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Review article

Recent insight into the biomedical applications of polybutylene succinate and polybutylene succinate-based materials

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Abstract. The development of biodegradable and biocompatible materials to replace non-biodegradable synthetic polymers has received significant interest in biomedical applications. Amongst all biopolymers, polybutylene succinate (PBS) possesses excellent properties, such as biocompatibility, easy processability, biodegradability, non-toxic, good mechanical and thermal properties, which makes it a suitable candidate to replace non-biodegradable synthetic polymers in biomedical applications. This review provides recent advancements, trends, and challenges for the utilization of polybutylene succinate (PBS) and PBS-based materials for biomedical applications, *viz*. drug delivery, tissue engineering, and biomedical devices. In addition, the design of medical devices from PBS using 3D and 4D printing is also presented. The market analysis, comparison of virgin PBS and synthetic polymer properties, as well as the end of service life, are summarized briefly. The current status, challenges, and future directions are also discussed.

Keywords: *biopolymers, polymer composites, polymer blends, properties, biomedical applications*

1. Introduction

In recent years, advances in material science have led to the discovery and development of novel biodegradable and biocompatible materials for biomedical applications as a substitute for non-biodegradable synthetic polymers [1]. Synthetic polymers contribute to waste disposal problems because they are resistant to microbial degradation [2]. The properties of biopolymers being biodegradable and biocompatible have garnered considerable attention in biomedical applications, such as tissue engineering, drug delivery system, and wound dressing, because, after the end of service life, they hydrolyze within the body system and do not leave any toxic byproducts thus, showing a potential for these applications. Aliphatic polyesters, such as polylactic acid (PLA), polycaprolactone (PCL), and polybutylene succinate (PBS) have demonstrated great potential in biomedical applications due to their attractive features, such as environmental friendliness, biocompatibility, non-immunogenicity, and good thermal and mechanical properties [3–7]. For example, PLA is the most studied biopolymer, however, it has shortcomings, *i.e.*, brittleness, and low impact resistance, which have been major concerns, especially for biomedical applications. PBS has recently become a research hotspot

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due to its impressive features, such as good processability, chemical and heat resistance, biodegradability, good mechanical and thermal properties, biocompatibility, and non-toxicity [8]. In addition, its properties can be tuned by copolymerization and other modifications to achieve desired application. Unfortunately, PBS has shown some drawbacks, which include insufficient osteoblast compatibility and bioactivity, poor wettability with a contact angle of ~130°, and high production cost [8–11]. These drawbacks have greatly hindered the wide-scale applications of PBS in biomedical applications, and hence, the modification of PBS is critical to expanding its applications.

Several approaches that are reported to mitigate PBS limitations include reinforcing, blending, and copolymerization. For instance, a copolymer poly(butylene-*co*-dilinoleic succinate) (PBS-*co*-DLS) was developed for heart tissue engineering in order to overcome some limitations associated with virgin PBS. The copolymer demonstrated good mechanical properties matching properties of cardiac tissues, improved cell proliferation, and excellent biocompatibility. In addition, PBS copolymer degraded into non-cytotoxic byproducts [12]. Generally, the science of modification of PBS is relatively new when compared to their synthetic polymer counterparts. Therefore, further research is necessary to achieve the full potential of PBS.

A number of reviews related to PBS properties, biodegradation, and expanded applications, such as food packaging, biomedical, tableware, and mulch films, as well as modification of PBS have been published [8, 13, 14]. However, reviews on PBS and PBS-based blends and composites focusing specifically on biomedical applications are very few. For instance, Gigli *et al*. [13] published a comprehensive review on PBS-based materials for biomedical applications. However, in their study, they only focused on the drug delivery system. This contribution is aimed at providing recent advances in PBS-based materials in biomedical applications, specifically for drug delivery systems, tissue engineering, and biomedical devices. The application of PBS and PBS materials in 3D and 4D are also highlighted for future healthcare purposes. Moreover, the end-of-service life options of PBS-based materials, current status, and future outlook will also be discussed.

2. PBS market size

PBS comprises repeated $C_8H_{12}O_4$ units as shown in Figure 2, and is synthesized via the polycondensation method from 1,4 butanediol and succinic acid, which can be obtained from both petroleum and biobased sources. However, PBS obtained from petroleum-based monomers is usually referred to as conventional PBS, whereas the one obtained from biobased monomers is often referred to as Biobased PBS or BioPBS. Although the sources differ, their characteristics remain the same.

PBS offers a great opportunity to replace non-biodegradable synthetic polymers, such as polypropylene (PP) and polyethylene (PE). Since the first synthesis of PBS in the 1930s, over the years, it has been synthesized by well-established companies as well as in some research laboratories. The major producers and suppliers are in China, the United States of America, Thailand, and Germany. The key producers and suppliers of commercially available PBS are Kingfa, BioAmber (DNP/ARD), Myriant, PTT MCC Biochem, Reverdia, and BASF, with a production capacity of 30 000 metric tonnes per annum. The global market of PBS is growing immensely, and it is projected to grow fast in the next few years. Recently, Data Bridge Market Research analyses have reported that the market PBS is expected to grow at a Compound Annual Growth Rate (CAGR) of 7.3% from 2021 to 2028 and is anticipated to reach a market of USD 242,803.69 thousand [15]. To achieve the predicted 7.3% increase, there is a need to start up new companies for PBS production as well as to expand the production capacity of the existing well-established companies. In addition, PBS is an emerging biopolymer and therefore, diversification of PBS applications is a necessity to ensure its market growth [15].

The growth in market size and the demand for PBS is attributed to the increasing demand for biodegradable and biocompatible based products in various sectors, such as food packaging, agricultural, automotive, biomedical, and others. Several program – circular economy. The main aim is to address plastic waste pollution and global warming in the long run. In addition, according to the Web of science, over the past 10 years, there has been a growth in the number of publications on PBS topic, as depicted in Figure 1. Another boost towards the growing market of PBS is its excellent properties which include biodegradability,

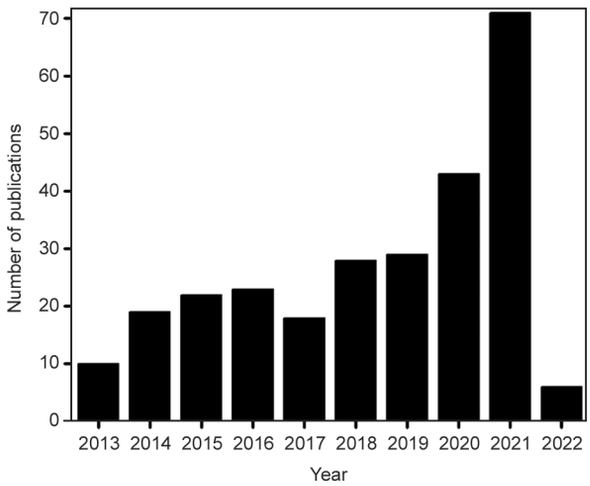

Figure 1. Publications of polybutylene succinate.

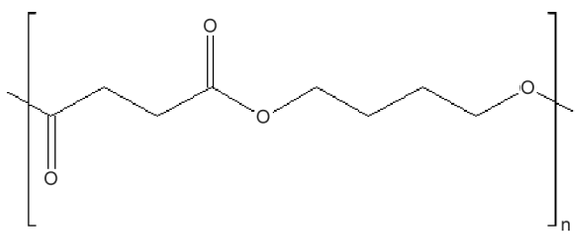

Figure 2. Polybutylene succinate (PBS).

eco-friendliness, good mechanical and thermal properties, as well as heat and chemical resistance. PBS properties are similar to those of non-biodegradable synthetic polymers, and they are summarized in Table 1. Moreover, the properties of PBS make it a suitable candidate for biomedical applications. However, further research is still needed to exploit PBS to achieve its full potential since it is an emerging biopolymer. Even though the projections demonstrated the rapid growth of the PBS market, PBS faces significant challenges that may negatively impact its market. The first challenge includes inadequate properties of PBS to be used as virgin biopolymer, and thus, it requires blending and reinforcing technology to improve their properties. The blending technique has shown several drawbacks, such as the immiscibility of polymers and the cost of the final product becoming high in most cases. On the other hand, the reinforcing challenge is agglomeration which affects the properties of the final product. The second challenge is the high cost and fluctuation cost of raw materials, which makes PBS expensive biopolymer and negatively impacts their market size.

3. Biomedical applications of PBS and PBS-based materials

Various processing technologies such as electrospinning, compression moulding, and 3D printing have been employed to develop PBS-based materials for biomedical applications, specifically, drug delivery, tissue engineering, wound dressing as well

Table 1. Mechanical and thermal properties (glass transition temperature (T_g), melting temperature (T_m)) of PBS and synthetic polymers counterparts.

PBS	Tensile strength [MPa]	Tensile modulus [MPa]	Elongation at break [%]	T_g [°C]	T_m [°C]	Molecular weight [g/mol]	Crystallinity [%]	References
Lab scale	31.08±0.3	513±60	8.9±0.2	n.r.	114.0	47 500	35.0	[16]
Lab scale	6.2±0.7	20±3	151±7	–32	114	50 000	n.r.	[17]
Lab scale	30±2	330±13	23±4	–32	115	48 300	56	[18]
Medical-grade PBS	33	–	700	–32	114	n.r.	n.r.	[9]
PBS (Bionolle 3001, Showa Denko)	37.29±2.01	287±16.7	605±62.19	n.r.	112.5	n.r.	3.2	[19]
PBS (Natureplast)	39.37±0.28	790±0.02	17.85±.02	n.r.	n.r.	n.r.	n.r.	[20]
PBS (Xinjiang Blue Ridge Tunhe Polyester Co. Ltd.)	41.5±2.8	554±45	324±36	n.r.	114.8	83 000	47.82	[21]
PBS (Bionolle 3002, Showa Denko)	18.3±1.6	159±61	432.7±57.4	–45	95.2±1.4	n.r.	n.r.	[22]
BioPBS (FZ71PM, PTT MCC Biochem Co., Ltd., Bangkok)	40.7	740	119	–17.0	115.4	n.r.	34.5	[23]
PP (Shazand Petrochemical Company)	29	850	28	n.r.	164.6	n.r.	51.5	[24]
High-density polyethylene (HDPE) (SABIC)	24.2±0.9	1220±29	50.0±14.9	n.r.	132.7	n.r.	71.0	[25]

n.r. = not reported

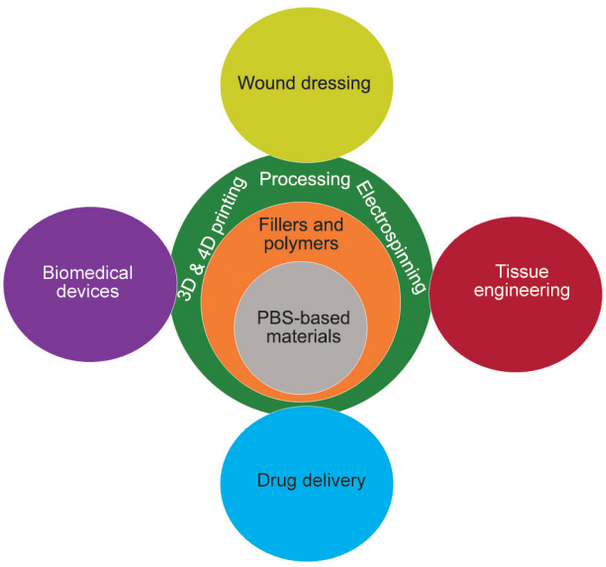

Figure 3. Biomedical applications of PBS-based materials.

as biomedical devices. Much research and development have been focusing on tissue engineering and drug delivery system. However, research on PBS-based wound dressing and biomedical devices is still in the developmental phase. Figure 3 summarizes the process of developing PBS-based material for medical applications. Due to the growing market size of PBS, it is anticipated that new applications such as 3D and 4D printing will be introduced yearly. In this section, the applications of PBS in drug delivery, tissue engineering, and biomedical devices will be discussed, citing recent literature on the new developments.

