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Graphical Abstract

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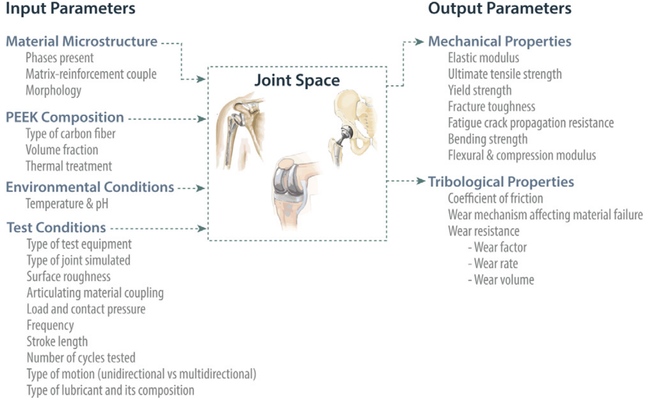

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Review article

An overview of the tribological and mechanical properties of PEEK and CFR-PEEK for use in total joint replacements

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ABSTRACT

Poly-ether-ether-ketone (PEEK) and PEEK composites are outstanding candidates for biomedical applications, such as orthopedic devices, where biocompatibility and modulus match with surrounding tissue are requisite for long-term success. The mechanical properties can be optimized by incorporating fillers such as continuous and chopped carbon fibers. While much is known about the mechanical and tribological behavior of PEEK composites, there are few articles that summarize the viability of using PEEK reinforced with carbon fibers in orthopedic implants. This paper reviews biocompatibility, tribological, and mechanical studies on PEEK and their composites with carbon fibers, notably PEEK reinforced with polyacrylonitrile (PAN)-based carbon fibers and PEEK reinforced with pitch-based carbon fibers, for application in orthopedics and total joint replacements (TJRs). The main objectives of this review are two-fold. Firstly, this paper aims to assist designers in making informed decisions on the suitability of using PEEK and PEEK composites in orthopedic applications; as it is not well understood how these materials perform on the whole in orthopedics and TJRs. Secondly, this paper aims to serve as a centralized paper in which researchers can gain information on the tribological and mechanical advancements of PEEK and PEEK composites.

1. Introduction

With an increase in life expectancy, patients demand orthopedic devices implanted into the body through total joint arthroplasty (TJA) surgeries, to last several decades in the body to minimize the number of revision surgeries over the patient's lifetime (Kurtz et al., 2009; Kremers et al., 2015). While a ten year implant lifetime was the standard at the inception of these devices (Kurtz et al., 2005), patients are now expecting more mobility and more cycles on their joints as the age demographics of patients is trending towards younger populations (Kurtz et al., 2009). This puts the implant at risk for premature failure since the original designs and selection of materials were for sedentary populations, but for the past few decades these implants have catered to a more active population.

In total joint replacement (TJR) surgery, a damaged joint is removed and replaced with a metal, plastic, or ceramic device. However, TJA designs can have the following material couplings: metal-on-metal (MacDonald, 2004), metal-on-ceramic (Bal et al., 2006), metal-on-polymer, ceramic-on-polymer (Bal et al., 2006), ceramic-on-ceramic (Clarke, 1992). Additionally, the fixation stem is usually composed of titanium or cobalt-chrome. While these materials are commonly found in TJA, they are far from being the perfect material. For instance, the go-to polymeric material is Ultra High Molecular Weight Polyethylene (UHMWPE), but it is challenged by wear, oxidation, and fatigue failures in the body (Ansari et al., 2016; Kurtz, 2009). Moreover, the metallic load bearing components are prone to stress shielding, resulting in bone resorption from the modulus mismatch between the surrounding bone and implant. Alongside, there is an ongoing concern of metal particles inside the body due to wear, corrosion, or fatigue failure of components as well as metal ion release culminating in metallosis (Kerner et al., 1999; Archibeck et al., 2000; Willis-Owen et al., 2011).

Therefore, materials such as carbon fiber reinforced (CFR) Poly-ether-ether-ketone (PEEK) have been proposed to replace the articulating and the load bearing portion of the device (Kurtz and Devine, 2007). PEEK is a polymer widely used in medical applications due to its biocompatibility and chemical stability, high toughness, fatigue resistance, and ability to tailor its mechanical properties to match those of bone (Kurtz, 2012b). There are several ways for designers to tailor the mechanical properties such as: thermal treatments (e.g. annealing) and adding a filler material (e.g. carbon fibers, β-tricalcium phosphate, titanium (Ti), calcium silicate (CS), hydroxy-apetite (HA), strontium containing hydroxyapetite, and nano-fluorohydroxyapetite

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(nano-FHA)) (Regis et al., 2017; Monich et al., 2016). Only certain fillers are appropriate for load-bearing orthopedic applications (Abdullah et al., 2015). In this review, the main focus will be on PEEK and PEEK reinforced with pitch-based and PAN-based carbon fibers for use in load bearing and articulating surfaces of TJRs. Unless otherwise specified, the aforementioned will be referred to as PEEK and PEEK composites in this article.

