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A systematic review of polymer composite in biomedical engineering

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ABSTRACT

This review focuses on 3D printing of calcium hydroxyapatite (cHAp) as a composite on poly-ether-ether-ketone (PEEK) scaffolds and related structures. The combination is made of cHAp and coated biocompatible PEEK, a composite material with improved mechanical, thermal and flow properties for biocompatibility and bone implant. The interactions of the PEEK/cHAp interfaces that allow biological fusion are investigated for new biomedical applications. This research demonstrates biocompatibility by reviewing conventional coating techniques for HAp and PEEK fusion interfaces and *in vitro* and *in vivo* studies of the interactions between proteins and composite. A cell study of interactions between cHAp and PEEK biomolecules and how these interactions are affected by specific pre-adsorption of proteins is discussed. This study offers concise knowledge and understanding of the nanomaterials used as modifiers for improving biological behaviours of PEEK/cHAp nanocomposites in bone implants and tissue engineering. The main applications of 3D printed cHAp scaffolds in bone tissue engineering are presented and discussed. This review emphasises the most recent development and testing of multifunctional cHAp-based systems combining multiple properties for advanced therapies such as bone regeneration, antibacterial effect angiogenesis and cancer treatment.

1. Introduction

The proliferation of osteoblasts in injection-moulded poly-ether-ether-ketone (PEEK) samples is higher than that of titanium. This means that injection-moulded PEEK exhibits osteointegration behaviour like titanium or even slightly better. However, the speed of osteointegration is more significant with autologous implants, where bones are removed from other parts of the body, unlike when biomaterials are used. To increase the osteointegration speed of PEEK implants, formulations of PEEK composites, calcium hydroxyapatite (cHAp) and beta-tricalcium phosphate (β-TCP) have been introduced. However, as noted by [1–3], cHAp particle adhesion with the PEEK matrix is very low, leading to a sharp drop in the composite's rigidity and toughness. This lack of interfacial adhesion can be seen in some analyses using scanning electron microscopy (SEM) [3–5].

Surface engineering techniques are good alternatives, as the bioactive ceramic has the desired property of being able to osseointegrate. This is only needed on the implant surface. Thus, the harmful consequences of using cHAp as reinforcement in a composite, such as increasing the elastic modulus and decreasing toughness, are not present. However, surface engineering techniques can negatively influence the PEEK matrix properties [6–8]. The high temperatures involved and the high-speed impact of the particles on the implant surface during the coating processes can alter both their short and long-term properties. This effect, especially the long term effect, is rarely evaluated. One of the few evaluations [8–10] presents data on the impact of cHAp coating on properties under fatigue in PEEK, concerning traction only (Fig. 1). However, there is greater criticality in bending, since the external fibre is subject to tension, leading to rupture of the cHAp layer. Evaluation is necessary to understand how the processing of PEEK resin affects its surface characteristics, and how the technique of applying a coating influences its short and long-term properties [10–12].

2. Fabric engineering

Tissue engineering is an interdisciplinary branch of science involving health sciences, materials engineering, mechanical engineering, and basic sciences. Its main objective is to develop biological substitutes to restore, maintain or improve tissue function. The formulation of substitutes requires various strategies, such as the direct transplantation of cells within damaged tissue and cell encapsulation. The implantation of scaffolds containing promoter cells leads to the regeneration of damaged

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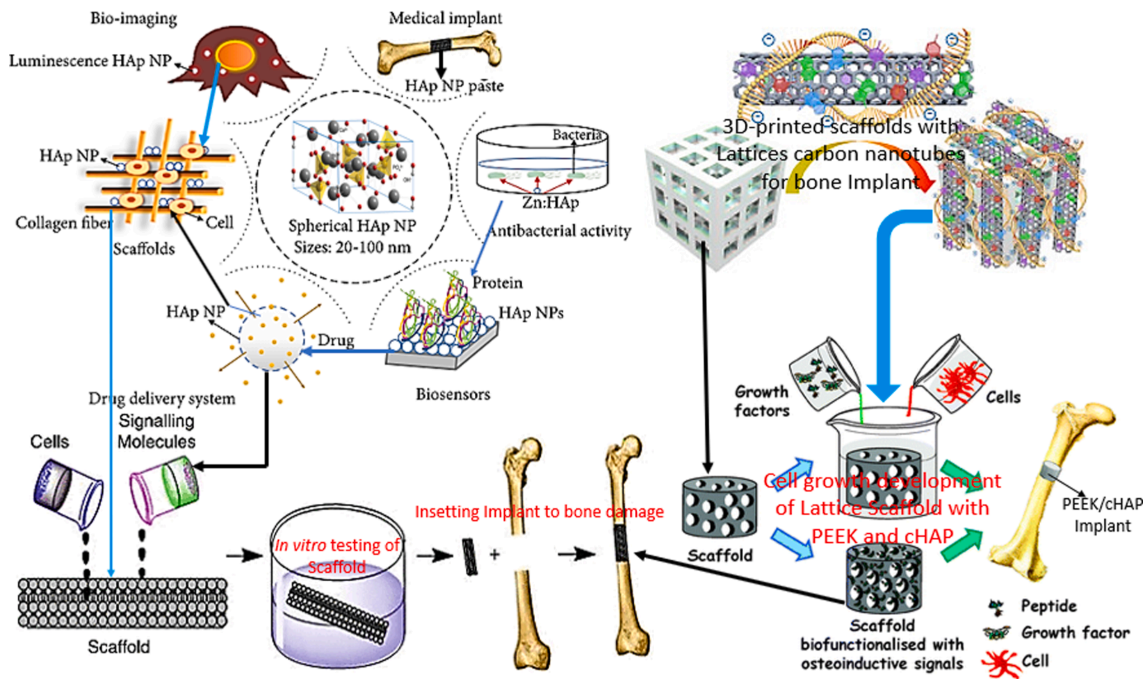

Fig. 1. Cell growth development of lattice scaffold with PEEK and cHAp nanoparticles, coating on polymer and 3D-printed scaffolds with carbon nanotube lattices to create effective bone-implant bioprinting.

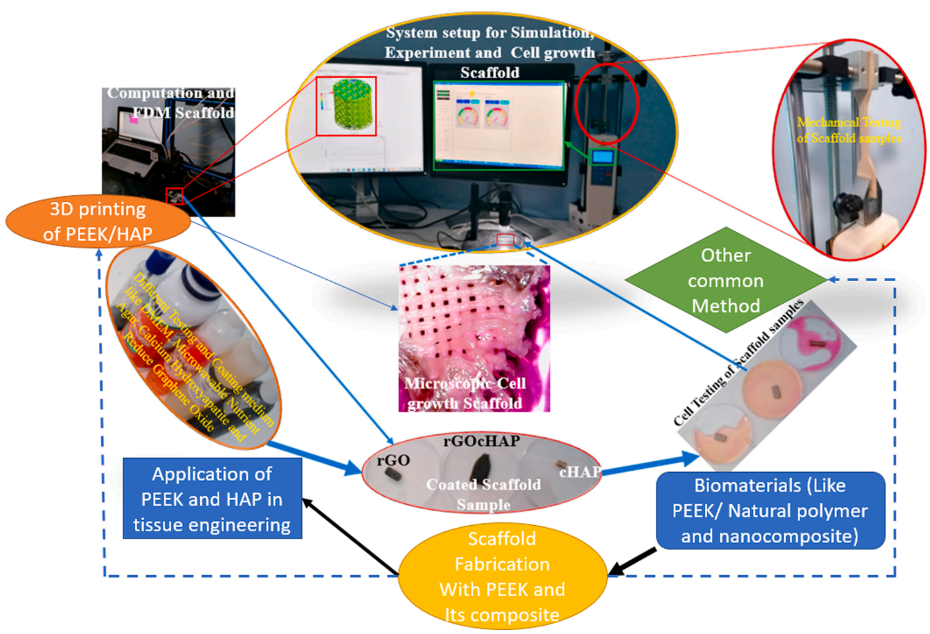

Fig. 2. PEEK/rGo/cHAp strength, biomechanical properties and osseointegration research methods: system set up, simulation and experiment for cell growth scaffolds; computer and FDM scaffolding; methods for testing samples of graphene oxides; mechanical testing of cell samples such as DMEM, microwavable nutrient agar, hydroxyapatite and graphenoxide reduction; 3D printing of hydroxyapatite (HAp)-based printed materials for regeneration of lost bone support tissue; possible application of PEEK and HAP [28].

