Progress in Biomaterials (2023) 12:89–111
https://doi.org/10.1007/s40204-022-00214-6

REVIEW PAPER

Mechanical performance and bioactivation of 3D-printed PEEK for high-performance implant manufacture: a review

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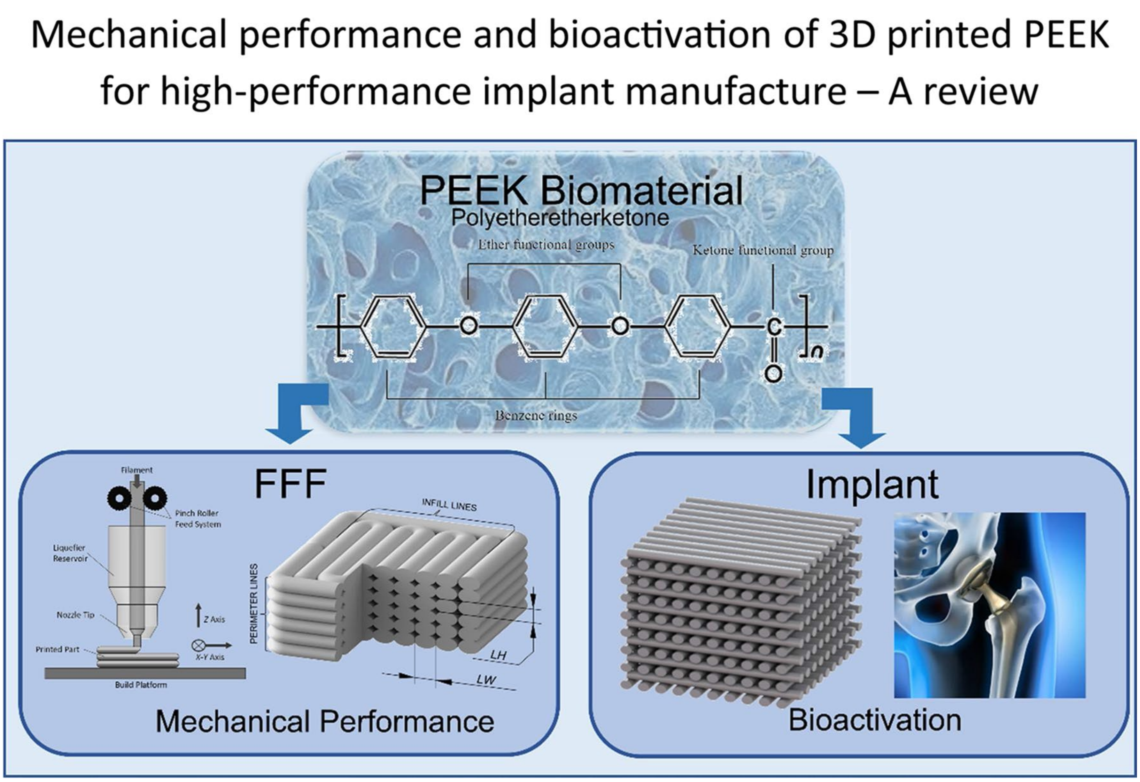
Received: 8 September 2022 / Accepted: 3 December 2022 / Published online: 10 December 2022

Abstract
Polyetheretherketone (PEEK) has stood out as the leading high-performance thermoplastic for the replacement of metals in orthopaedic, trauma and spinal implant applications due to its high biocompatibility and mechanical properties. Despite its potential for custom-made medical devices, 3D-printed PEEK's mechanical performance depends on processing parameters and its bioinertness may hinder bone opposition to the implant. Concerning these challenges, this review focuses on the available literature addressing the improvement of the mechanical performance of PEEK processed through "fused filament fabrication" (FFF) along with literature on bioactivation of PEEK for improved osseointegration. The reviewed research suggests that improvements can be achieved in mechanical performance of 3D-printed PEEK with adequate FFF parametrization while different bioactivation techniques can be used to improve the bioperformance of 3D-printed PEEK. The adequate approaches towards these procedures can increase PEEK's potential for the manufacture of high-performance custom-made implantable devices that display improved bone–implant integration and prevent stress shielding of the treated bone.

Graphical abstract



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Keywords PEEK · Implant manufacture · Additive manufacturing · 3D printing · Biomaterial · Bone

Introduction

Additive manufacturing (AM) refers to the process of fabricating a part by consecutively adding material until the desired 3D object is completed. AM techniques have been referred to as three-dimensional (3D) printing as the material is added layer-by-layer. AM has been used in "rapid prototyping" (RP) for the production of physical models based on the design's CAD data, thus enabling early fit and functional testing. This allows for early design adjustments and can reduce product development costs (Gibson et al., 2021). Additionally, due to its additive nature, AM technology enables the manufacture of complex geometries which are otherwise impossible to produce even through a "computerised numerical control" (CNC) subtractive manufacturing (Sachs et al. 1993). With these unique characteristics, different types of AM technologies such as material extrusion, powder bed fusion and vat photopolymerization have attracted the attention of various industries as potential manufacturing processes.

Extrusion-based AM, which is referred to "fused deposition modelling" (FDM®, Stratasys, USA) or "fused filament fabrication" (FFF), has experienced significant developments in the last years. The widespread of AM technology has increased the demand for both consumer and industrial-level FFF equipment which, in combination with new filament material options, sparked the development of material extrusion 3D printers that are more accessible and more capable of producing high-quality parts. These developments have sparked research on the use of FFF technology for different applications in various research fields. Vyavahare et al. (2020) present a review on different applications for FFF-produced components such as the intake manifold of a combustion engine (Williams and Ilardo 2010), sheet metal dies in "rapid tooling" (RT) (Durgun 2015) and electronic circuits using conductive plastics in curved layer FDM (Diegel et al. 2011a,b). In food science field, extrusion-based AM technology has used edible feedstock material to produce sustainable meat alternatives (Dick et al. 2019).

AM's use in the medical field is particularly interesting due to its ability to produce complex 3D structures based on 3D model's data which can be obtained through medical imaging techniques such as computed tomography (CT), magnetic resonance (MRI) or X-ray (Kumar et al. 2021). Furthermore, the use of AM in the medical field also presents a more sustainable and cost-effective form of manufacturing as its additive nature reduces the use of expensive biomaterials while its design flexibility enables the manufacture of different components with a single piece of equipment (Garcia et al. 2018; Haryńska et al. 2020; Park and Fu, 2021). With this, there is the possibility to enable in-house production of medical devices tailored to patient while the incorporation of AM's design flexibility with customer feedback can reduce manufacturing times. For these reasons, AM could potentially improve the patient's health care in the field of personalised medicine (Soares et al. 2021). These advantages along with current developments in AM-compatible biomaterials make additive manufacturing a top candidate for specialised fields of medicine such as tissue engineering and implant development (Ali et al. 2020; Bozkurt and Karayel 2021). FFF technology is an example of this, where new high-performance biocompatible thermoplastics have sparked research on the use of FFF in the medical field such as the production of a polycaprolactone–bioactive glass (PCL/BAG) scaffold structures (Korpela et al. 2012) and the manufacture of lumbar cages using a specially developed polycarbonate-hydroxyapatite (PC) composite (Serra et al. 2016).

As the interest in the FFF of biocompatible polymers in medical field grows, research has become more focussed on the processability of high-performance biocompatible thermoplastics and thermoplastic-based composites through FFF. Amongst the known biocompatible polymers, polyetheretherketone (PEEK) has stood out for orthopaedic, trauma and spinal implant applications. PEEK is the leading member of polyaryletherketone (PAEK) family of high-performance thermoplastics due to its mechanical and chemical properties. PEEK displays a high strength-to-weight ratio and is chemically inert making it resistant to in vivo degradation, namely lipid exposure (Kurtz and Devine 2007). PEEK is radiolucent, resistant to radiation damage and compatible with reinforcement fibres making it a suitable biomaterial for orthopaedic, trauma and spinal implants (Kurtz 2012). Additionally, as a thermoplastic polymer, PEEK can be processed through FFF which adds the advantages of AM in medical field and its use in the manufacture of load-bearing orthopaedic implants.

Due to its unique properties, PEEK has been the subject of research on its mechanical and clinical performances. However, there is still the need for further research on FFF of PEEK for medical applications. Previous works have reviewed the literature on PEEK's use in medical field (Verma et al. 2021) and even the use of additively manufactured PEEK in the medical field together with its use in the aerospace, electrical and chemical fields (Dua et al. 2021). Despite their interest, these works lack the detail of a focussed review on the processing of PEEK through FFF for load-bearing implant manufacture. Furthermore, this review covers specifically the FFF manufacturing process whereas other reviews on additively manufactured PEEK for the medical field, such as the one presented by Basgul et al. (2021a), focus more on the outcome of PEEK produced with different AM technologies. This review addresses the properties of this material and focuses on research documenting recent developments in FFF of PEEK for medical applications. More specifically, this work includes research concerning new approaches to the improvement of both mechanical and clinical performances of 3D-printed PEEK samples. The aim of this review is to highlight the potential of PEEK's 3D printing for the manufacture of high-performance load-bearing orthopaedic implants. For this, research documenting the manufacture and use of 3D-printed PEEK medical devices is included. Concerning the reviewed research, the remaining gaps are also identified in hopes to spark future developments in PEEK's FFF for orthopaedic implant manufacture.

