REVIEW ARTICLE

Application of Hydrophobic Polymers In Bone Tissue Engineering Scaffolds: A Review

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ABSTRACT

Fabrication of functional scaffolds that mimic the native bone is essential for bone osteogenesis. The latest generation of biomaterials is designed to imitate the structural characteristics of the extracellular matrix in promoting effective tissue integration and aiding long-lasting integration. One of high potentials biomaterials is hydrophobic materials that offer extended therapeutic advantages by offering sustained release over time. However, low water affinity and bio-inert are the most common drawbacks for hydrophobic polymers. Nevertheless, the combination of these hydrophobic polymers with other biomaterials offers great synergy in improving both mechanical and biological properties of a bone substitute. In this article, we highlight the application of hydrophobic polymers, such as Polyetheretherketone (PEEK), Poly-L-Lactic Acid (PLLA), Poly (lactic-co-glycolic acid) (PLGA)) and Polyethylene terephthalate glycol (PETG) for bone scaffold. This review briefly discusses the limitations and modifications of these hydrophobic polymers in enhancing bone regeneration based on recent in-vitro and in-vivo models.
Malaysian Journal of Medicine and Health Sciences (2025) 21(s2): 129–141. doi:10.47836/mjmhs.21.s2.18

Keywords: hydrophobic polymers, surface modification, composite, bone scaffold, tissue engineering

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INTRODUCTION

Bone tissue has a built-in potential for regeneration that is sufficient to repair minor injury sites such as cracks, bone deformities and some forms of fractures [1]. However, it is still very challenging to cure a bone defect of the critical magnitude caused by a pathological fracture or a high-energy injury in a clinical setting [1]. Thus, bone tissue from the patient or from appropriate donors is used for bone restoration. Due to a lack of tissue supplies, donor site morbidity and incompatibility, these procedures are only effective for smaller size abnormalities [2-3]. Autografting, or moving a patient's bone from another part of their body to the location of the bony defect, is still the gold standard for bone healing [4]. Nevertheless, there are few sources of autologous bone with risk of infection and subsequent damage [5-6]. Allogeneic bone grafting offers an alternative, although its broad use has been constrained by the immunological reaction [7-8]. Since the introduction of new biocompatible materials and the development of suitable implant structures, bone surgery has undergone a revolution. The initial non-toxic biomaterial scaffolds are inert with no influence on the surrounding tissues after implant procedure. Next, during the second generation, materials with bioactive properties are added, and biochemical interactions took place on their surface to connect them with host tissues. Then, the third generation of biomaterials are based on replicating naturally occurring structures like extracellular matrix (ECM) [9]. So, by mimicking the ECM, third-generation biomaterials have better integration with surrounding tissues and promote tissue regeneration for long-lasting treatments for patients.

For that reason, fabrication of functional scaffolds that replicate the structure and components of normal bone tissue is essential in enhancing bone osteogenesis. A scaffold is a three-dimensional (3D) biomaterial that provides good mechanical properties as well as good environment for cells to repair tissues and organ in enhancing bone regeneration and imitate how bone functions naturally [10]. Thus, high porosity and interconnected pores of 3D scaffolds enable cells adhesion, which promotes cells growth, cells proliferation and cells differentiation as well as the diffusion of waste and biodegradation's products. Besides, adequate pore size 3D scaffolds allow the mobility of cells within the scaffold [10-11].

In making a functional bone scaffold, the biomaterials must be bioinspired or tunable synthetic materials such as like metals, ceramics, and polymers [1]. Due to this, hydrophobic polymers have advantages in controlling the release of drugs or growth factors due to its hydrophobic nature [12-13]. Therefore, various type of polymers has been used in making bone scaffolds including hydrophobic polymers such as polyetheretherketone (PEEK), poly-L-lactic acid (PLLA), poly (lactic-co-glycolic) acid (PLGA) and polyethylene terephthalate glycol (PETG). However, these hydrophobic polymers are also known by their low water affinity and high resistance to wetting that does not favour cell proliferation and attachment [13].

Hence, surface modifications and combination with other biomaterials to form a composite able to overcome the shortcomings of these hydrophobic polymers. The mechanical characteristics and tissue interaction of composites have been improved by the development of materials consisting of a combination of natural and synthetic polymers, metals, and ceramics [14-15]. Synthetic polymers such as polylactic acid (PLA) and polyglycolic acid (PGA) are frequently being used to make it composites owing to their inherent capacity to modulate the rate of degradation [10, 16]. Nevertheless, their bioactivity is diminished as a result of their adaptable structure [10, 17]. Besides, the bioactivity of hydrophobic polymers was enhanced by surface modification with biomaterials such as hydroxyapatite (HA), gelatin, titanium, and alginate [18-20].

