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Poly-Ether-Ether-Ketone (PEEK) Biomaterials and Composites: Challenges, Progress, and Opportunities

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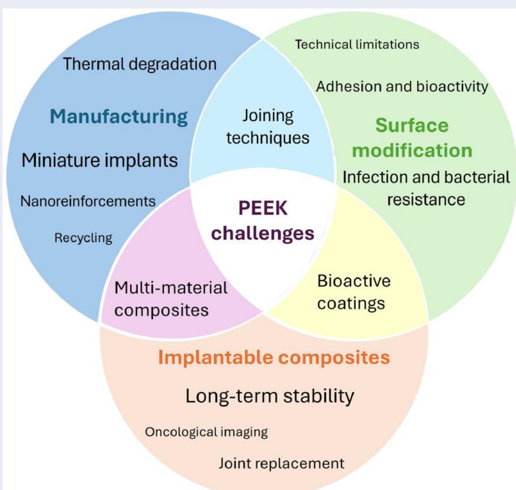
ABSTRACT

Polyetheretherketone (PEEK) is a lightweight, bioinert, high-performance thermoplastic that is beginning to see clinical use in orthopedic applications. PEEK outperforms conventional metallic counterparts in terms of reduced stress shielding and improved chemical resistance, making it highly suitable for implantable applications. However, despite its excellent mechanical properties, the elevated melting point (343 °C) presents significant challenges during manufacturing. Furthermore, PEEK requires surface modifications to enhance antibacterial, bioactive, and osseointegration properties suitable for *in vivo* applications. In this context, the present manuscript highlights current manufacturing challenges for implantable PEEK biomaterials and typical fiber reinforced PEEK composites. Emphasis is placed on reinforcements such as carbon fiber (CF), hydroxyapatite (HA) and titanium dioxide (TiO_2), along with multi-material PEEK composites and their applications. Opportunities are identified to address these challenges, contributing toward the development of synergetic, multi-functional PEEK biomaterials suitable for long-term implantable applications.

GRAPHICAL ABSTRACT



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1. Introduction

The global prevalence of bone-related disorders and diseases has increased significantly in recent years.[1] A report from Research and Markets[2] in 2018 noted that 22.3 million orthopedic surgical procedures were conducted worldwide, increasing to ~ 28.3 million by 2022. This trend has continued, driven by factors such as injuries (including fractures and dislocations from traffic accidents, sports, and falls),[1] bone tumors,[3] and degenerative conditions (*e.g.*, arthritis),[4] posing serious challenges in the field of orthopedics. Furthermore, the number of individuals aged 80 years or over is projected to triple to 426 million globally from 2020 to 2050 according to the World Health Organization (WHO).[5] This rate of aging will be accompanied by a rapid increase in orthopedic ailments: fractures; musculoskeletal diseases; osteoporosis; bone metastasis; and chronic-degenerative diseases.[6] Metal implants, such as titanium and its alloys, are frequently used in the context of orthopedics. However, issues related to wear are common, causing damage to bone tissue (osteolysis) and leading to adverse biological reactions such as metal allergies, inflammation and bone resorption.[7,8] Furthermore, the use of metals also compromises medical imaging (e.g. magnetic resonance imaging (MRI), X-ray) due to differences in magnetic susceptibility between the metal implant and the surrounding tissue, plus radiation scatter in the region of the implant. These factors lead to imaging artifacts and misleading medical diagnostics.[9] In light of such challenges, alternative polymer-based biomaterials have emerged for bone tissue engineering applications.

Polyetheretherketone (PEEK), a high-performance thermoplastic polymer from the polyaryletherketone (PAEK) family,[10] has been widely used as a biomaterial for orthopedic, trauma, and spinal implants. A number of mechanical characterization and *in vivo* simulation studies (such as degradation and corrosion damage) have demonstrated the suitability of PEEK for healthcare applications, including orthopedics[11,12] and trauma,[13] with the first PEEK biomaterial commercialized in 1998 for implantable applications.[14] PEEK displays superior mechanical properties when compared to other biomaterials used in orthopedics, as summarized in Table 1.

One of the key advantages of PEEK is the elastic modulus (3 – 4 GPa), which is much closer to that of human cortical bone (15 – 18 GPa) and cancellous bone tissue (0.3 – 1 GPa)[15,36] (Table 1), compared to titanium (103 – 110 GPa)[38] and titanium alloys (Ti-6Al-4V) (110 – 130 GPa).[33] Stress shielding, the reduction of bone density triggered by removal of typical stress from the bone due to the presence of an implant, occurs when the implant is significantly stronger or stiffer than the bone, leading to a disproportionate distribution of stress and ultimately to post-surgical complications.[39] Therefore, the use of biomaterials with similar elastic moduli to bone tissue is important to avoid stress shielding and to encourage stress transfer to the surrounding hard bone.[36] This can lead to a physiologically favorable mechanical environment to support long-term osseointegration[40] (the connection between living bone tissue and the surface of an implant). Implantable and non-implantable PEEK biomaterials have succeeded in clinical use,[41,42] driven by excellent mechanical properties, radiolucency, and biocompatibility. However, titanium continues to be the most widely used implantable biomaterial in clinical practice,[43] as the use of PEEK is currently limited due to poor

Table 1. Mechanical properties of PEEK, other implantable biomaterials and human bone.

Material	Tensile strength/MPa	Elastic modulus/GPa	Reference
Polyetheretherketone (PEEK)	103–110	3–4	[15–17]
Ultra-high molecular weight polyethylene (UHMWPE)	39–48	0.5–0.8	[18]
High-density polyethylene (HDPE)	29	1.1	[19]
Poly (methyl methacrylate) (PMMA)	30–50	2	[20,21]
Polycarbonate urethane (PCU)	20–60	0.01–0.1	[22,23]
Polyoxymethylene (POM)	50–60	2.5–5	[24–26]
Polylactic acid (PLA)	70	3.5	[26]
Carbon fiber reinforced (CFR) – PEEK composite (CF20%)	105–120	18	[27,28]
Carbon fiber reinforced (CFR) – PEEK composite (CF30%)	214	24	[29]
Hydroxyapatite (HA)	49–83	4–16	[30,31]
Ti-6Al-4V	976–1100	110–130	[32,33]
Cortical bone	104–114	15–18	[34,35]
Cancellous bone	5–10	0.3–1	[15,36,37]

surface osseointegration, high material and manufacturing costs, and the lack of data validating the long-term performance of PEEK implants.

Despite its well-suited mechanical properties, the elevated melting point (343 °C) of PEEK makes it challenging to process, as there are a number of process parameters that must be carefully considered in order to retain optimal mechanical performance post-processing.

This paper presents a comprehensive review of the current manufacturing challenges and future trends for implantable PEEK biomaterials and bio-composites. The review highlights opportunities for *(i)* the fabrication of innovative synergistic PEEK biomaterials and optimization of conventional & novel PEEK manufacturing processes; *(ii)* enhancement of PEEK bioactivity, osseointegration and antibacterial properties; and *(iii)* opportunities to accelerate the use of PEEK implants for regular clinical practice.

2. Bio-manufacturing using PEEK: Challenges and progress

The elevated melting temperature of PEEK requires highly specialized equipment and processing methods to control melting and molding of PEEK products, as very high melting temperatures often lead to micro-structural polymeric degradation and ultimately failure at the macroscale. Current PEEK processing techniques are limited to the development of non-complex implant geometries, which is an issue for personalized healthcare. In addition to these challenges, the other major concern is the elevated cost of PEEK materials, which can dominate the overall component cost depending on scale and production volume. The present section highlights some typical manufacturing challenges associated with PEEK, identifies solutions and emphasizes future trends for the manufacture of novel, synergistic PEEK biocomposites. These include: *(i)* Issues with thermal degradation and the resulting crystallographic properties. *(ii)* Manufacturing intricate components with complex geometries. *(iii)* Creating joints to produce complex assemblies. *(iv)* Homogeneously dispersing nanomaterial reinforcements to enhance performance. *(v)* Recycling of PEEK composite manufacturing waste.

2.1. Thermal degradation and crystallographic properties

Prolonged exposure of PEEK to temperatures beyond its melting point often leads to thermal degradation. Thermal degradation in PEEK occurs *via* a two-step mechanism, initiating with random chain scission of the ether and ketone bonds, followed by the oxidation of the carbonaceous char formed in the first step.[44] Hence, it is critical to control processing parameters such as cycle time, temperature, and heating/cooling rates to prevent the decline in mechanical performance.