Literature review methodology

The increasing relevance of AM technologies such as "fused filament fabrication" (FFF) and high-performance filament biomaterials such as PEEK motivated the investigation of available research in FFF of PEEK for medical implant applications. To better understand the current state of the available research, search terms such as "PEEK" or "polyetheretherketone" and "FFF" or "FDM" were used in search engines of Scopus, Science Direct and Web of Science databases (2022a, b, c). The search results, as of January 2022, for PEEK and FFF obtained from these databases, restricted to the material science, engineering and medical fields, can be seen in Table 1. The results from Scopus are also plotted considering the year of the publication in Fig. 1 which portraits a substantial increase in publications in recent years concerning both PEEK and FFF. As the Fig. 1 shows, research focussing on PEEK processed through FFF is still very scarce. The same tendency was also observed in the results from other mentioned databases. This outlines the demand for further research in FFF of PEEK and its use in the medical field.

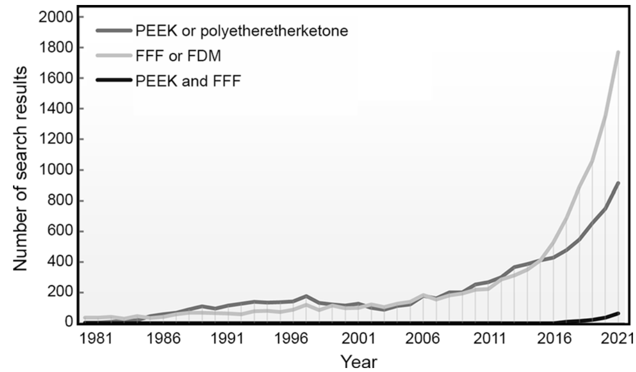

Fig. 1 Number of search results per year based on PEEK and FFF terms

For this review, keywords "PEEK" or "polyetheretherketone" were used in the Scopus search engine for the same mentioned research fields. The search results were filtered for works documenting PEEK's properties and its use in FFF or medical applications. With this, research reporting on the improvement of mechanical performance of 3D-printed PEEK samples and the improvement in bioperformance of 3D-printed and bulk PEEK samples was selected and included in this review. Additionally, research complementing the findings reported in the selected literature for PEEK and FFF was included, hoping to identify some research gaps in the use of 3D-printed PEEK for load-bearing implant applications. This resulted in selected publications from a variety of different fields such as material science, additive manufacturing, biomaterials and clinical orthopaedics (Fig. 2). This way, the review is intended to provide an appropriate understanding of the material and the process along with the most current research findings on "fused filament fabricated" PEEK in the interest of load-bearing implant manufacture.

The selected literature is reviewed in the following section which was divided in four subsections. The first subsection introduces research where PEEK's potential as a biomaterial is highlighted along with relevant concerns for the use of 3D-printed PEEK in medical implant applications. With this, the following two subsections address some of the highlighted concerns covering research documenting the improvement of the mechanical performance of 3D-printed

Table 1 Literature results focussing on PEEK and "fused filament fabrication" (January 2022)

Search terms	No. of results		
	Scopus	Science direct	Web of science
"PEEK"or "polyetheretherketone"	8946	13,980	7176
"FFF" or "FDM"	10,810	17,768	6302
"PEEK" or polyetheretherketone" and "FFF" or "FDM"	151	377	95

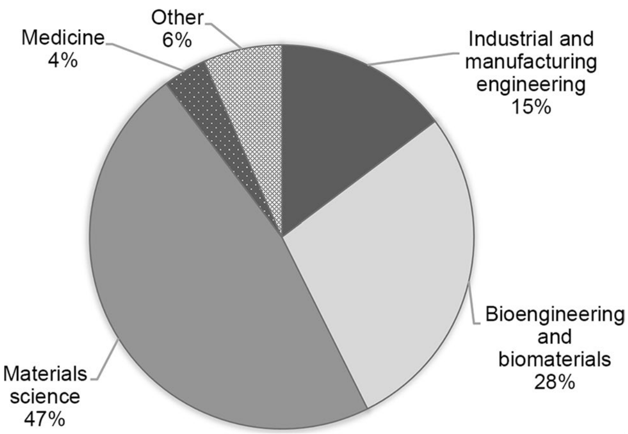

Fig. 2 Categorization of research fields included in this review

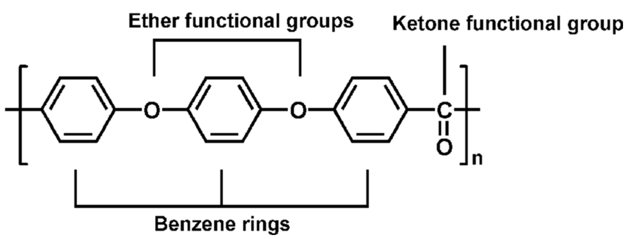

Fig. 3 Polyetheretherketone chemical formula; adapted from Kurtz and Devine (2007)

PEEK and the improvement in bioperformance of PEEK materials. Additionally, the fourth subsection covers the use of 3D-printed PEEK in medical applications further highlighting the potential of additively manufactured biomaterials for patient-specific implant manufacture. Lastly, the conclusion section of this review presents the final remarks along with the authors' insight to the future scope of research concerning FFF of PEEK in the medical field.

Research on 3D-printed PEEK biomaterial

PEEK's biocompatibility and processing

PEEK is part of the PAEK family of high-performance thermoplastic polymers. PAEK polymers have garnered interest in the scientific and engineering fields due to their temperature resistance and biocompatible properties. Similar to other PAEK polymers, PEEK is a linear homopolymer where each monomer has three aromatic benzene rings linked by two ether and one ketone functional group (Fig. 3). Its molecular constitution can vary in monomer repeatability resulting in variable molecular chain length which is related to the material's thermal sensitivity.

PEEK's chemical structure enables movement of the higher orbital electrons along the macromolecule which makes this material extremely unreactive and, consequently, resistant to chemical, thermal and post-irradiation degradation (Li et al. 1999; Kurtz and Devine 2007). This inertness makes PEEK highly biocompatible but its potential as a biomaterial is also highlighted by its high mechanical performance and ability to be easily processed as a thermoplastic. In addition to this, PEEK is translucent to X-ray and compatible with "computed tomography" (CT) scans, "magnetic resonance imaging" (MRI) and can be sterilised using different procedures such as gamma ray irradiation (Green and Schlegel 2001). However, the same inertness that makes PEEK biocompatible can also lead to poor implant performance. As PEEK is highly unreactive, bone attachement to its surface is hindered and results in poor osseointegration. This is one of the challenges to overcome for the use of PEEK as a biomaterial; for this, the present review attempts to address research on the improvements of 3D-printed PEEK's bioactivity.

Nevertheless, the use of metals in load-bearing orthopaedic implants can also be related to poor implant performance. These materials have stiffness much higher than human bone which can lead to stress shielding of the treated bone as the loads are mostly supported through the stiffer implant. Stress shielding of bone has been shown to lead to bone thinning and resorption which makes the patient's recovery difficult (Weinans et al. 1992). In addition to stress shielding, metal-based implants also have the disadvantages of interfering with therapeutic and diagnostic imaging techniques and producing long-term adverse physiological responses which is why biostable and bioabsorbable polymers have been mentioned as alternative materials (Figueiredo et al. 2018). As a biostable polymer, PEEK's potential as a candidate material for the replacement of metals in load-bearing implant manufacture has been mentioned early on (Williams et al. 1987) because bulk PEEK and reinforced PEEK composites present stiffness within the range of human trabecular and cortical bones. On top of this, PEEK's 3D printing can enable the manufacture of patient-specific devices with lower costs and faster design to manufacturing times which further highlights this potential.

Still, the potential in PEEK's mechanical behaviour as a requirement for the manufacture of load-bearing implants can present some challenges, namely its thermal processing. As a semi-crystalline thermoplastic, PEEK's molecular chain, which is mostly entangled in an amorphous region, has the ability to rotate around the ether and ketone-carbon bonds organising in folds which creates a crystalline region (Kurtz 2012) (Fig. 4). Early on, higher crystallinity percentages on PEEK materials were related to higher strength and fracture toughness; however, no significant effect was reported concerning stiffness (Talbott et al. 1987). The

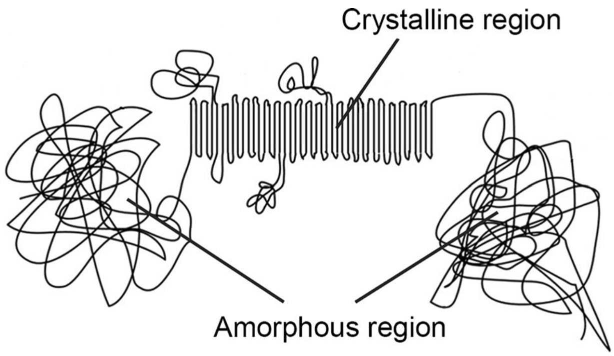

Fig. 4 Schematic representation of PEEK's microstructure; adapted from Kurtz (2012)

suggested reason for this is that the crystalline phase has stronger intermolecular bonding, and thus should require more energy to melt and to deform.

Differential scanning calorimetry (DSC) results show that PEEK displays a glass transition temperature around 140ºC and a melt temperature around 340ºC (Gupta and Salovey 1990; Naffakh et al. 2003; Regis et al. 2017; Seo et al. 2019). DSC has also been used to study PEEK's crystallisation which was reported to occur upon heating just after glass transition ("cold" crystallisation) and before the melt upon cooling ("hot" crystallisation) (Gupta and Salovey 1990). The "hot" crystallisation from the melt, which is more relevant for manufacturing techniques involving thermal processing such as FFF, has been observed to occur between 314 and 322ºC (Seo et al. 2019). Here, the degree of PEEK's crystallisation depends on the temperature rates involved in its processing; for this, slower cooling rates were reported to produce PEEK of higher crystallinity (Naffakh et al. 2003).

