl) triethoxysilane. The study concluded that both PHBV nanocomposites utilizing unmodified or modified montmorillonite have similar or improved mechanical and thermal properties, while it wasn't the case when organically modified halloysite nanofiller was used where it presented a general decrease in the properties compared to neat PHBV [176].

Other PHBV Composites and Applications

In a study to immobilize the enzyme acetylcholinesterase on a biopolymer, and among the three tested biopolymers [i.e. polylactic acid (PLA), polycaprolactone (PCL), and PHBV], PHBV was selected as the best support to immobilize the enzyme by cross-linking method. The ultimate purpose was to fabricate a biosystem that can detect organophosphate compounds based on optical bioassay as these pesticides inhibit the immobilized enzyme, and this in turn can be detected by Ellman colorimetric method. The developed bioassay has shown promising results in detecting organophosphate compounds down to detection limit of 10 part per billion, ppb [177].

A book-shaped triboelectric nanogenerator was fabricated by electrospinning fibers of PHBV and polyvinylidene fluoride, the purpose was to furnish a nanodevice that can harvest energy from various ambient mechanical motions and vibrations.

Being a direct power source, it was used to drive small electronics such as LED bulbs [178]. Also, cellulose nano crystals have been incorporated into a matrix of PHBV that was grafted with glycidyl methacrylate but the resultant nanocomposite has little increase in strength properties [179].

For the purpose of developing a delivery system for agricultural applications, PHBV has been fabricated as cylindrical pellets by extrusion to encapsulate dicyandiamide (a stabilizer for nitrogen fertilizers) and it is shown that PHBV could make a long-term slow release system for the nitrification inhibitor through an effective biodegradable matrix [180]. In another research, biochar has been used to accelerate the biodegradation of composites of PHBV with silver nanoparticles [181].

Extruded cast PHBV films mechanical and barrier properties have been studied after incorporating different plasticizers [182]. The study has shown that polyethylene glycol and triethyl citrate gave promising results on the enhancement of mechanical, thermal and permeative properties. In another research, carbon Fibers have been introduced into PHBV and the biocomposite have been extruded before injection moulding, and this has highly enhanced its mechanical and thermal properties [183].

Nanocomposites of PHBV/cellulose nanocrystal–graphene oxide nanohybrids were prepared through a simple solution casting method. The synergistic effect of cellulose nanocrystal and graphene oxide nanohybrids obtained by chemical grafting (nanocrystal–graphene oxide, covalent bonds) and physical blending (nanocrystal–graphene oxide, noncovalent bonds) on the physicochemical properties of PHBV nanocomposites was evaluated and the results compared with a single component nanofiller (nanocrystal or graphene oxide) in binary nanocomposites. Ternary nanocomposites—compared to bare PHBV and binary nanocomposites—displayed the highest thermal stability and mechanical properties. The ternary nanocomposites with 1 wt% covalent bonded nanocrystal–graphene oxide exhibited good antibacterial activity, excellent barrier properties and lower migration level [184].

A nanofibrous film from PHBV was fabricated by electrospinning and composited with hydroxyapatite which resulted in an extremely hydrophilic surface and enhanced biodegradability [185]. Also, carbon nanofibers and nanotubes have been used to enhance the thermal, conductivity, mechanical and gas barrier properties of PHBV [186].

Additionally, electrospinning method was used to produce nanofibers based on a composite of zinc oxide nanoparticles in PHBV, and it was shown that the addition of zinc oxide nanoparticles had decreased crystallinity and crystallization rate of the polymer [187].

PHBV was modified to have acyl chloride end groups and then grafted to the surface of chitin nanocrystals, as a result, the melting point of PHBV was increased and the crystallization was suppressed [188]. In another study, the biodegradability of PHBV hasn't changed much, though the mechanical properties has indeed improved by reinforcing the polymer with up to 5% organo-modified Mg–Al layered double hydroxide [189]. Also, hydroxyapatite crystals, both surface-treated and untreated—were incorporated into PHBV via melt extrusion process, the micromechanical models were used to correlate with experimental values [190].

A comparative study between cellulose nanoparticles and aluminum oxide as nano reinforcement fillers in PHBV matrix has been conducted, the study concludes that cellulose nanocrystals are better nano reinforcements than aluminum oxide nanoparticles [54]. Another research showed that boron nitride nanoparticles were incorporated into PHBV to form nanocomposites which have been investigated in terms of oxygen-barrier performance as a function of nanoparticle content and temperature. Oxygen-barrier properties have decreased with nanoparticles addition and increased with temperature, also the thermal stability of the composites has increased compared to neat PHBV [191].

Composite fibers of PHBV and tungsten disulfide were fabricated by melt reactive processing with dicumyl peroxide used as initiator. The fibers showed improved mechanical properties, a rapid crystallization rate and a higher nucleation temperature. Also, the tensile strength and elongation at break of the fibers were up to 189.8 MPa and 46.5%, respectively [192]. Ethylene-*co*-vinyl acetate was blended with PHBV, and [57] fullerene (C_{60}) was added as a filler with small amounts to form a nanocomposite with improved thermal properties [193].

Conclusion

PHAs are considered as the most readily biodegradable polymer, among many in literature, in both aerobic and anaerobic environments. PHBV is one of the most studied members of the PHAs family, with numerous applications. In this review PHBV based composites were well studied and found more suitable than neat PHBV as biomaterials for various applications. The limitations in PHBV properties that restricted its wide utilization have been overcome by the incorporation of many types of fillers, (i) natural fibers, (ii) agricultural waste, (iii) wood-derived materials, (iv) cellulose-derived materials, (v) clay, silicate minerals and others. The incorporation of bio-origin fibers and fillers can accelerate the rate of biodegradation based on the PHBV composition of fibers, while it isn't always the case for inorganic fillers. The produced composites have also opened new horizons and possibilities for the development of materials that highly add and contribute to the circular economy concept, and will definitely give a helping hand to the world in its fight against environmental challenges and global warming issues. Most of the developed new biocomposites have had fillers of bio-origin resulting in totally biodegradable materials. Though there has been huge research published in PHBV composite synthesis, there is still a big room for the introduction of new biocomposites especially with biodegradable and biocompatible metal–organic frameworks as there is very little research published in this field.

Acknowledgements This work was supported by the Scientific Research and Innovation Support Fund in Jordan (Project No. WE/2/12/2016). We thank Mr. Abdullah Medani (Naizak Lab Systems) for his support.