3.1. Polybutylene succinate (PBS) based materials for drug delivery system

In drug delivery systems, polymers are used to control the release of drugs into the body by either oral administration and/or implant [26]. A drug delivery system is used to sustain the release of drugs and avoid or minimize the daily taking of drugs as well as reduce the side effects [1].

Drug release depends on many factors to obtain the desired results. These factors include preparation method, distribution of drugs into the matrix, concentration of drug, and the interaction between drugs and polymer matrix [1, 26]. For instance, the direct compression process has been used to develop a drug delivery system to control the release of drugs. This is due to the low cost and industrial scalability of the process [1]. It was reported in the study of Llorens *et al*. [26] that poor interaction between drug and polymer matrix resulted in drug migration.

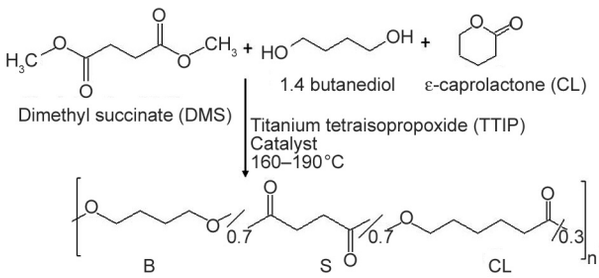

Figure 4. Synthesis of poly(butylene succinate-*co*-ε-caprolactone). Redraw from [1].

There are several methods reported in the literature used to fabricate drug delivery systems with prolonged release of drugs for oral administration and/or implant. These methods include compression moulding and melt extrusion. For instance, Fabbri *et al*. [18], Khalil *et al*. [27], and Galdón *et al*. [1] fabricated PBS-based materials for drug delivery using hot melt processing. In the case of Galdón *et al*. [1], a copolymer poly(butylene succinate-*co*-ε-caprolactone) (Figure 4) was developed to control the release of theophylline, a drug used for lung disease using direct compression, ultrasound-assisted compression, and hot melt extrusion.

A blend of 70/30 (PBS/ε-caprolactone) was prepared, and various loadings (12 to 47%) of theophylline were added to the blends. It was reported that 100% release in 240 min was achieved when 12% was loaded. However, higher loading of more than 12% has resulted in the prolonged release of 100% theophylline to 300 min [1]. Furthermore, the use of PBS-based blend controlled the release dosage of theophylline.

Even though the aforementioned methods (compression moulding and melt extrusion) are widely used in drug delivery systems, there are some inherent drawbacks. For instance, compression moulding and melt extrusion use high temperatures, which can destroy the integrity of the drug. In some cases, plasticizers are added during the melt extrusion processing to improve the processabilities of polymeric material, which is used for drug delivery systems. Some of the widely used plasticizers (*e.g.*, phthalate esters) have been found to be carcinogenic [28].

Most recently, the use of electrospinning techniques to fabricate drug delivery systems has become a research hotspot for developing PBS-based drug delivery systems [12, 17, 26]. Llorens *et al*. [26], a novel scaffold comprising PBS and poly(ethylene glycol) (PEG) for drug delivery system using coaxial electrospinning was developed to control the release

of triclosan and curcumin. This novel technology allows the fabrication of micro and/or nanofibers with a core-shell structure consisting of different compositions. The ensued PBS/PEG electrospun fibres were loaded with triclosan and curcumin. The results suggested that the release of triclosan in phosphate buffer saline was low. This was due to the adsorption of hydrophobic triclosan in hydrophobic PBS. However, it was reported that the lower release of triclosan was adequate to inhibit bacterial colonization. It was also highlighted that the addition of ethanol in phosphate buffer saline led to the higher release rate of triclosan. In the case of curcumin, the medium release was observed due to its hydrophobicity nature and good interaction with PBS. PBS can be functionalized to enhance the interaction with the cellular environment [29]. It is worth noting that the release of curcumin was independent of fibre structure and fibre composition, as well as the presence of ethanol in the medium. In addition, the adhesion and cell proliferation results revealed that both drugs were released during culture.

There are several methods reported to fabricate a drug delivery system. These methods include compression moulding, extrusion, and electrospinning. Recently, there has been a welcomed paradigm shift towards PBS-based nanospheres and microspheres as alternative drug delivery systems [30–33]. This is attributed to the fact that they can be tailored to attain desired particle size morphology and size distribution for good control of drug release.

Mohanraj *et al*. [30] developed PBS microspheres for the delivery of L-dopa. The cationic surfactant cetyl trimethylammonium bromide (CTAB), which produced smooth surface microspheres, as well as non-ionic poly(vinyl alcohol) (PVA), which produced porous microspheres were selected. Phosphate buffer saline and cerebrospinal fluid were used as release media. It was reported that the encapsulation efficiency for smooth and porous microspheres was 62.28±1.08 and 53.93±1.58%, respectively. In addition, the release of L-dopa using phosphate buffer saline from smooth and porous were 25.52 and 30.95%, respectively, within 1 hour. In the case of cerebrospinal fluid, the release of L-dopa within 1 hour from smooth and porous were 28.56 and 58.02%, respectively. Furthermore, the drug release rate was reported to increase over a period due to the slow degradation of microspheres. Based on their findings, the authors suggested that microspheres loaded with drugs can be administered by intravenous injection so that it reaches the target organ very quickly. Brunner *et al*. [32] reported similar observations. In their study, they investigated the effect of concentration of PVA, encapsulation efficiency of all-trans retinoic acid (atRA), and drug loading. The results revealed that atRA was successfully encapsulated with the encapsulation efficiency of 75% and drug loading of 14% when 4% of PVA concentration was used. The release rate was 9% in 4 weeks. In another study reported by Murase *et al*. [31] PBS microsphere was developed to control the delivery of indoles (indole, 1-methylindole, 2-methylindole, 3-methylindole, 2-phenylindole). The authors indicated that the encapsulation efficiency of the drugs studied was not the same. For instance, 1-methylindole had the lowest encapsulation efficiency, whereas 2-phenylindole had the highest when compared to all other drugs studied. It is worth mentioning that the lower the encapsulation efficiency, the weaker the interaction between the drug and the polymeric matrix. The major drawback of indoles is their slight solubility in water. The authors reported that about 80% of indoles were released from microspheres after 4 hours. However, due to the slight solubility in water, the release was halted after 4 hours of exposure. The solubility of drugs was improved by the addition of ethanol into a release medium (phosphate buffer saline). The authors reported that ethanol enhances the hydrophobicity and the swelling of microspheres which results in the improvement of drug diffusion to the medium. Moreover, the results demonstrated that indoles could be used as antiproliferative drugs for cancer cells.

Some of the drawbacks restricting the widespread use of PBS in the biomedical sector include hydrophobicity, slow degradation rate, inadequate biocompatibility, and lack of reactive centers for binding with drugs [29]. In recent years, three main strategies have been used to mitigate these challenges and expand its applications; these include copolymerization and developing blends of PBS with different polymers to improve their properties. The blending technique is an interesting solution to enhance the properties, but it is limited by compatibility considerations. The third strategy involves reinforcements with fillers or fibres to enhance their performance while the PBS matrix provides structural properties.

Different research groups synthesized various novel PBS copolymers possessing unique properties, such

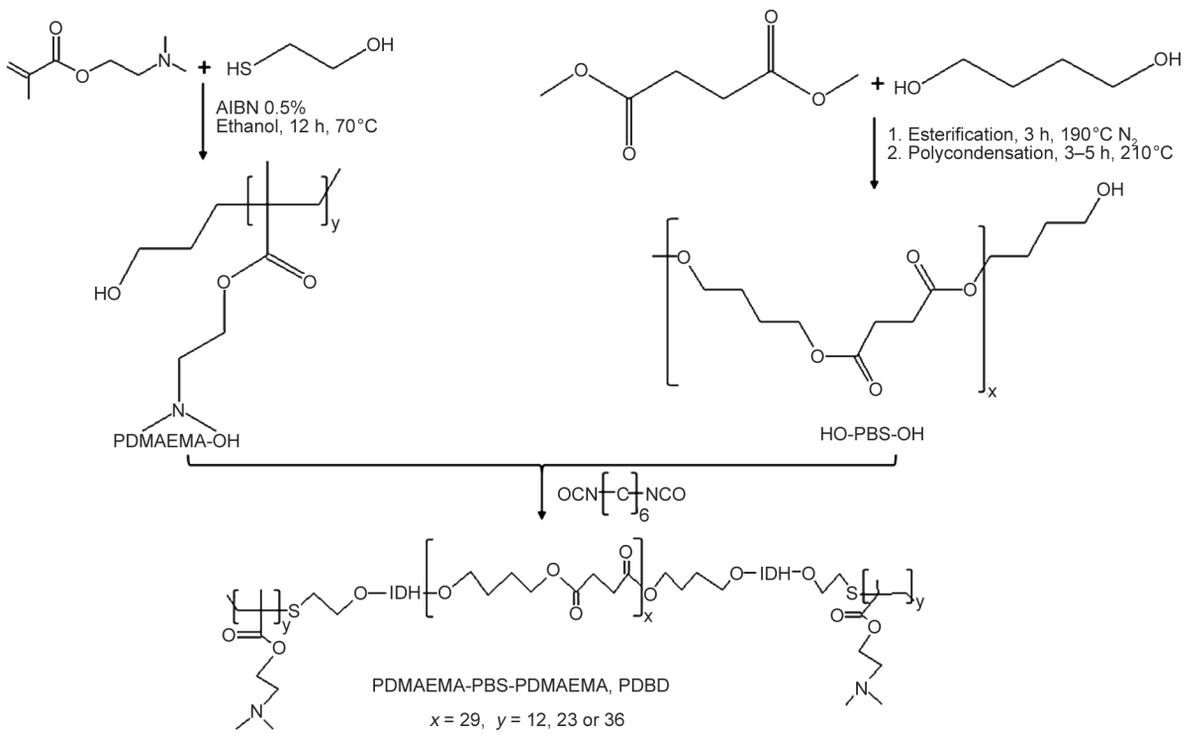

Figure 5. Synthesis of poly[2-(dimethylamino)ethylmethacrylate]–poly(butylene succinate)–poly[2-(dimethylamino)ethylmethacrylate] (PDMAEMA–PBS–PDMAEMA,PDBD). Redraw from [29].