As slower cooling rates produce PEEK with higher crystallinity, one of the challenges of processing PEEK is to control these cooling rates to obtain a stronger PEEK material. Another approach to this is to use high-temperature annealing treatments with slow heating/cooling rates which allow more time for the crystalline phase to form. Conversely, rapid cooling treatments such as quenching were found to produce mostly amorphous PEEK (Bodden et al. 2017). To demonstrate the effects of these low-rate temperature treatments, bulk PEEK and PEEK composites with crystallinity degrees by about 32%, created through annealing treatments, have displayed significant improvements in peak flexural load and flexural modulus compared to untreated samples (Regis et al. 2017).

PEEK's mechanical behaviour is not only related to its crystalline contents but also to the loading conditions. Similar to other thermoplastics, PEEK's behaviour is highly dependent on strain rate and temperature. Again, early on, higher strain rates and lower temperatures were related to higher yield strength and increased strain hardening for PEEK (Hamdan and Swallowe 1996). These relations were supported by more recent works which have also looked into the strain rate and temperature relation to the mechanical behaviour of PEEK (Rae et al. 2007; El-Qoubaa and Othman 2017; Barba et al. 2020; Zhang et al. 2021). In sum, high strain rates seem to favour PEEK's elastic behaviour as it displays higher yield strength and elastic modulus while high temperatures seem to favour PEEK's plastic behaviour as it displays lower yield stress but increased strain-at-break. This influence of load conditions in PEEK's behaviour must be acknowledged when comparing the results of mechanical testing of PEEK samples.

Lastly, PEEK's dynamic mechanical behaviour is also relevant for load-bearing implant applications. PEEK's fatigue is significantly influenced by stress amplitude and load frequency where hysteretic heating can lead to reduced fatigue life (Berer et al. 2014). Another issues noted in PEEK's fatigue studies are notch sensitivity and crack propagation. In the fatigue testing of micro-notched specimens, PEEK's crack closure seems to be supported by elastic deformation; however, once crack initiation occurs, PEEK displays high crack propagation rates (Colmer et al. 2017). PEEK has high notch sensitivity as most of its fatigue life is spent on crack nucleation, but after crack initiation, propagation occurs very fast (Avanzini et al. 2018). This suggests that PEEK's mechanical behaviour can be severely affected by the presence of defects, created during the manufacturing process, such as cracks or void.

In sum, PEEK's mechanical behaviour as a requirement for implant applications must consider the load conditions and the material's thermal processing history. This, in addition to its notch sensitivity, makes PEEK's mechanical performance significantly dependent on manufacturing process. This is especially relevant for AM processes where voids and porosities are largely unavoidable. For instance, PEEK samples produced through "high-temperature-laser sintering" (HT-LS) displayed about 12% lower "ultimate tensile strength" (UTS) and about 18% lower tensile elastic modulus relative to injection-moulded PEEK (Hoskins et al. 2018). In this sense, as FFF typically creates larger scale porosities than LS, PEEK samples produced through FFF should also display lower strength and stiffness compared to injection-moulded PEEK samples. To mitigate such issues, different approaches to improve the mechanical performance of 3D-printed PEEK through FFF parametrization will be reviewed in the following section. Additionally, bioactivation techniques of 3D-printed PEEK samples will also be reviewed in light of the development of high-performance 3D-printed PEEK for orthopaedic implants.

Mechanical performance of 3D-printed PEEK

PEEK's processing using AM techniques such as FFF further add to its potential as a biomaterial for personalised implant manufacture. As it was already stated, the FFF of PEEK enables the manufacture of high-performance custom-made medical devices based on medical imaging 3D data. Still, printing conditions should also have significant implications in the mechanical performance of 3D-printed PEEK parts due to the thermal processing and relatively high porosity percentages associated with this AM technique. For these reasons, this section will include research findings relevant for the improvement of 3D-printed PEEK's mechanical properties.

To better understand this AM technique, "fused filament fabrication" (FFF), or material extrusion AM, consists in layer-by-layer deposition of melted filament fed through a heated nozzle. The "slicer" software, a 3D model is divided into horizontal cross sections and the tool path for each section's profile is generated according to set parameters. This information is converted to a G-code instruction file read by FFF equipment. In Cartesian axis FFF machines, the material is deposited parallel to the XY plane while the layers stack along the Z axis as illustrated in Fig. 5.

Depending on FFF parameters, for fixed dimensions, an FFF-produced part displays a deposition path which can be observed even through unaided eye. This path creates a characteristic macromorphology typical of FFF 3D-printed samples and depends on different FFF parameters. Parameters that influence the macrostructure of a 3D-printed sample can be line dimensions, such as line width (LW) or line height (LH) which is equivalent to layer height, or tool path parameters such as build orientation (BO), infill percentage (IP), infill pattern and shell count for the perimeter lines and top/bottom layers. These parameters are illustrated in Fig. 6 which also conveys how the macrostructure of a 3D-printed part can be related to its void and porosity contents. Other FFF parameters are printing speed (PS) and the printing temperatures, nozzle temperature (NT), build platform temperature (BT) and printing ambient temperature (AT). Although these affect the deposition behaviour of the material, they do not affect the printing tool path and are adjusted mostly for the material and FFF equipment used. Nevertheless, all FFF parameters and their interplays can affect the quality and behaviour of a 3D-printed part which makes FFF parametrization an important step to meet the requirements for a 3D-printed component.

Concerning PEEK's FFF, the thermal processing involved in this process becomes even more relevant for print quality and performance of 3D-printed components. As it was already stated, PEEK is considered a high-temperature thermoplastic as its glass transition occurs at around 140 ºC and it melts at around 340 ºC. To reach the necessary PEEK fluidity, nozzle temperatures could be required to reach temperatures well above 450 ºC which is much higher than most thermoplastics used in FFF. Additionally, PEEK prints' cool-down rates should be controlled to avoid warping and to allow PEEK's crystalline phase to form. Reaching high temperatures and controlled cooling can be challenging and can only be achieved with more elaborate FFF equipment.

Some of the earliest research works in PEEK's 3D printing focussed on the improvement and upgrading of FFF equipment to improve its PEEK printing capability. One of the first reports of successful FFF of PEEK stresses the importance of a heated printing chamber (Valentan et al.

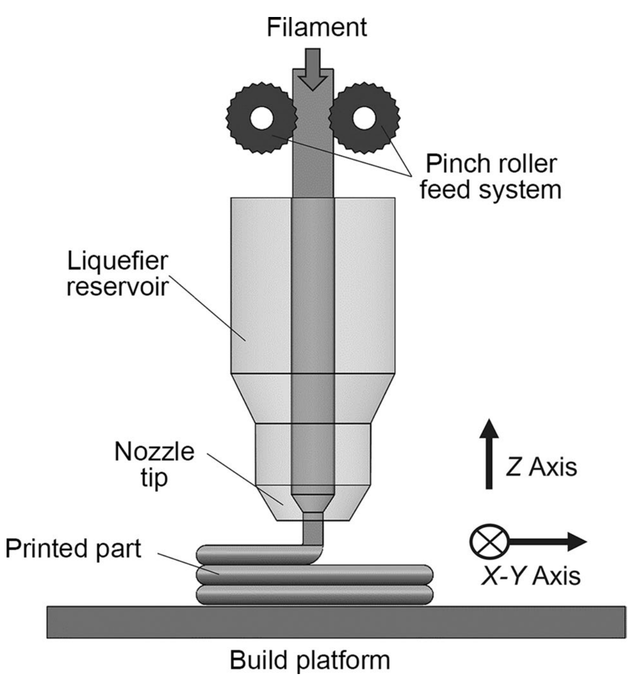

Fig. 5 Fused filament fabrication (FFF) process representation

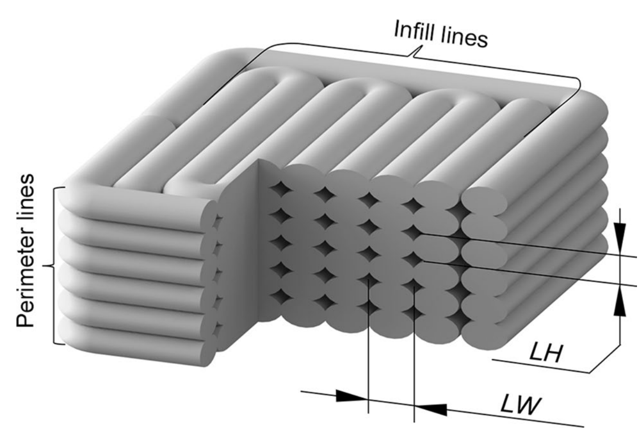

Fig. 6 Representation of FFF's typical macrostructure and dimensional parameters

2013). In this work, a filament drying chamber was included to reduce smaller scale porosities created by the evaporation of absorbed water evaporation upon extrusion. The issue of filament moisture absorption has been reported to have a negative impact not only on the quality but also on the mechanical performance of printed samples (Halidi and Abdullah 2012). Additionally, PEEK's 3D-printing with a heated chamber showed higher ambient printing temperatures that can reduce warping defects and improve printing quality (Wu et al. 2014).