References

1. Doppalapudi S, Jain A, Khan W, Domb AJ (2014) Biodegradable polymers—an overview. Polym Adv Technol 25:427–435
2. Torgbo S, Sukyai P (2018) Bacterial cellulose-based scaffold materials for bone tissue engineering. Appl Mater Today 11:34–49
3. Shrivastav A, Kim H-Y, Kim Y-K (2013) Advances in the applications of polyhydroxyalkanoate nanoparticles for novel drug delivery system. BioMed Res Int 2013:1–12
4. Reddy M, Vivekanandhan S, Misra M, Bhatia SK, Mohanty AK (2013) Biobased plastics and bionanocomposites: current status and future opportunities. Prog Polym Sci 38:1653–1689
5. Alsafadi D, Al-Mashaqbeh O, Mansour A, Alsaad M (2020) Optimization of nitrogen source supply for enhanced biosynthesis and quality of poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) by extremely halophilic archaeon *Haloferax mediterranei*. MicrobiologyOpen. https://doi.org/10.1002/mbo3.1055
6. Koller M (2019) Switching from petro-plastics to microbial polyhydroxyalkanoates (PHA): the biotechnological escape route of choice out of the plastic predicament. EuroBiotech J 3:32–44
7. Lemoigne M (1926) Products of dehydration and polymerisation of hydroxybutyric acid. Bull Soc Chim Biol 8:770–782
8. Khanna S, Srivastava AK (2005) Recent advances in microbial polyhydroxyalkanoates. Process Biochem 40:607–619
9. Lu J, Tappel RC, Nomura CT (2009) Mini-review: biosynthesis of poly(hydroxyalkanoates). Polym Rev 49:226–248
10. Ke Y, Zhang XY, Ramakrishna S, He LM, Wu G (2016) Synthetic routes to degradable copolymers deriving from the biosynthesized polyhydroxyalkanoates: a mini review. Express Polym Lett 10:36–53
11. Zinn M, Hany R (2005) Tailored material properties of polyhydroxyalkanoates through biosynthesis and chemical modification. Adv Eng Mater 7:408–411
12. Park SJ, Ahn WS, Green PR, Lee SY (2001) Biosynthesis of poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate-*co*-3-hydroxyhexanoate) by metabolically engineered *Escherichia coli* strains. Biotechnol Bioeng 74:81–86
13. Zhao W, Chen G-Q (2007) Production and characterization of terpolyester poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate-*co*-3-hydroxyhexanoate) by recombinant *Aeromonas hydrophila* 4AK4 harboring genes phaAB. Process Biochem 42:1342–1347
14. Liu Q, Chen G-Q (2008) In vitro biocompatibility and degradation of terpolyester 3HB-*co*-4HB-*co*-3HHx, consisting of 3-hydroxybutyrate, 4-hydroxybutyrate and 3-hydroxyhexanoate. J Biomater Sci Polym Ed 19:1521–1533
15. Madden LA, Anderson AJ, Asrar J, Berger P, Garrett P (2000) Production and characterization of poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate-*co*-4-hydroxybutyrate) synthesized by *Ralstonia eutropha* in fed-batch cultures. Polymer 41:3499–3505
16. Bugnicourt E, Cinelli P, Lazzeri A, Alvarez V (2014) Polyhydroxyalkanoate (PHA): review of synthesis, characteristics, processing and potential applications in packaging. Express Polym Lett 8:791–808
17. Zhao K, Deng Y, Chen JC, Chen GQ (2003) Polyhydroxyalkanoate (PHA) scaffolds with good mechanical properties and biocompatibility. Biomaterials 24:1041–1045
18. Modi S, Koelling K, Vodovotz Y (2011) Assessment of PHB with varying hydroxyvalerate content for potential packaging applications. Eur Polym J 47:179–186
19. Wang X, Chen Z, Chen X, Pan J, Xu K (2010) Miscibility, crystallization kinetics, and mechanical properties of poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV)/poly(3-hydroxybutyrate-*co*-4-hydroxybutyrate) (P3/4HB) blends. Appl Polym Sci 117:838–848
20. Endres HJ, Siebert-Raths A (2011) Engineering biopolymers markets, manufacturing, properties, and applications. Carl Hanser Verlag, Munich
21. Larsson M, Markbo O, Jannasch P (2016) Melt processability and thermomechanical properties of blends based on polyhydroxyalkanoates and poly(butylene adipate-*co*-terephthalate). RSC Adv 6:44354–44363
22. Weng YX, Wang Y, Wang XL, Wang YZ (2010) Biodegradation behavior of PHBV films in a pilot-scale composting condition. Polym Test 29:579–587
23. Avella M, Martuscelli E, Raimo M (2000) Properties of blends and composites based on poly(3-hydroxy)butyrate (PHB) and poly(3-hydroxybutyrate-hydroxyvalerate) (PHBV) copolymers. J Mater Sci 35:523–545
24. Malafaya PB, Silva GA, Reis RL (2007) Natural-origin polymers as carriers and scaffolds for biomolecules and cell delivery in tissue engineering applications. Adv Drug Deliv Rev 59:207–233
25. Ha CS, Cho WJ (2002) Miscibility, properties, and biodegradability of microbial polyester containing blends. Prog Polym Sci 27:759–809
26. Thorat Gadgil BS, Killi N, Rathna GVN (2017) Polyhydroxyalkanoates as biomaterials. MedChemComm 8:1774–1787
27. Kourmentza C, Plácido J, Venetsaneas N, Burniol-Figols A, Varrone C, Gavala HN, Reis MAM (2017) Recent advances and challenges towards sustainable polyhydroxyalkanoate (PHA) production. Bioengineering 4:1–43
28. Alsafadi D, Al-Mashaqbeh O (2017) A one-stage cultivation process for the production of poly-3-(hydroxybutyrate-*co*-hydroxyvalerate) from olive mill wastewater by *Haloferax mediterranei*. N Biotechnol 34:47–53
29. Alsafadi D, Ibrahim MI, Alamry KA, Hussein MA, Mansour A (2020) Utilizing the crop waste of date palm fruit to biosynthesize polyhydroxyalkanoate bioplastics with favorable properties. Sci Total Environ 737:139716
30. Zhang YZ, Liu GM, Weng WQ, Ding JY, Liu SJ (2015) Engineering of *Ralstonia eutropha* for the production of

poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) from glucose. J Biotechnol 195:82–88