A recent publication[45] reported the degradation behavior of PEEK for a range of different process parameters and material reinforcements. Thermal degradation was studied as a function of laser-heating time, where topographical, structural, compositional, and mechanical characterizations provided evidence of thermal effects (such as carbonization) on the PEEK surface. Short laser heating times improved the crystallinity (5.1%) and hardness (10.8%) of the surface modified area, but a further increase in the heating time resulted in surface carbonization and the development of a char layer, reducing the hardness (50%) and indentation modulus (45%). This study highlights the impact of thermal degradation on the micro-structural (crystallographic) properties of PEEK, which ultimately influence the mechanical properties at the macro scale. As such, the crystallinity of PEEK needs to be controlled *via* in-mold cooling at a specific cooling rate; therefore, special consideration is required when manufacturing implantable devices.

Studies regarding the relationship between micro-structural properties and macro-scale performance of PEEK materials have focused on multiple spherulites.[46] Figure 1 illustrates the hierarchical structure of PEEK spherulite crystals. Spherulite-type crystal fibrils are the basic building blocks for a range of semi-crystalline polymers, including the PAEK family. Importantly, spherulite-type crystals play a crucial role in determining

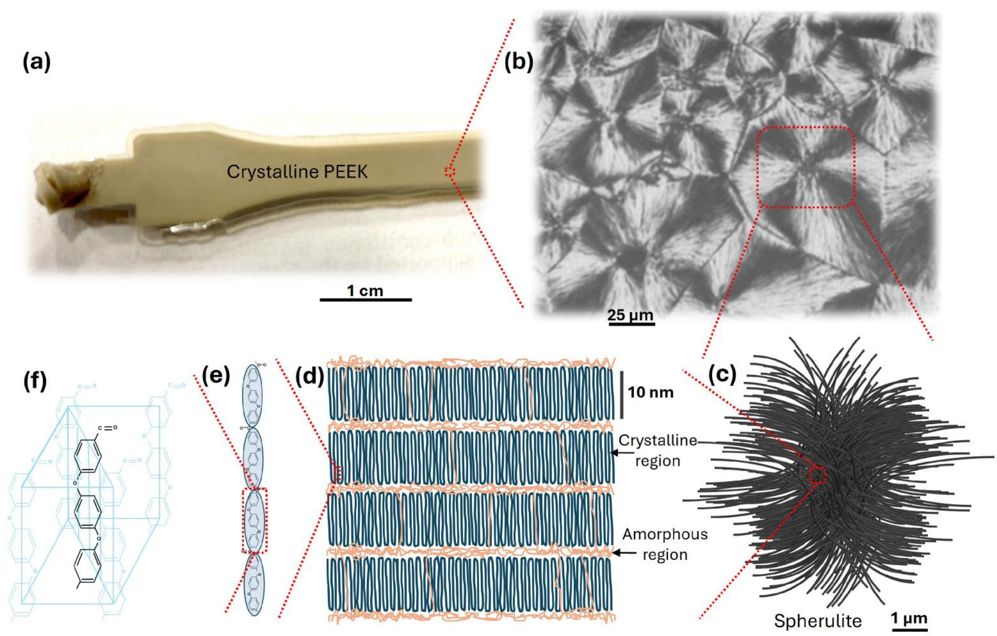

Figure 1. Illustrations and schematic representation of hierarchical structure of PEEK spherulite crystals. (**a**) Injection molded crystalline PEEK specimen, (**b**) micrographs of PEEK spherulites,[47] (**c**) spherulite schematic, (**d**) crystal lamellae and amorphous regions between lamellae, (**e**) individual lamellae, and (**f**) PEEK unit cell. Figures 1d-f reproduced from.[48]

the macroscale mechanical properties of PEEK, including fatigue performance and yield strength. The fracture of individual spherulites have been observed to control the crack mechanisms within polyetherketoneketone (PEKK), another member of this polymer family.[49] Spherulite anisotropy strongly influences the crack behavior of PEEK depending on the location of the crack and the direction of the crystal plane. Plastic deformation of an individual spherulite is determined by the direction of the nucleation site with respect to the applied force. Moreover, the presence of a filler, for example carbon fibers, can increase spherulite nucleation density compared to unfilled PEEK, driven by transcrystalline regions forming at the fiber/matrix interface.[50]

To prevent PEEK degradation, it is crucial to achieve precise and uniform heat distribution throughout molten PEEK during processing. This is a particular challenge in injection molding, a well-established manufacturing technique for developing PEEK-reinforced composites suitable for many clinical applications.[51] The main advantage of injection molding is the versatility to manufacture complex geometries *e.g.,* in total knee arthroplasty.[52] However, despite injection molding being one of the most important processes for mass production of thermoplastics, the complex behavior of molten PEEK, along with uneven heat management can result in thermal degradation and non-uniform crystallization. Moreover, achieving uniform heat distribution becomes more complicated when using complex-shaped molds, triggering internal stresses and undesired warping, compromising the mechanical performance of the final component.[53,54]

2.2. Manufacturing intricate components with complex geometries

Miniature medical devices with complex geometries and the requirement for high mechanical performance are driving the development of novel thermoplastic manufacturing methods, to deliver low-cost solutions to support minimally invasive surgeries. Miniature implants have been fabricated by using molding techniques such as injection molding, ultrasonic micromoulding, and additive manufacturing (AM) techniques, including selective laser sintering (SLS) and fused filament fabrication (FFF) (Figure 2).

Traditional injection molding is limited for achieving complex geometries for miniature components (Figure 2a), as these require smaller nozzles and molds, and shorter residence time to prevent degradation. An alternative method to conventional injection molding for producing miniature thermoplastic impacts is ultrasonic molding (Figure 2b), which uses high-powered ultrasound as a heating source to convey the molten thermoplastic into complex, micro-featured mold tools. This approach avoids the need for a conventional screw, such as for injection molding[58] (Figure 2a), by simultaneously melting and injecting the polymer by sonification. This results in very short exposure times (a few seconds) to the high temperatures, reducing energy consumption, reducing material wastage and minimizing polymer degradation.[55] This method has been used for the rapid manufacture of tailored micro-implants,[59] including PEEK,[60] reporting similar tensile properties between injection (87.6 MPa) and ultrasonic molded (87.4 MPa) samples, and similar crystallinity values between post-ultrasonic molding ($\sim$ 26%) and PEEK pellets prior to processing ($\sim$ 27%). However, these similar properties resulted from the prolonged exposure of PEEK to ultrasound energy, required to reach its melting point. As such, the method is not regularly used for PEEK despite its

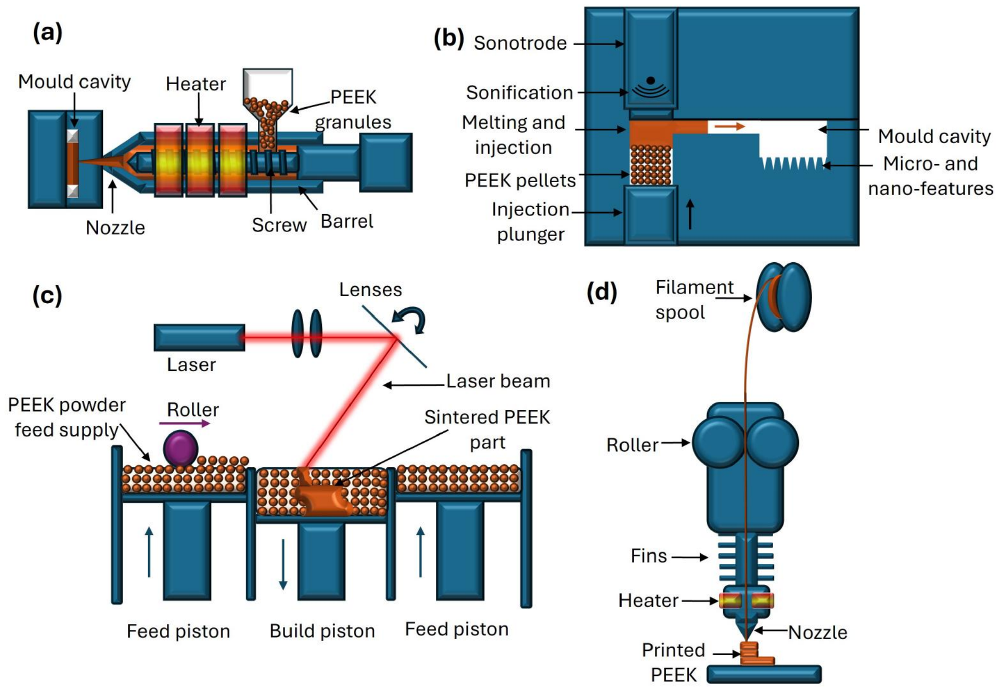

Figure 2. Schematic representation of processes used for manufacturing miniature PEEK composites. **(a)** Injection molding, **(b)** Ultrasonic molding[55] **(c)** Selective laser sintering (SLS),[56] and **(d)** Fused filament fabrication (FFF).[57] Schematics reproduced from citations.

potential for processing other thermoplastics with lower melting temperatures. Furthermore, there are also challenges associated with the reproducibility of the ultrasonic molding process. There is a lack of experimental and simulation investigations regarding reproducibility, with few reports on different machine configurations and experimental approaches. As such, manufacturing miniature components often results in poor replication of geometries with high aspect ratio micro-features (ratios between lateral dimensions and thickness).[61] In order to enhance understanding of the ultrasonic molding process, it has been suggested[58] the use of in-mold sensors for collecting more experimental data during the process. This approach could ultimately help to overcome the challenge of reproducibility. Nonetheless, still much work is needed in terms of process optimization.