As these developments allowed for successful PEEK prints, research has investigated the effects of more complex FFF equipment to further improve the parts' quality and performance. In one case, FFF equipment was upgraded with extruder cooling systems and forced-convection heated chamber which was able to produce PEEK samples with higher crystallinity and strength (Park et al. 2021a, b). The convection heating allows for a more uniform temperature distribution and better cooling control in the printing chamber, while the extruder cooling system allows for a more reliable printing at higher temperatures and can even improve flow stability through an increased temperature gradient between the feeding system and the extruder. In other cases, FFF upgrades have addressed the temperature difference between the printed part and the nozzle. Laser preheating of the deposition zone resulted in improved interfacial bonding and also increased the samples crystallinity (Luo et al. 2018). However, this is a highly focussed form of preheating that could create more thermal stresses and would be more difficult to implement. To preheat effectively, the laser would need to be focussed on the deposition zone which is relative to the print head movement's direction. With the same purpose, a different approach to deposition zone preheating was presented in the form of heat collector placed around the nozzle that reflects the heat from the extruder and preheats the surrounding deposition zone (Hu et al. 2019). To improve the quality of the printed samples, this work also presents a build plate that allows for thermal expansion of the print, which together with the heat collector resulted in PEEK prints with increased strength, stiffness and crystallinity.

These developments in FFF equipment have been essential for the achievement of high-performance PEEK 3D printing but further improvements in the mechanical behaviour of PEEK prints can still be achieved with FFF parametrization. The effects of FFF parameters in the mechanical properties of 3D-printed PEEK have been addressed in the literature and some of the findings can even be corroborated by studies on FFF with other materials. For instance, research reports that printed lines in FFF can be compared to fibres in anisotropic materials in the sense that loads carried axially through the lines will be supported better than those causing shear were the filament bonded (Es-Said et al. 2000; Ahn et al. 2002; Masood et al. 2010; Durgun and Ertan 2014). This makes the built orientation one of the most significant parameters for the mechanical performance of FFF parts. With PEEK, significant improvements in tensile, bending and compressive strength were observed for the samples where the lines were deposited parallel to the loads (Wu et al. 2015; Pu et al. 2021). Additionally, build orientation also defines layer orientation. As the temperature difference is greater for consecutive layers than for consecutive lines, lines from the same layer are expected to bond better than lines from consecutive layers. Due to this, PEEK prints with build orientations that avoided layer detachment displayed significantly better results in tensile and flexural testing while samples loaded for layer detachment displayed brittle fracture before yield (Arif et al. 2018). These findings highlight the relevance of the anisotropic behaviour presented by FFF parts and stress the importance of adequate build orientation for high-performance PEEK prints.

Still, even with the correct choice of built orientation, FFF prints can still display significant differences in their mechanical behaviour depending on the other parameters used. Interfacial bonding between lines and layers is another important factor at play in FFF which can be influenced by various parameters. One example of this is higher printing chamber temperature which, besides reducing warping defects, can also preheat the printed section and improve interlayer bonding. Higher chamber temperatures were shown to increase the tensile strength and modulus of PEEK prints even when no increases were observed in the samples' crystallinity suggesting that the improvements are attributed to improved bonding (Yang et al. 2017; Zhao et al. 2020). High chamber temperatures can also help mitigate some issues with uneven heat transfer throughout the print. Filament bonding can be worse in the bottom layers due to rapid cooling as heat dissipates to the build plate (Basgul et al. 2021b).

Furthermore, while bed temperature affects mostly the first layer and has a small effect on ambient temperature, nozzle temperature can also have significant effects in the part's interfacial bonding. Higher nozzle temperatures have been associated with PEEK prints with higher storage modulus in dynamic mechanical analysis (DMA) (Pu et al. 2021). Higher nozzle temperatures can improve weld conditions due to higher molecular chain mobility or to lower viscosity. Lower viscosity can translate into more material spread upon deposition which also increases the bonding contact areas of the deposited lines. With this, the printing temperatures can have a significant impact in the mechanical performance of PEEK 3D-printed samples for their effects in both the crystallinity of the samples and the interfacial bonding of printed material (Lee et al. 2022; Qu et al. 2022). For these reasons, the printing temperatures of PEEK should be considered as amongst the most impactful parameters for high-performance PEEK 3D prints.

Apart from printing temperatures, the effects of other FFF parameters in the mechanical behaviour of PEEK can be more difficult to assess. Printing speeds, despite being matched by material flow, can have effects on the line's stability, spreading and cooling. Higher printing speed was associated with lower tensile strength as it produced samples with higher void percentage, thus suggesting worse flow stability and line spreading (Wang et al. 2019). Layer thickness defines the number of layers in a print, and consequently the number of weak interfaces for layer detachment. Layer thicknesses of 0.3 and 0.35 mm have been related to samples with higher tensile strength (Wang et al. 2019). However, these relations have also been questioned by other results. Studies with design of experiment (DoE) for 3D parameter optimization reported optimal combinations which seem to favour thinner layers and higher printing speeds for the strength of PEEK samples (Deng et al. 2018; Mohamed et al. 2021; Wang et al. 2021b).Additionally, other optimization studies have suggested the use of wider line thicknesses to increase the samples' strength (Jiang et al. 2022). This highlights the need for parameter optimization studies to achieve the best results with PEEK prints. This way, FFF parametrization can consider the equipment and material's specifications and can also account for interplay of different parameters which can be very difficult to assess otherwise.

Considering all this, the best approach to PEEK's FFF parametrization seems to focus on aligning the printed lines with the loads and to print at higher nozzle and ambient temperatures while maintaining low cooling rates. Parameter optimization studies should be performed whenever possible to adjust printing parameters such as speeds and layer thickness to the equipment and material's characteristics. With this, it should be possible to achieve significant improvements in the performance of PEEK prints.

Despite this, there is still the issue with the voids and porosities typical of the material's deposition in FFF. These voids and porosities are largely unavoidable and, even for 100% infill PEEK prints, can account for as much as 8% in volume (Rinaldi et al. 2018). These void contents have been shown to be related to different FFF parameters where infill percentage, line orientation angle and wall line count affected the appearance of defects in the infill to wall transition zone. (Emolaga et al. 2022). As PEEK displays high notch sensitivity and crack propagation (Colmer et al. 2017; Avanzini et al. 2018), these discontinuities in PEEK prints can have a significant impact in the performance of 3D-printed samples. Higher void volume in PEEK samples was related to lower UTS (Vaezi and Yang 2015). For these reasons, FFF PEEK should always be outperformed by injection-moulded PEEK samples. For instance, PEEK 3D-printed lumbar cages only supported as much as 63% of the ultimate load of their moulded counterparts (Basgul et al. 2018). Still, due to the advantages of AM techniques such as FFF in the medical field, reducing the performance gap between injection-moulded and 3D-printed samples is becoming increasingly relevant.

Porosity percentages of PEEK 3D prints have been reduced with screw extrusion-based FFF equipment which allowed to lower PEEK's viscosity and increase its flow stability (Tseng et al. 2018). However, there are other approaches which do not require new developments in FFF equipment. Early studies on FFF with other materials have suggested that void contents in a print can be reduced using different parameters such as negative line distance (overlapping lines) and interlayer line translation (Rodriguez 1999; Rodriguez et al. 2000). With this, it is possible to obtain denser PEEK prints simply by adjusting these parameters. Although interlayer line translation has yet to be tested to the author's knowledge, negative line distance has been shown to improve the tensile and flexural strength and modulus of PEEK prints (Cicala et al. 2017). With these approaches, it is possible to obtain denser samples and further improve the mechanical performance of PEEK prints which can help reduce the gap between injection-moulded and 3D-printed PEEK samples.

So far, the reviewed research provides different approaches to improve the performance of PEEK prints using upgraded FFF equipment and FFF parametrization but there is still the possibility to improve the mechanical performance of PEEK prints using stronger reinforced PEEK filament materials. The use of reinforced PEEK materials such as carbon fibre-reinforced PEEK (CF-PEEK) in FFF for medical applications has also grown in relevance due to research supporting the biocompatibility these materials. Research on the use of reinforced PEEK filaments is very recent and results show that it is possible to increase printed samples' strength and stiffness for all static load conditions with the use of reinforcements such as 5% in weight of carbon fibres (Han et al. 2019). Despite this, the use of such materials can also be limited as the presence of glass fibres (GF) or carbon fibres (CF) in PEEK filament can lead to fibre pull-out and brittle fracture due to poor interfacial bonding between the fibres and the PEEK matrix (Wang et al. 2020). Still, lower fibre percentages in reinforced PEEK composites can reduce the issues with fibre–matrix debonding and result in composite PEEK samples with higher strength than neat PEEK (Qin et al. 2019).

The interfacial bonding issues of reinforced PEEK filaments have scarcely been addressed in research. In one instance, graphene nanoplatelets (GNP) and carbon nanotubes (CNT) were compared as reinforcements for PEEK filaments where GNP resulted in higher ductility for the composite (Arif et al. 2020). In another work, a titanium oxide (1% in weight) composite, PEEK filament also improved strength but still resulted in brittle fracture (Bragaglia et al. 2020). Interesting research has presented different techniques to improve the interfacial bonding between the PEEK matrix and the fibre reinforcements in PEEK composites using different reinforcement materials, fibre treatments or bonding agents (Monich et al. 2017; Chen et al. 2018, 2021; Martínez-Gómez et al. 2018; Hassan et al., 2019; Mao et al. 2019; Arevalo and Pruitt 2020; Lyu et al. 2021).Although the interfacial bonding of PEEK-based composites is not addressed in this review, the mentioned works suggest that these approaches have the potential to improve the mechanical performance of 3D-printed PEEK and result in samples with higher strength and stiffness. For example, Li et al. (2021a) have used the bonding agent approach with POSS (polyhedral oligomeric silsesquioxane) which increased the interfacial bonding of PEEK 3D prints after a pyrolysis reaction. This work highlights the potential in PEEK composites to obtain samples with improved interfacial bonding and mechanical performance.