31. Kunasundari B, Sudesh K (2011) Isolation and recovery of microbial polyhydroxyalkanoates. Express Polym Lett 5:620–634
32. Chen GQ (2010) Microbiology monographs, vol 14. Springer, Berlin
33. Li Z, Yang J, Loh XJ (2016) Polyhydroxyalkanoates: opening doors for a sustainable future. NPG Asia Mater 8:e265
34. Rivera-Briso AL, Serrano-Aroca A (2018) Poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate): enhancement strategies for advanced applications. Polymers 10:732
35. Zhang J, Shishatskaya EI, Volova TG, da Silva LF, Chen GQ (2018) Review polyhydroxyalkanoates (PHA) for therapeutic applications. Mater Sci Eng C 86:144–150
36. Koller M (2018) Review biodegradable and biocompatible polyhydroxy-alkanoates (PHA): auspicious microbial macromolecules for pharmaceutical and therapeutic applications. Molecules 23:362
37. Lim J, You M, Li J, Li Z (2017) Review emerging bone tissue engineering via polyhydroxyalkanoate (PHA)-based scaffolds. Mater Sci Eng C 79:917–929
38. Dwivedi R, Pandey R, Kumar S, Mehrotra D (2020) Poly hydroxyalkanoates (PHA): role in bone scaffolds. J Oral Biol Craniofac Res 10(1):389–392
39. Samui AB, Kanai T (2019) Review polyhydroxyalkanoates based copolymers. Int J Biol Macromol 140:522–537
40. Tarrahi R, Fathi Z, Seydibeyoğlu MO, Doustkhah E, Khataee A (2020) polyhydroxyalkanoates (PHA): from production to nanoarchitecture. Int J Biol Macromol 146:596–619
41. Raza ZA, Khalil S, Abid S (2020) Review recent progress in development and chemical modification of poly(hydroxybutyrate)-based blends for potential medical applications. Int J Biol Macromol 160:77–100
42. Tebaldi ML, Maia ALC, Poletto F, De Andrade FV, Soares DCF (2019) Poly(-3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV): current advances in synthesis methodologies, antitumor applications and biocompatibility. J Drug Deliv Sci Technol 51:115–126
43. Bugnicourt E (2014) Polyhydroxyalkanoate (PHA): review of synthesis, characteristics, processing and potential applications in packaging. Express Polym 8:791–808
44. Bucci DZ, Tavares LBB, Sell I (2005) PHB packaging for the storage of food products. Polym Test 24:564–571
45. Rhim JW, Park HM, Ha CS (2013) Bio-nanocomposites for food packaging applications. Prog Polym Sci 38:1629–1652
46. Castro-Mayorga JL, Fabra MJ, Lagaron JM (2016) Stabilized nanosilver based antimicrobial poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) nanocomposites of interest in active food packaging. Innov Food Sci Emerg Technol 33:524–533
47. Castro-Mayorga JL, Fabra MJ, Pourrahimi AM, Olsson RT, Lagaron JM (2017) The impact of zinc oxide particle morphology as an antimicrobial and when incorporated in poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) films for food packaging and food contact surfaces applications. Food Bioprod Process 101:32–44
48. Anzˇlovar A, Krzan A, Zagar E (2018) Degradation of PLA/ZnO and PHBV/ZnO composites prepared by melt processing. Arab J Chem 11:343–352
49. Gouvêa RF, Aguila EMD, Paschoalin VMF, Andrade CT (2018) Extruded hybrids based on poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) and reduced graphene oxide composite for active food packaging. Food Packag Shelf Life 16:77–85
50. Díez-Pascual AM, Díez-Vicente AL (2014) ZnO-reinforced poly (3-hydroxybutyrate-*co*-3-hydroxyvalerate) bionanocomposites with antimicrobial function for food packaging. ACS Appl Mater Interfaces 6:9822–9834
51. Zare M, Namratha K, Ilyas S, Hezam A, Mathur S, Byrappa K (2019) Smart fortified PHBV-CS biopolymer with ZnO–Ag nanocomposites for enhanced shelf life of food packaging. ACS Appl Mater Interfaces 51:48309–48320
52. Zhang H, Yu HY, Wang C, Yao J (2017) Effect of silver contents in cellulose nanocrystal–silver nanohybrids on PHBV crystallization and property improvements. Carbohydr Polym 173:7–16
53. Abdalkarim SYH, Yu H-Y, Song M-L, Zhou Y, Yao J, Ni Q-Q (2017) In vitro degradation and possible hydrolytic mechanism of PHBV nanocomposites by incorporating cellulose nanocrystal–ZnO nanohybrids. Carbohydr Polym 176:38–49
54. Ashori A, Jonoobi M, Ayrilmis N, Shahreki A, Fashapoyeh MA (2019) Preparation and characterization of polyhydroxybutyrate-*co*-valerate (PHBV) as green composites using nano reinforcements. Int J Biol Macromol 136:1119–1124
55. Malmir S, Montero B, Rico M, Barral L, Bouza R (2017) Morphology, thermal and barrier properties of biodegradable films of poly (3-hydroxybutyrate-*co*-3-hydroxyvalerate) containing cellulose nanocrystals. Composites A 93:41–48
56. Yu HY, Qin ZY, Sun B, Yang XG, Yao JM (2014) Reinforcement of transparent poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) by incorporation of functionalized carbon nanotubes as a novel bionanocomposite for food packaging. Compos Sci Technol 94:96–104
57. Mayorga JLC, Rovira MJF, Mas LC, Moragas GS, Cabello JML (2018) Antimicrobial nanocomposites and electrospun coatings based on poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) and copper oxide nanoparticles for active packaging and coating applications. J Appl Polym Sci 135:45673
58. Farmahini-Farahani M, Xiao H, Khan A, Pan Y, Yang Y (2015) Preparation and characterization of exfoliated PHBV nanocomposites to enhance water vapor barriers of calendared paper. Ind Eng Chem Res 45:11277–11284
59. Farmahini-Farahani M, Khan A, Lu P, Bedane AH, Eic M, Xiao H (2017) Surface morphological analysis and water vapor barrier properties of modified Cloisite 30B/poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) composites. Appl Clay Sci 135:27–34
60. Ajmal AW, Masood F, Yasin T (2018) Influence of sepiolite on thermal, mechanical and biodegradation properties of poly-3-hydroxybutyrate-*co*-3-hydroxyvalerate nanocomposites. Appl Clay Sci 156:11–19
61. Shakil O, Masood F, Yasin T (2017) Characterization of physical and biodegradation properties of poly-3-hydroxybutyrate-*co*-3-hydroxyvalerate/sepiolite nanocomposites. Mater Sci Eng C 77:173–183
62. Sanchez-Garcia MD, Gimenez E, Lagaron JM (2008) Morphology and barrier properties of solvent cast composites of thermoplastic biopolymers and purified cellulose fibers. Carbohydr Polym 71:235–244
63. Singh S, Mohanty AK, Sugie T, Takai Y, Hamada H (2008) Renewable resource based biocomposites from natural fiber and polyhydroxybutyrate-*co*-valerate (PHBV) bioplastic. Composites A 39:875–886
64. Ahankari SS, Misra M, Mohanty A (2011) Mechanical behavior of agro-residue reinforced poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate), (PHBV) green composites: a comparison with traditional polypropylene composites. Compos Sci Technol 71:653–657
65. Berthet MA, Coussy H, Chea V, Guillard V, Gastaldi E, Gontard N (2015) Sustainable food packaging: valorising wheat straw fibres for tuning PHBV-based composites properties. Composites A 72:139–147
66. Torres-Giner S, Hilliou L, Melendez-Rodriguez B, Figueroa-Lopez KJ, Madalena D, Cabedo L, Covas JA, Vicente AA, Lagaron JM (2018) Melt processability, characterization, and antibacterial activity of compression-molded green composite