Therefore, the aim of this review is to discuss the modification of these hydrophobic polymers in bone tissue engineering. The biological, physical and mechanical properties of the fabricated scaffold in-vivo and in-vitro where highlighted in Table I, to show the significant impact of these hydrophobic polymers in enhancing bone tissue engineering.

POLYETHERETHERKETONE (PEEK)

Polyetheretherketone (PEEK) is a thermoplastic material with exceptional mechanical attributes. PEEK is a semicrystalline polymer containing a ketone and ether group-linked aromatic backbone chain as shown in Fig. 1(a). PEEK and its co-polymer are acknowledged as high-performance polymer due to its remarkable chemical resistance, exceptional resistance to radiation and sterilisation, radiolucency properties, and near-bone mechanical characteristics with elastic modulus ranging from 3.7 to 4.0 GPa and tensile strength of 103 MPa [21-28]. PEEK and its composites have been utilised extensively in bone tissue engineering and orthopaedic surgery, for example in fracture fixation, bone replacement, and spinal fusion cages [28-29].

PEEK has the potential to serve as a viable alternative to conventional implant's materials commonly employed in orthopaedic surgery, such as titanium, titanium alloys, Cr-Co-Mo alloys, and biological ceramics [28, 30]. Study by [21] stated that hydrophobic PEEK exhibits poor osseointegration with bone tissues after implantation due to bioinert properties which lead to possible clinical failure. Regarding this inert property, another study also claimed was no chemical bond between PEEK and bone of sheep after 6 months implantation [31]. On other hand, there was no evidence of degradation or no adverse effect of releasing of PEEK ions [31].

Various adaptations have been derived from the constituents, structure, mechanical properties, and immunological response of bone in order to develop surface modification of (PEEK) and PEEK-based composites such as the addition of inorganic phases and minerals ions as coating deposition and reinforcing fillers with other materials [32]. These types of modifications have been used in development of PEEK implants to mimic closely to our natural bone in terms of mechanical properties, increasing efficacy of osseointegration, cytocompatibility, and anti-inflammation/infection. Numerous research endeavours have been conducted to assess the efficacy of reinforced (PEEK), yielding outcomes that have both unveiled novel opportunities and presented challenges.

Surface Modification of PEEK

PEEK exhibits inherent hydrophobicity and bioinertness, as evidenced by its water contact angle measuring between 80 and 90 [32]. This made the PEEK implants not suitable for the cells or proteins to adhere on its surface. Surface roughness influences surface wettability. By modifying the surface roughness of PEEK implant by using surface treatment or a combination of surface treatment can improve the wettability and the integration with host bone tissue. Currently, the suggested method, which needs further exploration, employs combination strategies of surface treatment to enhance both biological and mechanical performance [33-34]. Studies by Faadhila et al., this dual approach uses alumina sandblasting to improve surface roughness, which unfortunately also increases bacterial adhesion [35]. However, the addition of a novel coating, such as platinum, effectively counters this drawback but none mechanical performance was stated in this study [35]. Another study, a straightforward immersion process coated a PEEK implant, resulting in a dual-functional coating (polydopamine and manganese/silver) with both antibacterial properties and improved osseointegration [36]. The application of polydopamine (PDA) augmented surface roughness and decreased surface wettability,

