Surface Treatments of PEEK for Osseointegration to Bone

Subjects: Polymer Science

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Polymers, in general, and Poly (Ether-Ether-Ketone) (PEEK) have emerged as potential alternatives to conventional osseous implant biomaterials. Due to its distinct advantages over metallic implants, PEEK has been gaining increasing attention as a prime candidate for orthopaedic and dental implants. Although a myriad of permutations and combinations of different surface treatments are employed to alter the surface topography of PEEK, for the sake of simplicity, these treatments have been classified into the following categories: physical treatment, chemical treatment, surface coating, and composite preparation, with the first surface treatment in the combination determining the classification. Though these terms are arbitrary and could lead to considerable overlap, physical and chemical treatments can be grouped into a subtractive form of surface modification while surface coating can be regarded as an additive form.

Keywords: dental implant ; orthopedic implant ; implant biomaterial ; polymer

1. Physical Treatment

Physical treatments constitute plasma treatment, accelerated neutron atom beam (ANAB), photodynamic therapy, sandblasting, and laser irradiation.

1.1. Plasma Treatment

Plasma treatments primarily aim to decrease the contact angle of the PEEK surface by increasing the surface energy. Secondarily, the plasma treatments incorporate the element constituting the plasma onto the surface of a PEEK (Plasma Immersion Ion Implantation). This improves its response to human osteoblasts. Several elements have been successfully tested for the plasma treatment of PEEK (**Table 1**).

Table 1. Various plasma surface treatments of PEEK.

Treatment	Results	Author
Plasma		
Oxygen/Ammonia	**In-vitro: Increased adhesion, proliferation, and osteogenic differentiation of cells as compared to control**	**Althaus et al. [1]**
Nitrogen	**In-vitro: Increase in bioactivity and antibacterial properties with reference to *S. aureus*.**	**Gan et al. [2]**
Oxygen/Argon	**In-vitro: Increased wettability and cell adhesion, spreading, proliferation, and differentiation of SAOS-2 osteoblasts**	**Han et al. [3]**
Oxygen/Nitrogen	**In-vitro: Decrease in contact angle and no disadvantageous effect on cytocompatibility;**	**Ha et al. [4]**
Nitrogen/Argon/(Nitrogen + Argon)	**In-vitro: Increase in osteogenic activity (Highest: Nitrogen) and antibacterial property (Highest: Nitrogen + Argon)**	**Liu et al. [5]**
Oxygen	**In-vitro: Decrease in contact angle**	**Tsougeni et al. [6]**
Oxygen	**In-vitro: Increased cell adhesion and spreading of U2-OS osteoblasts in the presence of *S. epidermidis***	**Rochford et al. [7]**
Water vapour/Argon	**In-vitro: Increased wettability and cell adhesion, spreading, proliferation, and differentiation of osteoblast precursor cell line derived from Mus musculus (mouse) calvaria (MC3T3-E1).**	**Wang et al. [8]**