AM has enabled the fabrication of complex 3D medical devices & customized implants for biomedical applications.[62] AM technologies have shown potential for the production of complex-shaped miniature implants whilst reducing the wastage of raw materials to reduce production costs.[63] SLS and FFF (Figures 2c,d respectively) have both been used for 3D printing PEEK and its composites. However, SLS wastes large amounts of raw material, which cannot be reprocessed due to potential contamination.[64] Alternatively, FFF has experienced significant development for 3D-printing high-performance biocompatible PEEK[65] with research efforts mostly concerned with process control and composites design. Rodzeń et al.[66] enhanced the layer-by-layer tensile strength of PEEK components by introducing short carbon fiber reinforcement and by optimizing the FFF chamber temperatures with controllable crystallization conditions. Spherulite crystals arising from the carbon fibers acted as nucleation agents, producing thicker lamellae branches (from 25 nm to 50 nm) and enhanced tensile strengths (from ~7 MPa to ~36MPa), as a function of temperature (78 °C – 230 °C). Jiang et al.[67] designed and fabricated PEEK-CF/PEEK sandwich structures *via* layer-by-layer FFF and conducted compression investigations to assess the anisotropic bonding strength on different 3D-build orientations. Results revealed that the build orientation (flat, on-edge, and up-right) had a significant effect on the interface bonding strength (varying from 69.1 MPa to 80.4 MPa) and therefore the failure mode, due to interfacial porosity and poor interlayer bonding.

Moreover, FFF printers offer a layer thickness ranging from 100 to 400 µm,[68–70] contributing to higher resolution and smoother surfaces. Recently, FFF has shown relevance for the 3D printing of dental implants with a layer thickness of 160 µm.[71] However, whilst noting the potential of FFF for processing PEEK, weak inter-layer adhesion typically leads to poor surface quality and poor mechanical properties compared to classic molding routes.[72] Further improvements in mechanical performance of FFF printed PEEK composites are required, including improvements to the interfacial bonding of 3D-printed PEEK[73] and reduced porosity.[74] Whilst 3D-printing is time-consuming and an expensive manufacturing route for mass production of large components,[75] it has the potential to be used for printing miniature, complex PEEK implants for personalized applications.

2.3. Joining techniques for complex assemblies

Some implants, including dental prosthetics and joint replacements, require multiple components, which can also be made from different materials. Joining techniques offer a versatile option for the development of complex-shaped, customizable composite material implants, with recognition of the need for generating multifunctional biocompatible materials. However, selecting an appropriate joining technique for PEEK without compromising the integrity of the material is challenging. Most common approaches include injection overmoulding (Figure 3a) and ultrasonic welding (Figure 3b). As illustrated in Figure 3c, strong interfacial bonding requires an intimate contact between two compatible thermoplastics at a temperature sufficient to allow inter-diffusion of polymer chains across the interface.[78] Overmoulding is an injection molding-based process that can be used to combine two or more materials (*e.g.*, thermoplastics, metals, etc.) to create a single, integrated component. Beyond PEEK biomaterials, overmoulding has been successfully used to mold other biocompatible thermoplastics onto metal components (*e.g.*, titanium) to improve grip, comfort, or bioactivity in medical devices. This includes developing bioresorbable pedicle screws with over-injected polyglycolide (PGA), poly(lactic-co-glycolic acid) (PLGA), poly(δ-decalactone) (PDL), and poly(D,L-lactide-co-glycolide acid) (PDLG) onto a medical-grade metallic core (316 L stainless steel).[79]

Currently, the major challenge related to overmoulding is weak bonding. This occurs due to poor compatibility between materials and poor interdiffusion of the phases (healing). In light of such limitations, current investigations aim to enhance interfacial strength, reduce defects, and control interface temperature. Akkerman et al.,[76] studied the overmoulded interface strength of semi-crystalline thermoplastic composites,

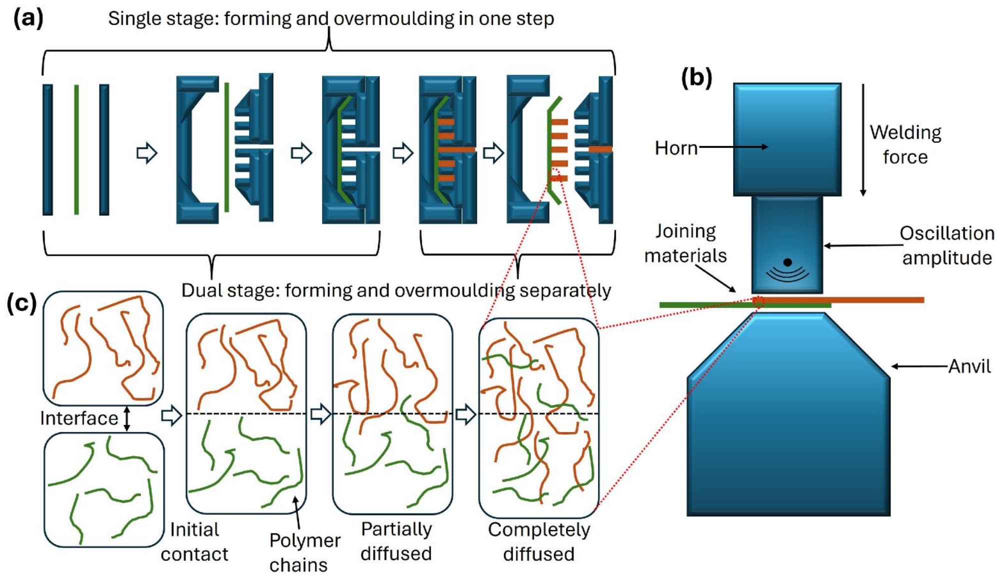

Figure 3. Schematic representations of **(a)** injection overmoulding,[76] **(b)** ultrasonic welding,[77] and **(c)** interdiffusion of polymer chains at thermoplastic interface.[78]

including PEEK onto CF reinforced-PAEK. Two process approaches were explored, denoted as *i)* single-step (the insert is heated above the melting point and formed whilst closing of the mold. Subsequently, a thermoplastic is injected onto the insert) and *ii)* dual-step (the insert is prepared in a separate mold and then transferred to a second mold for overmoulding). Such approaches were investigated *via* process modeling and mechanical testing using different coupon geometries. Small cracks emerged at the interface for specimens manufactured during the dual-step method, which were attributed to rapid cooling and thermal shrinkage. Conversely, the single-step approach showed no signs of micro-cracks. Instead, fiber migration was observed, which increased mechanical interlocking between the overmoulded thermoplastic and the insert, thus improving the interfacial strength.

Zhao et al.,[80] studied the effects of temperature of over injected *(i)* PEEK and *(ii)* short-carbon-fiber reinforced PEEK onto compression molded continuous carbon-fiber reinforced PAEK. For PEEK/PAEK, the interfacial shear strength indicated that the mold temperature had a strong effect on the bond strength of the composites (from 220 °C to 260 °C, shear strength increased from 56 MPa to 70 MPa, respectively). For over injected CF-PEEK/PAEK, the shear strength increased from 77 MPa at 220 °C to 85 MPa at 260 °C. Simulation work revealed that this effect was facilitated by molecular chains crossing the interface and becoming entangled. Furthermore, the increase in melting temperature influenced the interfacial shear strength of the over injected CF-PEEK/PAEK (83 MPa at 380 °C to 87 MPa at 410 °C). This effect was influenced by the migration of short carbon fiber across the overmoulded interface. Interestingly, both studies highlight the effect of short fibers on enhancing interfacial bonding strength.

Overmoulding has shown promise for long-term applications for PEEK dental prostheses (implant crowns). Wachtel et al.[81] overmoulded a screw-retained PEEK crown connected to a titanium implant with indicator-agar (kanamycin Aesculin Azide) to detect bacterial leakage. The investigation demonstrated the effectiveness of the overmoulded composite by resisting against E. faecium bacterial leakage during cyclic masticatory simulations (force of 50 N cm applied at 30° for 1.2 million cycles). Whilst overmoulding is at an early stage for healthcare applications, its versatility can provide a route for scaffold and dental implant fabrication with enhanced functional properties, such as antibacterial resistance and integration with AM molded components.