There are notable advantages to using CFR-PEEK over UHMWPE and metal-based biomaterials in TJRs, for instance, PEEK is able to maintain its mechanical properties during commonly employed sterilization processes such as gamma, steam autoclave, vaporized hydrogen peroxide, and ethylene oxide up to a certain number of cycles (Solavy, 2017; Kumar et al., 2018). Furthermore, using CFR-PEEK as a load bearing material to replace metallic components, may reduce stress shielding and bone resorption since the modulus will be a closer match to bone (de Ruiter et al., 2021), while also addressing long-term concerns of metals in the body. Using PEEK can mitigate allergic reactions to those patients with metal sensitivity (Thyssen et al., 2009). Lastly, the radiolucency of CFR-PEEK may enable in vivo imaging and monitoring of device (Kurtz and Devine, 2007). It is noteworthy to mention here that PEEK composites behave differently from their cross-linked counterparts. Thermoset systems may abrade but offer limited plastic deformation. Bio-active glass fiber-reinforced thermosets have been successfully employed in cranial implants (Aitasalo et al., 2014; Posti et al., 2016; Piitulainen et al., 2015). These thermosetting systems offer improved stiffness and osseointegration but have not been utilized in orthopedic bearing systems owing to their greater propensity for higher contact stresses and fracture. PEEK resins offer tailorable plasticity though the overall mechanical properties are linked to crystalline domain size, annealing conditions, and the degree of adhesion with reinforcing fibers (Bonnheim et al., 2019; Regis et al., 2018). It also comes with the caveat that there are still ongoing concerns surrounding carbon fiber debris from CFR-PEEK (Stratton-Powell et al., 2016), which warrants more research in this domain.

PEEK and PEEK composites have mechanical properties that can become an alternative material in TJRs. However, stringent assessment of the mechanical, biological, and tribological properties is needed to ensure its efficacy and suitability to serve in articulating and load bearing applications. Therefore, this review collects and critically assesses the existing research on mechanical, tribological, and biocompatibility research of PEEK composites to verify the validity of using these materials as articulating or load bearing applications. This review differs from the current literature (reported in Table A.1 in the Appendix) as it aims to bring PEEK and PEEK composites to the forefront of orthopedic bearing devices. This is accomplished by taking a deep dive into the biological and tribo-mechanical characteristics of PEEK and PEEK composites and in the process, generating a centralized resource to aid researchers, medical device engineers, and designers, who can then make informed decisions on orthopedic device-related matters. To the best of the authors' knowledge, this would be the first-of-its-kind review exclusively devoted towards the compilation and in-depth analysis of the bio-tribo-mechanical property literature of PEEK and CFR-PEEK, as a means to evaluate their feasibility in TJR.

2. PEEK and PEEK composites overview

PEEK is a dominant member of the polyaryletherketones (PAEK) family, which was introduced in the 1980s for use in trauma, orthopedic, and spinal implants (Kurtz and Devine, 2007). Prior to that, PEEK was already commercially used in aircraft and turbine blades (Kurtz and Devine, 2007). The arrival of PEEK coincided with the development of isoelastic hip stems and fracture fixation plates with stiffness comparable to bone (Kurtz and Devine, 2007). By the 1990s, PEEK emerged as the leading thermoplastic candidate for replacing metal implants, with an emphasis in orthopedics and trauma application. Shortly after, in 1998, PEEK was commercially offered as a biomaterial for implants (Kurtz and Devine, 2007). The wide range of applications PEEK has to offer is a testament to the microstructure of PEEK, enabling desirable mechanical behavior, manufacturability, resistance to chemical and radiation damage, and biocompatibility (Blundell and Osborn, 1983).

2.1. *Material overview — structure and morphology*

PEEK is a semicrystalline polymer, whose chemical structure consists of an aromatic molecular backbone, along with combinations of ketone and ether functional groups between the aromatic rings (Blundell and Osborn, 1983) as shown in Fig. 1(a). The large aromatic units inhibit chain mobility, thereby requiring large amounts of thermal energy for chain motion (Kumar et al., 1986). Thus, PEEK has a high glass transition temperature of 143 °C, a high melting temperature (343 °C) and is stable at room and body temperature (Bonnheim et al., 2019).

Through this distinct chemical structure, PEEK exhibits stable chemical and physical properties: chemical as well as wear resistance and stability at high temperatures, resistance to structural degradation resulting from sterilization. The mechanical properties of PEEK depend on the crystalline structure, chemical architecture, and morphology (Kurtz, 2012a). PEEK has a phase separated microstructure consisting of an amorphous and a crystalline phase (Kumar et al., 1986). The crystallinity content of PEEK can be controlled through thermal processes. Depending on the processing conditions, it can be up to 43% crystalline, but 30%–35% crystallinity is more common in medical devices (Kurtz, 2012a; Blundell and Osborn, 1983; Reitman et al., 2012). The crystalline domains are generally lamellar in structure and organize into spherulites (Kumar et al., 1986). Techniques to enhance the crystallinity are usually done by slow cooling from the molten state and annealing. The fillers, such as carbon fibers, affect the morphology by altering the geometry of crystalline domains of the PEEK matrix (Reitman et al., 2012). Fig. 1(b) illustrates the microstructure of PEEK reinforced with carbon fiber, imaged by scanning electron microscopy (SEM).

The fiber type in CFR-PEEK has an impact on the elastic modulus (pitch-based ~12.5 GPa and PAN-based ~18.5 GPa) and on ultimate tensile strength (pitch-based ~145 MPa and PAN-based ~192 MPa) for equivalent weight percent of fiber (Bonnheim et al., 2019). These can be adjusted by changing the weight percent of fiber, among other things. Additionally, PAN-based PEEK composites show better wear and friction properties than pitch-based at high pressures and low speeds (1 m/s) in a pin-on-disc wear experiment (Flöck et al., 1999). A schematic evincing the differences between the microstructures of the two different types of CFR-PEEK composites (i.e. pitch- vs. PAN-based) has been sketched in Fig. 1(c).