as biodegradation, hydrophilicity, and biocompatibility for drug delivery [18, 29, 34–36]. In addition, the introduction of functional groups in ether linkages of PBS chains triggers the hydrolysis degradation process and their flexibility [18]. These researchers successfully synthesized PBS copolymers by modifying PBS chains to control the delivery of drugs. In the case of Zhao *et al*. [29], a novel copolymer poly[2-(dimethylamino)ethylmethacrylate]–poly (butylene succinate)–poly[2-(dimethylamino)ethylmethacrylate] (PDMAEMA–PBS–PDMAEMA, PDBD) (Figure 5) was successfully prepared through a chain-extension reaction.

The results revealed that these copolymers formed spherical micelles with small particle sizes of about 90 nm. The micelles developed had a hydrophobic core structure of PBS and hydrophilic poly[2-(dimethylamino)ethyl methacrylate] outer shell. The introduction of doxorubicin drug into the micelles resulted in the micelles with small particle sizes with narrow size distribution, which suggest good performance of micelles. The authors reported that 34% of doxorubicin was released after 6 hours from micelles prepared at neutral pH. However, it was noticed that at lower pH (pH = 4) about 56% of doxorubicin was released. The increase in the release of doxorubicin at lower pH was due to higher solubility of the drug in acidic medium and swelling of micelles attributed to protonation of amino groups in the copolymer in an acidic medium. Furthermore, the resulting micelles demonstrated very low toxicity, making them a suitable candidate for drug delivery. In contrast, da Costa *et al*. [35] reported that the introduction of the drug (Meloxicam) did not significantly affect the size of particles. The results showed that the encapsulation efficiency of the drug was 79%. Unlike in Zhao *et al.* [29] study, in this study, the release of drug was faster at a higher pH medium than in a lower pH medium. This behavior was due to the good interaction between drug and polymer in alkali media. The developed materials showed the potential to be used as transdermal patches.

In another study [18], PBS copolymers containing ether-oxygen atoms were fabricated to deliver the drug dexamethasone. The results showed that the modification of PBS with triethylene glycol (TEG) resulted in improved hydrolytic degradation. In addition, copolymers sustained good cell adhesion and proliferation. The particle size of copolymers was larger than those of neat PBS. Also, the results revealed that copolymers had lower encapsulation efficiency than that neat PBS due to the high hydrophobicity nature of PBS. It was also observed that the drug release was faster in the copolymer in

comparison to neat PBS due to the higher hydrophilicity of copolymers and improved degradation rate. Most recently, Ferreira *et al*. [36] modified PBS using biobased rutin, also known as vitamin P and castor oil, in order to investigate their potential as a delivery system of silybin. The results revealed that the modification of PBS with rutin and castor oil led to the lower release of silybin.

In recent years, blending PBS with various polymers such as starch, keratin, and polyethylene glycol (PEG) as well as reinforcing PBS with fillers has received considerable interest in biomedical applications, especially in drug delivery [27, 37–39]. In general, the drug release depends on the blend composition and blend morphology [27]. For instance, Guidotti and coworkers [17, 38] prepared a blend of PBS and keratin at the ratio of 50:50 through electrospinning for drug delivery. The developed blend exhibited excellent drug release properties and improved the biodegradability of PBS. The release rate further improved when the loading of keratin was increased. Soares *et al*. [37] developed a blend of PBS/PEG, and PBS/PEG reinforced with montmorillonite (MMT) organoclay for the release of praziquantel. The addition of organoclay in a blend enables a controlled release of praziquantel dissolution process by allowing praziquantel to be in a dissolution medium for 72 hours. In the case of the neat blend, the dissolution of praziquantel in the medium occurred within 24 hours.

3.2. PBS-based materials for tissue engineering

Over the past decades, thermoplastic polymers have been widely used in biomedical applications because they can easily be designed into customized shapes depending on the intended applications. The selection of suitable polymeric materials for biomedical applications, such as scaffolds for tissue engineering, is the most crucial step toward the fabrication of the resultant materials [39]. Research on tissue engineering has gained considerable attention in the last decades for restoring, maintaining, and/or improving tissue functions that are damaged [40, 41]. Recently, tissue engineering has been used for the regeneration of different types of tissues such as bones, skin, *etc*. [39, 42]. For instance, Deepthi *et al*. [42] fabricated a ternary hydrogel scaffold comprising PBS/chitin/chondroitin sulfate nanoparticles for skin tissue engineering. The resultant scaffold demonstrated a large surface area suitable for more human dermal fibroblasts adhesion, better cell proliferation, and low cytotoxicity, thereby, promoting skin regeneration. Scaffolds for tissue engineering can be made from synthetic polymers or natural polymers, blend polymers, and/or polymer-based composites.

In recent years, there has been a paradigm shift toward the development of biopolymer-based scaffolds for tissue engineering. Poly(lactic acid) (PLA), polycaprolactone (PCL), poly(glycolic acid) (PGA), poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV), and poly-(butylene succinate) (PBS) are amongst the widely used biopolymers to fabricate scaffolds for tissue engineering. This is due to their unique properties, *i.e.*, biodegradability, biocompatibility, good mechanical, and non-toxicity [7]. PBS has been one of the most widely used biopolymers for developing scaffolds for tissue engineering due to its flexibility, biodegradability, high degree of crystallinity, and non-toxic [43].

Studies have demonstrated that PBS is biocompatible as it supports attachment, proliferation, and differentiation of human fibroblast cells [43]. PBS also possesses good degradation behavior in phosphate-buffered saline. The biocompatibility and degradation behavior together with other properties, such as good mechanical and thermal properties as well as good processability indicate that PBS is one of the most suitable biopolymers for tissue engineering applications [44, 45]. One of the most crucial advantages of PBS is that it can be easily tailored through copolymerization using various monomers (*e.g*., dilinoleic acid, lactic acid, terephthalic acid, *etc*.) to improve its properties to afford their application in tissue engineering [46]. Poly(butylene succinate-*co*-dilinoleic succinate) (Figure 6) has been explored as the material

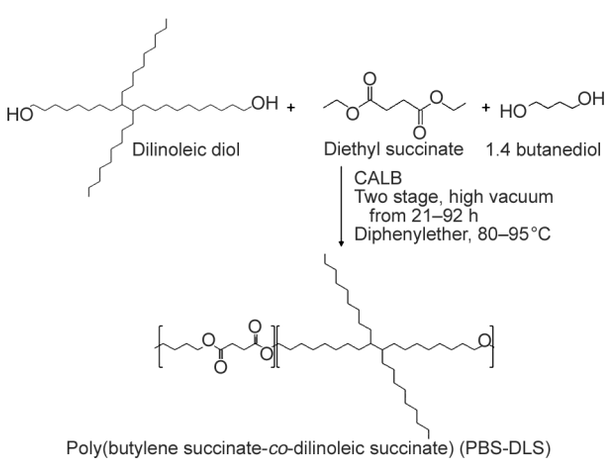

Figure 6. Synthesis of poly(butylene succinate-*co*-dilinoleic succinate). Redrawn from [47].

of choice to fabricate helically coiled scaffolds that can be used for heart-related tissue engineering.

The resulting three-dimensional (3D) materials were analogous in terms of architecture and behavior of human tissues, especially heart muscle perimysium which is composed of microscale coiled fibers [12]. On the other hand, copolymerization of PBS with carboxylic acid induces enzymatic degradation, making it a suitable candidate for different biomedical applications [46].

The ideal scaffolds should allow cells to adhere and proliferate, leading to the formation of an extracellular matrix (ECM), displaying high porosity, interconnected structure, good mechanical properties, and uniform distribution throughout the scaffolds [41], as depicted in Figure 7.

In this context, numerous researchers have developed highly porous electrospun fibres made from PBS for soft tissue engineering and wound dressing [12, 43, 46, 48]. The high-quality fibres with less bead