Table I: In-Vitro and In-Vivo Applications in Bone Tissue Engineering

Type of Polymer	Surface Modification/ Composite	In-vitro/In-vivo	Biological Properties	Mechanical/Physical Properties	Reference
Polyetheretherketone (PEEK)	Surface Modification (PEEK-PDA-Mn/Ag)	Osteoblast cell (MC3T3-E1)	Good biocompatibility, excellent osteogenesis induction, satisfactory antibacterial properties, and enhance osseointegration in vivo.	No studies	[36]
	Surface Modification (phosphate and calcium)	Mesenchymal stem cells (MSCs)	Enhancement of MSC osteogenesis in-vitro and osseointegration capability in-vivo.	Improvement of surface hydrophilicity.	[37]
	Surface Modification (PEEK/PDA-mediated)	Fibroblast and Osteoblast Cells	Good cell adhesion and proliferation, decreased the macrophage adhesion, decreased the inflammatory factor TNF-α expression and reduced S. aureus and S. mutans bacteria population.	Super hydrophilicity.	[39]
	Composites (PEEK-HA)	Osteoblast cell (MC3T3-E1)	Increased cell proliferation, good cytocompability and induced mineralization.	Improvement on the mechanical properties.	[51]
	Composites (PEEK/nano-HA, strontium (Sr)-doped nano-HA, and zinc (Zn)-doped nano-HA)	No studies	Simulated body fluid immersion showed the apatite formation on the surfaces of the samples containing HA, SrHA and ZnHA.	Slight reduction in ultimate tensile strength and Young's modulus in PEEK/HA as compared to pure PEEK.	[15]
Poly-L-lactic acid (PLLA)	Surface Modification (PLLA- thin nitrogen-titanium)	No studies	No studies	Improvement on the surface wettability.	[59]
	Surface Modification (PLLA-alginate)	L929 fibroblast cells	Decreased in cell proliferation and adhesion	High hydrophilicity.	[14]
	Surface Modification (PLLA- ε-polylysine (ε-PL) and alginate)	Osteoblast Cell (MC3T3-E1)	Facilitated cell adhesion and osteoblast differentiation with good antibacterial efficacy	No studies	[20]
	Surface Modifications (PLLA-gelatin)	Mesenchymal stromal Stem cells (mBMSCs) / Calvarial bone defect	Good cell affinity that promoted osteogenic differentiation and promoted new bone regeneration.	Controlled pore size, enhanced mechanical property, enhanced hydrophilicity and decreased the pH during degradation.	[61]
	Surface Modification (PLLA- Baghdadite)	Adipose-derived Mesenchymal Cells (AD-MSCs)	Improved osteogenic differentiation, induced osteogenic gene expression significantly and enhanced cell proliferation.	No studies	[62]
	Composites (PLLA-poly (ethylene glycol) (PEG))	Mouse embryonic fibroblast cells /Rat model with bone defects	Good cytocompatibility and enhanced bone formation.	Improved compressive strength and degradability.	[63]
	Composites (PLLA- chitin whisker (CHWs)	Osteoblast cell (MC3T3-E1)	Good cell adhesion and cell proliferation, anti-inflammatory properties, up-regulated alkaline phosphate activity and calcium deposition.	Superior hydrophilicity and compression performance.	[64]

	Composites (PLLA-Aragonite)	Osteoblast cell (SaOS-2) /Rabbit radius segmental bone defects	Improved cell proliferation and differentiation, increased osteogenic activity mad enhanced both mineralization and in-vivo bone regeneration.	High bending load of rabbit limb.	[66]
	Composites and surface modification (PLLA- hydroxyapatite (HA)/ decellularized extracellular matrix (ECM))	Human adipose stem cells (hASCs)	Increased cellular activity, enhanced mineralization and induced osteogenic differentiation.	Improved the compressive properties and surface roughness and also surface wettability.	[65]
Poly (lactic-co-glycolic acid) PLGA	Surface Modification (HA/PLGA with DOPA-IGF-1)	Rabbit bone mesenchymal stem cells (rMBSC)	Good biocompatibility and bioactivity. Enhanced osteogenesis differentiation with DOPA-IGF-1 group	No studies	[71]
	Surface Modification (PDA coated PLGA-gelatin)	L929 fibroblast cells and human osteosarcoma cell line/well (MG-63)	Good biocompatibility with more than 80% cell viability	Improved hydrophilicity and swelling ratio.	[72]
	Surface Modification (PLGA, PDA-nHA)	Mouse preosteoblast (MC3T3-E1)	Enhanced proliferation of osteoblast cells.	Incorporation of PDA improved the hydrophilicity properties.	[73]
	Composites (PLGA-HA)	Human bone marrow stromal cells (hBMSCs) and human adipose- derived stem cells (hADSCs)	Good biocompatibility with high cell viability and high cell proliferation	No differences in tensile strength with incorporation of nHA.	[74]
	Composites (PLGA/TCP/Mg (PTM))	SAON rabbit model	Good osteogenic and angiogenic abilities.	No studies	[76]
	Composites (TCP-PLGA)	Minipig model	Improvement on bone regeneration on mandibular defects	No studies	[75]
Polyethylene terephthalate glycol (PETG)	Composite (Silk-PETG)	L929 murine fibroblast cells	Good biocompatibility.	Increased of tensile modulus with addition of silk fiber.	[79]

while fluorescence microscopy indicated dispersed cytoplasm, lamellipodia, and filopodia, influencing cell interaction and differentiations [36].

Although surface modification techniques are crucial, whether simple or complex, the addition of inorganic or organic phases and mineral or metal ions, either as coatings or particles for release, is equally essential. The surface functionalization with calcium and phosphate materials dramatically enhanced both the in-vitro osteogenesis of mesenchymal stem cells (MSCs) and in-vivo osseointegration [37]. In vitro studies found that only hydroxyapatite (HA) coatings on PEEK formed an apatite structure, with titanium having the highest surface roughness, titanium dioxide (TiO_2) the lowest, and similar roughness values observed for single and double-layer HA coatings [38]. Another study using hybrid coating of PEEK implant using PDA and (TiO_2) creates synergetic effects that enhance the surface characteristics, for sustained biocompatibility, while also promoting super hydrophilicity and stimulating fibroblast and osteoblast cell proliferation while reducing inflammatory responses [39]. Przykaza et al. found that increasing the concentration of chitosan in a bio-glass and chitosan hybrid coating on plasma-activated PEEK polymer improves surface homogeneity and wettability, whereas lower concentrations lead to partial coverage and reduced wettability [40]. In various surface modification techniques, coating deposition of metal ions is more commonly used and tends to yield more remarkable results in terms of reducing surface roughness compared to mineral ions and organic/inorganic phases, according to numerous studies. More research is needed in extensive long-term clinical settings to address the existing gaps and ensure thorough understanding.