tissue. Scaffolds or cellular scaffolds are three-dimensional (3D) structures used in tissue engineering to direct cell culture growth *in vitro* or *in vivo*. The latter has received most attention since the support structure (Fig. 2) guarantees the implant's stability and mechanical functionality [12–14]. Using support structures made of resorbable materials that degrade as the healthy tissue develops is essential.

Various types of implants are used for tissue regeneration, classified according to their origin: in autografts, the cells used in the transplant come from the individual (Fig. 2); in allografts, the cells used come from an individual of the same species but not the treated patients; and in xenografts, the tissue comes from another species. The main advantage of using autologous tissue is that rejection is avoided. To carry out this type of procedure, it is necessary to perform a biopsy of healthy patient tissue to use directly or culture on a support matrix. The direct use of tissue is a one-stage procedure, and its main advantage is reducing the number of interventions to which the patient is subject [14–16]. To grow a culture on a support matrix, the process has two clinical phases, removing healthy tissue and the subsequent implant. The main limitation of autologous cell therapy is the difficulty in obtaining an adequate tissue sample and the risk of post-surgical morbidity.

Not all cell lines, however, have sufficient proliferation to guarantee this differentiated cell strategy. As an alternative, many authors propose the use of stem cells. Stem cells are indistinguishable cells, capable of giving rise to various types of cell lines. The potential for tissue

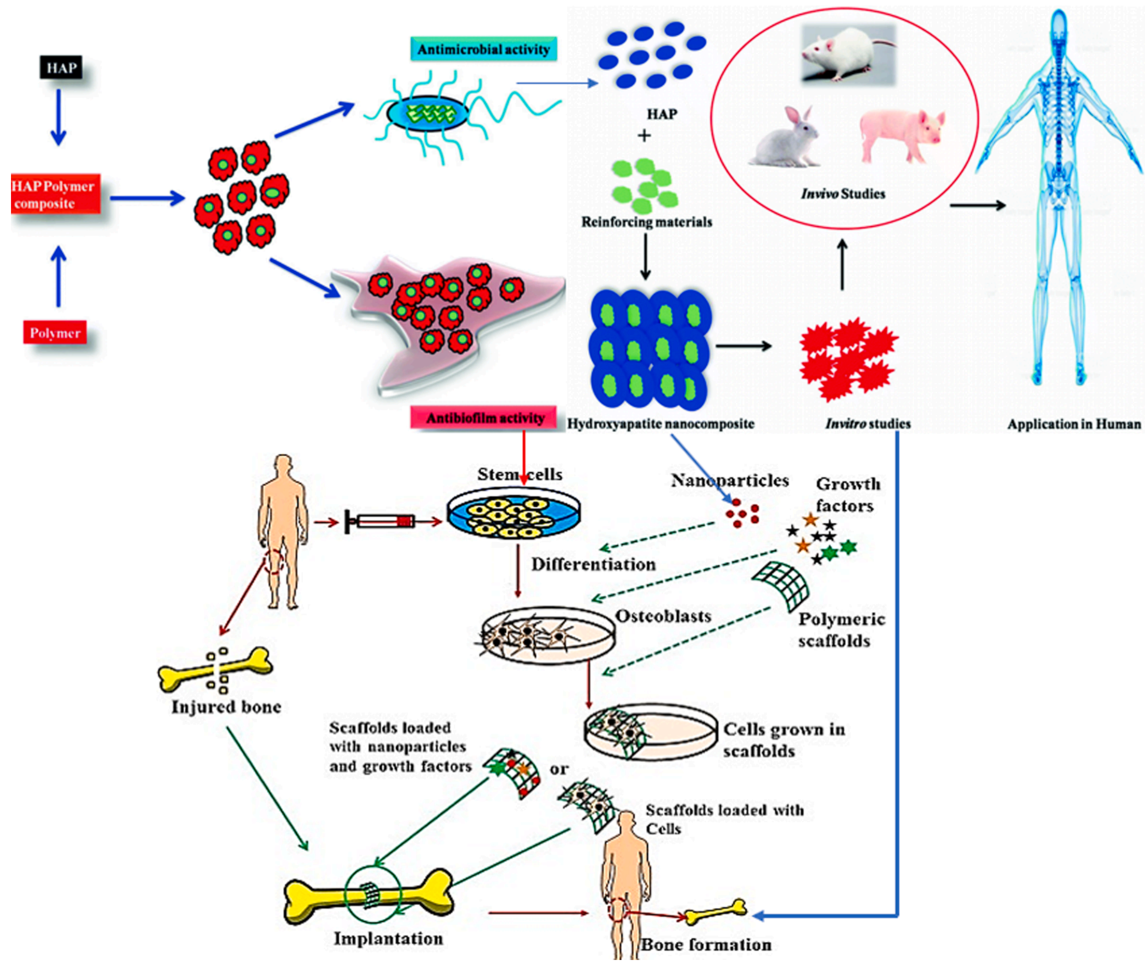

Fig. 3. Chitosan-based biocomposite scaffolds for bone tissue engineering, using cells and biomaterials or a mix of cells stacked onto biodegradable platforms used to treat essential measured bone imperfections [34–37]

engineering is indisputable, having all the advantages of autografts [17–19]. Depending on the origin, stem cells are classified into embryogenic and adult. Embryogenic cells have certain limitations in tissue engineering, including ethical implications and tumorigenic potential, which implies a restriction in terms of safety. Adult stem cells have a more limited differentiation capacity than embryogenic cells, but their pluripotential continues to be very wide, giving them the ability to treat multiple conditions. Obtaining them is simpler and does not carry the ethical implications inherent in using embryonic stem cells [20–22]. Therefore, there is a growing interest in this type of stem cell for the regeneration of various tissue types.

2.1. Polymer for tissue engineering

An ageing population, increased life expectancy, greater quality of life and high accident rates all lead to a significant increase in degenerative musculoskeletal diseases. Despite the rapid progress in bone regenerative medicine over the years, there are still many limitations to bone graft therapies. Tissue engineering is a discipline in biomedical sciences, concerning regenerative medicine. Cultivation and cell growth techniques have been used for many years, but with limitations due to the complex 3D structures. The development of functioning tissues is one aspect of modern research involving regenerative medicine in a multidisciplinary research field. There is a diversity of disciplines and groups with different specialisations studying specific problems related to the creation of functional living tissues, the repair of tissues damaged by longevity or with abnormal or irregular functions [22–24].