Ultrasonic welding is a versatile technique with many advantages for joining biocompatible thermoplastics together, such as PEEK,[75] ultra-high molecular weight polyethylene (UHMWPE)[82] and poly (methyl methacrylate) (PMMA).[83] Furthermore, it is applicable for joining dissimilar composite materials *e.g.*, semi-crystalline and amorphous thermoplastics, or thermoplastic and metals.[84] Ultrasonic welding outperforms other forms of welding in terms of the required energy input, the welding temperature and the speed,[85,86] with the possibility of *in situ* monitoring.[87,88] However, the penetration of the ultrasonic vibration is limited due to physical aspects, such as shear joints[89] and materials thickness (limit ~ 3 mm).[90] In addition, the stiffness and hardness of the thermoplastic can affect the amount of vibrational energy delivered to the interface, limiting the thermal energy.[91] As such, ultrasonic welding of PEEK biomaterials has been restricted due to inherent technical difficulties.

Ultrasonic welding has shown some relevance in manufacturing PEEK biomaterials. Abdulfattah et al.[92] recently investigated ultrasonic welding for joining PEEK-based denture frameworks. Ultrasonically welded dental grade PEEK was evaluated by assessing the shear bond strength to determine the optimum welding energy. Digital microscopy provided evidence of surface deformations as a function of welding time/energy (50, 70, 90 and 130 J). Mechanical tests (tensile and indentation) of ultrasonic welded PEEK coupons indicated that a weld energy of 90 J yielded the highest levels of shear bond strength (16.5 MPa) among the coupons, but this is still much lower than the required 65 MPa for polymer biomaterials and their application in dentistry according to ISO 10477.

2.4. Dispersing nanomaterial reinforcements

Researchers have been investigating the incorporation of nanomaterials into PEEK, such as multi-walled carbon nanotubes[93] in order to enhance tribological properties, wear behavior, and mechanical strength. Manufacturing nanocomposites using PEEK involves an initial dispersion stage, a molding process and post-molding processes. The initial dispersion stage is critical for achieving good compositional homogeneity. The most common PEEK matrix/filler mixing methods are ball-milling,[94–96] solvent-assisted dispersion,[97] and melt extrusion.[98] However, from a manufacturing perspective, the agglomeration of carbon nanotubes in PEEK remains a challenge because of the inert nature of PEEK to organic solvents.[99]

To address this issue, Ma et al.[100] utilized montmorillonite (a biocompatible, natural inorganic phyllosilicate mineral[101]) as a second filler to enhance the dispersion between PEEK and carbon nanotubes. The composite samples were prepared by using ultrasonification to disperse the carbon nanotubes in the montmorillonite suspensions (ratios of 1:0, 1:1, 1:2, and 1:4), followed by PEEK powder incorporation, stirring and water filtration. The composite was diluted with neat PEEK, melt-blended, and injection molded. The investigation revealed a clear difference between neat PEEK and montmorillonite modified PEEK/carbon nanotube composites, and highlighted the formation of smaller, more evenly dispersed spherulite crystals as the concentration of montmorillonite increased. Moreover, this study highlighted the effects of nanoreinforcements on PEEK, including at elevated temperatures. Dynamic mechanical analysis revealed that PEEK nanocomposites containing 0.5 wt% carbon nanotubes and 2 wt% montmorillonite exhibited a maximum increase of 48.1% in storage modulus at 240 °C when compared to untreated PEEK.

Moreover, recent studies have also focused on improving the interfacial bonding between PEEK and CF using carbon nanotubes. Zhou et al.[102] modified the surface of CF with sulfonated PEEK/carboxylated carbon nanotubes. The modified PEEK-CF showed a significant increase in flexural strength (75%) and interlaminar shear strength (86%) when compared to the unsized, PEEK/carbon nanotube control sample. Li et al.[103] modified the surface of PEEK-CF with sulfuric acid (98%) *via* sulfonation to generate a porous structure, and subsequently applied a graphene oxide coating. Electron microscopy of the sulfonated PEEK-CF/graphene oxide composites revealed a 3D porous nanostructured network with uniformly distributed layers of graphene. Sulfonated PEEK-CF/graphene oxide samples presented bioactivity in terms of upregulation (occurs when a cell increases activity in response to a stimulus, boosting cellular response or protein production) of osteogenic genes expression and improved apatite deposition, and also biocompatibility assessed *via in vitro* and *in vivo* studies.

Ji et al.[104] investigated the low-impact effect and damage mechanisms of PEEK-CF-Ti hybrid laminates with interfacial multi-walled carbon nanotubes. Two surface treatment methods were compared, including sandblasting and sandblasting followed by electrophoretic deposition of carbon nanotubes on the surface of Ti plates. Results showed that the initial delamination threshold can be considerably increased (15%) by incorporating carbon nanotubes networks. This effect was attributed to the inter-layered carbon nanotube network, which suppressed the deformation of the hybrid laminate. Moreover, carbon nanotubes are noted to enhance interfacial performance, such as crack bridging and toughness, through mechanical interlocking and chemical bonding (when using functionalized carbon nanotubes). The mechanical interlocking approach[105] offers stability levels comparable to those achieved *via* chemical modification, with the added benefit of avoiding saturation of sp^2 carbon,[106] which can affect mechanical properties.

Furthermore, the effects of CNTs on PEEK crystallinity have been investigated. Ye, et al.[107] reported on the micro-structural effect of carbon nanotubes (CNTs) incorporated into PEEK at different concentrations (0.5 – 10 wt%) *via* a parallel twin-screw extruder, and subsequent injection molding. A non-isothermal crystallization kinetics investigation revealed that the crystallinity of PEEK composites decreased (from 32% to 18%) as a function of increasing the concentration of carbon nanotubes. Both the tensile strength (from 98 MPa to 118 MPa with 5 wt% PEEK-CNTs) and electrical conductivity (from 0 S/cm to 2.13 S/cm, 0.5 wt% and 10 wt% respectively) increased compared to unfilled PEEK. The effect was attributed to CNTs hindering the movement of the PEEK chains, reducing the crystallinity of the composite.

Despite such studies highlighting the inherent advantages of carbon nanotubes, their use in healthcare has been limited. Researchers continue exploring alternative routes to address safety concerns on whether carbon nanotubes are biocompatible or carcinogenic[108] due to concerns regarding toxicity *via* inhalation.[109]

2.5. Recycling manufacturing waste

The Circular Economy Action Plan (CEAP) from the European Commission aims to ensure that materials wastage is eliminated in the European Union by 2030. In this context, there is a need for improved strategies to reduce PEEK material wastage during the manufacturing stage. The healthcare market consumes around 2% of all thermoplastics and recycling them is particularly challenging in the context of medical applications. For other industries, PEEK waste can be recovered and reprocessed within the manufacturing facility, but this is not feasible within the healthcare sector due to contamination. In situations where recycling or reprocessing is not feasible, PEEK waste is usually incinerated to generate energy *e.g.*, heat or electricity. Alternatively, it is suggested that PEEK be recycled within the manufacturing facilities and subsequently remanufactured for non-implantable applications, *e.g.*, insulin auto-injectors and inhalators. Importantly, PEEK composites can be thoroughly sterilized (*via* gamma radiation[110] and steam[111]) which opens up opportunities for non-implantable biomedical applications. Moreover, PEEK can be recycled for other industries, such as electronics and automotive. In this context, coordination is required between recyclers, the medical industry and other composite sectors.[112]

3. Surface modification of PEEK: Challenges and progress

Non-degradable polymers such as PEEK are suitable for applications requiring long-term stability,[16] including orthopedics and implants, but are bioinert and hydrophobic (water contact angle of 80 – 90°[113–115]). This hydrophobic nature can lead to a reduced wound healing capacity during osseointegration[16,41] due to poor cell attachment/migration, inflammatory responses, and microbial adhesion, resulting in clinical failure. Therefore, special attention must be given to the surface properties of PEEK, as the interface with human tissue is critical to the osteogenic function.[7] Surface topography modification and the incorporation of bioactive groups benefit the adhesion, proliferation and differentiation of osteoblasts,[116,117] as well as providing antibacterial/anti-infection properties (Figure 4). Importantly, surface changes usually do not affect the mechanical properties of PEEK.[119] The present section discusses *(i)* limitations associated with surface engineering techniques, *(ii)* strategies to enhance osseointegration, surface adhesion, bioactive properties, *(iii)* implant infection and bacterial colonization, and *(iv)* progress on *in vivo* validation of bioactive coatings.