PEEK-Based Composites

Although coating improves the surface wettability, PEEK has a significantly lower elastic modulus than human cortical bone and therefore insufficiently stiff to tolerate applied stress in load-bearing orthopaedic implants [33]. In order to increase the stiffness of PEEK for load-bearing applications, PEEK-based composites were offered to improve these properties [21, 41]. In biomedical applications, elastic modulus of any biomaterials must be comparable to cortical bone (7 to 30 GPa) for biological reasons. PEEK exhibits a relatively low elastic modulus, ranging from 3.7 to 4.0 GPa. In order to enhance the stiffness of PEEK for load-bearing purposes, many techniques are employed, including the incorporation of HA as micro or nanofillers, as well as the utilisation of continuous and discontinuous carbon fibres [21]. In comparison to HA micro or nanofillers, carbon fibres offer greater stiffness and load-bearing capacity [21]. For this reason, the tensile strength of carbon fiber reinforced PEEK implants similar to those cortical bone [21]. Inforcement of carbon fiber to PEEK implants have been reported to have a favourable degree of in-vivo osseointegration in comparison to titanium implants [41]. A more direct technique to improve tissue integration is to increase the material's biological activity [42-43]. PEEK-based composites are frequently utilised to increase the osteogenic capacity of PEEK by combining it with biological ceramics including calcium phosphate (TCP), hydroxyapatite, and bioglass (BGA) (HA) [4, 44-46]. Due to its great bioactivity, HA, the major component of natural bone, proved helpful for bone tissue healing [47-51]. Zheng et al, fabricated scaffolds using PEEK and HA with varied HA concentration [19]. The objective was to enhance the integration of the scaffolds with the surrounding bone tissue, leading to improved adhesion, proliferation, osteogenic differentiation, and mineralization capacity of bone marrow-derived mesenchymal stem cells (BMSCs) [19]. The results demonstrated a greater volume of bone in-growth in the scaffolds with higher HA content [19].
The development of composite structures utilizing PEEK and bioactive ceramics, such as HA has been thoroughly investigated in the literature [15, 52]. The study conducted by Ma & Guo, involved the investigation of in-vitro bioactivity through the simulated body fluid (SBF) immersion test over a period of 28 days [52]. The focus of the study was the analysis of the bioactivity of PEEK/HA composites, which were manufactured using injection moulding techniques and incorporated different concentrations of HA (0, 10, 20, 30, and 40 wt%) [52]. The inclusion of HA resulted in greater levels of cell attachment, proliferation, spreading, and alkaline phosphatase (ALP) activity compared to pure PEEK as well as the impact of HA loading on the mechanical properties and there was a decrease in tensile strength as the HA level increased [52]. Manzoor et al, employed hot-melt extrusion and fused deposition modelling (FDM) techniques to produce PEEK-based filaments containing 10 wt% of pure nano-hydroxyapatite (HA), strontium (Sr)-doped nano-HA, and zinc (Zn)-doped nano-HA [15]. The presence of apatite was seen on the surfaces of the samples containing HA, strontium-substituted hydroxyapatite (SrHA), and zinc-substituted hydroxyapatite (ZnHA) [15]. The bioactivity of 3D printed samples was evaluated by an in vitro test using SBF for a period of 28 days [15]. Based on the results obtained, it is evident that the fabrication of bioactive 3D printing (3DP) PEEK composites holds promise for addressing challenging scenarios such as the replacement of cranial bone [15]. Following a period of 14 days of immersion, there was seen an increase in both the size and quantity of the apatite precursors [15]. In contrast to coatings that primarily emphasize surface features, PEEK-based composites prioritize the enhancement of mechanical properties. However, achieving a balance between mechanical properties and biological activity is crucial to maximizing implant performance.

POLY-L-LACTIC ACID (PLLA)

Poly-L-Lactic Acid (PLLA) is a semicrystalline material with a consistent chain structure, good tensile strength, low extension rate, and low degradation rate [53]. PLLA is one of the homopolymers of PLA as shown in Fig. 1(b) is a food and drug administration (FDA)-approved, less toxic polymer with anti-infective effects in vivo and in vitro. It performs well during implantation, ensuring mechanical properties for long-term regenerative processes. However, concerns about its hydrophobic surface may jeopardise its biocompatibility, affecting protein absorption and cell adhesion [54]. PLLA is a hydrophobic polymer with a melting temperature, Tg of 175°C and a mechanical strength of 4.8 GPa [55]. PLLA has been used safely in a range of clinical applications for over 30 years, including dissolvable sutures, intra bone implants, and soft-tissue implants [56].