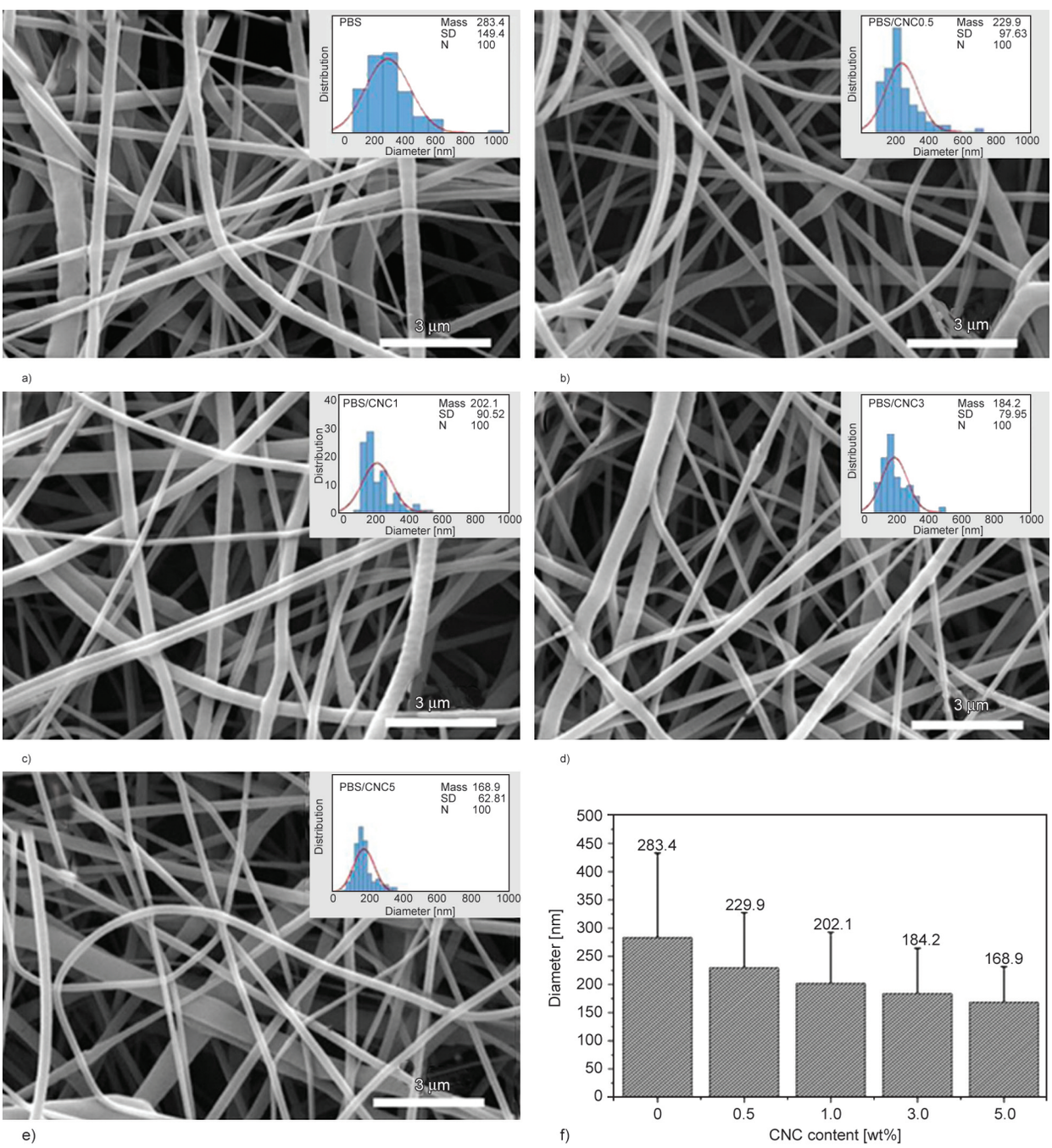

Figure 7. SEM micrographs of electrospun fibres. a) neat PBS, b) PBS reinforced with 0.5 wt% CNC c) PBS reinforced with 1 wt% CNC, d) PBS reinforced with 3 wt% CNC, e) PBS reinforced with 0.5 wt% CNC and f) electrospun fibre diameters reproduced from [41].

or bead-free are achieved by optimizing parameters such as the solvent system used, grade of PBS, the concentration of PBS, applied voltage, and distance between the electrodes [48]. For instance, 15% (w/v) of bio PBS was prepared by dissolving it in a mixture of chloroform and dimethyl sulfoxide (DMSO) at 50 °C under vigorous stirring for 2 hours. The electrospinning process was conducted at 15 kV applied voltage, 1.5 ml/h flow rate, 20 cm tip-top-collector distance, and 18-gauge blunt-tipped needle, under ambient conditions (19–21 °C, 55–65% relative humidity). The resultant electrospun fibres exhibited good tensile strength and modulus as well as high porosity at micro and nano levels which makes them preferable for soft tissue engineering [48].

The main challenge associated with conventional electrospinning is the production of two-dimensional (2D) non-woven mats, which limits their applications. In order to mitigate those challenges, a number of researchers fabricated 3D electrospun fibres [12, 41]. Sonseca *et al.* [12] developed 3D PBS-based scaffolds for smooth muscle tissue engineering. The scaffolds consist of large surface area, high porosity, and good elasticity which afforded the scaffolds with facilitated cell proliferation. The development of artificial scaffolds for peripheral nerve regeneration using electrospinning was demonstrated by Cicero and colleagues [49]. The resultant 3D PBS-based scaffolds were flexible thin sheets with diameters ranging between 1–5 microns. The scaffolds were implanted in rats to stimulate, and repair severed peripheral nerves, as shown in Figure 8. The findings revealed that after 120 days, there was a complete re-adsorption which indicates the biocompatibility of scaffolds and hence demonstrates that 3D PBS-based scaffolds have a great potential for nerve regeneration.

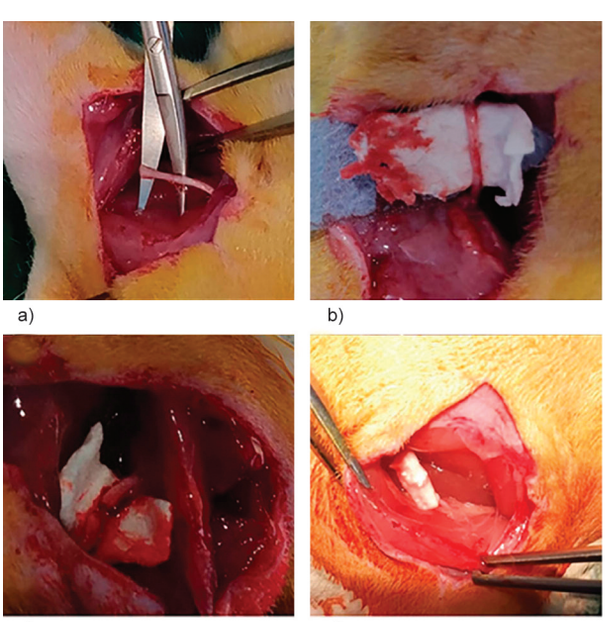

Figure 8. a) Nerve isolation, b) implantation of PBS scaffolds, c) nerve section, d) nerve wrapping. Reproduced from [49].

3D scaffolds made from PBS alone are, however, limited in terms of mechanical properties, performance, and surface structure. Huang *et al*. [41] and Ju *et al*. [50] incorporated cellulose nanocrystals (CNC) in PBS to address the aforementioned challenges of PBS. The findings revealed that the introduction of 3 wt% CNC into PBS led to the improvement in crystallinity, mechanical properties, and hydrophilicity. It is noteworthy mentioning that the incorporation of CNC into PBS also improved the overall porosity, biodegradation, and biocompatibility when compared to neat PBS. The cell proliferation was better in the case of PBS reinforced with CNC in comparison to neat PBS. This is because the NIH-3T3 cell spread very well in the PBS-based composite in comparison to neat PBS. In addition, PBS-based composite comprises an open pore and bimodal structure which favors cell attachment and proliferation.

A literature study indicates that the overall properties of PBS-based materials for tissue engineering were enhanced by blending with other polymers [43]. In this interesting study, the optimum properties and bioactivity were reported for PBS/PLA in ratios of 50/50 wt%. Additionally, blending PBS with PLA (50/50 wt%) resulted in uniform and smooth fibres without beads. The properties of PBS/PLA (50/50 wt%) blend were improved by reinforcing with cellulose nanofibres (CNF). The results revealed that the incorporation of CNF into the blend enhanced the mechanical performance of the blends due to the strong interaction between CNF and the polymer matrix. Also, the incorporation of CNF led to the reduction in fibre size and improved the human dermal fibroblast attachment of the resultant scaffold, cell proliferation as well as protein attachment on the scaffold due to the reduced size of the fibres. Therefore, the resultant scaffolds demonstrated a potential for vascular tissue engineering applications [43].

Another major drawback of PBS is inadequate osteoblast biocompatibility and bioactivity which limit their applications for bone tissue regeneration [9]. To overcome these challenges and to improve biocompatibility and bioactivity, surface modification

and reinforcing PBS should be considered [9, 51–53]. Wang, *et al*. [9] modified PBS with H_2O or NH_3 plasma immersion ion implantation (PIII) to enhance biocompatibility and bioactivity. The results revealed that plasma treatment improved the hydrophilicity and roughness of the polymer. As a result, osteoblast biocompatibility was enhanced after the treatment which suggests that the resultant material is suitable for bone replacement implant. Another strategy for improving biological performance such as biocompatibility and bioactivity is to introduce material which can readily degrade and maintain high bioactivity. Ceramics, such as hydroxyapatite, and nano-fluorapatite have been widely used as bioactive materials for bone regeneration because they can easily bond with living cells through the apatite layer formed on the ceramic surface [54]. However, natural bone tissue is made up of inorganic compounds (apatite) as well as organic material (collagen). Therefore, in order to promote bone regeneration and design bone tissue engineering the material must contain both inorganic and organic materials such as a polymer. The ensued material must have good properties in comparison to neat inorganic and organic material. In addition, the developed material must mimic the natural bone structure in terms of properties. Recent studies on PBS reinforced with bioactive materials such as hydroxyapatite [54], nano-fluorapatite [52], nanolaponite [11], silica-nanotubes, and strontium hydroxyapatite [55, 56], magnesium phosphate [57] have shown a significant improvement in bone functions. In the study investigated by Prowans and co-workers [54], poly(butylene succinate-butylene dilinoleate) (PBS-DLA) copolymer reinforced with 30 wt% hydroxyapatite was fabricated for bone healing. The incorporation of hydroxyapatite into PBS copolymer resulted in the increased tensile modulus while maintaining good elongation at break. The healing process of bone after fracture, as depicted in Figure 9, stabilized with implanted PBS copolymer reinforced with 30 wt% hydroxyapatite. The histology results revealed that the healing process was taking place after implanting PBS copolymer-based composites due to the presence of hydroxyapatite. In addition, the presence of calcium and phosphate ions in the hydroxyapatite triggered bone regeneration.

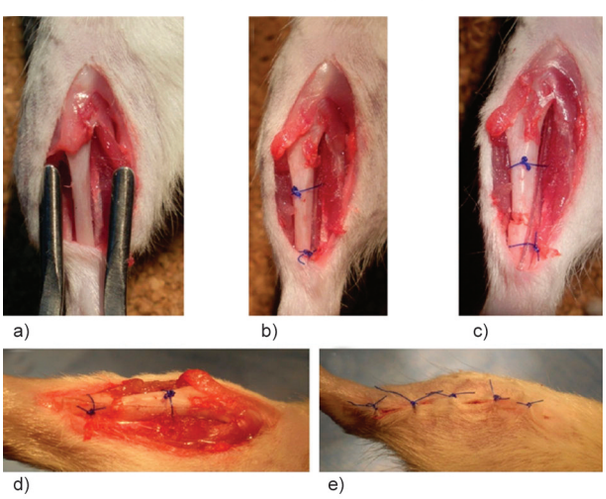

Figure 9. Images of a) limb prepared for a procedure, b) limb exposed in tibia, c) implanted composites stabilized with two nonabsorbable Prolen 5.0 stitches, d) bone cut and stabilized with the composites, e) stitched after surgery. Reproduced from [54].