Despite the support of these reinforced PEEK's biocompatibility, the use of materials such as CF-PEEK as a biomaterial can still be questioned due to the presence of fibres in the composition of an implantable device. In any case, the reviewed research still suggests that significant improvements in the performance of 3D-printed PEEK samples can be obtained without the use of reinforcements. With the adequate choice of FFF parameters and new approaches to lower the void volume of 3D-printed samples, it should be possible to achieve a mechanical performance closer to that presented by injection-moulded PEEK samples. Concerning this, Table 2 provides a summary of the mentioned research remarks for the increase of the strength and quality of 3D-printed PEEK. Additionally, some of the mechanical properties obtained in mentioned studies are provided in Table 4 along with the stiffness of human bone for comparison. With these approaches, the mechanical behaviour of 3D-printed PEEK samples can be improved to closely match the stiffness of the treated bone; thus, the issues of stress shielding that lead to the treated bone's resorption could be minimised. This, together with the design flexibility of FFF, makes 3D-printed PEEK a potentially better option than machined metals in high-performance load-bearing implants for trauma, orthopaedics and spinal treatment applications.

Bioactivation of 3D-printed PEEK

The improvement of performance and quality of additively manufactured PEEK components further adds to the potential of the use of 3D-printed PEEK for the manufacture of orthopaedic, trauma and spinal treatment applications. However, these applications also require bone–implant integration for effective load transfer between the treated bone and the implant. For this integration, PEEK's inertness that is responsible for its biocompatibility can be a disadvantage as it also makes it bioinert. This results in poor bone–implant bonding which can ultimately cause the PEEK implant's detachment from the treated bone.

PEEK's potential as a biomaterial has led to research in the improvement of its bioperformance. For this, different approaches have been reported, some of which were already reviewed by Verma et al. (2021). In this work, the potential of PEEK's 3D printing and of PEEK-based composite biomaterials for medical implant manufacture is highlighted. Additionally, the authors also underline the need for improvements of the mechanical properties and implant performance of PEEK materials. Nevertheless, there is unmentioned potential in PEEK's additive manufacturing to produce 3D structures that could enable biofunctionalities. Concerning this, this section will address research on the improvement of the bioperformance of PEEK materials with focus on bioactivation techniques compatible with FFF-manufactured PEEK.

The deposition of material in FFF enables the manufacture of 3D structures with tuneable porosity. The use of porous structures in orthopaedic materials has been stated to improve osseointegration. In these structures, pore interconnectivity allows the diffusion of cells and nutrients while pore size allows for cell attachment and vascularization of the biomaterial (Jarman-Smith et al. 2012). The use of FFF to manufacture porous scaffolds with different materials has been addressed in research with the use of composite bioactive filaments such as polycaprolactone filled with bioactive glass (PCL-BAG) (Korpela et al. 2012) and polypropylene containing tricalcium phosphate (PP-TCP) (Kalita et al. 2003).

Very recently, research started reporting on the use of FFF techniques to produce 3D-printed porous PEEK scaffolds with positive results. For instance, 3D-printed PEEK samples with controllable porosity were produced by varying infill percentages which displayed higher osteoblast cell proliferation compared to non-porous samples (Elhattab et al. 2020). Osteoblast cell proliferation and differentiation can be studied through in vitro cell culture assays with pre-osteoblast cell lines and higher values can be indicative of increased bone growth. In another work, highly porous (40–60% porosity) 3D-printed lattice PEEK scaffolds were tested both in vitro and in vivo (Wong et al. 2021). Here, all porous samples displayed increases in osteoblast cell proliferation and showed intense alizarin red staining which are indicative of increased mineralization compared to solid PEEK. Interestingly, the samples with the lowest porosity of 40% withstood the highest force in dynamic push-out tests performed on in vivo implanted samples suggesting that the highest degree of osseointegration is not achieved with the highest porosity but rather with a specific porous configuration. Different porosity configurations were obtained by

Table 2 Summary of fused filament fabrication of PEEK research remarks

Researchers	PEEK filament	Remarks
Valentan et al. (2013)	PEEK Optima® LT3 and LT1	-Importance of a heated chamber and filament drying chamber
Wu et al. (2014)	PEEK from Changchun Jilin University Special Plastic Engineering Research Co. Ltd	-Higher ambient temperature reduces warping and improves quality
Park et al. (2021a, b)	APIUM PEEK 450G	-Extruder cooling system improves flow stability -Forced-convection printing chamber increases crystallinity and strength
Luo et al. (2018)	PEEK filament reprocessed from Victrex® PEEK 450G pellets	-Laser preheating of the deposition zone improves interfacial bonding
Hu et al. (2019)	PEEK filament from Sting3d Technology Co. Ltd	-Heat form the nozzle was used to preheat deposition zone, control cool-down rates and increases crystallinity -Expandable build plate reduces thermal stresses
Wu et al. (2015)	PEEK from Changchun Jilin University Special Plastic Engineering Research Co. Ltd	- Build orientation with lines parallel to loads increases the samples' strength and reduces line/layer debonding
Pu et al. (2021)	Victrex® PEEK 450G from iMaker Ltd	-Nozzle temperature decreases the material's viscosity upon deposition which improves interfacial bonding shown by higher storage modulus in DMA
Arif et al. (2018)	Victrex® PEEK 450G	- Loads promoting layer detachment lead to brittle failure before yield
Yang et al. (2017)	PEEK filament reprocessed from Victrex® PEEK 450G pellets	-Higher ambient temperatures increase the samples' strength and stiffness by improving interfacial bonding
Zhao et al. (2020)	PEEK filament from INTAMSYS Technology	
Wang et al. (2019)	PEEK 450G	-High printing speeds can increase void percentage, and thus decrease strength
Deng et al. (2018)	PEEK-1000 bar from Zhongshan Yousheng Plastic materials Co. Ltd	-Results from DoE studies for optimum parameter combinations favour thinner layers and higher printing speed
Mohamed et al. (2021)	PEEK filament reprocessed from Victrex® PEEK 450G pellets from 3D4Makers	-Higher nozzle and bed temperatures produce samples with higher strength and stiffness
Wang et al. (2021b)	VESTAKEEP® PEEK i4G from Evonik Industries AG	-When infill percentage is considered, optimum parameter combination includes the maximum infill percentage tested -Results for optimum parameter combination can vary depending on the diameter of the nozzle used
Vaezi and Yang (2015)	Victrex® PEEK 450G	-Samples with higher porosity percentages display lower UTS
Tseng et al. (2018)	Victrex® PEEK 450G and 90G pellets	-Screw-extrusion FFF allows to print at higher temperatures for lower viscosity and increased flow stability which resulted in a reduction of the samples' porosity percentages
Cicala et al. (2017)	PEEK filament reprocessed from industrial-grade PEEK from Luvocomm, Germany	-Negative line distance can reduce the sample's porosity percentage and increase strength and stiffness

varying the infill percentage and pattern of PEEK 3D prints (Spece et al. 2020). Although the different samples were designed with the same pore size, different average pore sizes and porosities were measured through micro-CT. The samples were submitted to pre-osteoblast cell culture assays where the diamond pattern samples displayed the highest values of alkaline phosphatase (ALP) activity which can be indicative of higher osteogenic differentiation. This could be attributed to the pore size obtained with the diamond pattern as these samples had the average measured pore size closest to the designed value of 600 µm which is said to match the pore size of human cancellous bone (Lim et al. 2019). Furthermore, these diamond pattern samples displayed the highest values of elastic modulus and yield strength obtained from compression tests.

The use of porosity features to enable biofunctionalities on PEEK samples has the advantage of retaining PEEK's processability and biocompatibility but these features lower the samples' strength and stiffness due to the void contents and lower density created by lower infill percentages. Besides this, there are other FFF parameters for controlled porosity that could correspond to prints with lower mechanical performance. For instance, higher nozzle temperatures resulted in higher compressive strength while lower temperatures improved pore size control (Song et al. 2021). This means that the use of porous 3D-printed constructs for improved osseointegration can be limited for load-bearing applications depending on the applications' requirements for strength and stiffness. In such cases, the use of porous features can be focussed on the samples' surface where the bone–implant interface is located, thus retaining most of the samples' mechanical performance in its solid core. In such cases, surface porous 3D-printed PEEK samples have also been shown to increase ALP activity while displaying higher tensile strength than fully porous samples (Li et al. 2021b). Regarding this, the reviewed research seems to suggest that FFF also has the potential to create orthopaedic and trauma implantable devices with improved osseointegration through the use of controlled surface porosity features and without the use of bioactive materials.

Nevertheless, the use of bioactive fillers in PEEK matrix composites has been one of the main focuses of research concerning the use of PEEK as a biomaterial. Bioactive fillers to improve osseointegration consist mostly of calcium orthophosphate ceramics as their chemical composition that closely resembles the composition of human bone. These ceramics are included in PEEK matrix composites usually by powder compound mixing with PEEK in its molten state. Concerning this, the calcium orthophosphate that is perhaps the most widely covered in the literature is hydroxyapatite (HA). Apatite formation in "simulated body fluid" (SBF), which is usually related to bone mineralization, has been shown to increase with HA contents in PEEK-based materials (Yu et al. 2005). Additionally, PEEK–HA composites display higher stiffness than neat PEEK due to the presence of the rigid ceramic contents (Abu Bakar et al. 2003a,c,b). This suggests that there is a high potential in bioactive PEEK-based composites for orthopaedic implant applications. In light of this potential, research has investigated the use of different bioactive materials for PEEK's bioactivation such as β-tricalcium phosphate (β-TCP) (Petrovic et al. 2006), nano-calcium silicate ($CaSiO_3$, n-CS) (Ma et al. 2014) or fluorhydroxyapatite (FHA) (Wang et al. 2014). However, like reinforced PEEK composites, these bioactive PEEK composites also display weak bonding with the PEEK matrix. Stress concentrations created in HA agglomerates in PEEK–HA composites can lead to crack initiation in the filler–matrix interface which results in brittle fracture for these composites and could ultimately reduce the samples' strength (Tang et al. 2004).