sheets made of poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) reinforced with coconut fibers impregnated with oregano essential oil. Food Packag Shelf Life 17:39–49
67. Berthet MA, Angellier-Coussy H, Machado D, Hilliou L, Staebler A, Vicente A, Gontard N (2015) Exploring the potentialities of using lignocellulosic fibres derived from three food by-products as constituents of biocomposites for food packaging. Ind Crops Prod 69:110–122
68. Zhao X, Ji K, Kurt K, Cornish K, Vodovotz Y (2019) Optimal mechanical properties of biodegradable natural rubber-toughened PHBV bioplastics intended for food packaging applications. Food Packag Shelf Life 21:100348
69. Barouti G, Jaffredo CG, Guillaume SM (2017) Advances in drug delivery systems based on synthetic poly(hydroxybutyrate) (co)polymers. Prog Polym Sci 73:1–31
70. Poletto FS, Fiel LA, Donida B, Ré MI, Guterres SS, Pohlmann AR (2008) Controlling the size of poly(hydroxybutyrate-*co*-hydroxyvalerate) nanoparticles prepared by emulsification–diffusion technique using ethanol as surface agent. Colloids Surf A 324:105–112
71. Monnier A, Rombouts C, Kouider D, About I, Fessi H, Sheibat-Othman N (2016) Preparation and characterization of biodegradable polyhydroxybutyrate-*co*-hydroxyvalerate/polyethylene glycol-based microspheres. Int J Pharm 513:49–61
72. Vilos C, Gutiérrez M, Escobar RA, Morales F, Denardin GC, Velasquez L, Altbir D (2013) Superparamagnetic poly (3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV) nanoparticles for biomedical applications. Electron J Biotechnol 16:5
73. Oka C, Ushimaru K, Horiishi N, Tsuge T, Kitamoto Y (2015) Core–shell composite particles composed of biodegradable polymer particles and magnetic iron oxide nanoparticles for targeted drug delivery. J Magn Magn Mater 381:278–284
74. Augustine R, Hasan A, Patan NK, Dalvi YB, Varghese R, Antony A, Unni RN, Sandhyarani N, Al Moustafa A (2020) Cerium oxide nanoparticle incorporated electrospun poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) membranes for diabetic wound healing applications. ACS Biomater Sci Eng 1:58–70
75. Li H, Chang J (2005) Preparation, characterization and in vitro release of gentamicin from PHBV/wollastonite composite microspheres. J Control Release 107:463–473
76. Huang W, Wang Y, Ren L, Du C, Shi X (2009) A novel PHBV/HA microsphere releasing system loaded with alendronate. Mater Sci Eng C 29:2221–2225
77. Duan B, Wang M (2010) Encapsulation and release of biomolecules from Ca-P/PHBV nanocomposite microspheres and three-dimensional scaffolds fabricated by selective laser sintering. Polym Degrad Stab 95:1655–1664
78. Dai Y, Liu HR, Xia LI, Zhou Z (2011) Preparation and characterization of icariin/PHBV drug delivery coatings on anodic oxidized titanium. Trans Nonferr Met Soc China 21:2448–2453
79. Xia L, Li Y, Zhou Z, Dai Y, Liu H, Liu H (2013) Icariin delivery porous PHBV scaffolds for promoting osteoblast expansion in vitro. Mater Sci Eng C 33:3545–3552
80. Li W, Ding Y, Rai R, Roether JA, Schubert DW, Boccaccini AR (2014) preparation and characterization of vancomycin releasing PHBV 45S5 Bioglass-based glass–ceramic scaffolds for bone tissue engineering. J Eur Ceram Soc 34:505–514
81. Li W, Macias-Andres VI, Aguilar-Reyes EA, Ding Y, Roether JA, Harhaus L, Leon-Patino CA, Boccaccini AR (2014) Preparation and characterization of PHBV microsphere/45S5 bioactive glass composite scaffolds with vancomycin releasing function. Mater Sci Eng C 41:320–328
82. Miroiu FM, Stefan N, Visan AI, Nita C, Luculescu CR, Rasoga O, Socol M, Zgura I, Cristescu R, Cracium D, Socol G (2015) Composite biodegradable biopolymer coatings of silk fibroin–poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) for biomedical applications. Appl Surf Sci 355:1123–1131
83. Dalgic AD, Atila D, Karatas A, Tezcaner A, Keskin D (2019) Diatom shell incorporated PHBV/PCL-pullulan co-electrospun scaffold for bone tissue engineering. Mater Sci Eng C 100:735–746
84. Chen Y, Abdalkarim SYH, Yu HY, Li Y, Xu J, Marek J, Yao J, Tam KC (2020) Double stimuli-responsive cellulose nanocrystals reinforced electrospun PHBV composites membrane for intelligent drug release. Int J Biol Macromol 155:330–339
85. Perveen K, Masood F, Hameed A (2020) Preparation, characterization and evaluation of antibacterial properties of epirubicin loaded PHB and PHBV nanoparticles. Int J Biol Macromol 144:259–266
86. Otroj M, Taymouri S, Varshosaz J, Mirian M (2020) Preparation and characterization of dry powder containing sunitinib loaded PHBV nanoparticles for enhanced pulmonary delivery. J Drug Deliv Sci Technol 56:101570
87. Pettinelli N, Rodriguez-LIamazares S, Farraq Y, Bouza R, Barral L, Feijoo-Bandin S, Lago F (2020) Poly(hydroxybutyrate-*co*-hydroxyvalerate) microparticles embedded in κ-carrageenan/locust bean gum hydrogel as a dual drug delivery carrier. Int J Biol Macromol 146:110–111
88. Handali S, Moghimipour E, Rezaei M, Saremy S, Dorkoosh FA (2019) Co-delivery of 5-fluorouracil and oxaliplatin in novel poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate acid)/poly (lactic-*co*-glycolic acid) nanoparticles for colon cancer therapy. Int J Biol Macromol 124:1299–1311
89. Vidal LS, Rojas C, Padin R, Rivera M, Haensgen A, Gonzalez M, Rodriguez S et al (2016) Synthesis and characterization of polyhydroxybutyrate-*co*-hydroxyvalerate nanoparticles for encapsulation of quercetin. J Bioact Compat Polym 31:439–452
90. De Almeida Neto GR, Barcelos MV, Ribeiro MEA, Folly MM, Rodriguez RJS (2019) Formulation and characterization of a novel PHBV nanocomposite for bone defect filling and infection treatment. Mater Sci Eng C 104:110004
91. Álvarez-Álvarez L, Barral L, Bouza R, Farrag Y, Otero-Espinar F, Feijoo-Bandin S, Lago F (2019) Hydrocortisone loaded poly-(3-hydroxybutyrate-*co*-3-hydroxyvalerate) nanoparticles for topical ophthalmic administration: preparation, characterization and evaluation of ophthalmic toxicity. Int J Pharm 568:118519
92. Vardhan H, Mittal P, Adena SKR, Upadhyay M, Yadav SK, Mishra B (2018) Process optimization and in vivo performance of docetaxel loaded PHBV–TPGS therapeutic vesicles—a synergistic approach. Int J Biol Macromol 108:729–743
93. Gheibi A, Khoshnevisan K, Ketabchi N, Derakhshan MA, Babadi AA (2016) Application of electrospun nanofibrous PHBV scaffold in neural graft and regeneration: a mini-review. Nanomed Res J 1:107–111
94. Hutmacher DW (2000) Scaffolds in tissue engineering bone and cartilage. Biomaterials 21:2529–2543
95. Puppi D, Chiellini F, Piras AM, Chiellini E (2010) Polymeric materials for bone and cartilage repair. Prog Polym Sci 35:403–440
96. Wu J, Xue K, Li H, Sun J, Liu K (2013) Improvement of PHBV scaffolds with bioglass for cartilage tissue engineering. PLoS ONE 8:e71563
97. Smith JR, Lamprou DA (2014) Polymer coatings for biomedical applications: a review. Trans IMF 92:9–19
98. Galego AN, Rozsa C, Sanchez R, Fung J, Vazquez A, Tomas JS (2000) Characterization and application of poly(b-hydroxyalkanoates) family as composite biomaterials. Polym Test 19:485–492
99. Baek JY, Xing ZC, Kwak G, Yoon KB, Park SY, Kang PLS, IK, (2012) Fabrication and characterization of collagen-immobilized