This field of medicine strives to create self-regenerating bodies or cell cultures for situations where the body has limitations in its ability to regenerate itself. Various techniques and therapies are used in conjunction with tissue engineering to reproduce damaged tissue. Multidisciplinary tissue engineering uses procedures to stimulate cell growth and development, manipulating various biomaterials which provide temporary support for the steady development of specific tissues. The 3D printed models (Fig. 3), called scaffolds, have physical, mechanical and chemical requirements associated with cell adhesion and tissue growth. Bone, for example, is well known for its ability to self-regenerate, but the body cannot entirely regenerate extensive bone defects, and, in most cases, external interventions are required to aid bone repair. Tissue science focuses on bone scaffolds which meet essential biocompatibility criteria such as osteoconduction, pore measurements between 1 and 299 mc, biodegradability for osteointegration and biomonitoring capability. They must also have compatibility, bone-like mechanical properties and simple processing [25–27]. Scaffold structures consist of biomaterials with properties that permit cell growth in the conditions of the host organism, and must be non-toxic, biodegradable, bioresorbable, bioactive and biocompatible (see Fig. 4).

2.2. cHAp natural–synthetic polymer-based materials

Calcium phosphate-type ceramics as biomaterials are an object of study, especially for uses where they are in contact with bone structures, due to their chemical similarity to human bone [28–30]. Dental implants, periodontal treatments and orthopaedic surgery are among the

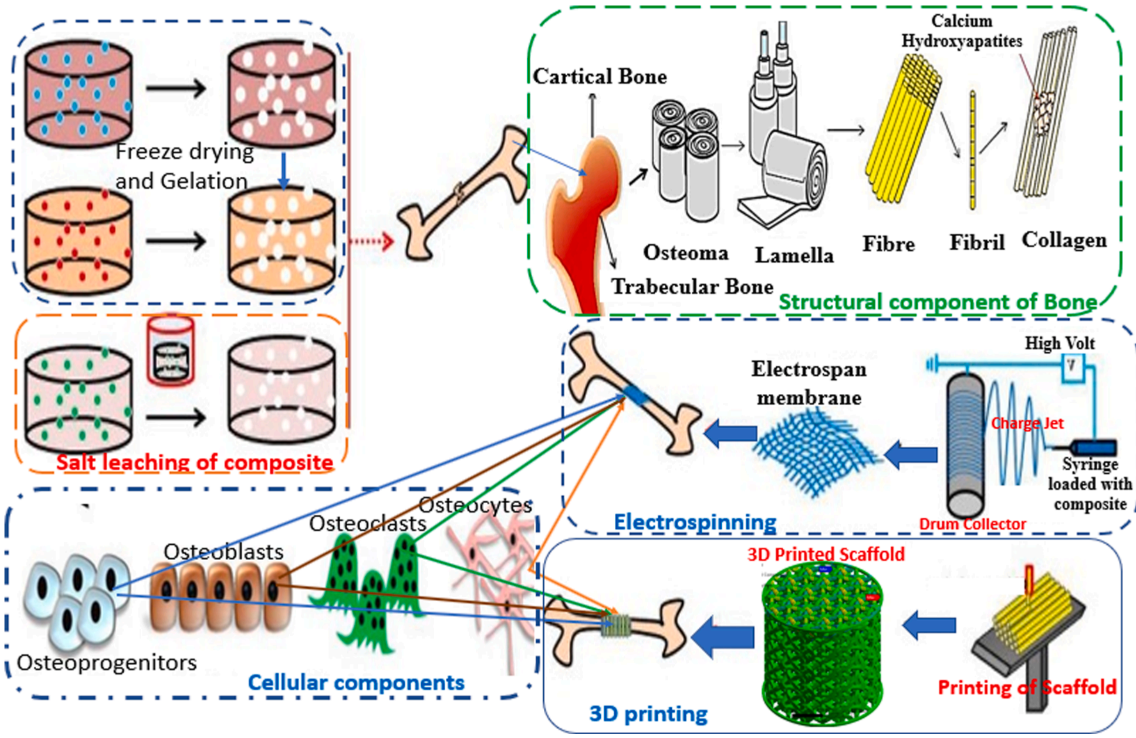

Fig. 4. The hierarchical structure of bone and 3D printed scaffolds [50–52]

Table 1
Main calcium phosphate compounds for applications as biomaterials [43,44].

Element	Chemical formula	Ratio Ca/P
DCPA (Phosphate dicalcium)	$CaHPO_4$	1.00
DCPD (Dicalcium phosphate dihydrate)	$CaHPO{\cdot}2H_2O$	1.00
OCP (Octacalcium phosphate)	$Ca_8H_2(PO_4)_6{\cdot}5H_2O$	1.33
OcHAp (Oxi-hydroxyapatite)	$Ca_{10}(PO_4)_6(OH)_{2\text{-}2x}O_x$	1.67
AO (Completely dehydroxylated)	$Ca_{10}(PO_4)_6O$	1.67
cHAp (Calcium Hydroxyapatite)	$Ca_{10}(PO_4)_6(OH)_2$	1.67

applications explored. There are several calcium phosphate compounds with applications as biomaterials, summarised in Table 1. Human bone has a Ca/P ratio of 1.65, showing significant chemical similarity to cHAp with a Ca/P ratio of 1.67. The unit cell consists of densely packed Ca, PO_4 and OH ions, representing a structure called apatite.

2.3. Properties of cHAp as a composite

The purity of the coating must be controlled and depends on the coating process and the chemical composition. Temperatures above 800 °C cause dehydroxylation and temperatures above 1050 °C cause cHAp decomposition, according to ISO 13779-2: 2008 Implants for surgery. cHAp has a maximum degree of phases of 5% [31–34]. The final post-process Ca/P ratio, according to the standard, should be in the range 1.67 to 1.76. During the coating process, cHAp particles usually have a solid core with a partially fused surface [35–37]. As a result, the coating crystallinity is solid core crystallinity with a recrystallised or amorphous form of the solidified liquid phase. The parameters such as the flame temperature and cooling rate of the coating process can be calculated. The ISO 13779-2: 2008 standard indicates a minimum percentage of crystallinity of 45% to guarantee good mechanical properties *in vivo* [38–40].

cHAp coating adhesion is similarly studied. The coating adhesion is mechanical, physical, and chemical, but the mechanical bonding is predominant. Not all the deposited layers are in contact with the substrate, so there are solder points or active zones. The larger the contact area, the better the adhesion. The ISO 13779-2: 2008 standard establishes a minimum adhesion value of 15 MPa for metallic implants, but this value is not defined for other types of implant. Another important factor is the cohesive strength of the covering. The cohesive strength depends on the adhesion between the individual particles. Cohesive force is recognised as one of the main weaknesses of the coating. Cohesive strength depends on several factors, including porosity, coating thickness and defects. The porosity is an inherent characteristic of the coating process and includes open pores in or under the surface [41–44]. Fig. 3 shows chitosan-based biocomposite scaffolds for bone tissue engineering, include cells and biomaterials or a mix of cells stacked onto biodegradable platforms used to treat fundamental measured bone imperfections. High porosity increases the penetration of bone cells in osteointegration but weakens the mechanical resistance of the coating. Therefore, a balance is necessary to determine the ideal porosity for optimal penetration of bone cells without impacting the mechanical resistance.

2.4. PEEK composite for bone implants

By 2050, the predicted population over 60 will be 1700 million, which gives an idea of the need to improve therapeutic alternatives for pathologies that significantly affect this segment of the population. Global ageing is one of the main factors in the growing interest in new therapeutic alternatives for the locomotor system, including tissue engineering. Tissue engineering for treating bone tissue lesions has its most important application in the regeneration of the significant defects caused by removing neoplasms or trauma. It is necessary to give a brief description of the main characteristics of bone tissue to understand the critical requirements for structures intended to regenerate this type of tissue [45–47].