Treatment	Results	Author
Plasma treatment + Radiation		
EUV + (low temperature Nitrogen/Oxygen)	**In-vitro: Decreased contact angle and increased cell adhesion of MG63 cells, Cell adhesion higher with Nitrogen plasma**	**Czwartos et al. [9]**
Oxygen/UV	**In-vitro: Increase in the bond strength to TiO_2 sol solution after exposure to O2 plasma/UV radiation**	**Kizuki et al. [10]**
Plasma + Chemical treatment		
Argon + Hydrofluoric acid	**In-vitro: Decreased contact angle and increased cell proliferation and differentiation of rBMS cells (Higher with Nitrogen)** **In-vivo: Increased resistance to *Porphyromonas gingivalis* (*P. gingivalis*)**	**Chen et al. [11]**
Argon/(Argon + Hydrogen peroxide)	**In-vitro: Increased cell adhesion, collagen secretion, and extra-cellular matrix deposition (Higher with Argon, Peroxide combination)** **In-vivo: Increased fibrous tissue filtration inhibition and osseointegration with Argon, Peroxide combination**	**Ouyang et al. [12]**
Plasma + Laser		
Oxygen + Nd:YAG	**In vitro: Decrease in contact angle**	**Akkan et al. [13]**
Plasma + Biomolecules/Inorganic coating		
Argon + Polydopamine (PDA) + Vancomycin gelatin nanoparticles	**In vitro: No cytotoxicity and increased antibacterial resistance to *Staphylococcus aureus* (*S. aureus*) and *Streptococcus mutans* (*S. mutans*)**	**Chen et al. [14]**
Nitrogen + Tropoelastin	**In vitro: Increased bioactivity of osteogenic cells**	**Wakelin et al. [15]**
Nitrogen + PDA + Poly (lactic-co-glycolic acid) carrying Bone Morphogenic Protein-2 (BMP-2) gene	**In vitro: Increased osteogenic activity**	**Qin et al. [16]**
(Argon/Oxygen) + Acrylic acid vapours + Polystyrene sulfonate (PSS) and polyallylamine hydrochloride (PAH) multilayers	**In vitro: Increased adhesion and proliferation of bone marrow stromal cells** **In vivo: Increased osseointegration**	**Liu et al. [17]**

As evident from the studies, plasma treatments are utilized as a pre-treatment for several other surface treatments. Oxygen plasma was tested with various forms of radiation, whereas Argon plasma was combined with various chemical treatments. However, the rationale for the preference for such combinations could not be deciphered. Considering the decrease in contact angle and increase in the bioactivity of PEEK, nitrogen plasma was found to be most suited for implant applications of PEEK. Plasma treatments and sulphonation are the most common surface treatments used to increase the surface energy of PEEK to receive a bioactive coating. The two treatments are also used extensively together. In addition to increasing the surface energy and hydrophilicity of the surface, plasma immersion ion implantation also increases the hardness of the surface [18]. This property may decrease the tribological wear of orthopaedic implants due to gliding surfaces but is not important for dental implants [19]. However, due to the nature of electromagnetic radiation, plasma treatments are restricted by line-of-sight limitations. Therefore, it is difficult to utilize plasma for modifying implants with complex geometry [20].

1.2. Accelerated Neutral Atom Beam (ANAB)

Accelerated Neutral Atom Beam (ANAB) is a technique for employing an intensely directed beam of neutral gas atoms that improves the bioactivity of PEEK without altering its chemical or mechanical properties. Studies have demonstrated a decreased contact angle and increased bioactivity of osteogenic cells in response to ANAB-treated PEEK in-vitro [21][22][23][24] and an increased bond strength to bone in-vivo [22], as shown in **Table 2**. An in-vitro decrease in the bacterial colonization of Methicillin-resistant *Staphylococcus aureus* (*MRSA*), *Staphylococcus epidermidis* (*S. epidermidis*), and *Escherichia coli* (*E.coli*) have been demonstrated following treatment of PEEK with ANAB [23]. Though ANAB has exhibited significant improvement when used as a solitary treatment, its synergy with other treatments is yet to be tested. ANAB-

treated PEEK surfaces are capable of osteoblast differentiation following osteoinduction in an osteogenic medium. However, ANAB-treated PEEK surfaces have not demonstrated independent osteoinduction ability [24].

Table 2. Results of ANAB of PEEK.

Treatment	Result	Author
ANAB	**In vitro: Decreased contact angle and increased bioactivity of osteogenic cells**	**Khoury et al. [21]**
ANAB	**In vitro: Increased wettability and cell adhesion, spreading, proliferation, and differentiation of SAOS-2 osteoblasts** **In vivo: Increased bond strength to bone**	**Khoury et al. [22]**
ANAB	**In vitro: Improved osteoblastic response and decrease in bacterial colonization of *MRSA*, *S. epidermidis*, and *E. coli***	**Webster et al. [23]**
ANAB	**In vitro: Decreased contact angle and increased bioactivity of osteogenic cells**	**Ajami et al. [24]**

1.3. Photodynamic Treatment

Photodynamic treatment is primarily a therapeutic approach to decrease the microbial load on the surface. It involves the introduction of a drug on the surface of the biomaterial, followed by irradiation with a laser beam. It has been proven to decrease the microbial load and can be used in cases of inflammation around PEEK implants [25][26] (as given in **Table 3**). However, any potential role of photodynamic treatment in improving osseointegration in the absence of a periodontal pathology is yet to be investigated. However, significant improvements are required in light sources, absorption rates, and penetrating abilities of photosensitizers to decrease the exposure time required to modify PEEK surfaces with photodynamic treatment [26].