Despite this, there is still potential in the use of bioactive PEEK composites in FFF of load-bearing orthopaedic implants as these materials present higher stiffness along with increased osseointegration ability. Reports of the use of bioactive PEEK filaments in FFF are also very recent and research presents positive results. PEEK-HA filament with up to 30% in weight of HA was used to produce samples which displayed higher elastic modulus than neat PEEK samples both in tensile and flexural testing (Rodzeń et al. 2021). In this work, PEEK-HA-printed samples with lower HA percentages of 10% also presented higher UTS and yield strain than neat PEEK samples. The lower concentrations of HA reduce the presence of agglomerates in the filament composition which avoids some of the issues with filler–matrix debonding and attenuates the brittle behaviour of the printed samples. However, there are also reports of decreased tensile strength and fracture strain even for low concentrations of HA in 3D-printed PEEK samples compared to neat PEEK prints (Zheng et al. 2021a).

Even so, the use of bioactive fillings in PEEK filaments can still improve the bone–implant bonding of 3D-printed PEEK implants. These materials can be combined with aforementioned porosity features enabled by FFF to produce devices with high osseointegration ability. For instance, 3D-printed porous PEEK–HA scaffolds submitted to osteoblast precursor cell culture assays displayed improved cell attachment and proliferation along with more intense alizarin red staining compared to neat PEEK scaffolds (Zheng et al., 2021b). In this work, it is suggested that pore interconnectivity improves mostly cell adhesion while the HA contents improve the samples' mineralization. As PEEK-HA filaments display such promising results, the possibility arises for the use of other bioactive fillings in PEEK filaments. PEEK filament containing amorphous magnesium phosphate (aMP) was also compared to neat PEEK in both in vitro and in vivo studies (Sikder et al. 2020). Although there are no reports of 3D printing with this filament, aMP–PEEK samples presented higher new bone formation and bone–implant contact than neat PEEK samples, both indicative of improved osseointegration. In another instance, PEEK–HA filaments were doped with zinc and strontium nutrients (Manzoor et al. 2021). This doping of PEEK–HA, despite resulting in lower material strength and stiffness, further increased the apatite formation in PEEK–HA during SBF immersion. Still, despite the available research on different bioactive PEEK composites, studies addressing the use of different bioactive PEEK filaments are still very scarce. Furthermore, as the trend in the research on these materials seems to be in transition to drug and nutrient-doped materials, the investigation gap available for research in the FFF with composite PEEK filaments becomes even larger. This stresses the need for further research in the FFF of different bioactive PEEK composites in search for an adequate filament material for implant 3D printing.

Again, as osseointegration is focussed on the bone–implant interface, the use of the mentioned bioactive compounds is mostly effective on the device's surface like it was previously suggested for the porosity features. The bioactivation of PEEK that focussed on the samples' surface has the advantage of maintaining neat PEEK's mechanical performance and processability. These techniques can be even more relevant for PEEK's FFF as some can be employed as a post-printing procedure. Once again, there are few research works on the use surface bioactivation techniques for 3D-printed PEEK such as coatings and surface treatments. In one instance, PEEK 3D prints were dip coated with antibiotic agents such as ampicillin or vancomycin using a poly (lactic-*co*-glycolic acid) (PLGA) as a binder agent (Lau et al. 2020). This suggests that the use of binder agents such as PLGA can be used to load PEEK's surface with other compounds that promote bone growth and improve the samples' osseointegration ability. Additionally, promising new techniques are still being developed which can ultimately be used to load the samples' bone–implant interfaces with bioactive materials which have yet to be tested with biocompatible polymers such as PEEK. One example of this is the use of friction stir processes to incorporate magnesium, hydroxyapatite and fluorapatite particles in metals (Vidal et al., 2022).

Apart from this, recent research documents various coating and surface treatment techniques used on PEEK samples which could also be tested for 3D-printed PEEK and its different surface morphology. Documented coating techniques include the plasma spray of titanium which improved neat PEEK's osseointegration shown by implant pull-out tests (Cheng et al. 2018) and the cold spray of HA which also showed results of improved osseointegration as micro-CT measurements of in vivo implanted samples indicate increases in bone–implant contact (Lee et al. 2017). Other coating techniques include enhanced variations of vapour deposition (VD) used to coat PEEK samples with magnesium for antibacterial activity (Yu et al. 2018) or silicon nitride for increased cell viability and improved osteogenesis (Xu et al. 2019). Moreover, PEEK samples were coated with polydopamine (PDA) which allowed for pH-responsive release of copper citrate that improved both antibacterial activity and in vivo osseointegration (Yan et al. 2021). This research shows that different coating techniques can be used to load 3D-printed PEEK's surfaces with various biomaterials. With this, PEEK coatings with different biomaterials can enable specific biofunctionalities in PEEK samples that improve its implant performance.

In addition to coatings, different surface treatment techniques were used to modify and functionalize PEEK's surfaces. Some of the techniques used for PEEK's surface modification are plasma treatments (Gao et al. 2020; Liu et al. 2021a; Porrelli et al. 2021) and "accelerated neutral atom beam" (ANAB) (Ajami et al. 2017; Khoury et al. 2017, 2019). Other techniques used for PEEK's surface functionalization include UV-induced graft polymerization (Liu et al. 2019, 2021b) and "plasma-immersion Ion implantation" (PIII) (Wakelin et al. 2018). In these works, PEEK's surface morphology modification is reported to improve cell adhesion while surface functionalization can improve osteogenic response. To the authors' knowledge, these techniques are yet to be tested with 3D-printed PEEK samples which display different surface morphologies than the previously tested moulded, extruded and machined samples.

As the morphology of PEEK' surface influences bone bonding, sulfonation presents an interesting technique reported in research for PEEK's surface bioactivation. The etching action of sulfuric acid in PEEK's surface creates a 3D nano-sized porous network that can resemble human bone's porosity. PEEK's sulfonation followed by water and acetone rinsing has been shown to improve cell adhesion and increase new bone formation and bone–implant contact of implanted PEEK samples (Zhao et al. 2013). Compared to some of the coatings and surface treatments mentioned, PEEK's sulfonation is a simple process and does not require additional equipment. Furthermore, PEEK's sulfonation can be combined with other techniques to augment the biofunctionalities enabled on PEEK samples. For example, the sulfonation of 3D-printed porous PEEK scaffolds resulted in combined macro- and nano-scale porosities which further improved cell proliferation and mineralization on the porous samples' surfaces (Su et al. 2020). This shows that PEEK's sulfonation has the potential to be combined with designed 3D-printed porous constructs. Additionally, the porous network created on PEEK's surface by sulfonation can also be impregnated by bioactive particles through continuous stirring of the samples immersed in a particle suspension. Using this technique, PEEK samples' surfaces were successfully loaded with HA (Sharifi et al. 2018), calcium sulphate (CS) (Miyazaki et al. 2017) and even zinc and strontium oxide nutrients (Wang et al. 2021a), all of which enhanced the osseointegration ability of the samples. Similar to this technique, a three-step procedure was developed consisting of sulfonation followed by O_2 plasma treatment ending in SBF immersion. With this technique, the porous network created in the surface of PEEK samples by the sulfonation is increased in its hydrophilicity by the plasma treatment which can further improve cell adhesion. Following this, the immersion in SBF would result in the mineralization of the samples surface with precursors of apatite which can promote bone growth and improve bone–implant contact. Studies reporting on this bioactivation technique have shown that the three steps of the procedure are essential for a good apatite layer on the surface of both neat PEEK and reinforced PEEK samples which resulted in higher cell viability in mice pre-osteoblast cell line assays. (Yabutsuka et al. 2017, 2018). Furthermore, despite decreases in the osteogenesis-related genes' expression, osseointegration quantified through implanted bone detachment tests was significantly higher on the samples submitted to the full procedure (Masamoto et al. 2019). The morphologies created some of the mentioned procedures for the surface bioactivation of PEEK samples that are displayed in Fig. 7 which represents examples of promising and simple procedures for PEEK's bioactivation that can significantly improve the bioperformance of 3D-printed PEEK implants where integration with bone is required.

Collectively, the reviewed research presents many different options for the bioactivation of 3D-printed PEEK, each with specific remarks which are summarised in Table 3. PEEK's FFF enables the manufacture of complex structures with controllable porosities that allow vascularization of the samples and can improve cell attachment and osseointegration. However, the void contents in porous samples are directly related to the structural integrity of 3D-printed parts and will lower the mechanical performance of the samples. This limits the use of porous 3D-printed PEEK scaffolds in load-bearing implant applications. On the other hand, PEEK's use as matrix material in a composite allows for the use of bioactive composite filaments. The presence of calcium orthophosphates such as HA in PEEK filaments can increase the osseointegration ability of 3D-printed samples and can even produce more rigid parts due to the higher stiffness of the ceramic fillings. Still, the issues with filler–matrix debonding added to the difficult interfacial bonding of 3D prints can lead to brittle failure of these samples which lowers the UTS presented by bioactive PEEK 3D prints.

From the reviewed research, the best approach to the bioactivation of printed PEEK seems to be focussed on the bone–implant interactions occurring on the samples' surface. For this, literature provides different approaches which can consist of coatings with bioactive materials, drugs or nutrients, and surface treatments that functionalize PEEK's surfaces. Research findings for these techniques are also included in Table 3. Additionally, the mechanical properties of some of these samples have also been included in Table 4 for comparison with human bones and neat 3D-printed PEEK's properties. Such techniques have the advantage of being employed as a post-printing procedure that could improve the bioactivity of 3D-printed PEEK samples.