Due its high melt viscosity, PLLA processing can be difficult, resulting in difficulties achieving uniform and defect-free products and concerns have been raised about the potential release of lactic acid during the degradation of PLLA, which could harm surrounding tissue or the environment [57]. Several modifications of PLLA have been offered to overcome those drawbacks such as surface functionalization (coatings) and make it composite depending on its application. Extensive research has been conducted on PLLA-based composites as biodegradable materials for biomedical applications such as bone fracture fixation, sutures, interference screws, and meniscus repair [58].

Surface Modification of PLLA

Pure PLLA scaffolds have excellent results, but their hydrophobic nature hinders cell-material interactions [54]. The most common surface modified technology which is plasma treatment has been used to change the physico-chemical surface properties. Studies that coat the PLLA with a titanium coating mixture of nitrogen and xenon by using reactive magnetron sputtering showed decreases of surface wettability compared to unmodified PLLA scaffold [59]. Coating with hydrophilic polymers such as alginate that formed soft hydrogel have no effect on compressive properties of scaffolds but have an effect on the cell differentiation and cell attachment [14, 20]. According to study by Bahcecioglu et al, the cell differentiation decreased due to softness of alginate and rapid degradation contribute to drop of pH of medium that affect the cell viability and in terms of cell attachment, it showed more dendritic/elongated morphology because of the stiffness of alginate same as fibroblasts [14]. Yao et al, conducted a study that employed PDA as a pre-treatment method prior to coating with ε-polylysine (ε-PL) and alginate using a layer-by-layer approach [20]. The aim of the study is to overcome the constraints associated with PLLA in relation to its osteogenic and antibacterial characteristics [20]. As results, it demonstrated that the material exhibited improved adhesion and differentiation of murine calvarial pre-osteoblast cell line MC3T3-E1, along with significant antibacterial activity against S. aureus and E. coli [20]. The bacterial survival rates were found to be 21.5 ± 3.5% and 13 ± 2.1% for S. aureus and E. coli, respectively [20].

Coating with natural polymer or bioactive molecules such as chitosan and baghdadite can improve PLLA surface bioactivity and cell adhesion due to naturally occurring polymers extracted from the native extracellular matrix (ECM) [54, 60]. Nonetheless, it depends on methods to develop scaffold and concentration of the polymer have been used for the coatings [58-59]. Chen et al, modified the surface of macroporous nanofibrous scaffolds with chitosan using cloud point thermally induced phase separation (CP-TIPS) where it showed improvement in terms controlling the pore size (300μm) without the loss of nanofiber structure on the pore wall (diameter of 250 μm), mechanical properties, hydrophilicity and decrease the pH throughout the degradation of scaffolds [61]). Interestingly, another material which is baghdadite (a combination of calcium silicate and zirconium) and then to be plasma-treated on the PLLA nanofibrous scaffold showed improved in osteogenic differentiation potential of AD-MSCs [62]. However, although it is said that the baghdadite improve cell proliferation but still more surface modification is needed to maximize the interaction and contact area in PLLA scaffold since 1% of baghdadite has been used [62]. Chitosan with 3% showed the best concentration for the bone growth consider it is challenging to maximize the contact area and interaction between chitosan and porous PLLA nanofibrous scaffold [61]. Coating is affected by the methods to surface functionalized as well materials so that it can be long-lasting on its surface to have a cell to proliferate and differentiate [14, 20]. Still, more research is needed to have more option of innovation biomaterials to be chosen as a coating on PLLA surface scaffold and have more remarkable results for specific application.

PLLA-based composites

Surface modifications improve cell adhesion and interaction, but can alter surface chemistry, causing protein absorption and undesirable reactions. Thus, to overcome this surface modification, PLLA-based composites were introduced to improve the properties of either reinforcing with other biomaterials. A lot of studies related to reinforcing PLLA with synthetic polymer (poly (ethylene glycol) (PEG), natural polymer (chitin whiskers (CHWs)), bioactive ceramic materials (hydroxyapatite), and natural composite materials (nacre and pearl) to form a composite where it gives an excellent bone property [63-66]. PEG incorporation enhances hydrophilicity, biodegradability, and compressive strength by adopting a structural modification processing approach with supercritical carbon dioxide (Sc-CO2) foaming [63]. Also, PEG incorporation increased cell viability and proliferation, while in vivo, mature osteoid tissues were found after 3 months post-implantation, confirming bone formation activity with Col1, BMP4, RUNX2, and BSP expression [63]. Liu et al, stated that well-dispersed chitin whiskers (CHWs) with a range of 5%-20% incorporated inside the PLLA matrix by using 3D printing showed good compressive strength compared to 40% of CHWs content [64]. The hydrophobicity of the PLLA scaffold significantly improved as the content of CHWs increased due to its properties that have a large number of hydrophilic groups [64]. Based on the ALP activity and calcium deposition, it promotes osteogenic differentiation [64]. Besides, 40% of CHWs content appeared to have anti-inflammantory properties for tissue repair as it transformed the macrophages from M1 to M2 phenotype [64].