2.2. *Applications*

The majority of current applications of PEEK within medical treatments are for orthopedic trauma internal fixation devices (Ma et al., 2021). The first medical use of PEEK, and now widely accepted, was for use as spinal implants (Kurtz and Devine, 2007; Kurtz, 2012b). CFR-PEEK has also been used as fracture fixation plates with promising results (Kurtz and Devine, 2007; Rotini et al., 2015; Schliemann et al., 2015). CFR-PEEK has the potential to eliminate stress shielding in applications such as femoral stems but is still undergoing research (Bonnheim et al., 2019). PEEK is also starting to be adopted in dental medicine and is a growing field of research (Rahmitasari et al., 2017; Schwitalla et al., 2015; Schwitalla and Müller, 2013). For example, PEEK composites are undergoing further study for use in implant abutment and implant body (Rahmitasari et al., 2017).

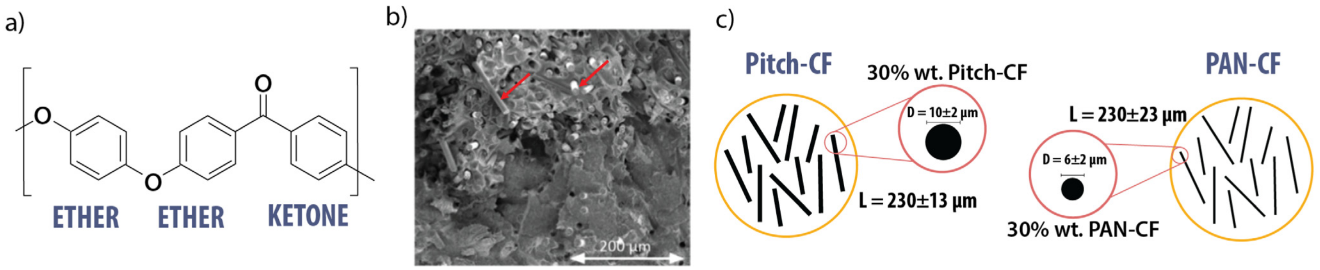

Fig. 1. (a) Chemical structure of PEEK molecule. (b) SEM image of a fractured surface of a CFR-PEEK composite (Arevalo and Pruitt, 2020). The white colored fibers are the carbon fiber reinforcements, marked by the red arrows in the diagram. (c) A schematic demonstrating the differences between pitch-based and PAN-based CFR-PEEK microstructures.

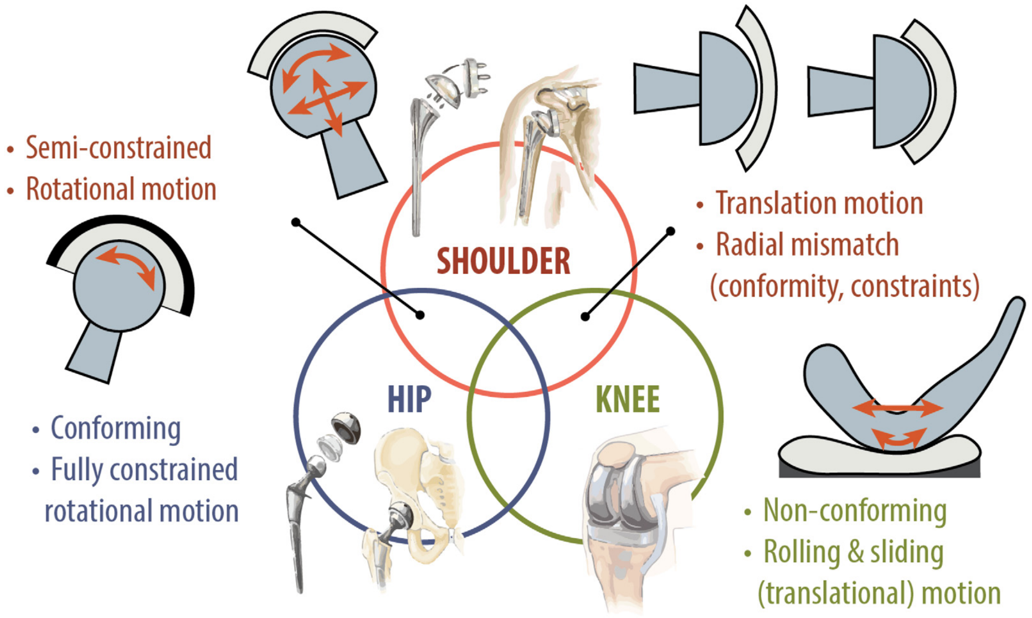

Fig. 2. The stresses and conformity variations across TJRs; and the biomechanical differences and similarities between the shoulder, hip, and knee joints. Hip joints are the most constrained while the knee is the least constrained. Knee and shoulder display translational motion and a radial mismatch. Shoulder and hip display rotational motion. The knee joint is the least conforming joint and thus displays a sliding motion.