Nevertheless, even with the significant improvements in bioperformance demonstrated through in vitro and in vivo assays, many of these techniques are yet to be tested for 3D-printed PEEK samples. The reviewed research presents different procedures that focus on the bioactivation of PEEK surface to improve bone attachment. Some of the mentioned techniques such as

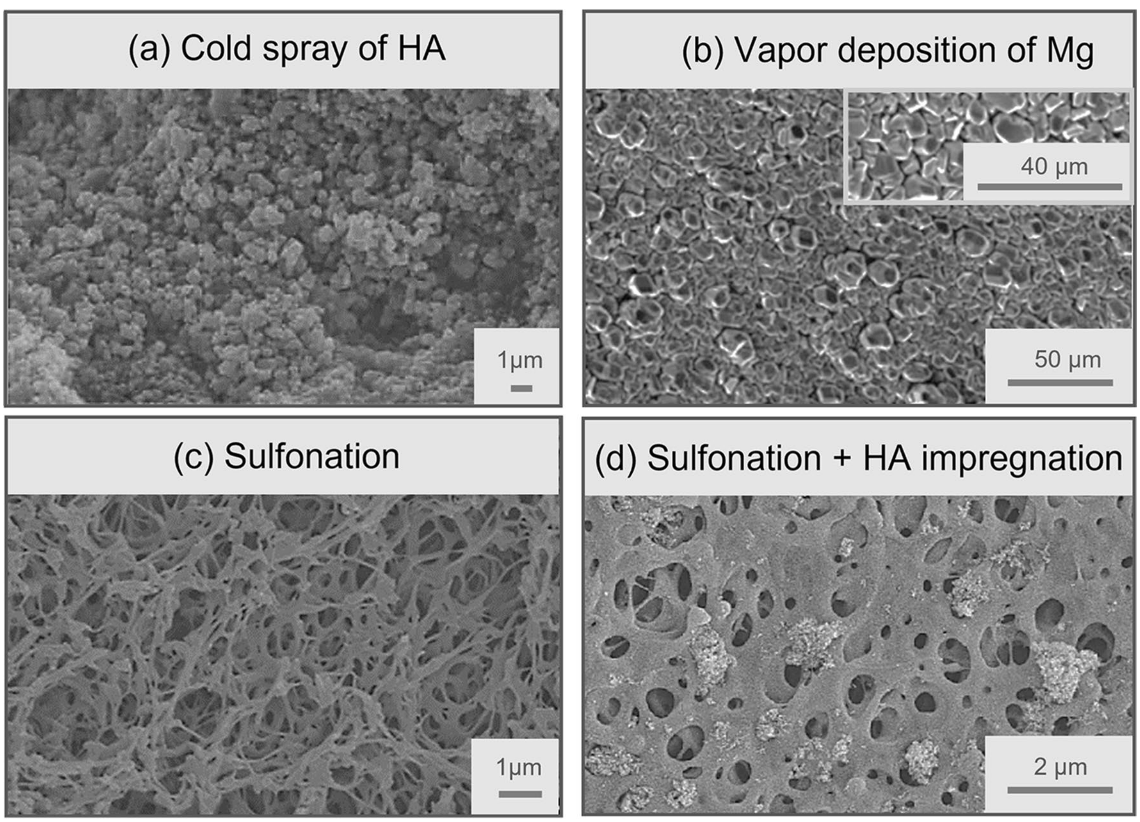

Fig. 7 Scanning electron microscopy (SEM) images of the surface morphologies created in PEEK samples (**a**) cold spray of HA (adapted from Elhattab et al. (2020)), **b** vapour deposition of magnesium [adapted from Yu et al. (2018)], **c** sulfonation [adapted from Zhao et al. (2013)] and (**d**) sulfonation followed by HA particle impregnation [adapted from Sharifi et al. (2018)]

Table 3 Summary of biological properties of bioactive PEEK samples

Researchers	Material/sample	Biological properties	
		Conducted assays	Observations
Elhattab et al. (2020)	Macroporous 3D-printed Victrex® PEEK scaffolds	Pre-osteoblast MC3T3 mouse cell culture assays	Increased cell proliferation rates with highest values displayed by samples with an average pore size of 800 µm
Wong et al. (2021)	Macroporous 3D-printed PEEK scaffolds2	Pre-osteoblast MC3T3-E1 cell culture assays In vivo implantation with dynamic push-out tests	Increased mineralization and osteogenic response -Improved osseointegration with the highest average push-out load withstood by the lowest porosity percentage tested (40%)
Spece et al. (2020)	Macroporous 3D-printed Victrex® PEEK 450G scaffolds	Pre-osteoblast MC3T3-E1 cell culture assays	Higher cell adhesion observed in SEM imaging for porous samples Improved osteogenic response from ALP activity Diamond pattern infill samples displayed the highest values of ALP activity and cells with more extended filopodia
Li et al. (2021b)	Surface porous 3D-printed PEEK	Pre-osteoblast MC3T3-E1 cell culture assays	Increased cell proliferation and ALP activity for surface porous samples compared to solid PEEK Samples with a designed pore diameter of 600 µm displayed the highest value of ALP activity after 7 days indicating a better osteogenic response for this pore size
Zheng et al. (2021b)	Custom-made HA–PEEK 3D-printed macro porous scaffolds	Pre-osteoblast MC3T3-E1 cell culture assays	Improved cell adhesion for HA–PEEK compared to neat PEEK porous samples Sample mineralization increased with HA contents
Sikder et al. (2020)	Custom-made AMP-PEEK filament	SBF immersion; Pre-osteoblast MC3T3-E1 cell culture assays In vivo implantation	Samples with higher AMP percentages displayed increased mineralization Cell proliferation and osteogenesis-related genes' expression indicate that AMP increases osteogenic response Implanted AMP-PEEK samples displayed more new bone formation and bone–implant contact
Manzoor et al. (2021)	3D-printed zinc-doped HA–PEEK samples 3D-printed strontium-doped HA–PEEK samples	SBF immersion	Apatite formation in the samples is significantly increased with the presence of HA in the composite and slightly increased with both the zinc and strontium nutrients
Lee et al. (2017)	Cold spray HA-coated PEEK samples	Bone marrow-derived mesenchymal stem cell (BM-MSCs) culture assays In vivo implantation	Higher ALP activity and bone sialoprotein presence were observed in HA-coated samples Ha-coated samples displayed a significantly higher bone–implant contact ratio than neat PEEK

Table 3 (continued)

Researchers	Material/sample	Biological properties	
		Conducted assays	Observations
Xu et al. (2019)	Silicon nitride (SN) plasma coated Victrex® PEEK 450G	S. aureus and E. coli culture assays -Rat bone mesenchymal stem cell (rBMSCs) culture assays	SN-coated samples displayed significantly higher antibacterial activity than uncoated PEEK samples -Cell adhesion was improved with the SN coating as the cells on the coated samples are more spread and display more filopodia and lamellipodia -Osteogenesis-related genes' expression also shows upregulation with the SN coating
Yan et al. (2021)	Sulfonated and polydopamine-coated PEEK with copper citrate release	E. coli antibacterial activity assay Ad-MSCs culture assays In vivo implantation	Antibacterial activity increases with the presence of copper citrate nanoclusters Calcium OD values are higher for the surface porous coated samples Bone volume fraction and bone mineral density measured for implanted samples suggests improvements in PEEK's ossseointegration with the coating and copper citrate release
Zhao et al. (2013)	Sulfonated surface porous PEEK	Pre-osteoblast MC3T3-E1 cell culture assays In vivo implantation with mechanical push-out tests	PEEK's sulfonation followed by water and acetone rinsing improved cell adhesion and proliferation Osteogenesis-related genes' expressions show upregulation for the sulfonated PEEK samples submitted to the complete rinsing procedure Implanted sulfonated samples display higher values of bone volume, bone–implant contact and osseointegration shown by push-out load
Su et al. (2020)	Sulfonated 3D-printed PEEK lattice scaffold	Pre-osteoblast MC3T3-E1 cell culture assays	The nanoporous surface created by sulfonation improves cell adhesion and increased cell proliferation -Sulfonated samples display a more intense alizarin red S staining indicating increased mineralization
Masamoto et al. (2019)	Plasma-treated sulfonated Ketron® 1000 PEEK impregnated with a precursor of apatite after SBF immersion	Pre-osteoblast MC3T3-E1 cell culture assays In vivo implantation with mechanical pull-out tests	Cell viability increased with the sulfonation and plasma treatments as well as with the presence of the precursor of apatite -ALP activity and osteogenesis-related genes' expressions decreased with the surface modification steps suggesting a decrease osteogenic response Implanted samples submitted to the three-step surface modification process showed higher osseointegration by displaying higher detachment load and increased new bone formation and bone–implant contact

Table 4 Mechanical properties of neat, reinforced and bioactive PEEK samples produced through FFF