Another possible method where the combination of incorporation and coating to enhance more the PLLA-based composite. Hwangbo et al, incorporated hydroxyapatite with PLLA by using methods of the in-situ plasma treatment 3D printing and coating with decellularized extracellular matrix (dECM) then thermal annealling to enhance the mechanical and biological properties [65]. In terms of mechanical properties, where due to in situ plasma treatment and HA particles size, it showed an increase 2.1-fold in flexural modules compared to the normal PLLA/HA composite [65]. For biological properties, human adipose stem cell (hASCs) was proliferated greater in PLLA/HA with plasma treatment and PLLA/HA/dECM compared to normal PLLA/HA [65]. According to the findings obtained from the reverse transcription-polymerase chain reaction (RT-PCR) analysis, it can be observed that the PLLA/HA/dECM biocomposite scaffold elicits a notable promotion of osteogenic differentiation [65]. This is evidenced by the upregulation of early osteogenic gene markers, such as runt-related transcription factor 2 (RUNX-2) and bone morphogenetic protein 2 (BMP-2), as well as the late osteogenic gene markers, namely osteopontin (OPN) and osteocalcin (OCN) [65]. As a results, the mechanical characteristics are similar to those of native trabecular bone [65]. Huang et al, compared incorporation between aragonite or vaterite pearl powders into PLLA scaffolds enhanced osteogenesis [66]. The in-vitro findings indicate that the PLLA-aragonite scaffold exhibits a more pronounced stimulatory effect on the proliferation and differentiation of ostoblast cells (SaOS-2) [65]. This is evidenced by increased cell viability, alkaline phosphatase activity, collagen synthesis, and gene expressions related to osteogenic bone markers [62]. While, in vivo by using rat bone defect as model showed aragonite enhanced woven bone formation [66]. Some studies reported that PLLA still presence even after three years implantation [67]. In addition, comprehensive investigations into the in-vivo degradation and biocompatibility of these composites over extended periods of time would yield significant knowledge that could be applied to their clinical translation.

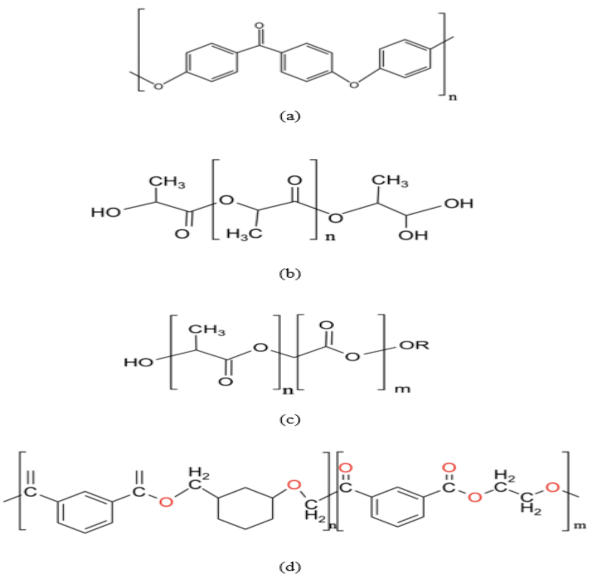

Fig 1: Chemical Structure of (a) PEEK, (b) PLLA, (c) PLGA and (d) PETG.

POLY (LACTIC-CO-GLYCOLIC ACID) (PLGA)

Another appealing aliphatic polyester with a linear structure is called PLGA. It is created by polymerizing its monomers, lactic and glycolic acids [68]. Due to its adaptable degrading behaviour and great biocompatibility, PLGA is regarded as a viable choice in biomedical applications such as implants, sutures, grafts, sealant films, pins, and micro- and nano-drug carriers [68-70]. Fig. 1(c) below shows the chemical structure of PLGA.

Surface modification of PLGA

The latest surface modification studies of PLGA involving coating with growth factor, bioactive molecules and natural polymer. In the study conducted by Liu et al, PLGA was coated with varying HA content by using the electrospinning process and subsequently coated with growth factors, insulin-like growth factor-1 (IGF-1) and dihydroxyphenylalanine-insulin-like growth factor-1 (DOPA-IGF-1) [71]. As HA content increased, cell's ability for adhesion and osteogenesis increased as well as their proliferative activity [71]. Further coated HA/PLGA microsphere with growth factor have better ability to induce cell proliferation [71]. The osteogenesis gene and the expression levels of COL1A1, Runx2, and bone morphogenetic protein 2, BMP-2 were both at their highest levels in 50%HA/PLGA/DOPA-IGF-1 [71].