Residual stresses are caused by differences in thermal expansion coefficients between coatings and substrates, and cause fatigue which impacts implant life. Coating thickness and roughness are both highly process dependent. The number of passes, feed speed of the particles in the gun, the distance between the gun and the substrate, and other

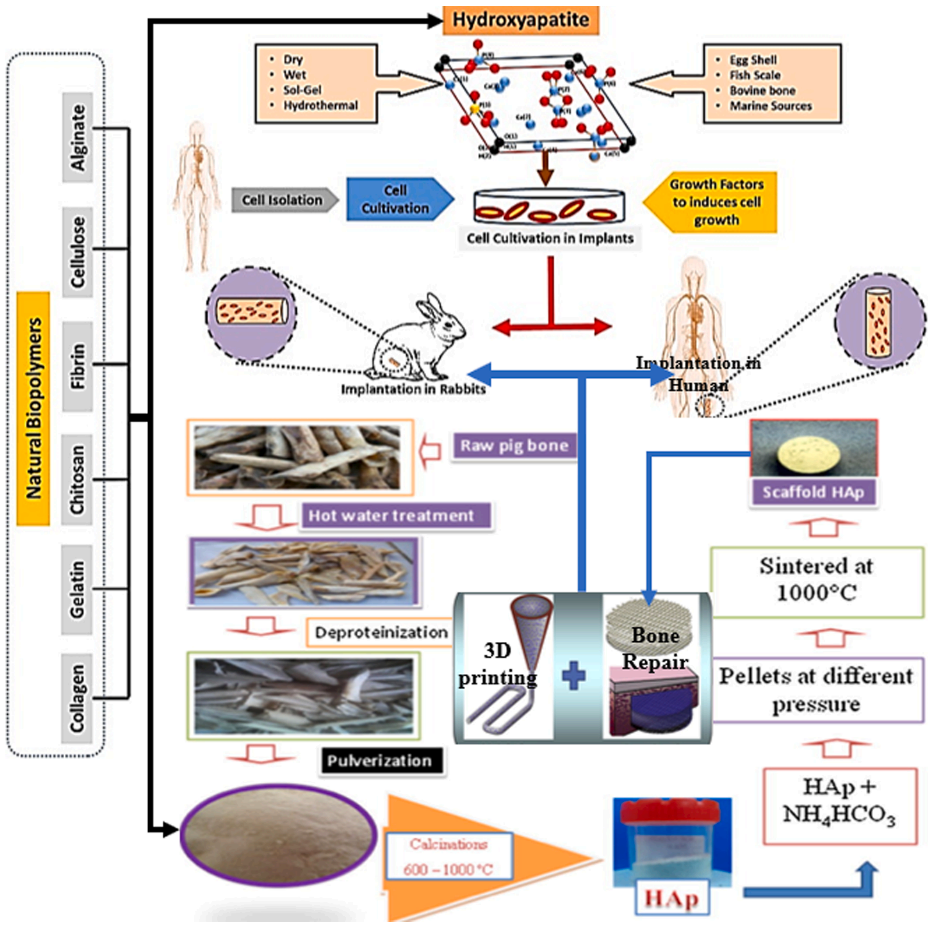

Fig. 5. Natural organic and inorganic–hydroxyapatite biopolymer composites for biomedical applications [99,100].

variables, impact both properties. Usually, coatings applied to implants have a thickness of 50 to 200 µm and a roughness of 4 to 6 µm, when powders of 20 to 30 µm are used. Several authors [48,49] report that osteoblasts adhere better to surfaces with higher roughness, although the optimum roughness value remains uncertain.

Fig. 5 shows natural polysaccharides organic and inorganic–hydroxyapatite biopolymer composites for biomedical application. The process of thermal coating of cHAp is complex. The coating quality depends not only on the gun used, but also on the powder, the nature of the flame and the substrate variables. Authors [48–50] divide the parameters into primary and secondary categories. Primary parameters are those that the technique directly controls, while secondary parameters depend on the primary parameters. Studies analysing the thermal coating process of cHAp on PEEK substrates have been carried out [50–52]. The authors coupled a sensor system close to the gun to monitor the secondary parameters that are considered most important, flame temperature and particle speed. Both parameters recorded affect the particles' effect on the substrate and the fatigue properties of the polymers at high temperature. The authors analysed the impact of the primary parameters, the current applied for the formation of plasma, the distance from the specimen to the gun, and the rate of feed of the cHAp particles, along with the two secondary parameters of most significance, but with greater focus on the speed of the particles [53–55] (see Fig. 6).

In addition, the processing parameters are determined that best ensure a high and uniform degree of crystallinity, including a high crystallinity value with minimal variation throughout the mould thickness and length, as well as a low level of residual stress frozen into the moulded parts by the PEEK injection. At this temperature, the total moulding cycle time does not increase too much to avoid compromising the quality of the PEEK moulding, due to probable degradation resulting from polymeric melt due to long residence time in the injector barrel between successive cycles. Another relevant processing parameter is the injection speed. Higher injection speeds contribute to maximising and standardising the degree of crystallinity in both the standard and parallel directions relative to the main melt flow direction when filling the mould cavity [55–58].

To correlate the influence of processing conditions on the degree of microstructure crystallinity and the short-term mechanical properties, data on the results of the mould temperature and injection speed on the elastic modulus, tensile yield stress and Izod impact resistance properties of PEEK injected moulds are reported [59–61].

During the injection moulding process of semicrystalline thermoplastics of high viscosity such as PEEK, the level of internal stresses frozen in the mould is a thermal and shearing function. The polymer melt is subject to the mould cavity filling and subsequent non-isothermal cooling until solidification in the mould at ambient temperature. The level of frozen internal stresses depends on the thermal gradient and crystallinity between the polymer layers on the surface and the crumb throughout the mould thickness, from the entrance region to the opposite end along the mould's length. Based on the temperature and type of aggressive service environment, the residual stresses can lead to the moulded parts warping due to differential shrinkage in the moulded part and mechanical failure or cracking, depending on the time under automatic loading. To measure the residual stresses in semicrystalline and amorphous injection-moulded PEEK, scientists [60–63] use the principle of incremental stress analysis in a crystallisation kinetics model with data on the constitutive properties of PEEK. They conclude that the presence of thermal stresses in moulded PEEK parts are a function of the cooling rate; the higher the cooling rate, the higher the level of residual stresses.