Another study investigated the incorporation of nano-fluorapatite into PBS. The results demonstrated that the presence of nano-fluorapatite promoted biocompatibility and bioactivity in the resulting composite material [52]. Similar observations were reported by other researchers [11, 57]. In addition, the fabricated PBS composites reinforced with nano-fluorapatite exhibited a highly reactive surface which enables it to combine with living cells of bone tissue without fibrous capsule tissue. Thus, displaying good osteoconductive [52]. Moreover, the presence of inorganic fillers in PBS inhibited the growth of *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) indicating that the resultant materials have antimicrobial activity [11]. The incorporation of inorganic fillers into PBS-based materials can also trigger the hydrolytic degradation process [55–57]. Other researchers have blended PBS with natural polymers such as chitosan to fabricate scaffolds for tissue engineering to overcome the aforementioned drawbacks of PBS [39, 58, 59]. Chitosan has been investigated in biomedical applications due to its advantages such as non-cytotoxicity, biodegradability, non-antigenicity, and biocompatibility. The results showed that the introduction of chitosan into PBS blends promoted the adsorption of human serum albumin (HSA) and human plasma fibronectin (HFN). However, the highest adsorption was noticed in the case of HSA. The *in vitro* studies revealed that the human osteosarcoma cell proliferated in the blend. In contrast, high proliferation was noticed in neat PBS [58]. Further studies were performed using human bone marrow mesenchymal stem cells (hBMSCs) on the PBS blended with chitosan scaffolds. The scanning electron microscopy (SEM) results showed excellent cell adhesion on the surface of the

scaffold and cell proliferation. The *in vivo* studies were performed on critical cranial bone defects in nude mice using PBS blend scaffold and hBMSCs. The micro-computed tomography (μCT) findings demonstrated that the cell construct enabled bone regeneration after 8 weeks of implantation [39].

3.3. PBS-based shape memory for biomedical devices

Shape memory polymers (SMP) are often fabricated based on the structure and the properties of the intended applications as depicted in Figure 10. PBS-based SMP has received great attention due to its biodegradability, biocompatibility, and non-toxicity. PBS based SMP are designed using various strategies; namely: (i) crosslinked homopolymer, (ii) segmented block copolymers, (iii) blending polymers, (iv) supramolecular polymer network, (v) polymer composites [60, 61]. Blending is the most popular strategy to design multi-shape materials with multiple properties. For instance, Zheng *et al*. [62] fabricated multiple shape memory consisting of PBS, PCL, and polyurethane (TPU). The resultant multi-shape memory is comprised of temporary and permanent shapes. The shape memory test results revealed that the system had a larger fixing ratio and recovery ratio. These results suggest that the resultant material has potential in the field of biomedical devices.

However, to the best of our knowledge, there is little information reported in the literature about designing biomedical devices from PBS-based SMP. Much research is only focusing on the synthesis and characterization of PBS-based SMPs [62, 64–70]. The newly developed PBS-based SMPs demonstrated good ductility which allows remarkable reversible deformation, good thermal properties, good crystallinity for biomedical devices, and are more hydrophilic [62, 64–70]. Huang *et al*. [66] synthesized and characterized poly(butylene succinate)-poly(ethylene glycol) (Figure 11) multiblock copolymer for biomedical devices.

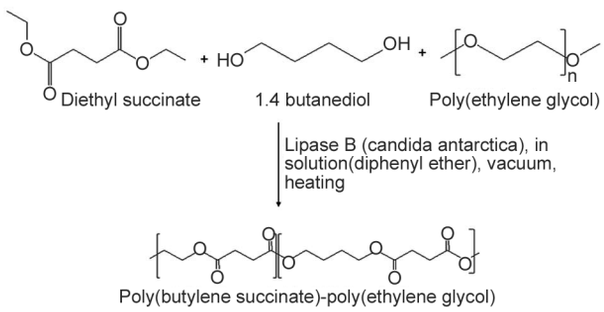

Figure 11. Synthesis of poly(butylene succinate)-poly(ethylene glycol). Redraw from [71].

The results showed that the synthesized multiblock possess two different crystalline regions. These crystalline regions showed both temporary and permanent shapes. In addition, multiblock demonstrated good elongation at break as well as high hydrophilicity, indicating that the material can be used to fabricate biomedical devices.

In another study, Lin *et al*. [72] designed a shape memory blend of PBS and PLA for biomedical

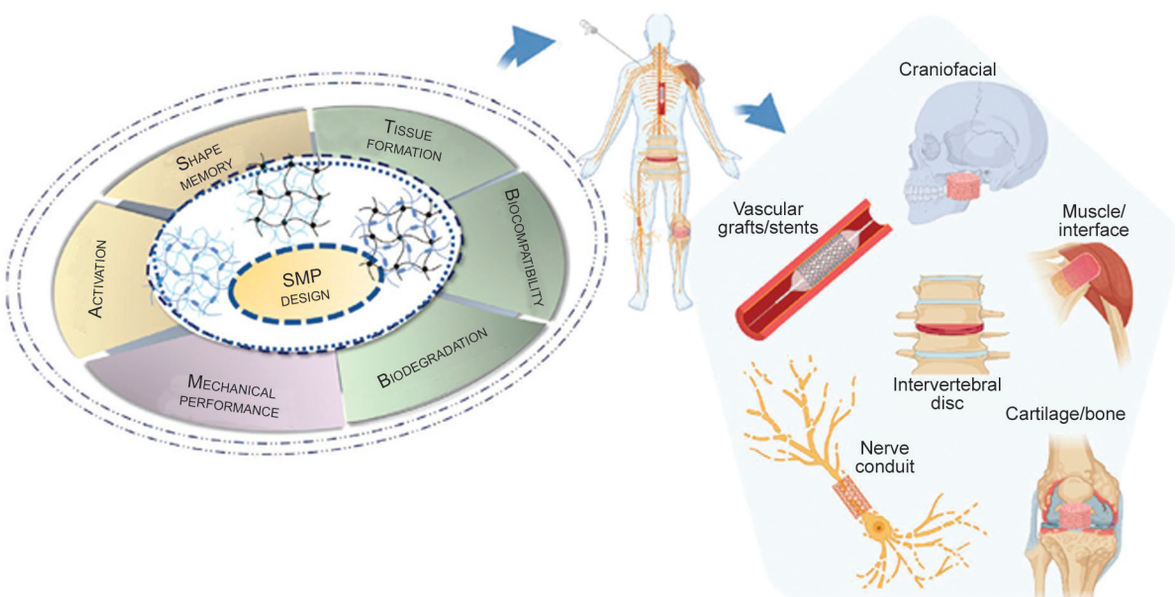

Figure 10. Shape memory polymers used in various biomedical applications. Reproduced from [63].

applications using 4D printing. 4D printing was used to develop the patient customized biomedical device, such as an aneurysm model because the structure and dimensions of the final product can be regulated. The resultant PBS SMP consisted of hard and soft phases. The soft phase is responsible for shape fixation performance whereas the hard phase is for shape recovery performance. In addition, the ensued SMP displayed improvement in flexibility which has potential in tissue engineering and photothermal therapy. Since the market for PBS is growing and the fact that it possesses good properties, it is projected that variety of applications such as biomedical devices, sensors and others will be explored.

4. Other applications of PBS-based polymers

PBS has garnered tremendous interest in other applications such as food packaging, the agricultural sector, *etc*., as shown in Table 2 [13, 73]. As previously mentioned, PBS offers unique properties which match those of non-biodegradable synthetic polymers

Table 2. Other applications of PBS-based materials.

Material	Processing methods	Intended applications	Summary of results	References
Aerogel PBS	Compression moulding	RF and Microwave	A composition of 97 wt% PBS and 3wt% silica aerogel PBS covered a bandwidth of 9.4 GHz with stopbands from 5.5 to 5.8 GHz and 7 to 8.3 GHz.	[78]
PBS reinforced with inorganic fillers (ZnO, silver zeolite)	Twin screw extruder and blown film	Food packaging	– The incorporation of 0.5 to 6 wt% of ZnO and silver zeolite into PBS resulted in decrease in mechanical properties of PBS films – Also, cold crystallization temperature (T_{cc}) and T_g of composites decreased whereas crystallinity increased – PBS-based composites reinforced with ZnO and silver zeolite displayed antimicrobial properties. Release test in the case of PBS reinforced with ZnO demonstrated that Zn^{2+} migrated over 15 days	[79, 80]
Poly(butylene succinate-*co*-hexamethylene succinate) (Figure 12a)	Melt polycondensation	Greener coatings for paper packaging	– PBS copolymer composed of 1:1.1 ratio of succinic acid and diol(s) resulted in decreased crystallinity while flexibility increases – The solubility of the resultant copolymer increased with the loading of hexamethylene succinate (HS) was increasing	[81]
Poly(butylene succinate co-propylene succinate) (Figure 12b)	Esterification and polycondensation	Medical support, coating, and phase-change material	– T_m, T_{cc}, crystallinity, T_g, and degradation temperature decreased with an increase propylene succinate (PS) loading up to 40% – In addition, tensile strength and modulus decreased with increasing PS loading	[82]
PBS/curaua fibres	Compression moulding	Rigid packaging or interior car parts	– Incorporation of 20 wt% of fibres into PBS improves impact and flexural strength and water absorption of composites	[83]
PBS/PCL membranes	Immersion precipitation.	Wastewater treatment	– Blending 30 wt% PBS and 70 wt%PCL improved water uptake due to increased porosity – The blend had high water flux, flux recovery, and permeate flux of 106, 26, and 37%, respectively – In addition, the blend demonstrated higher rejection of pollution indices when compared to neat PCL	[84]
Poly(butylene succinate-*co*-terephthalate) (PBST) (Figure 12c)	Electrospinning	Wastewater treatment	– Functionalized PBST with cyclodextrin demonstrated higher efficiency in removing methylene blue (MB) dye – Also, functionalized PBST membrane exhibited a maximum adsorption capacity of 90.9 mg/g	[85]

Table 2. Continuously 1.