1.4. Sandblasting

Sandblasting is a widely used procedure in the surface treatment of titanium implants. It was broadly used when the surface roughening of implants was first advocated to enhance osseointegration. It is a process of physically roughening the surface by subjecting it to a stream of abrasive particles. This method has been shown to increase the proliferation and differentiation of mesenchymal stem cells and also to mitigate inflammatory mediators around the implant [27] (**Table 3**). As observed in titanium implants, blasting is one of the most widely used surface treatments but is insufficient to improve tissue response and bone-implant contact. [18] Due to the advent of newer physical methods to treat PEEK surfaces, sandblasting has been restricted as a pre-treatment before the application of a bioactive coating.

1.5. Laser

A femtosecond laser can be employed to induce periodic grooves on the surface of the PEEK implant, which improves the surface characteristics. Xie et al. confirmed that the PEEK surface after exposure to a femtosecond laser showed increased adhesion, proliferation, and differentiation of mouse bone marrow mesenchymal stem cells (mBMSC) cells and increased expression and activity of alkaline phosphatase [28] (**Table 3**). However, these findings will require substantiation with in vivo studies.

Table 3. Results of photodynamic therapy, sandblasting, and laser on PEEK.

Treatment	Result	Author
Photodynamic therapy		
(Temporfin/Ampicillin) + Diode laser	**In vitro: Increase in resistance to microbial load**	**Peng et al. [26]**
PDT/Sulphuric acid (H_2SO_4)/Air abrasion (Al/Diamond)	**In vitro: Lower shear bond strength and microroughness of samples treated with PDT as compared to H_2SO_4 and Alumina particle air abrasion (Highest: H_2SO_4)**	**Binhasan et al. [25]**
Sandblasting		
Alumina particles	**In vitro: Increased proliferation and differentiation of rat MSCs and mitigation of inflammatory chemokine (C-C motif) Ligand 2 (CCL2)**	**Sunarso et al. [27]**
Laser		

Treatment	Result	Author
Femtosecond laser	**In vitro: Increased adhesion, proliferation and differentiation of mBMSC cells and increased expression and activity of alkaline phosphatase**	**Xie et al. [28]**

2. Chemical Treatment

2.1. Sulphonation

One of the most common surface treatments employed for PEEK, sulphonation, involves the exposure of the surface to concentrated sulphuric acid. (H_2SO_4). The term 'sulphonation' refers to the exposure to H_2SO_4 as well as its removal from the surface by an alkali, although in some studies it has been used exclusively for the exposure to the acid.

Studies demonstrating the exposure time of H_2SO_4 have yielded conflicting results; however, most studies have employed an exposure time of 3–5 min. Ma et al. proved that an exposure time of 5 min to 98% sulphuric acid yielded optimal surface topography [29]. Cheng et al. demonstrated that a 3 min sulphonation decreased the contact angle and increased pre-osteoblastic activity [30]. On the other hand, Wang et al. found that a short exposure time of 30 s was optimal for decreasing the contact angle of PEEK; however, the longest time of exposure in the study was only 90 s [31]. If an additive coating will be applied after sulphonation, the time of exposure is determined by the other treatments used in the combination, as well as the nature of the coating. The time of exposure is a critical factor as the chemical composition of PEEK, which imparts superior mechanical properties to PEEK, gets altered as a function of time.