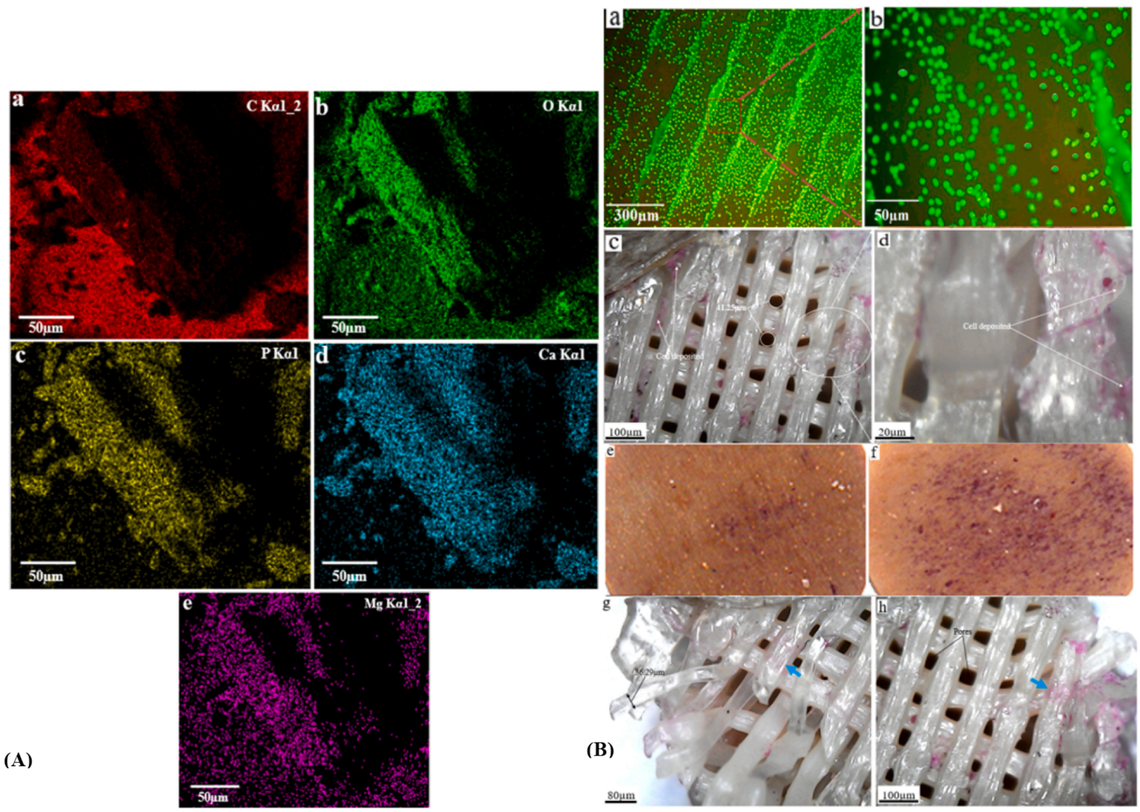

Fig. 6. **(A)** Layers of cHAp scaffold for bone implant shown by energy dispersive X-ray spectroscopy (EDS) analysis: (a) C Kα1_2, (b) O Kα1, (c) P Kα1, (d) Ca Kα1, (e) Mg Kα1_2. **(B)** Cells attached to PEEK and PEEK/cHAp composite scaffold surfaces after culturing for days: (a) 50× magnification, (b) 200× magnification, (c) 100 μm of the with the pore of 41.25 μm, (d) corresponding magnification of 20 μm of cell deposition, (e–f) spreading and alkaline phosphatase activity of cells with different material surfaces after 14 days of PEEK and PEEK/cHAp, (g–h) fracture after test showing pores, dimensions, and cell attachment [28].

3. Fatigue of PEEK and other polymers

Fatigue is defined as failure resulting from mechanical loading in traction, flexion, torsion, and compression, applied cyclically. Such failure occurs at stress levels below the yield stress limit of the materials involved. In the specific case of polymeric materials, the mechanisms involved are more complicated. Due to polymers' macromolecular structure, crack initiation mechanisms differ from those associated with metals and ceramics, although their propagation is similar [63–65]. The non-linear viscoelastic behaviour of polymeric materials makes them highly sensitive to the test frequency and subject to other variables peculiar to fatigue, such as stress–strain levels and the form of loading application if a simulated type of load wave is used.

Thermal failure is caused by heating the polymer during the application of cyclic loads, due to its inherent damping combined with low thermal conductivity and high mechanical hysteresis. If the temperature increase is sufficient to reach the glass transition temperature (T_g) of the polymer, for amorphous polymers, or the melting temperature (T_m), for semicrystalline polymers, failure due to thermal softening occurs. For PEEK, its high T_m of 343 °C makes the chance of thermal fatigue failure remote, meaning mechanical failure by crack propagation is predominant. Heterogeneity associated with the microstructure of materials gives rise to defects, the geometry, size and orientation of which are random. In the case of cHAp-coated PEEK parts, particles under the surface of the pieces give rise to heterogeneity, leading to the appearance of complex growth and an interaction of defects that leads to the initiation of macroscopic cracks.

Cracks first propagate steadily to the stage where a transition to an unstable or uncontrolled propagation begins. The failure process occurs through the propagation of damage, and the fracture surface is, in general, perpendicular to the direction of the stress applied. The most common way of measuring crack propagation is the crack growth rate per cycle (da/dN). This parameter is a function of the stress intensity factor (ΔK). During the application of dynamic loading to the material, especially in simulated tests, the stress amplitude applied is constant. Failure is caused by the development of pre-cracks of a subcritical initial size before the critical dimension of material fracture toughness (K_c) is reached [66–68]. Therefore, cyclically loaded material fatigue life depends on the initial size, propagation rate and critical crack size. The relation between da and dN, in the form of a power-law, is known as the Paris Erdogan equation, with the strength factor of voltage (K).

4. Fracture mechanics of PEEK under fatigue

Various tests have been conducted to investigate fatigued PEEK, considering the effects of several variables on the spread of cracks. These variables include the wave used, molecular orientation, molecular weight, and crystallinity [69,70]. Using the Paris Erdogan model, studies demonstrate that the wave effects and molecular orientation have little influence on the crack propagation in PEEK. Better crystallinity and greater molecular weight indicate less crack propagation than lower crystallinity, see Fig. 7(a–c) (see Fig. 8).

Fig. 7**a** shows the influence of injection speed on crystallinity distribution along the length of samples moulded by PEEK injection at rates of 5.2 and 23.2 cm^3/s, retention times of 1, 4 and 10mins of PEEK 380 G at a temperature of 150 °C. The effect of mould retention time on crystallinity variation along the length of PEEK injection moulded samples, and elastic modulus with increase in temperature are shown in Fig. 7b and c. The yield stress under tension for PEEK mouldings, depending on the mould temperature and two injection speeds of PEEK 380 G, is shown in Fig. 7d. The RII values tend to decline to a temperature of approximately 70 °C initially, then increase when the mould