3. Tribo-mechanical properties

Carbon fiber type, volume fraction, and thermal history inform the mechanical and tribological properties of PEEK and PEEK composites. Literature in this section demonstrates how wide ranging testing methodologies and a lack of standardization lead to conflicting results. The literature highlights the need for tailoring testing conditions towards the specific type of joint being studied, i.e., knee, shoulder, or hip. The conformity differences and similarities are highlighted in Fig. 2. Most notable are the differences in rotational and translational motion between joint types. In general, the design requirements of a material used in a specific orthopedic application vary depending on the location. This is because there is significant variation in the loading pattern experienced in each joint space. Regardless of the location however, a good candidate material for orthopedic joint replacement must meet certain basic requirements such as biocompatibility, wear resistance, low friction, and high impact toughness. This section will delve into the mechanical properties (monotonic, fatigue, nanoindentation) and tribological properties (wear) of PEEK and PEEK composites.

3.1. Mechanical properties

This section focuses on the mechanical properties of interest for TJR applications and the results obtained by numerous researchers, using different testing methodologies (Dworak et al., 2017; Bonnheim et al., 2019; Kim et al., 2013; Arevalo and Pruitt, 2020; Regis et al., 2017; Qin et al., 2019). A summary of the experiments performed in these studies is detailed in Table 1. For instance, Dworak et al. (2017) studied the dynamic performance of layered PEEK composites. The authors found no signs of degradation induced by the simulated body fluid, suggesting that this was potentially due to the cyclic load frequency used (50 Hz and 1 Hz). Furthermore, the dynamic test to failure conducted in bending and compression modes did not show a significant difference in the material's performance, with the exception of the case where all fibers are aligned, which decreased the mechanical strength after 10^6 fatigue cycles by about 10%. However, for all the composites tested under dry ambient conditions, the bending strength ranged from 416.8 to 780.6 MPa, with the upper value being similar to that of the titanium-based alloys used in TJR. Flexural and compression modulus (both ranged from 19 to 38 GPa) are similar to that of cortical bone, making these composites an ideal candidate for structural implants in orthopedic applications.

Bonnheim et al. (2019) investigated the elastic properties and fatigue crack propagation (FCP) behavior of PEEK and PEEK composites, as well as the effect of annealing on the FCP behavior. Their experimental results demonstrated the superiority of PAN-based PEEK over pitch-based PEEK in terms of the monotonic elastic modulus and the ultimate tensile strength (UTS) as shown in Fig. 3. In terms of FCP, PAN-CFR-PEEK exhibited a higher resistance compared to the unfilled and pitch-based PEEK composite as illustrated in Fig. 4. Moreover,

Table 1
Summary of mechanical experiments.

Material	Type of test	Conditions	Ref
Layered PEEK composites (CF) (cross ply 0/90, +/−45, multidirectional and 1D fibers)	Static (3-point- bending, axial compression) and 10^6 cycles under cyclic flexural or compression loads	Dry and simulated body-fluid (pH 6.5, 37 °C)	Dworak et al. (2017)
PEEK (unfilled) and PEEK composites (PAN and Pitch)	Monotonic and cyclic loading	Ambient	Bonnheim et al. (2019)
PAN PEEK with different CF orientations and thermal pretreatments vs CFR/Epoxy	Tension, compression, and short beam	Ambient	Kim et al. (2013)
PEEK and composites (thermally pretreated and untreated)	Nanoindentation	Ambient	Arevalo and Pruitt (2020)

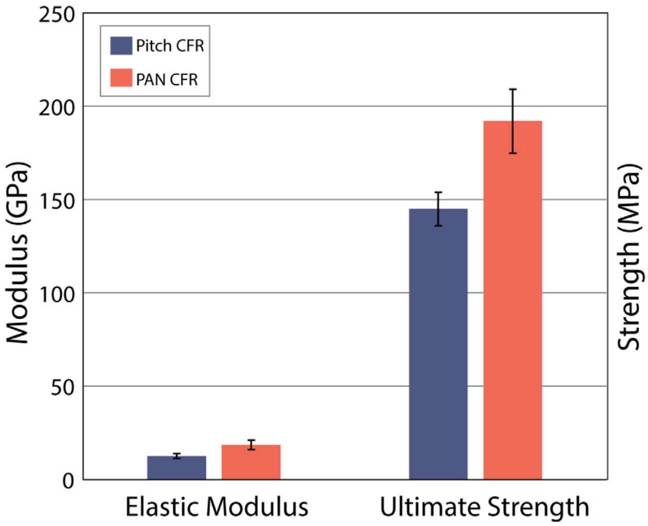

Fig. 3. Elastic modulus and ultimate tensile strength comparison of pitch-based and PAN-based CFR.
Source: Data from Bonnheim et al. (2019).

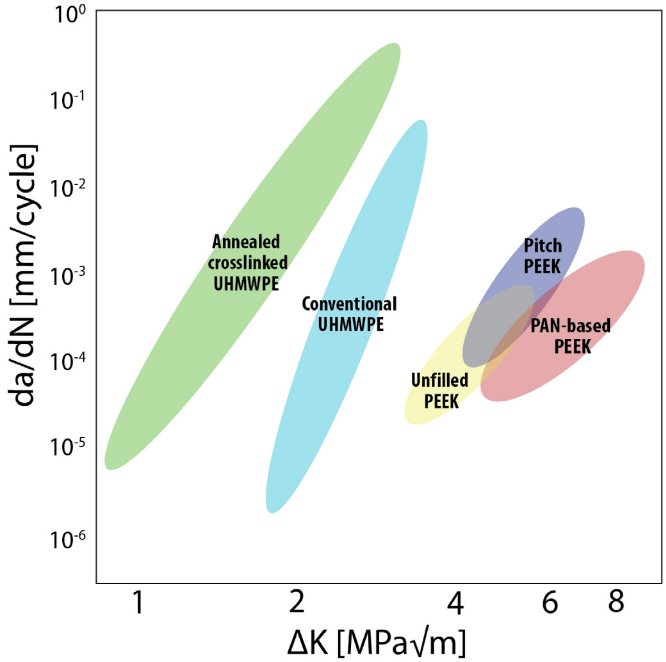

Fig. 4. FCP plot of PEEK and PEEK composites compared with UHMWPE.
Source: Data compiled from Bonnheim et al. (2019), Gencur et al. (2006).