Researchers	Material/sample	Mechanical properties		
		Tensile	Flexural	Compressive
Figueiredo et al. (2018)	Trabecular bone	Strength–10 to 20 MPa Modulus–0.05 to 0.5 GPa	–	–
	Cortical bone	Strength–50 to 150 MPa Modulus–7 to 30 GPa	–	–
Edward Guo(2001)	Human tibia	Modulus–10.4 to 18.6 GPa	Modulus–4.6 to 6.8 GPa	–
Arif et al. (2018)	Victrex® PEEK 450G 3D-printed samples	Strength–82.6 MPa Modulus–3.8 GPa	Strength–142 MPa Modulus–3.1 GPa	–
Han et al. (2019)	Custom-made 5% CFR-PEEK 3D-printed samples	Strength–101.4 MPa Modulus–7.4 GPa	Strength–159.3 MPa Modulus–5.4 GPa	Strength–137.1 MPa Modulus–3.5 GPa
Spece et al. (2020)	Macroporous 3D-printed Victrex® PEEK 450G scaffolds	–	–	Strength–6.6 to 17.1 MPa Modulus–0.21 to 0.27 GPa
Song et al. (2021)	Macroporous 3D-printed PEEK scaffolds	Strength–18.5 to 34.7 MPa Modulus–2.5 to 4.8 GPa	–	Strength–26.2 to 38.8 MPa
Li et al. (2021b)	Surface porous 3D-printed PEEK	Strength–28 to 39 MPa Modulus–1.3 to 1.7 GPa	Strength–24 to 36 MPa Modulus–0.6 to 0.9 GPa	–
Rodzeń et al. (2021)	5 to 30 wt% custom-made HA–PEEK 3D-printed samples	10% HA: Strength–94.2 MPa Modulus–4.7 GPa 30% HA: Strength–84.9 MPa Modulus–6.1 GPa	5% HA: Strength–171 MPa Modulus–4.8 GPa 30% HA: Strength–171 MPa Modulus–4.8 GPa	–
Zheng et al. (2021b)	Custom-made HA–PEEK 3D-printed macroporous scaffolds	–	–	Strength–5 to 30 MPa Modulus–0.1 to 0.6 GPa
Manzoor et al. (2021)	3D-printed zinc-doped HA–PEEK samples	Strength–47.9 MPa Modulus–0.75 GPa	–	–
	3D-printed strontium-doped HA–PEEK samples	Strength–51.5 MPa Modulus–0.79 GPa	–	–
Su et al. (2020)	Sulfonated 3D-printed PEEK lattice scaffold	–	–	Strength–33.5 MPa Modulus–0.5 GPa
Oladapo et al. (2021)	Macroporous samples 3D-printed with custom-made cHAp-PEEK filament	Strength–45 Mpa (at 40% UTS) Modulus–7 GPa	–	–

sulfonation combined with HA impregnation represent simple procedures that can significantly improve the osseointegration of 3D-printed PEEK implants. With these improvements focussed on the samples' surfaces, the issues with bone resorption and implant detachment observed with neat PEEK implants can be addressed while the mechanical properties of 3D-printed PEEK samples are mostly retained.

Medical applications of 3D-printed PEEK

Even with significant improvements in the mechanical behaviour and implant performance, the use of 3D-printed PEEK in orthopaedic, trauma and spinal implants is far from widespread. Despite the potential in the FFF of PEEK for patient-specific medical device manufacture, the lower stiffness and strength presented by 3D-printed PEEK samples can limit their use in load-bearing implant applications. The interfacial bonding between the lines and layers of 3D-printed samples needs to be improved to take advantage of the high mechanical performance of PEEK for these applications. This issue has been highlighted by Oladapo et al. (2020) where PEEK-HA-GO filament was used to print samples for orthopaedic prosthesis applications. These samples displayed defects and gaps which promoted line detachment and could have led to the samples' failure. This work also highlighted the necessity for numerical simulation to determine which areas of the print should be strengthened through FFF parametrization. Despite these issues, there are examples in the literature of studies which have successfully used FFF of PEEK and PEEK-based materials for different types of prosthetics and implant devices.

One example of an implant application for 3D-printed PEEK is the manufacture of cranial plates. Berretta et al. (2018) produced various samples of additively manufactured PEEK cranial plates. Although this study reports on PEEK implants manufactured through high-temperature laser sintering, some of the parameters studied can be similar to FFF parameters in their effects. This work investigated the effects of different build orientations in the mechanical performance and the best results were achieved with the horizontal build orientations. In FFF, this orientation would correspond to the longitudinal layer alignment which would avoid layer detachment as it was already recommended in this review. In another instance, cranial plates were also printed using a bioactive PEEK filament containing calcium hydroxyapatite (cHA) in the work presented by Oladapo et al. (2021). Here, despite presenting a brittle behaviour, the composite PEEK 3D-printed samples displayed higher stiffness than neat PEEK and showed more intense ALP staining compared to neat PEEK which suggests improved osteogenic response. In this work, the authors state that the 3D printing of bioactive PEEK filaments is a viable option for load-bearing implant manufacture.

In another work which was already mentioned in this review, Basgul et al. (2018) used FFF to produce intervertebral lumbar cages. In this work, the 3D-printed cage's mechanical behaviour was compared with machined PEEK counterparts. Despite being outperformed by machined samples, the 3D-printed PEEK samples still complied with the lumbar cages' requirements. Additionally, the effects of annealing treatments were studied for these 3D-printed cages which could further improve their mechanical performance of 3D-printed samples by increasing interfacial bonding (Basgul et al. 2020). Unfortunately, no significant improvements in the compressive behaviour of the 3D-printed cages were observed as the compressive loads may not promote layer or line detachment in 3D-printed samples.

Besides its potential for load-bearing implants, 3D printing of PEEK prosthesis only displays its full potential in the manufacture of complex geometries and patient-specific implants. In implant applications, PEEK 3D printing can be used to take advantage of FFF's ability to produce adapted designs of prosthetics and devices. One example of this is the work presented by Zhang et al. (2020) where the design of a coastal cartilage prosthesis can be adapted to the patient's cartilage elasticity requirements, and thus help restore breathing function. Other works documented the use of PEEK 3D printing to produce medical devices such as extra vascular stents to treat nutcracker syndrome (He et al. 2020) and implant fixations to attach external prosthesis after canine limb amputation (Mendaza-DeCal et al. 2021).

Nevertheless, the medical applications addressed by the works mentioned in this section are only examples of 3D-printed PEEK's possible uses in the medical field. A search with the keyword "PEEK" in the "clinicaltrials.gov" database (2022d) displayed 166 results, of which only 11 have published results. In these trials, PEEK is mostly used in devices such as cages and spacers to treat spinal-related conditions through interbody fusion procedures or in implant fixations such as anchors and screws. However, only when considering trials without results, there are four trials which have used 3D-printed PEEK implants for maxillofacial trauma, cranioplasty and occlusal caries treatment. These are examples of patient-specific implant applications where the use of AM techniques such as FFF display the most potential. These search results attest to the relevance of PEEK in medical applications and further support 3D-printed PEEK's potential for the manufacture of custom-made medical devices.

As recent and more advanced FFF equipment has been reported to have the ability to produce high-quality PEEK prosthesis with flexible design and complex geometries in a hospital environment (Honigmann et al. 2018, 2021), 3D-printed PEEK becomes increasingly relevant for more demanding implant applications. With the correct approaches to design, FFF parametrization and surface bioactivation, the performance of 3D-printed PEEK can be improved substantially which would make PEEK's FFF suitable for the manufacture of custom-made high-performance implantable medical devices where strength and osseointegration are important requirements. Although further research is still required for the widespread use of 3D-printed PEEK for these applications, together, the works mentioned in this review attest to the potential of FFF of

PEEK for the manufacture of high-performance patient-specific implants.

Conclusion

Research articles from a variety of different fields have been selected and combined in this review to highlight current developments in the FFF of PEEK in the interest of load-bearing and patient-specific implant manufacture. As a high-performance thermoplastic, PEEK presents a stiffness that is closer to that of human bone and for this it has been considered as a candidate biomaterial for the replacement of metals in orthopaedic, trauma and spinal implants. Additionally, PEEK's processing using AM techniques such as FFF can enable the manufacture of complex 3D devices tailored to the patient and with decreased design-to-manufacture times. Concerning this, PEEK's 3D printing has the potential to significantly improve the patient's healthcare while presenting a more cost-viable option for medical device manufacture.

Nevertheless, the use of PEEK's FFF for these applications still seems to be in its early stages. The mechanical behaviour of PEEK 3D-printed samples is highly dependent on FFF's parametrization and high-performance good-quality PEEK prints can be difficult to obtain even with advanced FFF equipment. Furthermore, despite its biocompatibility, neat PEEK is also bioinert which hinders the implant's integration with the treated bone and could ultimately lead to implant detachment or bone resorption. Concerning these challenges, this review highlights research findings that relate to the improvement of the mechanical performance of PEEK 3D-printed samples and to the increase of PEEK prints' osseointegration ability.

High-performance PEEK 3D prints can be obtained with the right approach to FFF parametrization. For this, the reviewed research provides different approaches to improve the mechanical performance of PEEK samples through the increase of the interfacial bonding and reduction void defects in PEEK prints. Additionally, the bioactivation of 3D-printed PEEK can be achieved through surface modification which can be employed as a post-printing procedure and retains most of the prints' mechanical performance with the denser PEEK core. For PEEK's bioactivation, porosity features designed for FFF or produced through acid etching can be loaded with bioactive materials which combined with surface activation treatments can increase the cell adhesion and bone integration with the implants' surface. With such developments, future research can address the design for additive manufacturing even including topology optimization to focus the strengthening and bioactivation of PEEK 3D-printed samples for specific implant applications. Through these approaches, PEEK 3D prints can display strength and stiffness in the range of human bone's while also displaying improved osseointegration. With such improvements, the use of PEEK's 3D printing combined with surface bioactivation displays its full potential for the manufacture of patient-specific high-performance implantable medical devices for orthopaedic, trauma and spinal treatment applications.

Funding The authors acknowledge Fundação para a Ciência e Tecnologia (FCT, I.P.) for its financial support through the PhD scholarship UI/BD/151082/2021 and through UNIDEMI, project UIDB/00667/2020.

Data availability Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Conflicts of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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