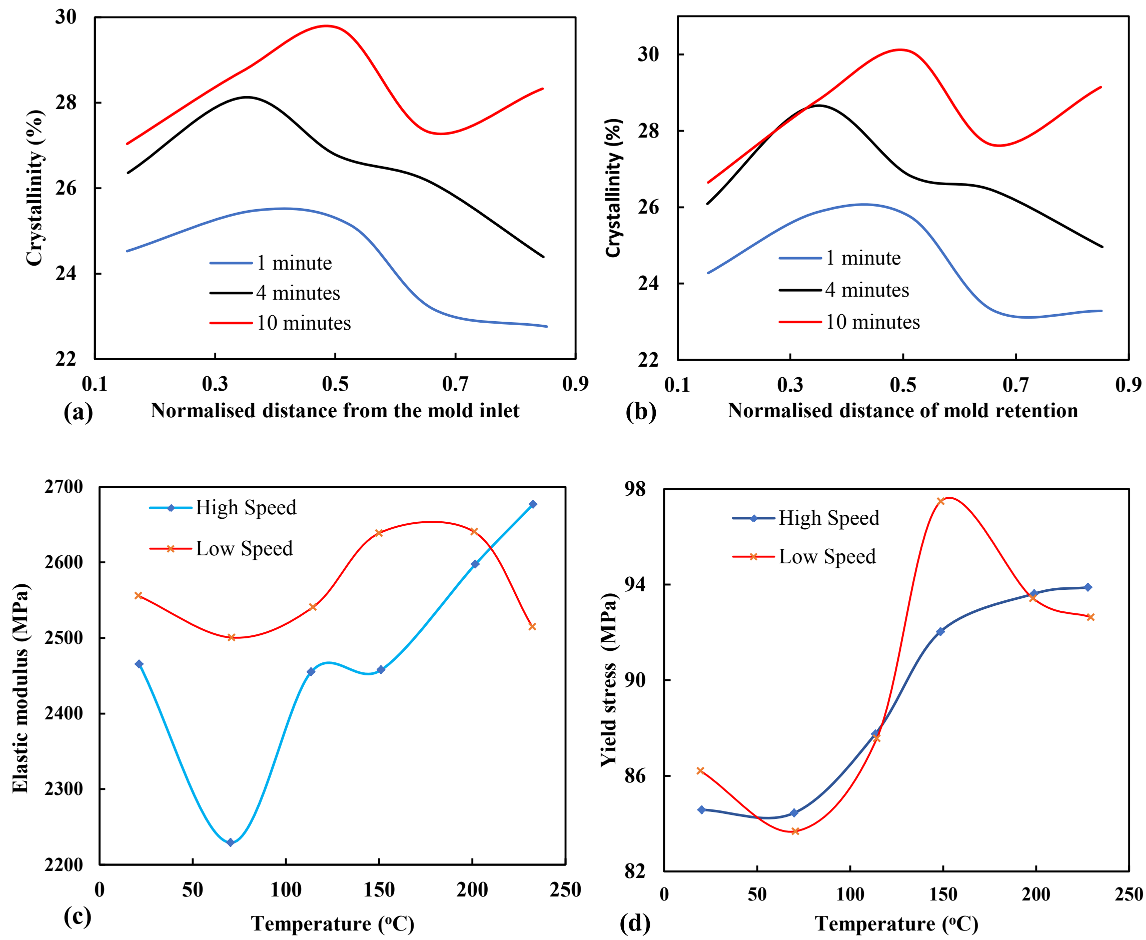

Fig. 7. (a) Influence of injection speed on crystallinity distribution along the length of samples moulded by PEEK injection with rates of 5.2 and 23.2 cm^3/s, retention times of 1, 4 and 10 mins of PEEK 380 G at temperature of 150 °C; (b) effect of mould retention times on the crystallinity variation along the length of PEEK injection moulded samples; (c) elastic modulus; (d) yield stress under tension for PEEK mouldings, depending on the mould temperature and two injection speeds of PEEK 380 G [85–87].

temperature approaches T_g of the polymer. Above T_g, the RII tends to level off with a slight decrease at temperatures between 200 and 230 °C. At mould temperatures between 180 and 230 °C, the effects of low, medium, and high injection speeds become almost constant.

Based on studies [70–72] of the effects of the temperature and thickness of PEEK pieces on fatigue fracture mechanics, larger thicknesses exhibit more fragile modes of fracture, presenting the phenomenon of crazing, micro fibrillation under tension, in the area around the fracture. Smaller thicknesses have two fracture modes, brittle and ductile. At a temperature range between 75 and 100 °C, a critical change in fatigue behaviour is reported. In this type of test, the data are presented on a graph with the applied stress value in loads of traction, flexion, compression, and torsion arranged on the coordinate axis according to the log of the number cycles (N) at which failure occurs for each specimen. Another concept is life under fatigue (N_f), which is shown on a durability graph, where N_f represents the number of cycles required. A few studies on the exhaustion of cHAp coated PEEK parts are available, for instance comparative traction results between PEEK specimens with and without cHAp coating and sandblasted specimens [72–74]. The results show a slight post-coating drop, from 91 to 85 MPa, in static yield stress. Fatigue durability tests of PEEK using sine waves at 5 Hz have been performed, showing a stress of 77 MPa for a fatigue life of 1 million cycles.

4.1. Mechanical properties

The mechanical property of the scaffold is an essential factor in selecting a biomaterial for an application. Each tissue needs to be regenerated with varying mechanical properties. The mechanical properties included under ASTM F 2150-13 relate to stress, tension, and physical force reaction. Scaffolds must have sufficient mechanical strength to withstand the stresses caused by the implant process and subsequent physiological loading demands in the implant environment. The compatibility of the mechanical properties of the scaffold with the ideal conditions for cell growth is fundamental to the tissue reconstruction process [74–76]. Therefore, scaffolds need to meet the implant site's mechanical specifications and requirements to avoid compromise in low mechanical strength and, consequently, cell proliferation.

4.2. Morphological properties

The scaffold must have a porous microstructure capable of expanding and constantly distributing tissue cells. More importantly, the interconnectedness between the pores must provide a facilitating environment for the insertion of blood cells and vessels that propagate nutrients and oxygen essential for new tissue growth. The existence of interconnected pores favours connection between the cells of the newly developing tissue. Human osteoblasts can penetrate interconnections with a diameter greater than 20 μm, but a larger diameter favours cell distribution. Interconnections with a diameter greater than 50 μm are

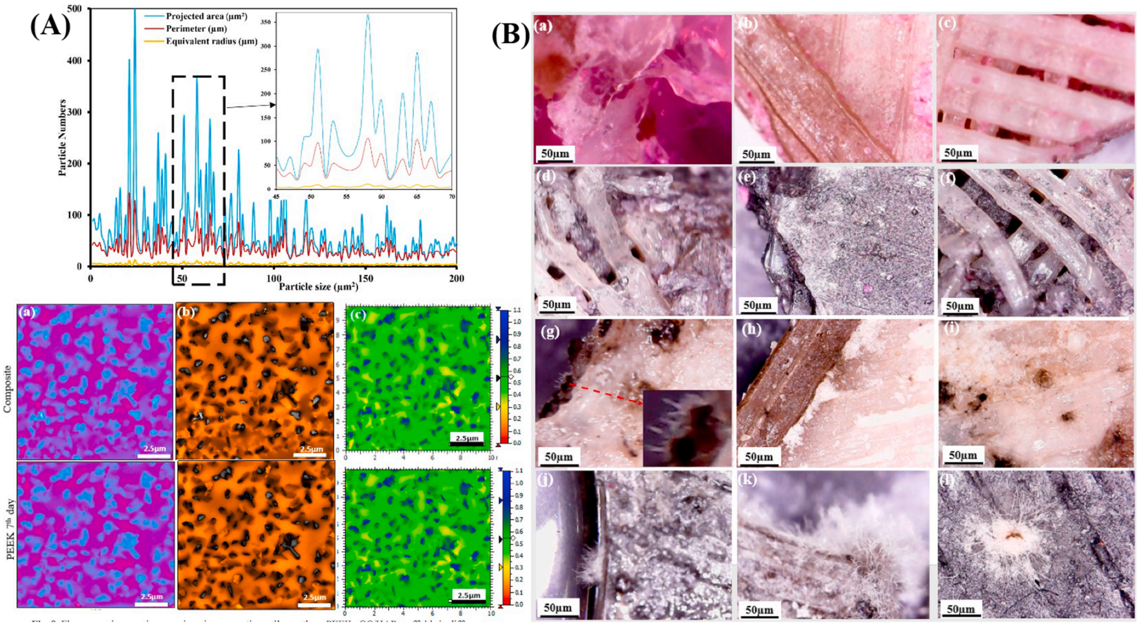

Fig. 8. Fluorescent pictures of tissue engineering cell development of PEEK/rGO/HAp scaffolds at various days of analysis: **(A)** PEEK/rGO/cHAp: (a) sample cell profile for Gaussian 0.8 mm filter, (b) extracted cell amplitude-roughness profile for the samples of cell threshold sets 60.8 nm by 39.12 nm, (c) number of particular analysis motifs for micrometre thresholds; **(B)** days after using a DMEM crop medium, sample scaffold cells with: (a) 50 μm of PEEK after more than 24 h, (b) 50 μm of PEEK after three days rGO/cHAp, (c) a better spread of cell-alkaline phosphatases after seven days of PEEK cultivation, (d–e) 50 μm of PEEK/rGO/cHAp composite scaffold after over 24 h, (f) A better life cell attachment on PEEK/rGO/cHAp composite scaffold; (g-o) live/dead colouring of the composite sample surfaces FDM 3D-printed PEEK after cultivation with nutrient agar solution: (g) for 24 h, 50 μm PEEK, (h) more 3rd day cell activity in 50 μm PEEK, (i) 50 μm PEEK cell propagation on the 7th day, with small dead cell, (j) 50 μm of PEEK/rGO/cHAp for 24 h, (k) 50 μm of PEEK/rGO/cHAp cell growing on the 7th day to spread to small dead cells PEEK/rGO/cHAp cells [11].