Material	Processing methods	Intended applications	Summary of results	References
PBS/acrylonitrile butadiene styrene (ABS)	Solvent casting	Wastewater treatment	– Tensile strength and modulus of the blends improved with increasing ABS loading from 10–30wt% – Blends had less irreversible fouling and the water filtration suggested that chemical oxygen demand rejection dropped whereas permeable flux increased with the increasing ABS loading from 10–30 wt%. In addition, all membranes rejected 100% of turbidity	[86]
PBS/cyclic olefin copolymer (COC)	Solvent casting	Packaging	– Blending 30 wt% PBS and 70 wt% COC enhanced mechanical properties and demonstrated good resistance to the bacterial growth	[87]
PBS/starch, chitin, and cellulose nanocrystals	Chill-roll cast film extrusion, twin screw extruder	Packaging	– Incorporation of 1 wt% nanocrystals into PBS enhanced tensile and barrier properties. In addition, the increase in nanocrystals loading to 3 wt% results in to increase in both mechanical and barrier properties – The composites were biodegraded in approximately 3 months using wastewater treatment sludge	[88, 89]
PBS/geraniol	Twin screw extruder	Bread shelf-life extension	– PBS-based material containing 10 wt% geraniol showed good antimicrobial properties – Release test revealed that the migration concentration of geraniol increased with increasing humidity – Shelf-life extension results indicated that the spoilage of bread stored using the resultant material was delayed by three weeks	[90]
PBS/Curcumin and Carvacrol	Solvent casting	Active packaging	– The PBS films containing 1 wt% of curcumin and carvacrol demonstrated antimicrobial properties and improved antioxidant activities	[91]
Poly(butylene-succinate-*co*-adipate) (PBSA) based materials (Figure 12d)	Melt mixer and blown film	Active packaging of bread	– The films possess lower tensile strength and modulus while elongation at break was higher when compared to neat PLA – Mould was observed after 7 days on the bread package in comparison to 6 days observed when neat PLA was used	[92–95]
PBS/quercetin	Solvent casting	Food packaging	– Introduction of quercetin 0.05 to 0.25 phr resulted in changing of color, opacity, and UV-blocking effect – There were no significant changes observed in mechanical properties of the resultant PBS-based films – The resultant films displayed some bactericidal activity	[96]
PBS/modified tapioca starch/natural fibres	Twin screw extruder and compression moulding	Agricultural Mulch Films	– PBS composites reinforced with natural fibres (5 to 30 wt%) exhibited decreased tensile modulus, elongation at break, and flexural properties – Biodegradation was enhanced in the soil burial test	[97, 98]
PBS/maghemite	Hot melting	Oil spill clean-up	– Results showed that 1g of the PBS-based composites containing 5 wt% maghemite was able to remove 11 g of the petroleum from the water.	[99]
PBS/CNC	Melt mixing and supercritical CO_2	Thermal insulation	– Composite containing 1 wt% CNC demonstrated a high volume expansion ratio of 37.1 times and outstanding thermal conductivity of 0.021 $W(m \cdot K)^{-1}$	[100]

Table 2. Continuously 2.

Material	Processing methods	Intended applications	Summary of results	References
PBS containing thioether-linkages	Melt polycondensation	Food packaging	– Co-polymers exhibited lower tensile strength and modulus and higher elongation at break when compared to neat PBS – Co-polymers displayed improved barrier properties to both CO_2 and O_2 gases when compared to neat PBS	[101–103]
PBS and PBSA	Blown film	Poultry meat packaging	– Both films had higher water vapor transmission rate (WVTR) and oxygen permeability than commercially used polyamide (PA)/PE film – Both PBS films produced complied with European legislation (Regulations 1935/2004 and 10/2011)	[95, 104]
PBS/PLA reinforced with cellulose fibres	Melt mixer, compression moulding, injection moulding	Hot cups and food packaging	– Blend composition of 20 wt%PBS and 80 wt% PLA containing various loading (0.5 to 15 wt%) of cellulosic fibres were investigated – Results revealed that low loadings (0.5 to 1.5 wt%) reduced the mechanical properties of the blend whereas high loadings (5 to 15 wt%) improves mechanical properties – Addition of low loadings improved the thermal stabilities of the composites whereas the incorporation of high loadings resulted in intermediate thermal stabilities	[105, 106]

with the added biodegradable and sustainable features. As a result, these materials are anticipated to replace non-biodegradable synthetic polymers and alleviate environmental pollution caused by plastics. Although PBS-based products have demonstrated potential in various applications, however, the shelf life and disposal should be taken into consideration to alleviate environmental pollution. Unlike a biomedical application, PBS-based products after the end of service life undergo biodegradability in soil and compost conditions. Numerous studies have investigated the biodegradation of PBS-based materials in soil and compost [74–77]. The findings revealed that the rate of biodegradation of PBS was slower than that of PBS composites reinforced with natural fibres. In addition, composting environmental conditions provide a high rate of biodegradability for both PBS and its biocomposites in comparison to soil environmental conditions.

5. End-life options of PBS biobased materials

Figure 13 shows a variety of mechanisms responsible for biodegradable poly(butylene succinate) PBS-based polyesters degradation. Polymer chemical bond degradation mainly takes place through polymer chain scission either through the main chain or side chains of polymer molecules, induced by their thermal

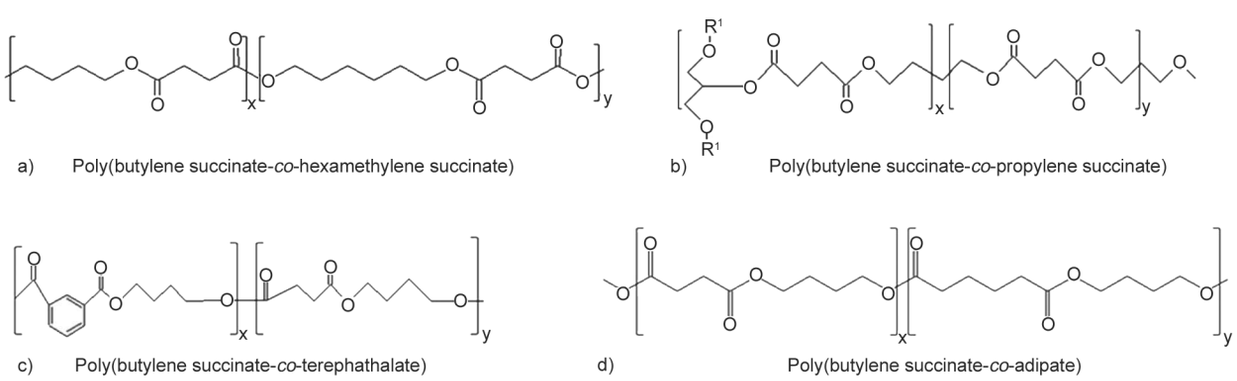

Figure 12. Structure of copolymers presented in Table 2. a) Poly(butylene succinate-*co*-hexamethylene succinate, b) poly (butylene succinate-*co*-propylene succinate, c) poly(butylene succinate-*co*-terephathalate), and d) poly(butylene succinate-*co*-adipate).

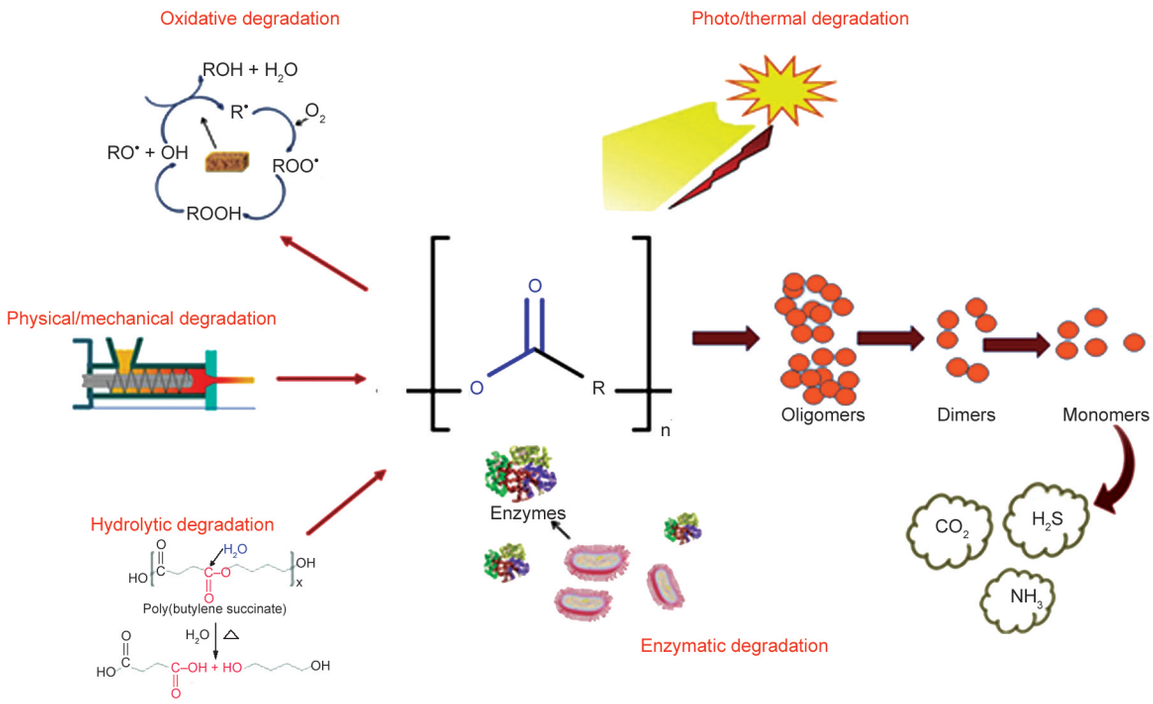

Figure 13. Modes of polymer degradation. Redrawn from [13, 73, 107].

activation, oxidation, photolysis, and hydrolysis (Figure 13). Photodegradation refers to polymers degraded by photolysis to give lower molecular weight molecules, whereas mechanical degradation refers to polymers that can be degraded into smaller pieces by an external load, such as polymer processing, shearing forces, and others. Oxidative degradation refers to polymer degradation induced by atmospheric oxygen, especially in the autocatalytic process of attack on the hydrogen atoms, to form hydroperoxides. Hydrolytic degradation refers to polymers having hetero backbone chains degradation induced by hydrolysis reaction either biotic (living cell or microorganisms) or abiotic (mainly pH) or both. Biodegradation of polymers refers to polymers undergoing degradation in biological environments when living cells or microorganisms are present around the polymers. Such biological conditions include soil and water as well as the body of human beings and animals [73].