porous PHBV/HA nanocomposite scaffolds for bone tissue. Eng J Nanomater 2012:171804

100. Gonzalez Ausejo J, Rydz J, Musiol M, Sikorska W, Janeczek H, Sobota M, Wtodarczyk J, Szeluga U, Hercog A, Kowalczuk M (2018) A comparative study of three-dimensional printing directions: the degradation and toxicological profile of a PLA/PHA blend. Polym Degrad Stab 152:191–207
101. Pan W, Xiao X, Li J, Deng S, Shan Q, Yue Y, Tian Y, Nabar NR, Wang M, Hao L (2018) The comparison of biocompatibility and osteoinductivity between multi-walled and single-walled carbon nanotube/PHBV composites. J Mater Sci Mater Med 29:189
102. Jack KS, Velayudhan S, Luckman P, Trau M, Grøndahl L, Cooper-White J (2009) The fabrication and characterization of biodegradable HA/PHBV nanoparticle–polymer composite scaffolds. Acta Biomater 5:2657–2667
103. Khoshraftar A, Noorani B, Yazdian F, Rashedi H, Ghaemi RV, Alihemmati Z, Saleheh Shahmoradi S (2018) Fabrication and evaluation of nanofibrous polyhydroxybutyrate valerate scaffolds containing hydroxyapatite particles for bone tissue engineering. Int J Polym Mater Polym Biomater 17:987–995
104. Rasoga O, Sima LE, Chiritoiu M, Popescu-Pelin G, Fufă O, Grumezescu V, Socol M, Stanculescu A, Zgura I, Socol G (2017) Biocomposite coatings based on poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate)-calcium phosphates obtained by MAPLE for bone tissue engineering. Appl Surf Sci 417:204–212
105. Wang N, Zhou Z, Xia L, Dai Y, Liu H (2013) Fabrication and characterization of bioactive β-Ca_2SiO_4/PHBV composite scaffolds. Mater Sci Eng C 33:2294–2301
106. Paşcu EI, Stokes J, McGuinness GB (2013) Electrospun composites of PHBV, silk fibroin and nano-hydroxyapatite for bone tissue engineering. Mater Sci Eng C 33:4905–4916
107. Unalan I, Colpankan O, Albayrak AZ, Gorgun C, Urkmez AS (2016) Biocompatibility of plasma-treated poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) nanofiber mats modified by silk fibroin for bone tissue regeneration. Mater Sci Eng C 68:842–850
108. Kouhi M, Prabhakaran MP, Shamanian M, Fathi M, Morshed M, Ramakrishna S (2015) Electrospun PHBV nanofibers containing HA and bredigite nanoparticles: fabrication, characterization and evaluation of mechanical properties and bioactivity. Compos Sci Technol 121:115–122
109. Kouhi M, Morshed M, Varshosaz J, Fathi M (2018) Enhanced proliferation and mineralization of human fetal osteoblast cells on PHBV-bredigite nanofibrous scaffolds. Mater Today Proc 5:15702–15709
110. Bai J, Dai J, Li G (2015) Electrospun composites of PHBV/pearl powder for bone repairing. Prog Nat Sci Mater Int 25:327–333
111. Silverman T, Naffakh M, Marco CG, Ellis G (2016) Morphology and thermal properties of biodegradable poly(hydroxybutyrate-*co*-hydroxyvalerate)/tungsten disulphide inorganic nanotube nanocomposites. Mater Chem Phys 170:145–153
112. Zhang S, Prabhakaran MP, Qin X, Ramakrishna S (2015) Biocomposite scaffolds for bone regeneration: role of chitosan and hydroxyapatite within poly-3-hydroxybutyrate-*co*-3-hydroxyvalerate on mechanical properties and in vitro evaluation. J Mech Behav Biomed Mater 51:88–98
113. Ye X, Li L, Zefeng Lin Z, Yang W, Duan M, Chen L, Xia Y, Chen Z, Lu Y, Zhang Y (2018) Integrating 3D-printed PHBV/calcium sulfate hemihydrate scaffold and chitosan hydrogel for enhanced osteogenic property. Carbohydr Polym 202:106–114
114. Bakare RA, Bhan C, Raghavan D (2014) Synthesis and characterization of collagen grafted poly(hydroxybutyrate−valerate) (PHBV) scaffold for loading of bovine serum albumin capped silver (Ag/BSA) nanoparticles in the potential use of tissue engineering application. Biomacromol 15:423–435