Table 2
Comparison of methods of improving PEEK quality characteristics and other bone implant materials.

Material	Major property	Method	Results/findings	References
PEEK/Alumina	Mechanical	Composite fabrication	The use of alumina reinforcement, 60 wt%, increases the dynamic strength of the resulting composite by 78%.	[50–53]
PEEK/HAp	Mechanical		The tensile strength of the resulting composite is increased due to good interactivity between HAp and PEEK.	[53–55]
PEEK/Carbon nano-tubes	Mechanical and crystalline		The use of reinforcement enhances the mechanical properties and reduces the crystallisation rate of PEEK.	[55–57]
PEEK/β-TCP	Biological		The proliferation rates of normal human osteoblast cells' growth on β-TCP/PEEK are lower than PEEK	[58–60]
Titanium	Biological	Electron beam deposition	In vivo tests show that the coating of titanium on PEEK implants results in an enhanced bone in-contact ratio.	[60–62]
PEEK/ Polytetrafluoroethylene	Tribological	Blending	With the use of polytetrafluoroethylene in PEEK, the resulting coefficient of friction is reduced.	[63–65]
	Biological	Plasma immersion ion deposition	The experimental treatment helps develop next-generation orthopaedic implants.	[65–68]
PEEK, PEKK	Chemical	Plasma treatment	Plasma treatment of PEEK at atmospheric pressure works remarkably to improve the adhesive strength of the polymer.	[69–72]

favourable for new bone growth within the pores. Blood vessels have been shown to penetrate a scaffold with a minimum pore size of 45 to 100 μm, but these are not as useful as scaffolds with 100 to 150 μm pores, which allow a better blood supply. The minimum pore size for perfect osteoconduction is 80 to 100 μm. An increase in porosity and pore size favours both bone growth and nutrition supply. However, increased porosity and pore size decrease mechanical strength, which is essential for bone graft functionality. It is not easy to obtain a structure with a large pore size and adequate mechanical strength. Scaffold construction architecture, voids caused by porosity, the interlacing strategy between layers and the arrangement of layers all influence scaffold rigidity and, consequently, its mechanical properties [76–79].

Current research into PEEK technology and its applications covers a wide range of fields, from dental, orthopaedic, spinal or trauma implants to advancements in PEEK additives and traditional medical efficacy. HAp improves postoperative evaluation. The fracture fixing potential of carbon fibre reinforced composite sheets of PEEK (CFR-PEEK) appears clear and very promising, mainly due to their excellent fatigue resistance and good modulus of elasticity. The potential benefits of a less rigorous wound-healing preparation are incredibly encouraging. The first comparative clinical study results are sure to increase interest in these materials. A study has been conducted comparing the mechanical stability of locking screws depending on whether they are placed in a CFR-PEEK or stainless steel humerus plate. The holding force of the screws in the CFR-PEEK is similar or better than that of the screws in the stainless-steel plate. Also, the resistant pre-fracture loading of the CFR-PEEK plate is comparable, or significantly higher in parts, to the stainless steel, to the extent of blocking the nearby humerus plate. Extensive research and clinical experience validate the reliable placement of implants using PEEK polymer, offering potential benefits for patients and a wide range

Table 3
Production processes (additive manufacturing) that could benefit PEEK-based biomedical components and improve PEEK quality characteristics.

Method	Material system	Affected property	Significant outcome	References
FDM	PEEK, Carbon fibres and nano-ZrO2	Mechanical and tribological	The use of nano-ZrO2 reinforcement reduces the stress concentration on the carbon fibre interface and the shear stress between sliding surfaces.	[44,46]
	PEEK/HAp	Mechanical	The tensile strength of the resulting composite is increased due to good interactivity between HAp and PEEK.	[47,80]
	PEEK/Carbon nano-tubes	Mechanical and crystalline	The use of reinforcement enhances the mechanical properties and reduces the crystallisation rate of PEEK.	[49,81]
Processing temperature	Injection moulding process	Mechanical and tribological	The hardness of the material increases with processing temperature and reduces the coefficient of friction.	[81,82]
Use of additives	Polyetherimide	Mechanical	The use of additive benefits the mechanical and thermal processing of PEEK-based products.	[54,83]
Pre-treatment of PEEK	Piranha solution etching and abrasion followed by chemical treatment	Chemical	Airborne particle abrasion in combination with piranha solution etching improves the adhesive properties of PEEK.	[83,84]
Sterilisation	– – –	Mechanical	Steam treatment is more efficient than others.	[84,85]

of developments. The planning of additive manufacturing in the medical industry is still in its early stages. However, it is believed that this technology can revolutionise implant production in terms of ease, speed, and precision. Table 2 shows some of the materials used, significant properties obtained, methods adopted and their outcomes to enhance the quality characteristics of PEEK.

4.3. PEEK as polymer and its merit

Unlike metallic implants, PEEK structures have all the advantages of radiolucency, such as much more precise implantation procedures and quicker diagnosis of postoperative complications. Biomaterial scientists are proud to have sponsored the mission to facilitate innovation in medical devices by offering new solutions and supporting research into PEEK [44,46,47,49,80]. *In vitro* is an innovation applying implantable polymers based on high-performance PEEK, such as PEEK-OPTIMA or PEEK-OPTIMA HA Enhanced. Additive manufacturing can create custom implants and significantly alter preoperative planning and surgery by directly correlating digital patient models. Therefore 3D printing specialists Apium Additive Technologies GmbH market a 3D printer with PEEK processing capabilities. Work continues the performance obtained in compression and compression shear, which are excellent. Future additive technology has the potential to achieve as much as the mechanised cage. Table 3 summarises the activities that could benefit PEEK-based biomedical composites and improve the quality characteristics of PEEK.

5. Dynamic mechanical analysis

Polymeric materials exhibit viscoelastic behaviour, which implies both elastic and viscous behaviours under mechanical loading. When a polymer is mechanically subjected to a cyclic sinusoidal tension, it responds in the form of deformation, also sinusoidally, but delayed from the application, that is, an out-of-phase response. Due to the time needed for macromolecular rearrangement and polymer relaxation of segments and side groups, polymeric materials display viscoelastic behaviour. The dynamic mechanical, thermal analysis uses minute deformation values to obtain the polymer elastic modulus constant in a region where the response is linearly viscoelastic, i.e. a region where the stress is directly proportional to the deformation provided. Thus, the ratio between stress and deformation is constant in tension (E) and shear (G). Regardless of the deformation provided, preventing the material from undergoing plastic deformation, the linear viscoelastic model equations are no longer valid. Deformation dissipates heat in polymeric materials from the stored potential energy due to internal damping or friction [86–88].