Since this review is dedicated to describing the application of PBS in biomedical applications, our discussion on the degradation of biodegradable polymers will only focus on the degradation processes that occur under biological environments either through enzymatic or non-enzymatic hydrolysis and/or oxidation. In this context, the degradation of PBS and PBS-based materials will be described in comparison with other bio-polyesters. Biodegradable polyesters (*e.g.*, polybutylene succinate PBS, polylactides PLAs, and other biodegradable aliphatic-aromatic co-polyesters) are hydrolyzed in our body to their respective monomers and oligomers that are soluble in aqueous media [13].

The rate of degradation of PBS-based biodegradable polymers and blends is mainly dependent on polymeric characteristics, such as chemical structure, distribution of repeating units, molecular weight, polydispersity, presence of low molecular compounds (monomers, oligomers, solvents, plasticizers, presence of ionic groups, presence of chain defects, morphology (crystallinity, microstructure, orientation), processing methods and conditions and mechanism of hydrolysis (enzymes *vs* water) [13].

Generally, the weight loss of biopolymers that occur over time in the living body is referred to as absorbable or resorbable polymers under enzymatic or non-enzymatic hydrolysis or/and both conditions. The term 'biodegradable' is often used only for such industrial and ecological applications which have been developed aiming to address post-consumer pollution issues in natural environments (terrestrial and aquatic). Polymers used for medical purposes by implanting or contact with the human body should not be called biodegradable but can be called resorbable or adsorbable polymer or even sometimes polymeric biomaterials [13, 73].

In this review article, however, the term biodegradable is used since the term has been widely utilized

in the polymeric biomaterials world the biomedical polymers that are absorbed in the body even through non-enzymatic hydrolysis. In other words, the term biodegradable is used here with the broad meaning that polymer will eventually disappear after introduction into the body.

Hydrolytic and enzymatic degradation

In biomedical applications, the degradation of biodegradable polymers in hydrolytic and enzymatic conditions is widely studied under physiological conditions (mostly at 37 °C, pH 7.4, phosphate-buffered saline). In in-vitro conditions, the hydrolytic degradation of aliphatic polyesters is influenced by different factors, *e.g.*, chemical structure, hydrophilic–hydrophobic nature of materials, molecular weight and molecular weight distribution, surface morphology and degree of crystallinity, and the physiological conditions exposed [13]. The hydrolytic degradation of polyesters, including PBS and its biodegradable blends and composites, undergo two-step processes. In the first step, a random chain scission occurs on the polymeric molecules where a decrease in the molecular weight, weight loss, and increasing water-soluble low molecular compounds during incubation time occurs [13, 108]. In the second step, when the polymeric material undergoes molecular weight reduction of less than 13 000 Da, the low molecular compounds of oligomers, dimers, and monomers become water soluble with less incubation time. Understanding each polymeric system and its composition degradation behavior requires an extensive study of the degradation profile, molecular weight changes, and weight losses as a function of incubation time by various analytical techniques. Table 3 provides the hydrolytic and enzymatic degradation studies conducted on PBS and PBS-based polymeric materials under different degradation conditions.

Many authors observed that neat PBS undergoes slow hydrolytic degradation under physiological conditions and the molecular weight remains the same for several weeks due to its molecular weight distribution, high crystallinity, and hydrophobicity [44, 110, 118–120]. On the other hand, copolymerization

Table 3. Hydrolytic and enzymatic degradation studies of PBS-based systems. The copolymers' molecular structures are presented in Figure 14.

Polymeric material	Degradation conditions	Time [d]	Weight loss [%]	Refences
Poly(butylene succinate) (PBS)	Hydrolytic: physiological conditions (37 °C, pH = 7.4).	105	65	[44]
Poly(butylene succinate-*co*-cyclic carbonate)s (PBS-*co*-CC)	Hydrolytic: physiological conditions (37 °C, pH = 7.4).	40	0	[109]
	Enzymatic: lipase Novozyme 435	25	40–70	
	Enzymatic: lipase porcine pancreas	20	40–90	
Poly(butylene succinate-*co*-dimethyl 5-sulfoisophtalate sodium salt)s (PBS-*co*-BSi)	Hydrolytic: physiological conditions (37 °C, pH = 7.4).	80	3–5	[110]
Poly(butylene succinate)-*block*-poly(triethylene succinate) (PBS-*b*-PTES)	Hydrolytic: physiological conditions (37 °C, pH = 7.4).	225	0–35	[111]
Poly(butylene succinate)–silica nanocomposites (PBS/Si); poly(butylene succinate)–strontium hydroxyapatite nanocomposites (PBS/SrHA)	Enzymatic: *R. delemar* and *P. cepacia lipases*	30	2–16	[55]
Poly(butylene succinate) urethane ionenes (PBSUI)	Hydrolytic: physiological conditions (37 °C, pH = 7.4).	4	5–35	[112]
Poly(butylene terephthalate)-*co*-poly(butylene succinate)-*block*-poly(ethylene glycol) (P(BSBT)-*b*-PEG)	Hydrolytic: physiological conditions (37 °C, pH = 7.4).	63	3–33	[113]
Poly(butylene succinate)-*blend*-chitosan (PBS/Chitosan)	Hydrolytic: physiological conditions (37 °C, pH = 7.4).	30	1–7	[114]
Poly(butylene-*co*-2,4,:3,5-di-*O*-methylene-D-mannitol succinate) (PB*x*Manx*y*S)	Hydrolytic: phys. cond.; pH 2.0, 37 °C	56	10–15	[115]
	Enzymatic: porcine pancreas lipase	56	24–29	
Poly(butylene-*co*-2,4,:3,5-di-O-methylene-D-glucitol succinate) (PB*x*GluxyS)	Hydrolytic: phys. cond.; pH 2.0, 37 °C	40	10–24	[116]
	Enzymatic: porcine pancreas lipase	40	15–25	
Poly(butylene succinate-*co*-butylene sulphonated succinate) (PBS_xSS_y)	Hydrolytic: physiological conditions (37 °C, pH = 7.4).	56	1–25	[117]
	Hydrolytic: pH 4.0, 37 °C	56	5–35	
	Hydrolytic: pH 10, 37 °C	56	15–60	

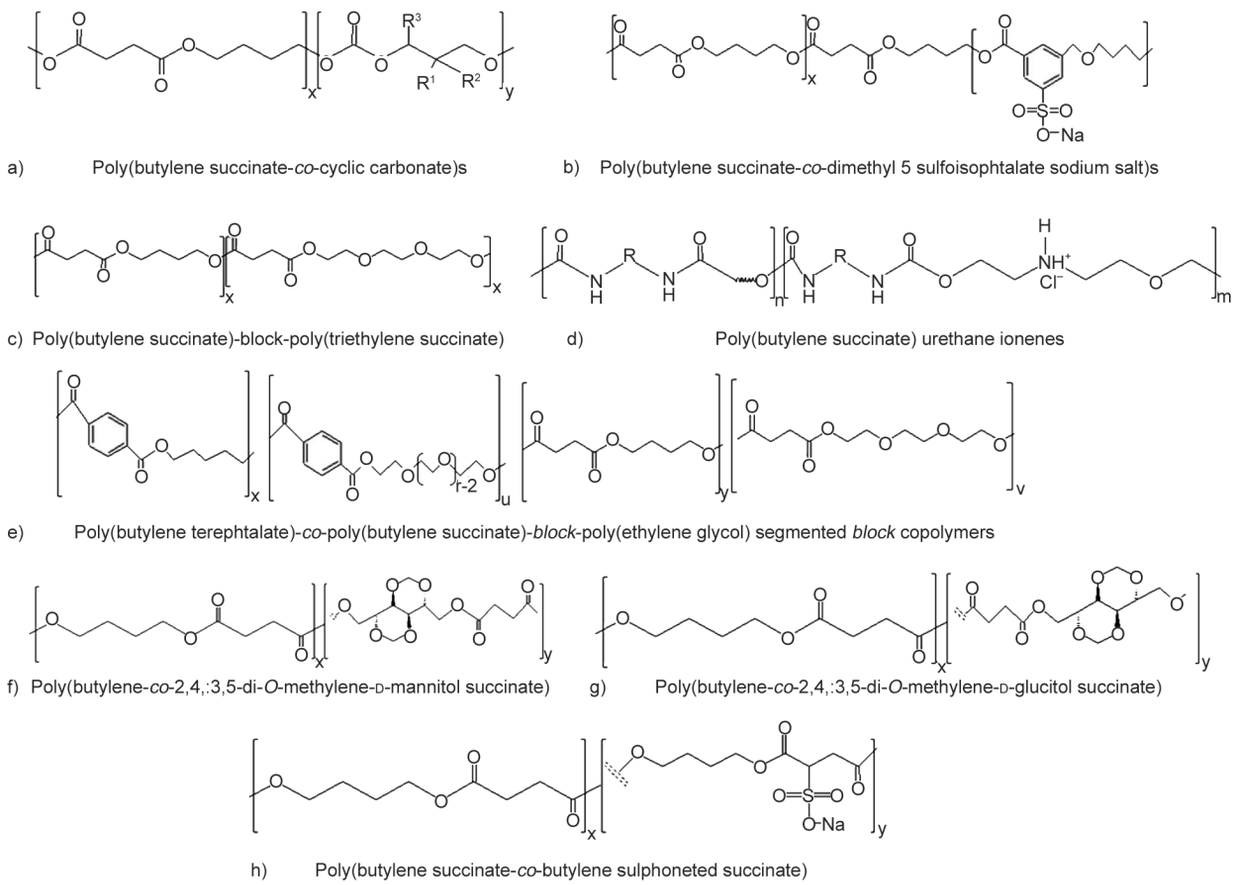

Figure 14. Structure of copolymers presented in Table 3. a) Poly(butylene succinate-*co*-cyclic carbonate)s, b) poly(butylene succinate-*co*-dimethyl 5 sulfoisophtalate sodium salt)s, c) poly(butylene succinate)-*block*-poly(triethylene succinate), d) poly(butylene succinate) urethane ionenes, e) poly(butylene terephtalate)-*co*-poly(butylene succinate)-*block*-poly(ethylene glycol) segmented block copolymers, f) poly(butylene-*co*-2,4,:3,5-*di*-*O*-methylene-*D*-mannitol succinate), g) poly(butylene-*co*-2,4,:3,5-*di*-*O*-methylene-*D*-glucitol succinate), and h) poly(butylene succinate-*co*-butylene sulphonated succinate).

of PBS with hydrophilic molecules showed a noticeable effect on the hydrolysis rate [118, 119, 121]. The increased degradation was mainly due to the cleavage of the ester bonds of chain segments. Also, it was reported that the introduction of ionic groups into PBS increased the hydrolytic degradation with the increased amount of urethane ionenes groups [110, 112, 113, 118]. On the other hand, the introduction of carboxylic groups into the PBS matrix is the key to increasing and controlling the rate of degradation by catalyzing the hydrolysis of the macromolecular chains [119, 122]. These demonstrate that PBS copolymerization with the water-soluble molecule, viz. PEG and other hydrophilic molecules, help in increasing the rate of degradation in both enzymatic and non-enzymatic conditions.