115. Bakare RA, Hawthrone S, Vails C, Gugssa A, Karim A, Stubbs J, Raghavan D (2016) Antimicrobial and cell viability measurement of bovine serum albumin capped silver nanoparticles (Ag/BSA) loaded collagen immobilized poly (3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV) film. J Colloid Interface Sci 465:140–148
116. Sajesh KM, Kiran K, Nair SV, Jayakumar R (2016) Sequential layer-by-layer electrospinning of nano $SrCO_3$/PRP loaded PHBV fibrous scaffold for bone tissue engineering. Composites B 99:445–452
117. Montanheiro TLDA, Montagna LS, Patrulea V, Jordan O, Borchard G, Ribas RG, Campos TMB, Thim GP, Lemes AP (2019) Enhanced water uptake of PHBV scaffolds with functionalized cellulose. Polym Test 79:106079
118. Ko GT, Korkusuz F, OzkuI A, SoysaI Y, Ozdemir T, Yildiz CU, Hasirci V (2005) Tissue engineered cartilage on collagen and PHBV matrices. Biomaterials 26:5187–5197
119. Bretcanu O, Misra SK, Yunos DM, Boccaccini AR, Roy M, Kowalczyk T, Blonski S, Kowalewski T (2009) Electrospun nanofibrous biodegradable polyester coatings on Bioglass®-based glass–ceramics for tissue engineering. Mater Chem Phys 118:420–426
120. Wu J, Sun J, Liu J (2014) Evaluation of PHBV-calcium silicate composite scaffolds for cartilage tissue engineering. Appl Surf Sci 317:278–283
121. Gorodzha SN, Muslimov AR, Syromotina DS, Timin AS, Tcvetkov NY, Lepik KV, Petrova AV, Surmeneva MA, Gorin DA, Sukhorukov GB, Surmenev RA (2017) A comparison study between electrospun polycaprolactone and piezoelectric poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) scaffolds for bone tissue engineering. Colloids Surf B 160:48–59
122. Nair MB, Baranwai G, Vijayan P, Keyan KS, Jayakumar R (2015) Composite hydrogel of chitosan–poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) with chondroitin sulfate nanoparticles for nucleus pulposus tissue engineering. Colloids Surf B 136:84–92
123. Duan B, Wang M, Zhou WY, Cheung WL, Li ZY, Lu WW (2010) Three-dimensional nanocomposite scaffolds fabricated via selective laser sintering for bone tissue engineering. Acta Biomater 6:4495–4505
124. Feng P, Kong Y, Yu L, Li Y, Gao C, Peng S, Pan H, Zhao Z, Shuai C (2019) Molybdenum disulfide nanosheets embedded with nanodiamond particles-co-dispersion nanostructures as reinforcements for polymer scaffolds. Appl Mater Today 17:216–226
125. Wu C, Liao HT (2017) Interface design of environmentally friendly carbon nanotube-filled polyester composites: fabrication, characterisation, functionality and application. eXPRESS Polym Lett 3:187–198.
126. Hsu YC, Wu CS, Liao HT, Cai YX (2015) Improvement of the biocompatibility of polyhydroxyalkanoate by filling with hyaluronic acid. J Mater Sci 50:7790–7799
127. Qian J, Ma J, Su J, Yan Y, Li H, Shin JW, Wei J, Zhao L (2016) PHBV-based ternary composite by intermixing of magnesium calcium phosphate nanoparticles and zein: in vitro bioactivity, degradability and cytocompatibility. Eur Polym J 75:291–302
128. Pramanik N, Bhattacharya S, Rath T, De J, Adhikary A, Basu RK, Kundu PP (2019) Polyhydroxybutyrate-*co*-hydroxyvalerate copolymer modified graphite oxide based 3D scaffold for tissue engineering application. Mater Sci Eng C 94:534–546
129. Rivera-Briso AL, Aachmann FL, Moreno-Manzano V, Serrano-Aroca A (2020) Graphene oxide nanosheets versus carbon nanofibers enhancement of physical and biological properties of poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) films for biomedical applications. Int J Biol Macromol 143:1000–1008
130. Mutlu G, Çalamak S, Ulubayram K, Güven E (2018) Curcumin-loaded electrospun PHBV nanofibers as potential wound-dressing material. J Drug Deliv Sci Technol 43:185–193