On the other hand, Rezaei et al, conducted a study by incorporating gelatin and PDA as the surface modifier for PLGA [72]. The hydrophilicity and biodegradation ratio of PLGA-gelatin scaffolds increased after being coated with PDA [72]. Furthemore, PLGA-gelatin-PDA scaffolds increased cellular adherence and spreading on PLGA-gelatin-PDA scaffolds since PDA layer enhanced the structure's hydrophilicity and surface roughness, which in turn encouraged cell attachment and growth that increased the cell viability [72]. PLGA-gelatin-PDA scaffolds also show good biomineralization property with the formation of uniform layer of precipitated surface after being submerged in SBF solution for 14 days [68]. Besides, PLGA-gelatin-PDA scaffolds also displayed increased levels of ALP activity ALP expression when compared to control groups [67].

Chen et al, developed a hybrid coating method of PDA-induced nHA on 3D printed PLGA scaffolds by treating with Tris-HCl in forming the micro-/nano-porous structures on the surface of PLGA that able to enhance cell adhesion [73]. Besides, PDA and nHA coatings able to improve the surface hydrophilicity while maintaining the stiffness and effective Young's modulus of the 3D printed PLGA scaffolds [73]. The hybrid coating of PDA at the moderate level of PDA did not impede cell attachment and considerably boosted cell development demonstrating the efficacy of PDA-based hybrid coatings in functionalizing polymer substrates for tissue engineering [73]. There, the use of PDA coating able to enhance cell proliferation and biodegradation ratio on PLGA scaffold [72-73]. This is because the chemical composition of PDA contains hydrophilic functional groups like catechol and amine, and the lamellar microstructure of the scaffolds boosted hydrophilicity, swelling ratio, and ultimately cell proliferation [72-73]. By introducing HA, DOPA, IGF-1, and PDA to scaffolds surfaces, hydrophobicity of the scaffold is modified, and this is good beginning to enhance cell proliferation, and differentiation thus making the scaffold ready for the clinical application.

PLGA-based composites

PLGA is a hydrophobic polymer and incorporation of other materials into the polymer to produce composite is necessary to ensure the high performance of PLGA. Babilotte et al. created 3D porous scaffolds using fused deposition modeling and medical-grade poly(lactic-co-glycolic acid) (PLGA) combined with hydroxyapatite nanoparticles (nHA) [74]. The PLGA-HA scaffold showed biocompatible properties with higher ALP activity and osteopromotive potential. In-vivo studies showed modest inflammatory reactions but no material absorption after 4 weeks, with significant cell infiltration likely caused by macrophages [74]. This is because HA degradation products might have buffered the acidic products of PLGA that reduce the impact of inflammation from the released lactate [74]. Therefore, this scenario proved the biodegradation properties from each materials synergized the biocompatible of the composite [74].

Probst et al, investigated bone regeneration in mandibular defects a minipig model by using a combination of adipose-derived mesenchymal stem cells (ADSCs) and tri-calcium phosphate-poly(D,L-lactide-co-glycolide) (TCP-PLGA) scaffolds [75]. After 12 weeks, scaffolds with ADSCs seeded revealed significantly more bone volume and osteocalcin than scaffolds without cells [75]. To put this idea into practice in clinical settings, further advancements in the osteogenic and neo-angiogenic capacities are required. Besides, previously, Lai et al. developed a scaffold using Magnesium (Mg), poly(lactic-co-glycolic acid) (PLGA), and β-tricalcium phosphate (β-TCP) through low-temperature rapid prototyping [76]. They assessed its osteogenic and angiogenic effects in a rabbit model of steroid-associated osteonecrosis (SAON) [76]. After 12 weeks, the scaffold led to increased bone formation in SAON-induced bone defects, showing continuous osteogenesis [76]. The scaffold was gradually replaced by new bone ends, with magnesium ions aiding in tissue rebuilding and mechanical strength restoration [76]. Magnesium's inclusion aimed to enhance vessel growth, facilitating bone creation and remodelling in challenging SAON-associated defects [76]. Progressing to be high performance of PLGA can be achieved through incorporation of other material to produce PLGA composite by providing finer mechanical strength and great cell-scaffold interaction.

POLYETHYLENE TEREPHTHALATE GLYCOL (PETG)

PETG is a common 3D-printing material with proven biocompatible, sufficient strength and strong chemical resistance [77-79]. Fig. 1(d) shows the chemical structure of PETG. PETG has been utilized for various biomedical applications including scaffold, hip implant, prostheses, drug delivery, bio-and electrochemical sensors, dental and vascular applications. A self-deployable spiral stent, mechanical fasteners and a self-conforming supporting splint are just a few examples of mechanical and biomedical applications that might benefit from the shape transformation capabilities of 3D printed PETG parts [79-80].