the annealed versions of PAN-CFR-PEEK showed further improvements in FCP resistance compared to the unfilled and pitch-based annealed samples.[2] These differences in the results were attributed to the cumulative effect of the following factors: (1) PAN-based CFR is stiffer than pitch-based CFR, (2) more PAN-based CFR are present compared to pitch-based CFR for the same wt.%, and (3) potentially the presence of more CFR surface area for bonding in case of PAN-based CFR-PEEK.

Kim et al. (2013) studied the mechanical behavior of heat treated PAN-based CFR-PEEK and CFR-Epoxy as alternative materials for artificial hip replacement. The composites had different ply configurations ranging from (0), (+/−45)(0/90)(+/−45) to (+/−45). The [(0)6] configuration exhibited considerably higher strength than the other configurations for both the matrix materials tested. The CFR-PEEK composites showed higher tensile strength (~800 MPa) and compressive strength (~600 MPa) when juxtaposed against the epoxy composites and its heat treated versions.

Understanding the nanoscale behavior of these materials as they interact within the body at all possible length scales is paramount since the nanoscale phenomena affect the long-term integrity and biocompatibility of the implant as well as influence the macro-scale behavior. Although, there is a dearth of research in this realm, Arevalo and Pruitt (2020) evaluated the mechanical behavior of PEEK and PEEK composites in their untreated and thermally treated forms. The methodology they adopted involved conducting nanoindentation using conospherical tips of two different diameters, in order to determine the nanoindentation modulus at different length scales and thereafter, establish a correlation to previously gathered microindentation data (Regis et al., 2017; Arevalo and Pruitt, 2020). The results unequivocally showed that nanoindentation using a smaller spherical tip is an effective characterization tool to understand small scale fiber–matrix interactions and to optimize the composite properties for eliciting the desired behavior for orthopedic implant applications. In Arevalo's study, the PAN-based composite exhibited higher nanoindentation elastic modulus in its heat treated and untreated versions compared to the unfilled and pitch-based PEEK composite samples tested, thereby reaffirming the superiority of PAN-based CFR-PEEK vis-a-vis pitch-based PEEK composites.

3.2. *Tribological properties*

It is evident from the literature that there exists a correlation between the results (wear performance, coefficient of friction (COF), other tribological parameters of interest) and the type of tribological testing methodology employed, best illustrated through Fig. 5. For

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[2] To propagate a crack at a da/dN = 2×10^4 mm/cycle, ΔK for pitch-based and unfilled samples were 4.7 vs. 4.8 MPa$\sqrt{m}$ respectively, compared to 7.0 MPa$\sqrt{m}$ for PAN-based samples.

instance, the wear rate obtained using linear reciprocating or unidirectional pin-on-plate wear testing equipment was radically different when the same material (UHMWPE) was tested under the same test conditions using a modern hip joint simulator predicated on multi-axial motion (Wang et al., 1997). The literature also highlights the limitations of the conventional wear testing (i.e. pin-on-plate) technique. *In-vitro* pin-on-plate wear testing is not representative of the intricate joint bearing/sliding material interactions. Particularly when the *in-vitro* tests or joint simulators use only unidirectional linear motion, which radically alters the wear mechanism and is significantly different from the *in-vivo* experience (Wang et al., 1998a), where cross-shear and multi-directional motion dominate. Hence, custom equipment have been created without standardization to simulate the knee joint and the hip joint.

Tables A.2 and A.3 in the Appendix of this article compile an array of *in-vitro* tribological tests conducted on PEEK and PEEK composites. While Table A.2 provides a comprehensive tabulation of each study's objectives and results, Table A.3 focuses primarily on the experimental conditions and tribological testing parameters utilized in these studies. In particular, the latter table gleans the tribological material coupling, the type of CFR-PEEK as well as its composition, the mode of *in-vitro* testing used, and which joint was being simulated alongside the lubricant used (if any) and test temperature. Given the wide diversity of testing parameters involved and the lack of uniformity between them, there is an urgent need to standardize these tests, which implies establishing a set protocol involving the material against which PEEK or PEEK composites articulate in the tribological test, the lubricant used and its composition, test temperature, load, frequency of testing, sliding distance or number of wear cycles tested, amongst many other parameters of interest. The lack of standardization across different research groups and medical-device organizations also drives home the need for more uniformity in equipment. Having more uniform standards for tribo-testing equipment as well as testing parameters would make it easier to compare the tribological performance of different sets of material couplings utilized for orthopedic bearing applications.