There is a statistically significant influence of sulphonation on the contact angle of PEEK. This phenomenon makes sulphonation acceptable as a pre-treatment before the application of a surface coating on PEEK. Furthermore, sulphonation has been extensively used in combination with plasma treatment for activation of the PEEK surface to receive organic and inorganic coatings and continues to be the most studied chemical treatment for the PEEK surface.

2.2. Phosphonation

Phosphonation is the introduction of a phosphate group on the surface of a biomaterial. Various methods, such as diazonium chemistry and polymerization of Vinyl phosphonic acid, have been used to graft the functional group on the surface of PEEK, which has increased cell adhesion, spreading, proliferation, and differentiation in vitro and the bone–implant contact ratio in vivo [32][33][34]. It serves as an optimal surface treatment, but the compatibility of phosphonation with other treatments will have to be assessed.

2.3. Silanization

Silanization is the introduction of a silane group to an object or surface. Silanization is utilized to improve the surface characteristics of materials like glass and metal oxides. It has been proven to increase the cell adhesion, spreading, proliferation, and differentiation of pre-osteoblasts in vitro, but in vivo studies confirming the same are not available.

3. Surface Coatings

3.1. Hydroxyapatite Coating

Hydroxyapatite (HA) is the main inorganic component of the human bone; hence, it is intuitive to incorporate HA on the surface of PEEK to increase its bioactivity. HA has regularly been employed as a surface treatment to increase the bioactivity of metallic implants. However, the temperature required to incorporate HA is higher than the temperature range at which PEEK is chemically stable. Hence, in most studies, an intermediate layer of Titanium or Yttria Stabilized Zirconia (YSZ) was used to shield PEEK from thermal insult [35][36][37] (**Figure 1**). The thickness of the intermediate layer has been found to influence the coating's bond strength to PEEK. [37] HA coating is thermally treated to transform it into a crystalline state from an amorphous bioinert state. This finding is consistent with the fact that HA found in the human bone occurs in a crystalline state. In terms of bioactivity and bone strength to PEEK, heat-treated crystalline HA outperformed untreated amorphous HA [35][36][37][38] (**Table 4**).

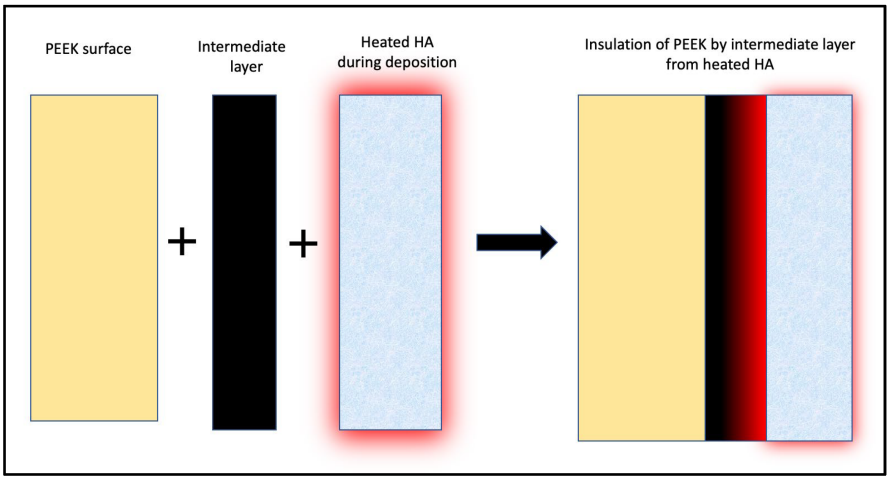

Figure 1. Insulation of PEEK by Titanium or YSZ intermediate layer from heated HA during crystallisation process.

Table 4. Results of Hydroxyapatite coating on PEEK.