The results of this analysis provide information about the relationships between the mechanical properties of the material and its structural parameters such as crystallinity, molecular orientation, along with external variables such as temperature, stress, time, and frequency [89–91]. The experimental parameters of the test, such as frequency, amplitude of deformation and heating rate, strongly influence this technique. Thus, the dynamic mechanical analysis technique gives results that allow the temperature parameter to determine linear viscoelastic nature of the polymer's mechanical properties. The conclusion of the dynamic storage module in traction in shear is the absolute modulus, which is directly related to the elastic fraction stored as potential energy. This allows for the determination of the dynamic loss module (E'') in case of traction/flexion and (G'') in case of shear, called the imaginary modulus, which is related to heat dissipation because of the response. The dimensionless ratio of energy lost per cycle, generally dissipated as heat, to the maximum power stored per cycle that is fully recoverable, is the mechanical damping, internal friction, or loss tangent, tan δ [92–94].

6. Applications of cHAp and PEEK

The systematic review carried out in this study compiles the current information on PEEK, cHAp, and the PEEK plasma coating process with cHAp. The data collected show that the coating process can positively influence PEEK properties. Also, the PEEK surface hardness affects the cHAp particle penetration before the coating process. Greater crystallinity results in more rigid surfaces and less penetration of cHAp particles [95–97].

The coating process at high temperatures alters the post-process part crystallinity, which can cause localised degradation and thermal stresses in the polymer. The mechanical characteristics of the covered component affect both effects. The mechanical aspects of PEEK are sensitive to temperature effects, as widely discussed within this review, such as the effects of mould temperature and mould retention time during processing. Significantly, the presence of cHAp particles can induce pre-cracks in implants and behave as stress concentrators. It appears from this review that crack propagation is the primary means of failure under fatigue of PEEK implants, and occurs around T_g of 143 °C and crystalline fusion of 343 °C, given a temperature of use of around 37 °C. The presence of cHAp particles can generate pre-cracks in PEEK, decreasing the stress intensity factor required for crack propagation. The depth of particle penetration, crystallinity, and stiffness of resin around particles are added as variables [98–100].

In addition to the effects on the PEEK substrate, interfacial adhesion must be adequate, as any detachment of the cHAp layer can impair the bone consolidation, making it difficult for the patient to recover. Therefore, it is important to improve the interfacial adhesion while having a low impact on the moulded part properties. The cHAp coated PEEK moulded surface depends on the plasma coating process parameters and surface properties. Parameters such as particle temperature and speed significantly impact the resulting interfacial adhesion, negatively impacting the PEEK resin properties [101–104]. The surface crystallinity can affect the cHAp particle penetration and influence the coating morphology.

It is evident that the coating process quality depends on the correct

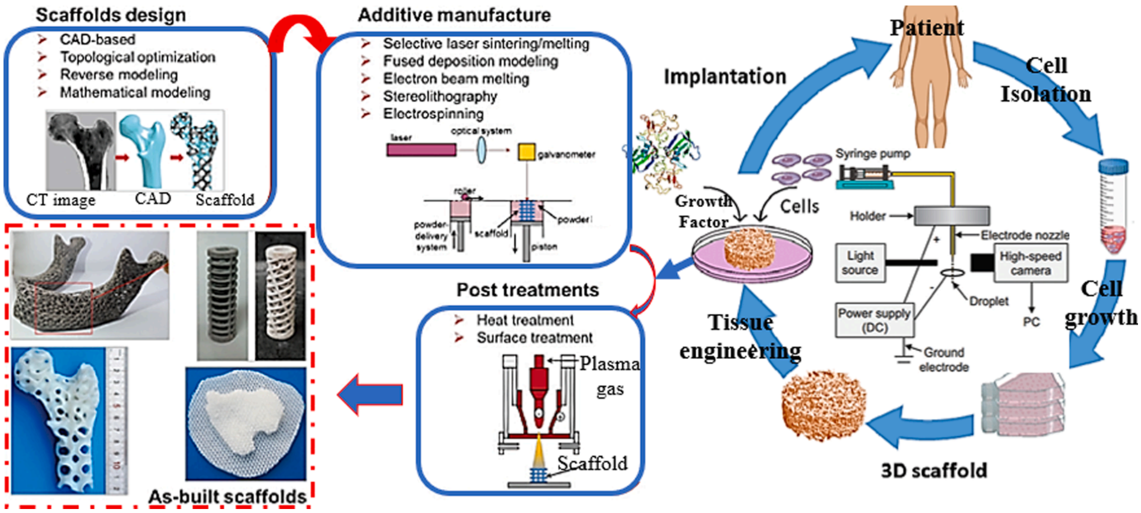

Fig. 9. Applications of electrohydrodynamic 3D printing of PEEK/cHAp with a scaffold-based tissue engineering approach [95–98].

specification of the plasma coating process variables and the appropriate identification of the PEEK moulding conditions. The thermal coating process is complex, and relies on several variables, as elucidated. Much of the available literature presents data only on the mechanical properties in a static regime, making it challenging to use in surgical applications, considering that arthrodesis implants undergo a lifetime under fatigue of at least 5 million cycles and up to 10 million [85–87] in the case of hips. Despite there being little published data on the long-term mechanical properties, the PEEK coating technique with cHAp for surgical implants is used commercially, although its development is embryonic [105–108]. Fig. 9 shows the applications of PEEK/cHAp using a scaffold-based tissue engineering approach. It is crucial to evaluate the effects of the coating process on fatigue properties so that the technique can be used safely for surgical implants.

7. Conclusions

The search for new materials for the manufacture of support structures for bone tissue regeneration is an area of great interest in developing new alternatives to treat musculoskeletal injuries. Following the literature review, it is possible to conclude that, due to the complexity of mimicking biological tissue, there is a tendency to combine materials relative to their advantages. This combination can be done either through composite material coating or extrusion of multilayer structures. Another alternative for improving the system properties of supports and promoting bone regeneration is surface treatment. Essential *in vitro* and *in vivo* results, based on tissue-specific printed constructs fabricated by various AM-based methods, are given for complex tissue regeneration.

Surface treatments are based on plasma functionalisation and the use of bioactive coatings. In both cases, the purpose is to increase the cellular affinity of the surface and the differentiation capacity in the interest of pluripotential cells. PEEK/cHAp, biocompatible polymers and their compounds are extensively studied both *in vitro* and *in vivo,* in terms of their biomolecular reactions for biomedical cHAp applications. For inorganic bone and tooth compositions, it remains the most suitable biomaterial. The cHAp-PEEK interface has been developed such that the implant bonds correctly to the bone, to ensure bone regeneration, with bioactive and biocompatible interfaces. The ability to form cells gives PEEK a continuous flexible structure. The support structure for cell growth at PEEK/HAp interfaces depends on their interactions with the biological environment due to their chemical compositions and surface structures.

Various methods have been developed to deposit cHAp on PEEK. Of these, biological growth is a promising approach because it produces HAp that is structurally like biological PEEK/HAp in bone and allows for better absorption of absorbable implants. Since cell adhesion, migration and diffusion are strongly influenced by pre-adsorbed proteins, it is necessary to develop HAp fusion interfaces bound to specific proteins, such as fibrin proteins, to increase cell adhesion and growth.

Finally, this work evaluates the activation of PEEK-based composites and the surface treatment of the same material. Due to its potential for bone tissue regeneration, this material is selected, as evidenced by the research. This review demonstrates the advantages of additive manufacturing techniques over other conventional manufacturing techniques for obtaining porous tissue. The analysis reveals some vital discoveries about how HAp interfaces with PEEK stimulate body fluids. Future research could significantly improve existing experimental methods for preparing and characterising functional nano ceramic polymer fusion interfaces with cHAp. Such studies would lead to a deeper understanding of nano biomaterial interfaces.

Declaration of Competing 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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