3.1. Technical limitations

Different surface modifications and functionalisation strategies have advanced into clinical applications.[31,120–125] Such surface strategies are useful to promote roughness,

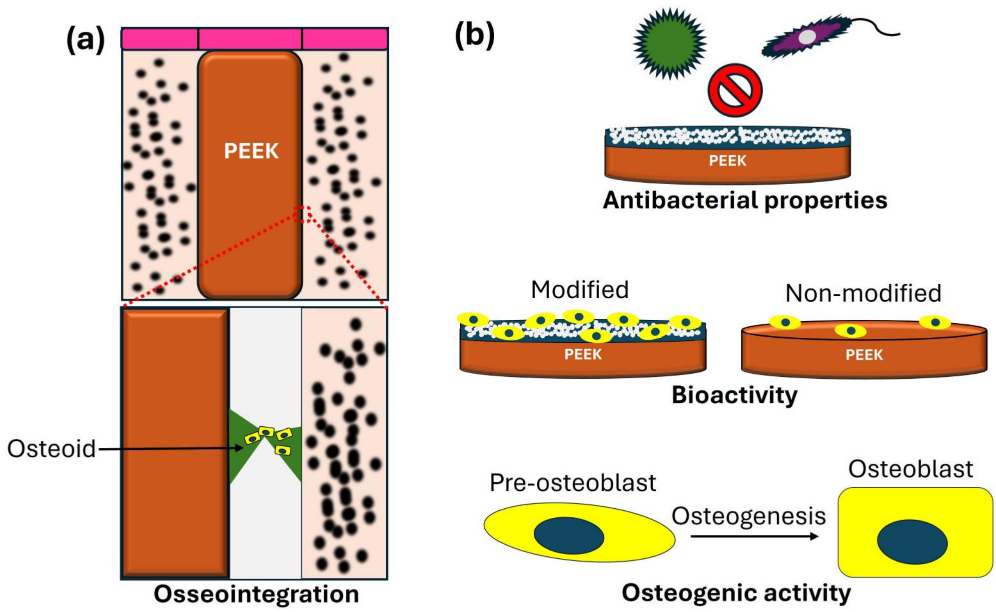

Figure 4. Functional properties of surface modified PEEK implants. **(a)** *In vivo* osseointegration after 6-8 wk of implantation,[118] and **(b)** *in vitro* antibacterial, bioactivity and osteogenic properties.[31] Schematics reproduced from citations.

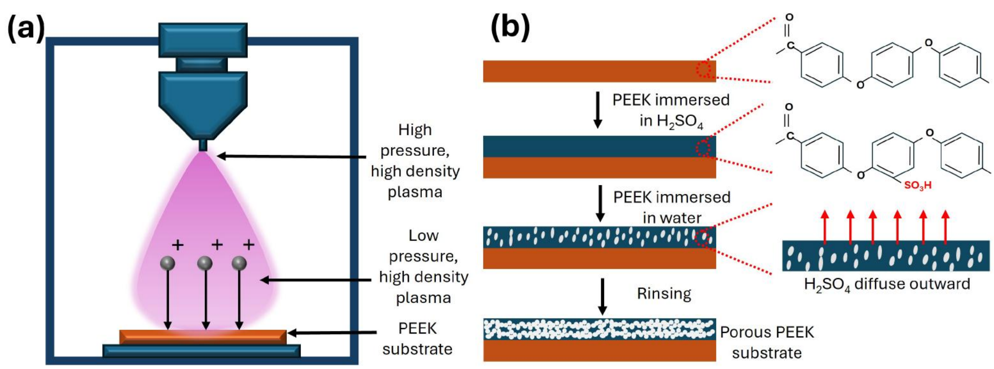

Figure 5. Schematic representation of **(a)** plasma immersion ion implantation (PIII) and **(b)** sulfonation.[129]

which is considered to be one of the most significant parameters for cell activity,[126,127] and wettability, which promotes the adsorption of proteins onto the surface for the osteogenesis of bone cells. Sulfonation and plasma treatment are the two most common surface modification strategies used to increase surface energy and bioactivity of PEEK.

Plasma treatment has been successfully used in combination with other surface modification techniques for the development of multi-functional, novel PEEK-based (bio)materials. These include PEEK surface functionalized with PLGA microspheres encapsulating the BMP-2 gene, which was used to enhance bioactivity.[128] In particular, Plasma Immersion Ion Implantation (PIII) (Figure 5a), a single-step plasma treatment technique, has been successfully used to modify the surface of PEEK.[130] PIII accelerates plasma ions toward the polymer surface to break bonds and disrupt polymer chains. During the restructuring of bonds, radicals containing reactive unpaired electrons are produced, which diffuse throughout the polymer surface to covalently immobilise/attach bioactive molecules *e.g.*, proteins.[131] This helps to improve bioactivity and osteogenic/angiogenic properties on PEEK-CF surfaces. However, plasma treatment suffers from line-of-sight limitations, which complicates the surface modification of implants with complex geometries.[125] In order to address this limitation, plasma treatment is commonly used as a pretreatment in synergy with other PEEK surface modification approaches, including chemical modifications such as sulfonation.

Sulfonation (Figure 5b) refers to the incorporation of sulfuric acid (H_2SO_4) or gaseous sulfur trioxide onto the PEEK backbone to promote inter-chain interactions, modifying the physical and functional surface properties.[114] As a result, a three-dimensional porous network with -SO_3H functional groups is produced. This strategy promotes osseointegration by increasing roughness and hydrophilicity.[132] Due to its advantages, sulfonation is often combined with plasma treatment, ultra-violet (UV) treatment (for wettability and adhesion) and material deposition techniques. However, the drawback of sulfonation relates to residual sulfuric acid remaining within the pore cavities, which triggers adverse biological effects such as an acidic microenvironment and cytotoxicity.[129] The reduction of residual sulfuric acid has been addressed by concentrated H_2SO_4, immersion in water and sodium hydroxide (NaOH).[117]

An alternative approach to clean the sulfonated PEEK is hydrothermal desulfonation. A study[133] showed progressive sulfur removal from PEEK as a function of the hydrothermal temperature. At 25 °C the sulfur content decreased to 2%, whereas at 120 °C the sulfur content decreased to only 0.7%. Similarly, a recent study[134] evaluated the effectiveness of hydrothermal treatment to remove sulfur content from sulfonated PEEK/CF composites. The results showed *a* ∼2.4% sulfur concentration when applying a hydrothermal treatment at 25 °C, and *a* ∼0.4% concentration at 120 °C (notably, similar outputs to the study above). Moreover, the application of temperature progressively reduced the concentration of sulfur (83.1%, 90.1% and 93.2% reduction at 90 °C, 120 °C and 150 °C respectively). The hydrothermal temperature of 90-120 °C showed improved cytocompatibility levels when compared to samples held at 150 °C. This effect was attributed to the removal of particles from the PEEK surface when applying hydrothermal treatment at 150 °C, which compromised its bioactivity and cytocompatibility.

Furthermore, a range of candidate modification strategies have already been proven effective for PEEK surface engineering. As summarized in Table 2, researchers have explored novel combinations of two or more approaches, resulting in enhanced levels of adhesion, bioactivity, osteogenesis and antibacterial properties.

3.2 Porous adhesive and bioactive surfaces

Achieving optimal surface properties for cell adhesion and promoting bioactivity is an ongoing challenge for PEEK. Surface modification strategies can be used to develop porosity on implant surfaces, which locally decrease the Young's modulus of the implanted material and promote cell adhesion and proliferation.[113,145,146] Appropriate

Table 2. Strategies explored for the surface modification of PEEK.