Treatment	Result	Author
Surface coatings—Hydroxyapatite		
Hydroxyapatite	**In vivo: Increased removal torque and biocompatibility**	**Johansson et al. [38]**
[Hydroxyapatite/(Hydroxyapatite + Microwave annealing)] + YSZ intermediate layer	**In vitro: Increased cell adhesion and proliferation with Hydroxyapatite crystallization with microwave annealing**	**Rabiei et al. [36]**
Hydroxyapatite + Titanium intermediate layer + Hydrothermal treatment	**In vitro: Bond strength of HA with PEEK with <10 nm Ti layer greater than that with >50 nm Ti layer**	**Ozeki et al. [37]**
[Hydroxyapatite/(Hydroxyapatite + Microwave annealing + Autoclaving)] + YSZ intermediate layer	**In vitro: Increased cell adhesion and proliferation with Hydroxyapatite crystallization with heat treatment**	**Durham et al. [35]**

3.2. Titanium Coating

Titanium is the most widely used implant biomaterial due to its biocompatibility and osseointegration potential. The phenomenon of osseointegration was also accidentally discovered using titanium when titanium chambers that were used for studying the circulation of a healing fibula in a rabbit could not be removed due to their fusion with the bone [39]. A stable layer of titanium dioxide is formed on the surface of titanium on exposure to air [40][41]. This oxide layer has a high dielectric constant, which leads to the adsorption of proteins from blood on the surface, which is the first step in the cascade of events leading to osseointegration. Therefore, a coating of titanium or titanium oxide on the surface of PEEK would give the implant the favorable mechanical properties of PEEK and the higher bond strength of titanium with bone. In vitro studies have shown an increase in adhesion, proliferation, and differentiation of pre-osteoblasts in reaction to a titanium coating. In vivo studies have also inferred that the coating increases osseointegration and bond strength with bone (**Table 5**).

Table 5. Results of Titanium coating on PEEK.

Treatment	Result	Author
Surface coatings: Titanium		
Titanium [Pre-treated with grit blasting + Vacuum plasma (element unspecified)]	**In vitro: Increased proliferation and differentiation of MC3T3-E1 cells** **In vivo: Increased osseointegration**	**Liu et al. 2021 [42]**
Titanium + alkali treatment	**In vitro: Increased adhesion and proliferation of pre-osteoblasts**	**Yang et al. [43]**
(Oxygen plasma/Sandblasting) + Titanium sol + Hydrochloric acid	**In vitro: Increased cell response** **In vivo: Increased osseointegration**	**Shimizu et al. [44]**

Treatment	Result	Author
Titanium dioxide (Pre-treatment: Argon ion + Titanium layer)	**In vivo: Increased osseointegration and bond strength in pull-out test**	**Tsou et al. [45]**

3.3. Anti-Microbial Agent Coating

Anti-microbial coatings like gentamycin and selenium have been used in vitro [46][47] as well as in vivo [46] in combination with a carrier agent. These coatings have also been shown to increase the bioactivity of PEEK in addition to its antimicrobial activity against microbes, such as *S. aureus* and *Pseudomonas aeruginosa* (*P. aeruginosa*), as shown in **Table 6**. However, the sustainability of the release of these agents will have to be titrated against the complexity of the surface treatments to determine their feasibility. Additional studies quantifying antimicrobial action as a function of time are required to establish the durability of these coatings in an in vivo environment.

Table 6. Results of anti-microbial agent coatings on PEEK.

Treatment	Results	Author
Surface coatings—Antibiotic agents with carrier		
Brushite + Gentamycin sulphate	**In vitro: Sustained biocompatibility and increased proliferation and differentiation of pre-osteoblastic cells** **In vivo: Increased antimicrobial resistance and osseointegration**	**Xue et al. [46]**
Antimicrobial peptide (AMP) of GL13K/[AMP of GL13K + 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)]	**In vitro: Increased antibacterial activity against *S. aureus***	**Hu et al. [48]**
Red selenium nanorods/Gray selenium nanoparticles	**In vitro: Increased antimicrobial activity to *P. aeruginosa***	**Wang et al. [47]**

3.4. Biomolecule Coating

Anti-inflammatory agents such as dexamethasone have been used to combat acute and chronic inflammatory responses of the body to noxious stimuli. Combinations of dexamethasone with other anti-inflammatory agents like interleukin-6 (IL-6) or metal-organic frameworks like Zn-Mg-MOF-74 have been proven to increase the anti-inflammatory response and antimicrobial activity of PEEK, respectively [49][50] (**Table 7**). Dexamethasone can be used as an implant coating in cases where the prognosis is compromised due to decreased local host immunity to infections, as supported by the current evidence.