Due to its thermal properties, PETG that is synthesized through polycondensation reactions of cyclohexanedimethanol CHDM, ethylene glycol (EG), and terephthalic acid (TPA) is easily molded through injection molding, pressure molding, 3D printing and thermoforming [81]. Therefore, PETG has become a very promising candidate for bone tissue engineering applications due to its due to its scaffolding ability that advantage for bone regeneration [81-82]. Previously, a study has been conducted to compare the performance between 3D-printed PETG and PCL as the bone scaffolds [82]. PETG scaffolds demonstrated better mechanical properties with enhanced cell adhesion, proliferation and differentiation in biomechanical environment that give advantages for bone tissue application [80]. Recently, 3D-printed PETG demonstrated good biocompatibility with bone marrow and peritoneal lavage cells [83].

Surface modification of PETG

Few studies have been conducted to analyze the effect of surface modification on PETG for tissue engineering application. In one of the studies, PETG surface has been treated with high amount of UV-C in improving hydrophilicity and cellular adhesion in making artificial blood vessels [84]. However, based on our knowledge, no specific studies have been done by using the surface modified or coated PETG scaffolds for bone regeneration.

Therefore, further studies on surface modifications for PETG scaffold should be conducted to study the biocompatibility, cell viability and hydrophobicity of the scaffold.

PETG-based composites

Due to their better qualities over individual materials, polymer composites are in high demand for a variety of biomedical applications such as implants, prostheses, and orthoses. Polymer composites offer a greater range of structural biocompatibility opportunities than homogenous monolithic materials [79]. Composites made of PETG may be an ideal choice for biomedical applications due to its distinctive attributes, which include biocompatibility, ease of formability, stable thermomechanical properties, and strong chemical and abrasion resistance [79]. Vijayasankar et al, presented a novel PETG composite reinforced with short silk fibers that was developed using a wet-mixing method [79]. One of the many natural fibers with great mechanical qualities is silk, which has been employed as a reinforcing fiber in a variety of thermoplastic matrices [79]. In the study, pure PETG film (0% Silk-PETG) and PETG-Silk composite films with 2%, 5%, and 10% weight of silk fibers were characterized and investigated [79]. Due to the stiffening action of fiber with matrix or constrained polymer chain movement, the storage modulus increases along with the fiber concentration [79]. After annealing, it was discovered that the tensile modulus of the composites and pure PETG had increased [79]. This might be as a result of the enhanced interfacial bonding during annealing [79]. According to a biocompatibility examination, the inclusion of silk increased cell adherence, demonstrating the materials were cell friendly [79]. In all situations, the cell number was declining or remained unchanged on day 14 as compared to tissue culture plates (TCP) [79]. This is anticipated to be the result of cell confluence on samples, where there is no room for additional growth. In conclusion, the produced composites are biocompatible and suitable for biomedical applications [79].

Recently, PETG was combined with polyurethane (TPU) making a hybrid 3D printed maxillofacial implant that demonstrated cell-friendly behavior due to the chemical constitution of the TPU and great impact stability because of the crack-absorbing TPU/PETG combination [85]. Therefore, to produce scaffold with good biocompatibility, mixing PETG with other hydrophilic materials is a good alternative to achieve the objective if producing scaffold with high cell proliferation rate.

CONCLUSION

Surface modifications and composite of hydrophobic polymers demonstrated a promising strategy in utilizing the benefits of these polymer in bone tissue engineering. By introducing surface modifications, biocompatibility and bioactivity of the scaffold are increasing compared to the unmodified polymer. Meanwhile, composite approach able to synergize the benefits of all biomaterials involved. Therefore, the modified polymers able to achieve biological properties and mechanical properties of bone scaffold. However, one criterion that need to be concern during the selection of these hydrophobic polymers is the degradation effect toward towards long term implantation. Overall, PLLA and PLGA have high potential in releasing the lactate during degradation either in short-term or long-term observation. On the other hand, PETG does have the potential to release degradation products during long-term implants due to release of terephthalic acid and ethylene glycol. Among these polymers, PEEK is the most stable that does not release harmful ions or acids to the surrounding body during degradation. However, if compared to other polymers, pure PEEK is the most inert material that will affect osteointegration property. Therefore, the venture into these uncommon polymers should be widen to assess its benefit to tissue engineering and cell interaction studies.

ACKNOWLEDGEMENT

This work was supported by RUG-UTM Matching Grant (Q.J130000.3023.04M47) from Universiti Teknologi Malaysia, Malaysia.

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