Technique	Coating/materials	Application	Outcome	Ref
Sandblasting, ultrasonification, solution immersion and film lamination	$CeCl_3$ powders / ethanol surface	Enhance the adhesion of PEEK-CF/titanium	Wettability and interfacial shear strength of PEEK-CF/titanium are improved (from 10 to 27.8 MPa)	[135]
Ultra-violet (UV)-initiated graft polymerization *via* vinyl phosphonic acid	Phosphate groups	Chemical incorporation of phosphate groups and hydrophilic enhancement of surface-modified PEEK	*In vitro* studies showed enhanced cell adhesion, proliferation and osteogenic differentiation of MC3T3-E1 osteoblast on surface-modified PEEK. *In vivo* investigation (rabbit tibiae proximal defect model) demonstrated an improved bone-implant contact	[136]
Atom transfer radical polymerization (ATRP)	Grafting biocompatible 2-(dimethylamino)ethyl methacrylate (DMAEMA) and poly(2-hydroxyethyl acrylate) (PHEA) brushes	Increase the biocompatibility of PEEK	Homogeneous distribution of hydroxyapatite was confirmed using microscopy, with good levels of mineralization confirmed *via in vitro* simulated body fluid investigations.	[137]
Accelerated neutral atom beam (ANAB)	Surface nanotexture (2-3 nm)	Controlling extracellular matrix protein adsorption on polymers	Reduction in bacterial attachment with low levels of inflammation surrounding implant	[138]
		Osteoblast functions and bacterial colonization	Enhanced osteoblast responses and protein absorption, demonstrating increases in PEEK bioactivity	[139]
Oxidation treatment	Carboxylic acid (COOH)	Anti-inflammatory	COOH groups promoted anti-inflammatory responses *in vitro*	[140]
Formation of hydroxylated surface-pores, polymer grafting, and chlorination	N-Halamine polymeric coating	Antimicrobial, anti-inflammatory, and pro-osteogenic properties	Mouse subcutaneous implant demonstrated *in vivo* antibacterial, anti-inflammatory effects of porous PEEK- (N-Halamine)	[141]
Physical vapor deposition (PVD)	TiO_2 coating (Ti 99.99%)	Improve mechanical and bioactive properties	Improved hardness (from $\sim$0.3 to $\sim$4.3 GPa), elastic modulus (from $\sim$3.6 to 21.8 GPa) and wear resistance (61% increment compared to uncoated PEEK). Furthermore, simulated body fluid investigations revealed the formation of apatite.	[142]
Liquid phase deposition (LPD)	Polydopamine (PDA) nanogranular TiO_2 coating	Inflammatory resistance, and hydrophilicity enhancement	Increased levels of hydrophilicity as the amount of TiO_2 increased. *In vitro* investigations demonstrated that TiO_2 coatings decreased the inflammatory reaction and enhanced antibacterial activity in both, fibroblasts and osteoblasts.	[143]
Plasma immersion ion implantation (PIII) and PDA-assisted covalent immobilization	Active sites of titanium, and hybrid polydopamine (PDA) ZnO nanoparticles	Antibacterial properties	Favorable stability and cytocompatibility levels.	[144]

interconnectivity levels, pore textures and surface compositions in bone scaffolds are crucial factors influencing bioactivity, such as cell adhesion, migration and differentiation.[147] The ability to combine both interconnected porosity and bioactivity into PEEK composites has been successful for the manufacture of PEEK-hydroxyapatite (HA) biocomposites.[148] Siddiq and Kennedy[149] developed a simple method for the manufacture of homogeneous, porous PEEK *via* sintering-infiltration of molten PEEK into a packed bed of salt beads. In order to support compressive loads to alleviate stress yielding and protect the porous structure, porous specimens were drilled and injection over-molded, creating "pillar" structures with PEEK-salt inserts. The investigation demonstrated an adaptable process to generate porous PEEK (75 – 85% porosity) with stiffness (386 ± 35 MPa) and yield stress (13 ± 0.4 MPa) at similar levels to those of trabecular bone (65 – 80% porosity, 300 MPa stiffness, and 2 MPa yield stress).

Alternative porous PEEK structures have been created by combining additive manufacturing and surface modification strategies. Zhong et al.[150] 3D-printed a series of hydroxyapatite (HA) scaffolds with varying pore and HA-filament sizes and then overmoulded them to investigate PEEK infiltration depths *via* scanning electron microscopy (SEM) and computerized tomography (CT). Cell cultures validated the cytocompatibility of PEEK-HA composites and mechanical assessments confirmed that the ultimate stress (110 ± 7 MPa) was within the range of human cortical bone. Liu et al.[151] manufactured an interconnected macroporous PEEK scaffold surface *via* FFF 3D-printing and sulfonation. In order to promote apatite formation and protein adsorption, the macroporous PEEK scaffold was coated with methacrylate chitosan/polyhedral oligomeric silsesquioxane nanocomposites through UV-polymerization. Subsequent *in vitro* and *in vivo* evaluations showed that methacrylate chitosan provided a bioactive coating for cell adhesion and proliferation, whereas polyhedral oligomeric silsesquioxane promoted calcium deposition and cell osteogenic differentiation. Furthermore, Luo et al.[152] used an advanced femtosecond laser microfabrication technique to generate porous PEEK, with C-OH groups and amorphous carbon on the surface to improve its bioactivity.

3.3. Infection and bacterial resistance

The risk of bacterial infection around the surface of medical implants is a concern. The uncontrolled growth of biofilms contributes to long-term bacterial infection[153] and, in the worst cases, can lead to implant failure. Biofilms are complex, dynamic organized microorganisms developed by the irreversible adherence of bacteria onto the surface of inert bodies capable of withstanding harsh environments.[7] PEEK does not possess natural antibacterial properties, which makes it susceptible to infections and bacterial adherence. Hence, researchers have focused on developing effective methods for bacterial-resistant coatings suitable for PEEK and its composites.

For a decade, TiO_2 coatings have demonstrated relevance in decreasing inflammation and bacterial colonization on PEEK surfaces. Wang, et al.,[154] developed a PEEK/nanofluorohydroxyapatite (FHA) (the release of fluoride ions from nano-FHA imparts antimicrobial properties[155]) biocomposite with enhanced antibacterial and biocompatible properties. Manufacturing consisted of uniformly dispersing the nanoFHA and PEEK powders in alcohol using an electric blender. The dispersed mixture was then placed into disc-shaped tools (15 mm diameter and 2 mm thick) and compression molded (pre-heated to 150 °C at 35 MPa load, and temperature increased to 375 °C under a load of 15 MPa), followed by mechanical grinding to control the surface roughness prior to being blasted with TiO_2 particles and ultrasonic cleaning. Biofilm formation assay investigations were performed to assess the bacterial cell viability (MG-63 cells) over a 21-day period on the PEEK composite surfaces. Furthermore, an *in vivo* study was conducted with a post-surgical intervention period of 4 and 8 wk. Both the cell viability and *in vivo* results showed that PEEK/nano-FHA biocomposites possessed good antibacterial activity and osseointegration due to the effects of the nano-FHA crystals and the rough surface of the PEEK composite.

More recently, researchers have explored innovative techniques such as physical vapor deposition (PVD) and liquid phase deposition (LPD) TiO_2 coatings for antibacterial applications (Table 2).

3.4. In vivo validation of bioactive coatings

Along with carbon fiber, the most common PEEK reinforcements are hydroxyapatite and titanium. Hydroxyapatite (HA) is an inorganic mineral that is the most commonly used bioactive material for PEEK surface coatings[31] and fillers.[156] Titanium is widely used in the medical sector for hard tissue replacements (*e.g.,* orthopedic joint arthroplasties)[157] and dental applications. The combination of these (bio)mechanically stable materials with bioactive properties,[158] and the mechanical properties of PEEK, are highly desirable for orthopedics, particularly for spine fusion, joint components & dental implants.

As summarized in Table 3, the *in vivo* applications of hydroxyapatite and titanium PEEK composites are well advanced. Current research is focused on validating the *in vivo* performance of hydroxyapatite and titanium coatings onto PEEK. Durham et al.[197] functionalized the surface of cylindrical PEEK implants with a bioactive two-layer coating consisting of HA and yttria-stabilized zirconia (YSZ) *via* ion beam assisted deposition (IBAD). Post-deposition, the coated PEEK implants were processed *via* two heat treatments: *(i)* microwave annealing & *(ii)* microwave annealing plus autoclave processing, to crystallize the as-deposited amorphous HA layer. Implantation investigations (18 wk) of heat-treated HA/YSZ PEEK coatings revealed improved levels of osseointegration, higher bone-implant contact area and improved implant fixation, when compared to untreated PEEK. Lee et al.[198] coated a HA-layer onto PEEK, demonstrating an improved osseointegration rate and an overall increase in the fusion rate and adherence of the PEEK/HA implants. Furthermore, titanium reinforced PEEK composites have shown relevance *in vivo*. McGilvray et al.[199] examined the interbody fusion mechanisms of a porous PEEK-titanium cage for lumbar fusion using an ovine model. Results highlighted that porous PEEK-titanium implants were effectively bonded to vertebral plates by bone-like ingrowth and ongrowth. Bone graft growth and solidification mechanisms were successfully monitored whilst taking advantage of the radiolucent properties of PEEK.

Table 3. Clinical & *in vivo* investigations of PEEK-based (bio)composites. CF: carbon fiber; HA: hydroxyapatite.