3.5. Polymer Coating

A coating of polymers like 2-methacryloyloxyethyl phosphorylcholine (MPC) on PEEK surfaces has been studied and shown to decrease the contact angle of PEEK, increase its wettability, and facilitate osseointegration [51] (**Table 7**). However, in vivo demonstration of the increase in hydrophilicity has not been documented.

Table 7. Results of biomolecule and polymer coatings on PEEK.

Treatment	Results	Author
Surface coatings—Biomolecules		
Dexamethasone + Nitrogen plasma treatment + IL-6	**In vitro: Decreased peri-implant inflammatory mediators** **In vivo: Increased osseointegration**	**Xie et al. [49]**
Zn−Mg-MOF-74 + Dexamethasone	**In vitro: Increased antimicrobial activity against *S. aureus* and *E. coli* and angiogenic ability** **In vivo: Increased antimicrobial activity and angiogenic ability and osseointegration**	**Xiao et al. [50]**
Surface coatings: Polymers		
2-methacryloyloxyethyl phosphorylcholine (MPC)	**In vitro: Decrease in contact angle**	**Kyomoto et al. [51]**

4. Composites of Poly (Ether-Ether-Ketone)

Composites of PEEK with various metals, oxides, inorganic fibers, and polymers have been used for improving the clinical performance of individual constituent biomaterials. The selection of material to be used with PEEK and the method of fabrication depend on the intended use of the implant. However, the main purpose of combining PEEK with other biomaterials is to improve the mechanical properties, with the improved surface characteristics being a by-product of the combination. Moreover, most composites of PEEK require an additional surface treatment for osseointegration. An exception in the following studies is a composite of HA and PEEK that did not require additional surface treatment and increased the adhesion, proliferation, and differentiation of pre-osteoblasts (**Table 8**), though in vivo studies are missing to substantiate the same. Most composites of PEEK are carbon-fiber reinforced PEEK (CFR PEEK) composites, which always require additional additive treatments for osseointegration.

Table 8. Composites of PEEK and surface treatments.

Treatment	Results	Author
PEEK + Poly (ether imide) +Titanium dioxide coating	**In vitro: Antibacterial resistance against gram-positive and gram-negative bacteria**	**Díez-Pascual et al. [52]**
3D printed PEEK + crystalline Hydroxyapatite	**In vitro: Increased adhesion, proliferation and differentiation of pre-osteoblasts and osteogenesis**	**Oladapo et al. [53]**
Carbon reinforced PEEK + Zirconium ions using PIII	**In vitro: Increased bioactivity of mBMSC cells and increased expression and activity of alkaline phosphatase, increased antibacterial activity against *S. aureus*, no effect against *E. coli***	**Li et al. [54]**
Carbon reinforced PEEK + H_2SO_4 + Oxygen plasma + Calcium phosphate	**In vitro: Increased precipitation of apatite nuclei in SBF medium**	**Yamane et al. [55]**
Carbon reinforced PEEK + H_2SO_4 + Dopamine HCl + Titanium carbide	**In vitro: Evidence of photothermal antibacterial activity and cytocompatibility** **In vivo: Evidence of osseointegration**	**Du et al. [56]**
Carbon reinforced PEEK + H_2SO_4 + Calcium chloride	**In vitro: Increased precipitation of apatite nuclei in SBF**	**Miyasaki et al. [57]**
Carbon reinforced PEEK + H_2SO_4 + Oxygen plasma + amorphous Calcium phosphate	**In vitro: Increased precipitation of apatite nuclei in SBF medium**	**Yabutsuka et al. [58]**
Carbon reinforced PEEK + H_2SO_4 + Hydroxyapatite	**In vitro: Decrease in contact angle**	**Asante et al. [59]**

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