Jager *et al*. [123] reported that nanoparticles made of poly(butylene succinate-*co*-dilinoleate showed a substantial decrease in molecular weight after 3 weeks of incubation. The rate of hydrolysis was mainly influenced by nanoparticle structure that contains a high amount of water molecules. Grigoriadou *et al*. [55] studied the effect of silica-nanotubes and strontium hydroxyapatite incorporated PBS composites on the degradation behavior. The increased hydrolytic degradation was mainly influenced by the presence of hydroxyl groups on the surface of both nanoparticles and porous structure formation which helps to facilitate the lipase diffusion in the polymer matrix and accelerate the degradation. Costa-Pinto *et al*. [124] reported that the presence of chitosan in the PBS/chitosan composite increased hydrolytic degradation with surface erosion and water uptake due to swelling and higher hydrophilicity.

Enzymatic degradation of PBS-based polymeric materials have conducted in the presence of various enzymes, *i.e.*, *Pseudomonas cepacia lipase*, *Candida antartica lipase* (Novozyme 435), *Aspergillus oryzae lipase*, *lysozyme*, *Rizopus delemar* [52, 109, 124]. Lipases are well-known enzymes for catalyzing

hydrolytic degradation of aliphatic polyesters, however, the degradation kinetics depends on various factors *i.e.* chemical structure, hydrophilic–hydrophobic balance, molecular weight, morphology, degree of crystallinity, and others. Therefore, the approach of copolymerization or blending favored the enzymatic degradation of PBS-based biodegradable polyester materials.

6. Current status and future directions

It is worth mentioning that PBS is facing some challenges such as high production costs and inadequate properties which make it difficult for PBS to be used as a virgin polymer for product development without blending, reinforcing, and copolymerization. Despite these challenges, the production of PBS has been showing an exponential increase in various countries, such as North America, Europe, and Asian countries such as China.

The increase in the market and the demand for PBS has opened opportunities for exploring PBS in both research and industry. The growth in the market size of PBS has encouraged research and innovation to diversify the applications of PBS leading to the development of PBS and PBS-based products for a variety of applications such as food packaging, agricultural and biomedical. The biocompatibility, non-toxicity, and biodegradability have widened the use of PBS in biomedical applications. Extensive research has focused on biomedical applications, such as tissue engineering, drug delivery, wound dressing as well as biomedical devices as they provide a platform for the development of biodegradable products. The increase in medical needs has further the interest in the development of PBS-based products for biomedical applications due to the aforementioned features. The research for biomedical applications has led to the design and fabrication of scaffolds for tissue engineering as well as drug delivery system. The current progress on designing 3D scaffolds for smooth tissue engineering has become a research hotspot. The ideal scaffolds for tissue engineering require high porosity which enables proper integration of cells as well as blood vessels and allows the movement of nutrients and waste [48]. 3D PBS-based scaffolds have proved to be biocompatible as the osteoblast proliferates and degrades in the system without leaving toxic byproducts. Additionally, PBS-based scaffolds have demonstrated potential in nerve regeneration, vascular tissue engineering, bone tissue regeneration as well as skin tissue regeneration. Moreover, since the body system is very complex, it is necessary to perform modeling studies to predict the challenges of PBS-based products prior to conducting clinical trials [125].

Although investigations have been conducted for the fabrication of PBS-based products for wound dressing, there are few reports documented on PBS and PBS-based products for wound dressings. The ongoing research on wound dressing is focusing on designing smart and bioactive products. This can be achieved by introducing antimicrobial agents and therapeutic elements into bandages for various types of wounds to accelerate the healing process of the wound [126]. This opens doors for further investigation to explore PBS for wound dressings. For instance, the design and fabrication of biodegradable wound dressings which have controlled porosity contained antimicrobial agents, and had similar features to natural extracellular matrix (ECM) could benefit from the progress in the fabrication of PBS fibrous wound dressings. The PBS wound dressing possesses good mechanical properties, a large surface area-to-volume ratio, and increased levels of porosity. In addition, they allow cell proliferation, removing exudates, moisture retention, and haemostasis [126]. Furthermore, PBS-based wound dressing shows potential and they open opportunities for designing bioactive and cost-effective biobased wound dressing.

In the case of medical devices, 3D printing has been used to design patient-customized biomedical devices. 3D printing can also enhance the uniformity of mechanical properties as well as allow the spatial localization of bioactive agents within the devices [127]. Currently, best to our knowledge there are only two studies reported about 3D printing of virgin PBS and few PBS-based materials [21, 128]. These researchers investigated the printability of PBS using fused deposition modeling (FDM) or fused filament fabrication (FFF) 3D printability. They reported that PBS was successfully printed via FDM or FFF. In addition, PBS demonstrated good thermal and mechanical properties. PBS has low melt strength which makes it difficult to form filament thus, limit their printability. Therefore, due to the limitations of printing PBS Candal *et al*. [128] investigated the effect of talc on the printability of PBS. In this study, the PBS reinforced with talc filament was obtained from the twin-screw extruder and the filaments were fed

into FDM 3D printer. The incorporation of talc resulted in the improvement in processability, increased crystallization temperatures, enhanced mechanical properties, and improved rheological properties. Other researchers [129] blended PBS with PLA to improve the printability of PBS. The results indicated that the bending of PBS with PLA improved the printability of the blend. However, it was noticed that the increase in PLA loading led to the improvement in melt viscosity and increased tensile properties which is the requirement for FDM 3D printing. Although various researchers have demonstrated that PBS and PBS-based materials can be printed via FDM or FFF, there is still little information about the fabrication of medical devices using 3D printing. This has opened opportunities for designing various biomedical devices from PBS-based materials using FDM 3D printing due to its simplicity and low-cost production. Moreover, much research is required to explore PBS and to develop biomedical devices from PBS since it has demonstrated excellent properties, and its market is growing at a rapid rate.

Even though 3D printing of PBS and PBS-based materials were successful, some drawbacks of 3D printing were identified. The major drawback of 3D printing is that the printed objects are static and cannot undergo any dynamic reshaping when subjected to external stimuli. Many scholars have proposed the use of 4D technology to address the limitations associated with 3D technology [72, 130, 131]. The concept of 4D technology is regarded as an emerging area to design customized patient designs which can provide researchers with a wide range of therapeutic control personalized to each patient [63]. Up to date, there are very few studies on the fabrication of 4D printed PBS-based biomedical devices. A recent study [72], investigated the 4D printing aspects of PBS/PLA blends. PBS/PLA blends were prepared by melt compounding and 3D printed into two types of prototypes: Starfish and Endoluminal stents). The shape memory behaviors of the printed stents were investigated by placing them in a hot water bath and observing smooth and complete shape recovery processes. Additionally, graphene oxide functionalized PBS/PLA blends were also prepared and displayed photothermal properties and 4D transformation of a porous scaffold under near-infrared (NIR). The 4D printed PBS/PLA filament showed promising application prospects in tissue engineering and photothermal therapy.

4D printing of biopolymers is at a nascent stage but has enormous potential for developing customized materials that react to various stimuli. These smart materials have the potential to be used in advanced industrial sectors, such as aerospace, medical and defense industries. No study, to the best of our knowledge, has reported on the printing of virgin PBS using 4D printing technology. In the near future, there will be a shift towards 4D printing because of the low production cost, simple processing, and the realization of fabricating complex structures and composites [132].

Despite the fact that 3D PBS-based scaffolds have shown potential in tissue engineering and drug delivery systems, significant challenges still remain when considering the use of PBS in the long run for biomedical applications. For instance, one of the major challenges of PBS is the high production cost which limits its full potential. The issue of inadequate properties such as required melt strength in the case of developing medical devices will be addressed by either reinforcing, blending, and/or copolymerization. In addition, the material that will be used for reinforcing, blending, and/or copolymerization PBS should be eco-friendly and sustainable to avoid compromising the biodegradation feature of PBS. It is worth noting that the temperature of a body system differs from those of room temperature.

The clinical studies of PBS-based scaffolds have been conducted using rats in various labs such as Istituto Zooprofilattico Sperimentale della Sicilia in Italy which was authorized by the Ministry of Health. The findings indicated that PBS scaffold has the potential as an implantable material for improving the regeneration of injured tissue in rats as well as shortening the time for nerve regeneration [49]. However, to the best of our knowledge, there is no study performed clinical trials on humans. Further investigation is required for the exploration of PBS-based products in human trials. In addition, although various grades of PBS are available on the market, according to our understanding, there is little information reported about medical grades which limits PBS for clinical applications. This opens opportunities for suppliers to carefully consider producing medical-grade PBS.

7. Summary

The growing concerns over non-biodegradable conventional plastics derived from petroleum-based

resources have encouraged the use of biodegradable polymers. Amongst biopolymers, polybutylene succinate is a suitable alternative to conventional plastic materials. The market and the research outputs of PBS and PBS-based materials over the last 10 years have been growing immensely. The properties of PBS are similar to those of synthetic polymers such as polypropylene (PP) and polyethylene (PE) with the added biodegradable and biocompatible features. These properties make PBS a favorable material for biomedical applications while demonstrating some shortcomings. The limitations of PBS include inferior properties and high production costs, which can be addressed by blending or reinforcing with cheap materials to reduce the cost as well as enhance the properties.

This study presents the current status and the future directions of PBS-based materials in biomedical applications. Extensive investigations have been conducted on the fabrication of PBS and PBS-based products for tissue engineering and drug delivery with a focus on the biological response to these materials. The areas that remain not sufficiently explored are wound dressing and biomedical devices 3D and 4D printing of PBS-based materials present an opportunity for the development of customized biomedical devices and need to be explored further. *In vivo* studies were performed in a rat model for the implantation of PBS-based scaffolds. The results revealed that the scaffolds integrated well with surrounding tissue and showed degradation after one month, although their degradation is slow. Even though PBS-based products displayed potential in various biomedical applications, there are no studies on clinical trials in humans. Therefore, much research focusing on i*n vitro* and *in vivo* testing and optimization is required before the material will be applied in clinical trials. Additionally, the production of PBS with medical grade is needed to ensure the material is suitable for medical procedures and clinical trials. Furthermore, to the best of our knowledge PBS based products have not yet been approved by Food and Drug Administration for biomedical applications, especially clinical trials.

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