131. Wu CS (2019) Comparative assessment of the interface between poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) and fish scales in composites: preparation, characterization, and applications. Mater Sci Eng C 104:109878
132. Demirkıran ND, Havıtçıoğlu H, Ziylan A, Cankurt U, Hüsemoğlu B (2019) Novel multilayer meniscal scaffold provides biomechanical and histological results comparable to polyurethane scaffolds: an 8 week rabbit study. Acta Orthop Traumatol Turc 53:120–128
133. Abdalkarim SYH, Yu HY, Wang C, Yang L, Guan Y, Huang L, Yao J (2018) Sheet-like cellulose nanocrystal–ZnO nanohybrids as multifunctional reinforcing agents in biopolyester composite nano fibers with ultrahigh UV-shielding and antibacterial performances. ACS Appl Bio Mater 1:714–727
134. Idris MI, Zaloga J, Detsch R, Roether JA, Unterweger H, Alexiou C, Boccaccini AR (2018) Surface modification of SPIONs in PHBV microspheres for biomedical applications. Sci Rep 8:7286
135. Li W, Zaloga J, Ding Y, Liu Y, Janko C, Pischetsrieder M, Alexiou C, Boccaccini AR (2016) Facile preparation of multifunctional superparamagnetic PHBV microspheres containing SPIONs for biomedical applications. Sci Rep 6:23140
136. Xing ZC, Chae WP, Baek JY, Choi MJ, Jung Y, Kang IK (2010) In vitro assessment of antibacterial activity and cytocompatibility of silver containing PHBV nanofibrous scaffolds for tissue engineering. Biomacromol 5:1248–1253
137. Zine R, Sinha M (2017) Nanofibrous poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate)/collagen/graphene oxide scaffolds for wound coverage. Mater Sci Eng C 80:129–134
138. Ma Y, Zheng Y, Wei G, Yang H, Xue R (2012) Processing, structure, and properties of multiwalled carbon nanotube/poly(hydroxybutyrate-*co*-valerate) biopolymer nanocomposites. J Appl Polym Sci 125:620–629
139. Farukad O, Biedzki AK, Fink H-P, Sain M (2012) Biocomposites reinforced with natural fibers: 2000–2010. Prog Polym Sci 37:1552–1596
140. Seggiani M, Cinelli P, Mallegni N, Balestri E, Puccini M, Vitolo S, Lardicci C, Lazzeri A (2017) New bio-composites based on polyhydroxyalkanoates and *Posidonia oceanica* fibres for applications in a marine environment. Materials 10:326
141. Seggiani M, Cinelli P, Balestri E, Mallegni N, Stefanelli E, Rossi A, Lardicci C, Lazzeri A (2018) Novel sustainable composites based on poly(hydroxybutyrate-*co*-hydroxyvalerate) and seagrass beach-CAST fibers: performance and degradability in marine environments. Materials 11:772
142. Torres-Tello EV, Robledo-Ortíz JR, González-García Y, Pérez-Fonseca AA, Jasso-GastineI CF, Mendizábal E (2017) Effect of agave fiber content in the thermal and mechanical properties of green composites based on polyhydroxybutyrate or poly(hydroxybutyrate-*co*-hydroxyvalerate). Ind Crops Prod 99:117–125
143. Teramoto N, Urata K, Ozawa K, Shibata M (2004) Biodegradation of aliphatic polyester composites reinforced by abaca fiber. Polym Degrad Stab 86:401–409
144. Javadi A, Srithep Y, Pilla S, Lee J, Gong S, Turng LS (2010) Processing and characterization of solid and microcellular PHBV/coir fiber composites. Mater Sci Eng C 30:749–757
145. Rossa LV, Scienza LC, Zattera AJ (2013) Effect of curauá fiber content on the properties of poly(hydroxybutyrate-*co*-valerate) composites. Polym Compos 34:450–456
146. Cheikh RB, Michel A, Billington S (2014) Mechanical characterization and modeling of poly (b-hydroxybutyrate)-*co*-poly(b-hydroxyvalerate)–alfa fiber-reinforced composites. Polym Compos 35:1758–1766
147. Tengsuthiwat J, Boonyasopon P, Dangtungee R, Siengchin S (2016) Characterization of poly(hydroxybutyrate-*co*-hydroxyvalerate)/sisal fiber/clay bio-composites prepared by casting technique. Period Polytech Mech Eng 60:103–112
148. Muniyasamy S, Osei Ofosu O, Thulasinathan B, Rajan AST, Ramu SM, Soorangkattan S, Muthuramalingam JB, Alagarsamy A (2019) Thermal–chemical and biodegradation behavior of alginic acid treated flax fibres/poly(hydroxybutyrate-*co*-valerate) PHBV green composites in compost medium. Biocatal Agric Biotechnol 22:101394
149. Miller SA (2018) Natural fiber textile reinforced bio-based composites: mechanical properties, creep, and environmental impacts. J Clean Prod 198:612–623
150. Wang B, Li J, Zhang J, Li H, Chen P, Gu Q, Wang Z (2013) Thermo-mechanical properties of the composite made of poly(3-hydroxy butyrate-*co*-3-hydroxyvalerate) and acetylated chitin nanocrystals. Carbohydr Polym 95:100–106
151. Lammi S, Gastaldi E, Gaubiac F, Angellier-Coussy H (2019) How olive pomace can be valorized as fillers to tune the biodegradation of PHBV based composites. Polym Degrad Stab 166:325–333
152. Solle MA, Arroyo J, Burgess MH, Warnat S, Ryan C (2019) Value-added composite bioproducts reinforced with regionally significant agricultural residues. Composites A 124:105441
153. Harmaen AS, Khalina A, Ali HBM, Azowaet IN (2016) Thermal, morphological, and biodegradability properties of bioplastic fertilizer composites made of oil palm biomass, fertilizer, and poly(hydroxybutyrate-*co*-valerate). Int J Polym Sci 12:3230109
154. Senthil Muthu Kumar T, Yorseng K, Rajini N, Siengchin S, Ayrilmis N, Varadarajulu A (2019) Mechanical and thermal properties of spent coffee bean filler/poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) biocomposites: effect of recycling. Process Saf Environ Prot 124:187–195
155. Hassaini L, Kaci M, Touati N, Pillin I, Kervoelen A, Bruzaud S (2017) Valorization of olive husk flour as a filler for biocomposites based on poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate): effects of silane treatment. Polym Test 59:430–440
156. Singh S, Mohanty AK (2007) Wood fiber reinforced bacterial bioplastic composites: fabrication and performance evaluation. Compos Sci Technol 67:1753–1763
157. Srubar WV, Pilla S, Wright ZC, Ryan C, Greene OR, Frank CW, Billington SL (2012) Mechanisms and impact of fiber–matrix compatibilization techniques on the material characterization of PHBV/oak wood flour engineered biobased composites. Compos Sci Technol 72:708–715
158. Chan CM, Vandi LJ, Pratt SL, Halley PJ, Richardson D, Werker AG, Laycock B (2018) Mechanical performance and long-term indoor stability of polyhydroxyalkanoate (PHA)-based wood plastic composites (WPCs) modified by non-reactive additives. Eur Polym J 98:337–346
159. Vandi LJ, Chan CM, Werker AG, Richardson D, Laycock B, Pratt S (2019a) Experimental data for extrusion processing and tensile properties of poly(hydroxybutyrate-*co*-hydroxyvalerate) (PHBV) polymer and wood fibre reinforced PHBV biocomposites. Data Brief 22:687–692
160. Vandi LJ, Chan CM, Werker AG, Richardson D, Laycock B, Pratt SH (2019b) Extrusion of wood fibre reinforced poly(hydroxybutyrate-*co*-hydroxyvalerate) (PHBV) biocomposites: statistical analysis of the effect of processing conditions on mechanical performance. Polym Degrad Stab 159:1–14
161. Singh S, Mohanty AK, Misra M (2010) Hybrid bio-composite from talc, wood fiber and bioplastic: fabrication and characterization. Composites A 41:304–312
162. Bledzki AK, Jaszkiewicz A (2010) Mechanical performance of biocomposites based on PLA and PHBV reinforced with natural fibres—a comparative study to PP. Compos Sci Technol 70:1687–1696