Orthopedic application	PEEK (bio) composite/ reinforcement	Coating/ Surface feature	Implant	Type of study/model	Reference
Spine	PEEK-CF	–	Pedicle screw system	Clinical/human	[159–165]
			Anterior cervical plating		[166]
	PEEK-HA	–	Anterior cervical fusion cages		[167]
	PEEK-HA- B tricalcium phosphate	–	Anterior cervical fusion cages		[168]
	PEEK-HA- demineralized bone matrix				
	PEEK-Ti	–	Spinal interbody fusion cages		[169]
	PEEK (unfilled)	–	Anterior cervical fusion cages		[170–173]
			Lumbar interbody fusion cages		[174,175]
		Ti	Lumbar interbody fusion cage		[176,177]
Joint replacement	PEEK-CF	HA	Hip prosthesis	*In vivo*/ovine	[178]
		–	Total knee arthroplasty	Clinical/human	[179]
Trauma	PEEK-CF	–	Proximal humerus plate	Clinical/human	[180–182]
			Intramedullary nails		[183]
			Distal radius fractures		[184,185]
			Distal femur fractures		[186,187]
			Ankle fractures		[188]
Maxillo-facial and cranial implants	PEEK (unfilled)	Porous	Skull plates	*In vivo*/rabbits	[189]
		–	Cranioplasty	Clinical/human	[190–192]
			Orbital prosthesis		[193]
			Mandible prosthesis		[194]
Dental	PEEK-CF	Porous	Dental	*In vivo*/rats	[195]
	PEEK-CF-HA (nanofillers)	–	Dental	*In vivo*/canine	[196]

4. PEEK (bio)composites: Challenges and progress

PEEK has been approved by the US Food and Drug Administration (FDA) for healthcare and has applications in many different areas of medicine, including spine, trauma, and dental applications. Table 3 summarizes some clinical and *in vivo* investigations of natural PEEK, and PEEK (bio)composites, including carbon fiber, hydroxyapatite, and titanium reinforcements. Unfilled PEEK biomaterials are used in craniofacial[200] applications. Reinforced and/or coated PEEK implants are typically used in trauma[201] and spinal[202] applications.

Despite the clinical progress made for PEEK (bio)composites, researchers continue to improve their (bio)mechanical and functional properties. The present section highlights promising applications of functional PEEK (bio)composites.

4.1. PEEK-CF (bio)composites

PEEK-CF has been explored as a substitute for cobalt chrome in the femoral component of total knee[52,203] and hip[204] replacements. Despite technological advancements and favorable mechanical properties that enable the use of PEEK-CF composites in high demand applications like joint replacements, critical complications such as wear, fatigue, squeaking and osteolysis have limited their clinical application for load-bearing implantable applications.[205] With only one study reporting fretting wear resistance suitable for artificial joint applications,[206] PEEK-CF (bio)composites are often overlooked for hip-joint applications compared to UHMWPE,[207] despite efforts to lubricate joints[208] and improve wear resistance.[209]

An all-polymer tibial component offers a desirable weight reduction over traditional metallic solutions. Whilst noting the potential of PEEK composites as joint replacements, current investigations are concerned with the wear performance. Cowie et al.[210] compared the wear performance of UHMWPE-on-PEEK against UHMWPE-on-cobalt chrome, using a multi-axial pin-on-plate test that revealed similar trends for both materials. Zhang et al.[203] conducted *in vitro* wear loss tests for PEEK-on-cross-linked polyethylene (XLPE) (30.9 ± 3.2 mg over 5 million cycles) and CoCrMo-on-XLPE (32.1 ± 3.1 mg over 5 million cycles). The main wear mechanism for the PEEK was plastic deformation, adhesive wear and abrasive wear. For CoCrMo it was related to abrasive wear and corrosion.

The development of biomimetic joint lubrication systems and self-healing surfaces is driving the development of PEEK – hydrogels.[211] A study[212] modified PEEK with acid-co-acryl amide hydrogel *via* UV-initiated polymerization. Subsequently, the prepared PEEK substrate was immersed in ferric nitrate solution to create a cross-linkage between -COOH groups (hydrogel) and Fe^{3+}. The investigation highlighted low-friction and a wettable surface, with the possibility for repair due to the reversible nature of the network structure. Nevertheless, hydrogels and self-healing applications of PEEK are at a very early stage.

PEEK-CF is considered to be the next generation orthopedic/oncology biomaterial, offering a promising alternative in the fields of spinal tumors and metastases imaging[213] due to its favorable (bio)mechanical and radiolucent properties.[214] The radiolucency of PEEK-CF is particularly advantageous for artefact-free medical imaging, with studies suggesting strong potential for the effective monitoring of treatments, such as radiotherapy for spinal neoplasms.[215] As such, PEEK-CF could play an increasingly vital role in managing spinal tumors and metastases, thereby enhancing diagnostic precision and treatment effectiveness. Currently there are two commercially available (titanium coated) PEEK-CF systems for spinal tumor applications. Both include pedicle screws and rods, and both include intervertebral and corpectomy cages.[216] Recent studies have highlighted the effectiveness of radiolucent PEEK-CF in spinal oncological imaging *via* computerized tomography (CT),[217] MRI,[218] and X-ray fluoroscopy.[219] Shen et al.[220] evaluated the postoperative performance and reviewed the short-term clinical and radiographic outcomes of a fully radiolucent PEEK-CF vertebral body replacement, designed for spinal tumor reconstruction. This investigation demonstrated the versatility of the PEEK-CF system to be integrated either on the anterior plate system or the posterior screw-rod system. This enabled postoperative surveillance imaging *via* computer tomography (CT) scanning and adjacent radiotherapy. Hubertus et al.[160] investigated the performance of intraoperative imaging and navigation systems, including intraoperative CT, robotic cone-beam CT and cone-beam CT, for instrumentation and precision assessment of PEEK-CF pedicle screws across the thoraco-lumbar spine. Results revealed that intraoperative CT imaging of PEEK-CF yielded the highest navigation precision, demonstrating their suitability for standard procedures in the field of CT for spine surgery.

4.2. Multi-material PEEK-(bio)composites: PEEK-HA and PEEK-TiO_2

The development of multi-material composites refers to the combination of three or more dissimilar materials to enhance functional properties (Figure 6). In this section,

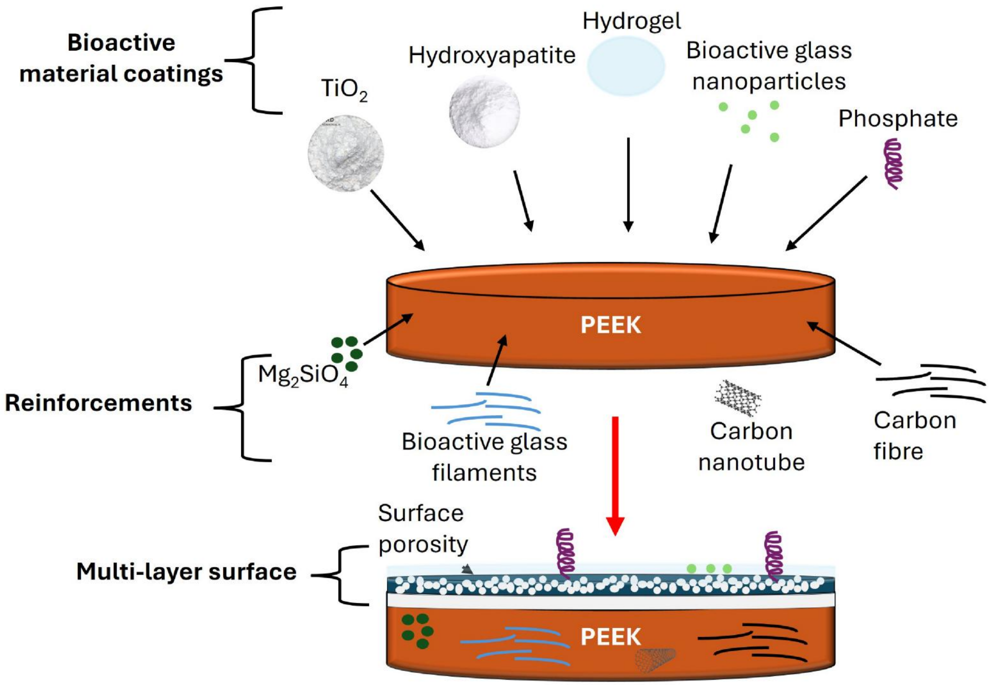

Figure 6. Multi-material PEEK composites.

emphasis is placed on PEEK-HA and PEEK-TiO_2. Hu et al.[221] fabricated and characterized a porous Ti-hydroxyapatite composite coating on PEEK to enhance bioactivity, by vacuum plasma spraying. The three-layer structure presented different roughness and porosity levels (bottom Ti – porosity 10%; intermediate Ti – porosity 35%; top HA – 90% crystallinity). The plasma spraying process had no effect on the thermal/chemical properties of the PEEK. Boonpok et al.[222] fabricated a TiN-HA coating *via* pulsed DC magnetron sputtering on the surface of PEEK, followed by a hydrothermal treatment. The dissolution behavior of TiN-HA coated PEEK was evaluated through simulated body fluid solution at different time-points. The immersion results revealed that both physical and chemical properties of coated PEEK were affected by the Ca/P ratio. The surface roughness of the TiN-HA coating increased from ~51 nm (control) to ~95 nm (day 56 of immersion) and the Ca/P ratio reduced from 1.28 (control) to 1.16 (day 56 of immersion). Nevertheless, the TiN-HA coating remained in the substrate after 56 days, providing evidence of improved levels of PEEK bioactivity.