It has been observed that for PEEK and PEEK composites articulating against zirconia-toughened alumina, low carbon and high carbon cobalt-chromium-molybdenum, UHMWPE, and self-mating couples (i.e. PEEK on PEEK), there is evidence to suggest that PEEK composites' wear rates are comparable to that of the conventional configurations with UHMWPE (Scholes and Unsworth, 2007, 2009; Evans et al., 2014; Koh et al., 2019; Cowie et al., 2020; Scholes and Unsworth, 2010; Joyce, 2005). Additionally, a few studies have reported other polymers (i.e. highly cross-linked polyethylene - HXLPE) that demonstrate better wear resistance when articulating against PEEK (East et al., 2015). So while the aforementioned tribological trends had initially pointed towards utilizing PEEK and PEEK composites as a potential substitute for UHMWPE in TJR applications, several studies have suggested otherwise. Testing PEEK and PEEK composites against Co-Cr in low conformity knee simulators (which are more representative of the real-life *in-vivo* experience) resulted in higher wear rates. Furthermore, there have been reports of PEEK and its composites' mechanical failure (delamination and cracking) vis-a-vis UHMWPE's performance under similar testing conditions. This has led to the inference that PEEK and PEEK composites would not be suitable candidates for replacement of UHMWPE under these low-conformity total knee replacement (TKR) applications (Brockett et al., 2017; Grupp et al., 2010).

It is interesting to note here that conflicting results have been found in hip simulator investigations. Lower wear rates were observed in PEEK composites articulating against Co-Cr and zirconia ceramic heads with and without lubrication (Wang et al., 1998b; Brockett et al., 2012; Polineni et al., 1998) with specific configurations (30 wt.% pitch-based CFR PEEK against zirconia ceramic head) having wear rates nearly two orders of magnitude lower than UHMWPE/metal and UHMWPE/ceramic couplings. In addition, Kandemir et al. (2019) have clearly evinced that there is no significant difference in wear rates when PEEK composites are tested under different contact stresses (similar to that of natural hip joints) with a pin-on-flat scenario, although there are definitely reservations concerning the use of a pin-on-disk setup to evaluate the true tribological performance for reasons explained previously. Moreover, it was observed that the Co-Cr discs articulating against PEEK composites experienced a reduction in weight, pointing towards metallic wear. In the long run, this could potentially culminate in metallosis.

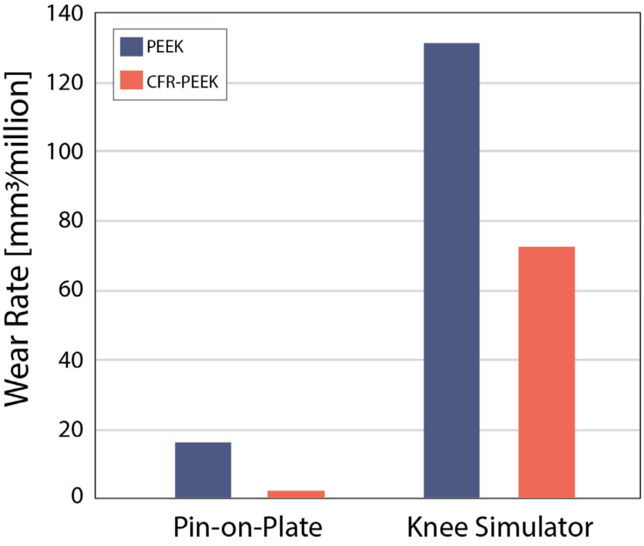

Fig. 5. Comparison of wear rate results obtained with pin-on-plate and knee simulator for PEEK and CFR-PEEK.
Source: Adapted from Koh et al. (2019).

Authors have investigated the effect of ambient test conditions by attempting to simulate the joint's biological environment, i.e. under dry vs. wet conditions (Polineni et al., 1998; Regis et al., 2018). For instance, Regis et al. (2018) tested PEEK and annealed PAN- and pitch-based PEEK composites against alumina spheres on a pin-on-flat test in two lubrication regimes, i.e. dry and bovine serum. Under dry ambient conditions, the experiments revealed that PEEK composites have improved wear resistance in comparison to the unfilled formulation. The wear rate reduction under lubricated conditions is much higher in the unfilled formulation vis-a-vis the CFR-PEEK composites. However, the wear rate is still much higher for the unfilled formulation in comparison to the composites. Additionally, the annealed versions of the materials under-performed in terms of wear resistance with respect to the non-annealed versions. This can be attributed to the increase in crystallinity and material strength resulting in deleterious effects on the wear rate; a hardened structure obtained through annealing (annealing increases crystallinity and consequently hardness and strength) enhances the second-body abrasion, generating more wear debris and in turn, culminating in higher wear volume. Further, it was observed that these effects were diminished in the samples tested with bovine serum.

In terms of the effect of CFR content, Flöck et al. (1999) found that when testing PEEK composites on a pin-on-disc wear machine at two different sliding velocities, the 10% pitch-based CFR and 10% PAN-based CFR exhibited outstanding friction and wear characteristics, except at high sliding velocities. Moreover, they noticed that with an increase in the weight percentage of the fiber reinforcements, there was a concomitant increase in the abrasive wear rate, applicable to both the PEEK composite formulations. However, when probing the wear behavior in a high-stress line-contact reciprocating wear machine, Wang et al. (1999) found that the smaller wear rates resulted for CFR content of 30% and that they were lower in pitch-based CFR PEEK (against alumina) than in the PAN-based counterpart at 10% and 50%. Despite the initial success with pitch-based CFR PEEK composites against alumina,