163. Ten E, Jiang L, Wolcott MP (2013) Preparation and properties of aligned poly(3-hydroxy butyrate-*co*-3-hydroxyvalerate)/cellulose nanowhiskers composites. Carbohydr Polym 92:206–213
164. Yu HY, Qin ZY (2014) Surface grafting of cellulose nanocrystals with Poly (3-hydroxybutyrate-*co*-3 hydroxyvalerate). Carbohydr Polym 101:471–478
165. Srithep Y, Ellingham T, Peng J, Sabo R, Clemons CM, Turng LS, Pilla S (2013) Melt compounding of poly (3-hydroxybutyrate-*co*-3-hydroxyvalerate)/nano fibrillated cellulose nanocomposites. Polym Degrad Stab 98:1439–1449
166. Qiang T, Wang J, Wolcott MP (2018) Facile fabrication of 100% bio-based and degradable ternary cellulose/PHBV/PLA composites. Materials 11:330
167. Zheng T, Clemons CM, Pilla S (2020) Comparative study of direct compounding, coupling agent-aided and initiator-aided reactive extrusion to prepare cellulose nanocrystal/PHBV (CNC/PHBV) nanocomposite. ACS Sustain Chem Eng 2:814–822
168. Jun D, Guomin Z, Mingzhu P, Leilei Z, Dagang L, Rui Z (2017) Crystallization and mechanical properties of reinforced PHBV composites using melt compounding: effect of CNCs and CNFs. Carbohydr Polym 168:255–262
169. Moigne N, Sauceau M, Benyakhlef M, Jemai R, Bénézet JC, Rodier E, Lopez-Cuesta JM, Fages J (2014) Foaming of poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate)/organo-clays nano-biocomposites by a continuous supercritical CO_2 assisted extrusion process. Eur Polym J 61:157–171
170. Wang S, Song C, Chen G, Guo TY, Liu J, Zhang BH, Takeuchi S (2005) Characteristics and biodegradation properties of poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate)/organophilic montmorillonite (PHBV/OMMT) nanocomposite. Polym Degrad Stab 87:69–76
171. Khankrua R, Pivsa-art S, Hiroyuki H, Suttiruengwong S (2013) Thermal and mechanical properties of biodegradable polyester/silica nanocomposites. Energy Procedia 34:705–713
172. Carli LN, Daitx TDS, Soares GV, Crespo JDS, Mauler RS (2014) The effects of silane coupling agents on the properties of PHBV/halloysite nanocomposites. Appl Clay Sci 87:311–319
173. Carli ALN, Crespo JDS, Mauler RS (2011) PHBV nanocomposites based on organomodified montmorillonite and halloysite: the effect of clay type on the morphology and thermal and mechanical properties. Composites A 42:1601–1608
174. Choi WM, Kim TW, Park OO, Chang YK, Lee JW (2003) Preparation and characterization of poly (hydroxybutyrate-*co*-hydroxyvalerate)–organoclay nanocomposites. J Appl Polym Sci 90:525–529
175. Crétois R, Follain N, Dargent E, Soulestin J, Bourbigot S, Marais S, Lebrun L (2014) Microstructure and barrier properties of PHBV/organoclays bionanocomposites. J Membr Sci 467:56–66
176. Daitx TS, Carli LN, Crespo JDS, Mauler RS (2015) Effects of the organic modification of different clay minerals and their application in biodegradable polymer nanocomposites of PHBV. Appl Clay Sci 115:157–164
177. Cacciotti I, Pallotto F, Scognamiglio V, Moscone D, Arduini F (2020) Reusable optical multi-plate sensing system for pesticide detection by using electrospun membranes as smart support for acetylcholinesterase immobilization. Mater Sci Eng C 111:110744
178. Huang T, Lu M, Yu H, Zhang Q, Wang H, Zhu M (2015) Enhanced power output of a triboelectric nanogenerator composed of electrospun nanofiber mats doped with graphene oxide. Sci Rep 5:13942
179. Zheng T, Zhang Z, Shukla S, Agnihotri S, Clemons CM, Pilla S (2019) PHBV-graft-GMA via reactive extrusion and its use in PHBV/nanocellulose crystal composites. Carbohydr Polym 205:27–34
180. Levett I, Pratt S, Donose BC, Brackin R, Pratt C, Redding M, Laycock B (2019) Understanding the mobilization of a nitrification inhibitor from novel slow release pellets, fabricated through extrusion processing with PHBV biopolymer. J Agric Food Chem 67:2449–2458
181. Gonçalves SPC, Strauss M, Martinez DST (2018) The positive fate of biochar addition to soil in the degradation of PHBV–silver nanoparticle composites. Environ Sci Technol 52:13845–13853
182. Jost V, Langowski HC (2015) Effect of different plasticisers on the mechanical and barrier properties of extruded cast PHBV films. Eur Polym J 68:302–312
183. Reddy JP, Ahankari S, Misra M, Mohanty A (2013) Influence of processing parameters on the impact strength of biocomposites: a statistical approach. Macromol Mater Eng 298:789–795
184. Li F, Yu HY, Wang YY, Zhou Y, Zhang H, Yao JM, Abdalkarim SYH, Tam KC (2019) Natural biodegradable poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) nanocomposites with multifunctional cellulose nanocrystals/graphene oxide hybrids for high-performance food packaging. J Agric Food Chem 39:10954–10967
185. Ito Y, Hasuda H, Kamitakahara M, OhtsukI C, Tanihara M, Kang IK, Kwon OH (2005) A composite of hydroxyapatite with electrospun biodegradable nanofibers as a tissue engineering material. J Biosci Bioeng 100:43–49
186. Sanchez-Garcia MD, Lagaron JM, Hoa SV (2010) Effect of addition of carbon nanofibers and carbon nanotubes on properties of thermoplastic biopolymers. Compos Sci Technol 70:1095–1105
187. Yu W, Lan CH, Wang S, Fang PF, Sun YM (2010) Influence of zinc oxide nanoparticles on the crystallization behavior of electrospun poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) nanofibers. Polymer 51:2403–2409
188. Wang J, Wang Z, Li J, Wang B, Liu J, Chen P, Miao M, Gu Q (2012) Chitin nanocrystals grafted with poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) and their effects on thermal behavior of PHBV. Carbohydr Polym 87:784–789
189. Ciou CY, Li SY, Wu TM (2014) Morphology and degradation behavior of poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate)/layered double hydroxides composites. Eur Polym J 59:136–143
190. Öner M, İlhan B (2016) Fabrication of poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) biocomposites with reinforcement by hydroxyapatite using extrusion processing. Mater Sci Eng C 65:19–26
191. Oner M, Ç¨ol AA, Pochat-Bohatier C, Bechelany M, (2016) Effect of incorporation of boron nitride nanoparticles on the oxygen barrier and thermal properties of poly(3-hydroxybutyrate-*co*-hydroxyvalerate). RSC Adv 6:90973–90981
192. Xiang H, Chen Z, Zheng N, Zhang X, Zhu L, Zhou Z, Zhu M (2019) Melt-spun microbial poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) fibers with enhanced toughness: synergistic effect of heterogeneous nucleation, long-chain branching and drawing process. Int J Biol Macromol 122:1136–1143
193. Omri N, Oualha MA, Brison L, Vahabi H, Fouad Laoutid F (2020) Novel nanocomposite based on EVA/PHBV/[60]fullerene with improved thermal properties. Polym Test 81:106277