Combinations of PEEK, hydroxyapatite and carbon fiber materials have also been explored. Jiang et al.[223] 3D-printed *via* fused filament fabrication (FFF) a novel core-shell composite structure using PEEK-CF (honeycomb core) and PEEK-HA (dense shell). The effects of printing deposition paths and its mechanisms were investigated. Baligidad et al.[224] developed HA/reduced graphene oxide wear resistant coatings, applied to PEEK *via* a dip coating method. The evidence showed that graphene oxide improved the friction and wear properties of the PEEK-composite.

Kumar et al.[225] manufactured different weight concentrations of PEEK-HA-Mg_2SiO_4 *via* a 3D-filament process for spinal implants. The materials' cytotoxicity and imaging compatibility *via* CT & MRI were also evaluated. The prepared PEEK (75 wt%) – HA (20 wt%) - Mg_2SiO_4 (5 wt%) composite revealed superior cell viability with minimal MRI and CT artifacts when compared to other compositions. Moreover, the field of nano-reinforcements also opens opportunities for PEEK enhancement. Liu et al.,[226] dispersed β-SiC nanoparticles into PEEK and investigated the tribocorrosion performance of PEEK-steel joints whilst exposed to simulated body fluid. It was concluded that β-SiC nanoparticles promoted the formation of a tribofilm that provided anti-wear properties and corrosion resistance. Ma, et al.[227] modified the surface of PEEK using bioactive glass nanoparticles (BGNs) and polydopamine (PDA) *via* an *in situ* polymerization process to improve osseointegration, osteogenesis and anti-infection activity. The multifunctional biomaterial showed good anti-inflammatory properties, osteogenic differentiation, along with enhanced osseointegration and osteogenesis in an implant model of femoral condyle defects.

Notably, the development of novel multi-material PEEK-(bio)composites is at an early stage, with most research focused on process optimization and materials-property-processing interrelationships, encompassing different research areas, such as wear resistance, osseointegration, medical imaging and anti-infection properties.

5. Future outlook

5.1. Optimization of manufacturing techniques

- **PEEK-CF crystallization kinetics:** The crystallization kinetics of PEEK have been thoroughly reported.[228–230] However, despite the progress made to date, further work needs to be conducted to further understand and enhance the interfacial bond between carbon fibers and PEEK. Studies need to be conducted under different processing conditions to understand the effect of the processing temperature, the heating rate and the number of thermal cycles.
- **Real time monitoring**: Monitoring polymer temperature during molding or joining processes would enable better understanding of the fusion mechanisms at critical interfaces,[231] helping to improve the quality of the bond. Similarly, further in-line process monitoring is needed to investigate the suitability of ultrasonic micromoulding for manufacturing PEEK biomaterials and composites.
- **Joining techniques:** Further investigations on welding and overmoulding strength, durability, and the long-term performance of welded PEEK (bio)composites are needed to ensure the safety and effectiveness of joined implants. Moreover, additional investigations are required to study the interfacial bond strength of PEEK to dissimilar biomaterials, including thermoplastics, ceramics and metals. As such, overmoulding of PEEK-CF materials under different pressure and temperature conditions would be beneficial. Moreover, the principles of injection overmoulding can be applied to fabricate multi-material solutions,[232] involving multi-stage injection strategies of dissimilar polymers.
- **Combining manufacturing techniques**: It is also suggested that the combination of joining methods with additive manufacturing[75] facilitates the development of miniature, complex shaped biomaterials with improved bonding strength. Such combinations can benefit the rapid bonding of PEEK biomaterials with similar

and/or dissimilar materials, enhancing the mechanical properties and fusion rates of *e.g.*, FFF components,[233–235] opening up the opportunity for the development of custom-designed orthopedic PEEK implants. Furthermore, combined additive/compression molding[236–238] technologies for next-generation PEEK composites look promising.

- **Multi-scale reinforcements:** Further research is required to generate systematic methodologies for the incorporation of micro- and nano-reinforcements into PEEK polymers for *e.g.*, injection molding and additive manufacturing. The use of micro- and nano-scale adhesive reinforcements are under intense research,[232] which could potentially boost the design and fabrication of hybrid, novel PEEK biocomposites such as micro/nano-hierarchical carbon fiber reinforced composites.[239,240]
- **Remanufacturing and recycling:** The reduction in the demand for virgin materials decreases the overall energy consumption and raw material extraction associated with PEEK production. Further research into cleaner and more energy-efficient recycling technologies can enhance the environmental benefits of repurposing medical-grade PEEK for broader industrial use. Alternatively, due to its high strength, fatigue resistance, low moisture absorption, and lightweight properties, recycled PEEK could be explored for reuse within the same facility for non-implantable medical applications, such as inhalers, electronic monitoring devices and autoinjector insulin pens, reducing the need for external disposal.

5.2. Enhancement of PEEK bioactivity, osseointegration and antibacterial properties

- **Removal of sulfonate remnants**: There is a need to effectively remove all sulfonate remnants to prevent contamination. Work still needs to be conducted to establish multi-functional PEEK-composite scaffolds for clinical trials.
- **Further surface modification techniques.** In addition to plasma and sulfonation, ultra-violet polymerization is a versatile and promising single-step technique for the rapid coating of bioactive nanomaterials on PEEK surfaces. Most efforts have focussed on improving the bioactive and hydrophilic properties of PEEK surfaces *via* UV-initiated graft polymerization,[241,242] therefore an opportunity for further research work in this area is recognized. Similarly, researchers have recently explored laser surface texturing (LST) for metal-PEEK hybrid joints, *e.g.* aluminum alloys to PEEK,[243,244] with recent efforts placed on improving the bonding performance of PEEK.[245,246] Due to its versatility, LST is relevant in the micro-fabrication of PEEK biomaterials, to generate porosity and enhance hybrid joints.
- **Pre-clinical investigations**: Research investigations are well advanced in terms of preparation of bioactive PEEK-composites, with tuned biological, anti-infection and antibacterial properties. However, there is a lack of pre-clinical investigations of multi-composite materials. Similarly, limited attention has been given to the anti-infection and anti-inflammatory capabilities of modified PEEK.[247]

5.3. Accelerating bench-to-bedside development of PEEK composites

- **Joint replacement:** Further computational and experimental investigations on molded and 3D printed PEEK structures are needed, including *in situ* wear studies *via* simulated body fluids and the development of mineralized collagen scaffolds. Moreover, investigations on hydrogels and self-healing biomaterials to enhance the tribological properties of PEEK are encouraged. Accordingly, further strategies to minimize wear debris are also encouraged.
- **Multi-material composites**: Further studies are required to investigate novel combinations of bioactive surfaces and reinforcements. For example, PEEK composites containing bioactive materials and carbon nanotubes,[248,249] and hybrid coatings such as bioglass-chitosan.[250]
- **Long-term clinical studies:** Most retrospective postoperative surveillance investigations of PEEK (bio)composites are typically limited to 6-12 months.[217,251–254] There is a strong need to ensure the long-term integration of PEEK implants with surrounding tissues, extending over several years. This is particularly crucial for applications including dental,[255] spinal[156] and orthopedic oncology,[256] assessing the stress distribution surrounding implants,[257] studying PEEK implants under disease conditions,[258] evaluating fusion rates[176] and the rate of bone resorption.[259]

6. Conclusions

PEEK biomaterials and their associated composites offer a versatile matrix for the development of innovative, multi-functional, complex-shaped orthopedic (bio)composites. The present review has highlighted challenges, recent advances and opportunities in manufacturing, surface modifiers and applications of PEEK biomaterials.

Researchers are continually developing novel manufacturing methods to enhance the functional and mechanical properties of PEEK (bio)composites. Molding routes are well-established for developing implantable PEEK biomaterials, but most challenges are associated with polymer thermal properties and the incorporation of nano-scale reinforcements. Additive manufacturing and joining techniques are under intense research for the development of miniature PEEK (bio)composite implants with complex-geometries. Nevertheless, current challenges associated with joining techniques relate to weak bonding, necessitating further *in situ* real time investigations into fusion mechanisms and interfacial interactions. In addition, strategies for recycling PEEK composites have also been discussed.

PEEK composites, including carbon fiber, hydroxyapatite or titanium reinforcements are concerned with antibacterial, osseointegration and long-term performance for medical investigations. Despite current advancements in surface modification, much work is still needed to translate multi-material PEEK composites from the laboratory setting into clinical use.

Disclosure statement

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