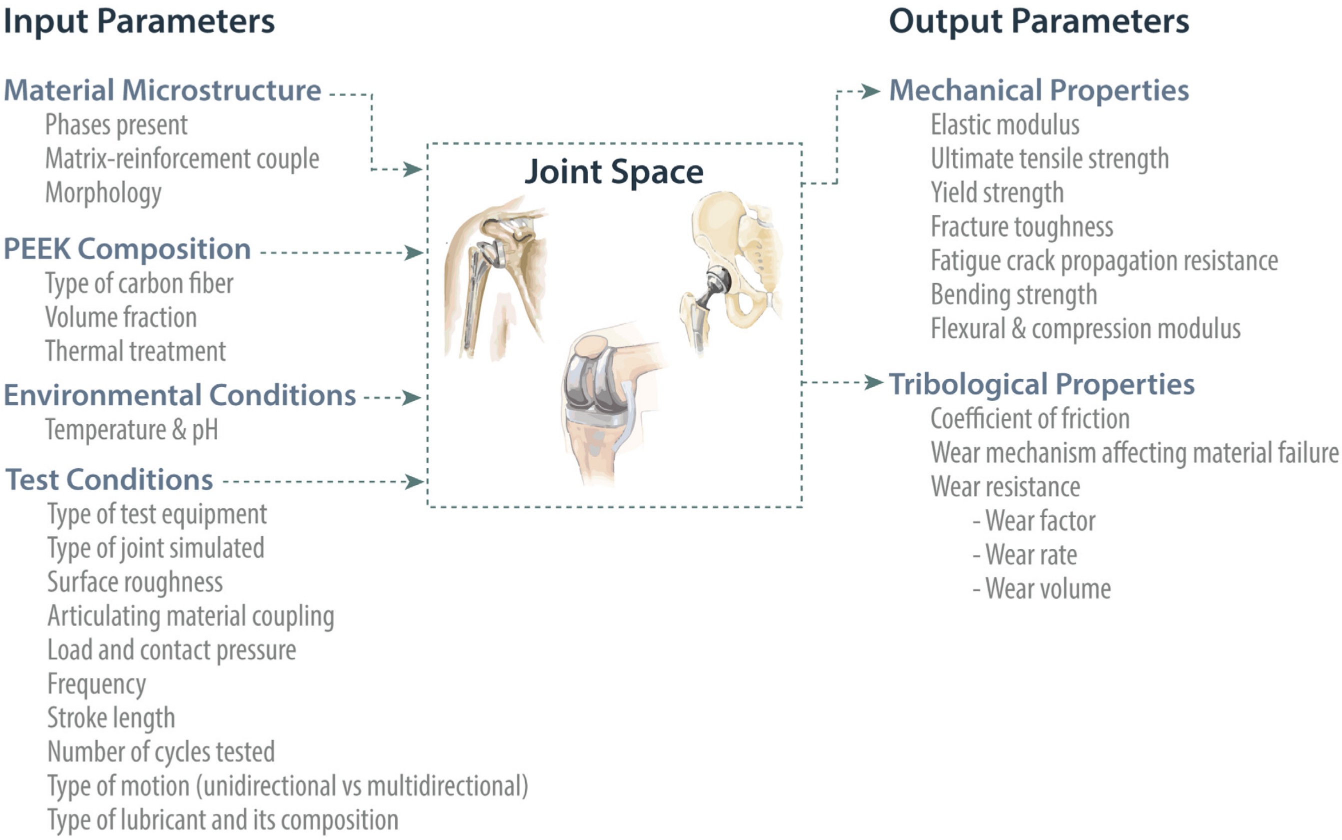

Fig. 6. Illustration to demonstrate the key input and output parameters of interest in the tribo-mechanical landscape of PEEK and PEEK composites.

their wear rates were still an order of magnitude higher than those of UHMWPE articulating against CoCr (control), reiterating the caveat concerning using CFR-PEEK composites as a substitute to UHMWPE in high-stress non-conforming situations such as those experienced in TKR. On the other hand, when tested in a ball-in-socket hip simulator, the best material combination was 30% pitch-based CFR PEEK and zirconia femoral head, for which the wear rates were one to two orders of magnitude lower than those of PAN-based composites, unfilled PEEK, and UHMWPE sliding against CoCr and alumina heads.

PEEK behaves like many thermoplastic polymers and is capable of plastic deformation, delamination, adhesion, and abrasive wear mechanisms. Regis et al. (2018) have observed plastic deformation of the polymer matrix within the PEEK composites. Debris formation and delamination were noted when wear tests were performed in bovine serum. For CFR-PEEK, researchers noted some evidence of fiber rupture; yet, fibers remained embedded within the polymer matrix. Differences in crystallization mechanisms between PAN- and pitch-based CFR-PEEK contribute to differences in interfacial bond strength as a function of annealing, even for similar crystallinity (Regis et al., 2017). Similar findings were observed under crack propagation conditions where PAN fibers offered substantially improved fatigue resistance owing to improved interface adhesion (Bonnheim et al., 2019).

A useful way to visualize the tribo-mechanical landscape of PEEK and PEEK composites is through a parametric table, illustrated in Fig. 6. Based on all the references compiled in Tables A.2 and A.3 in the Appendix of this article, all the parameters of interest in the design space have been classified into either input or output parameters. The tribo-mechanical properties of PEEK and PEEK composites (output parameters) cannot be altered directly, but can be affected indirectly by tailoring other parameters of interest (input parameters) such as the material's microstructure, its composition, the articulating material coupling, as well as the testing and environmental conditions under which the experiments are performed (Flöck et al., 1999; Scholes and Unsworth, 2007, 2009; Evans et al., 2014; Cowie et al., 2020; Scholes and Unsworth, 2010; East et al., 2015; Brockett et al., 2017; Grupp et al., 2010; Wang et al., 1998b; Brockett et al., 2012; Polineni et al., 1998; Kandemir et al., 2019; Regis et al., 2018; Wang et al., 1999; Chamberlain et al., 2019; Brockett et al., 2016). The definitions are as follows: input parameters (also known as control parameters) are the ones which can be controlled directly during experiments while the output parameters can be indirectly influenced by adjusting the input parameters but there exists no way to alter them through a direct route. Therefore, to optimize the tribo-mechanical performance of the material, there is a need to repeatedly undertake parametric studies to decipher not only the individual but also the synergistic effect of the input parameter(s) and to optimize the performance from the vantage of tribo-mechanical behavior of PEEK and PEEK composites. It is equally important to emphasize that Fig. 6 attests to the multi-factorial nature of PEEK's tribo-mechanical landscape. The multi-factorial (multiple input-multiple output) system implies that each input parameter influences a majority of, if not all of the output parameters. On a similar note, to optimize any of the tribo-mechanical properties, one can circle back to any and all input parameters and tailor them accordingly. The aforementioned tables provide a comprehensive account of the existing studies in the literature encompassing the input–output relationships while also stating the objectives and results from each of those studies.

4. Biocompatibility and toxicity

In this review, the biocompatibility literature pertaining to PEEK and PEEK composites is explored at various length-scales and the different modalities for evaluating biocompatibility of a material are presented. A biocompatible material will be stable in the biological ambience prevalent inside the body and will not exhibit cytotoxicity, mutagenicity, or carcinogenicity. Literature has shown that PEEK is neither cytotoxic nor mutagenic (Katzer et al., 2002; Wenz et al., 1990;

Morrison et al., 1995). This has been demonstrated using tests, such as, hypoxanthine–guanine–phosphoribosyl-transferase test (HPRT) test, direct contact cell culture evaluation (ASTM F813 American Society for Testing and Materials, 2012), tetrazolium dye-based colorimetric assay (MTT assay) (Sgouras and Duncan, 1990), the Ames test (Ames et al., 1975), etc. Furthermore, PEEK is biocompatible in the bulk form (Williams et al., 1987; Scotchford et al., 2003; Wenz et al., 1990; Jockisch et al., 1992; Morrison et al., 1995; Cook and Rust-Dawicki, 1995; Toth et al., 2006; Nieminen et al., 2008; Petillo et al., 1994) and demonstrates the ability to stay relatively inert in other aggressive media, for instance, aerospace and high moisture environments (Cogswell and Hopprich, 1983).

However, the biocompatibility of a material is dependent on the length scale of the foreign particles, not just their presence in the bulk form. Thus, a material that is biocompatible in bulk might not be at the micron or sub-micron level, particularly in the phagocytozable size range (~0.1–10 μm). More so for particles in the size range <1 μm which tend to exhibit the maximum biological reactivity (Glant and Jacobs, 1994; Green et al., 1998, 2000; Matthews et al., 2000a,b; Shanbhag et al., 1995; Stratton-Powell et al., 2016). An immunological response is nonetheless elicited for any foreign particle irrespective of its size, with a stronger response being provoked by smaller particles (<2 μm) (Zysk et al., 2005). This immunological response is often also accompanied by inflammation (Zysk et al., 2005). In light of this, biocompatibility tests need to consider the entire spectrum of particles' sizes before a material can be certified as biocompatible and consequently used in an implant for a medical device application.

The biocompatibility of any implant material is influenced by wear particles' size (Green et al., 1998, 2000; Gelb et al., 1994), mass distribution (Ingram et al., 2002), material type (Hallab et al., 2012; Rader et al., 1999; Shanbhag et al., 1995; von Knoch et al., 2004; Glant and Jacobs, 1994), dosage/concentration of wear particles at the implant site (Green et al., 2000; Ingram et al., 2002; Matthews et al., 2000a), surface area and volume of the wear debris formed (Shanbhag et al., 1994; Gelb et al., 1994), their morphology (Gelb et al., 1994), composition (Glant and Jacobs, 1994), and volume fraction of carbon fiber reinforcement particles (pitch and PAN) (Lorber et al., 2014; Utzschneider et al., 2010). Numerous studies support PEEK and PEEK composites as biocompatible (Scotchford et al., 2003; Wenz et al., 1990; Katzer et al., 2002; Williams et al., 1987; Rivard et al., 2002; Jockisch et al., 1992; Hallab et al., 2012; Howling et al., 2003; Morrison et al., 1995; Cook and Rust-Dawicki, 1995; Cunningham et al., 2013; Utzschneider et al., 2010; Latif et al., 2008; Grupp et al., 2014; Bao et al., 2007; Toth et al., 2006; Nieminen et al., 2008; Petillo et al., 1994). However, a couple of studies have concluded otherwise (Lorber et al., 2014; Khonsari et al., 2014). The aforementioned biocompatibility investigations have inherent methodology variations such as testing *in-vivo* (Cunningham et al., 2013; Grupp et al., 2014; Latif et al., 2008) or *in-vitro* (Scotchford et al., 2003; Hallab et al., 2012; Howling et al., 2003; Morrison et al., 1995; Katzer et al., 2002; Petillo et al., 1994). Even within *in-vivo* explorations, biocompatibility can be evaluated via animal studies such as in rats (Williams et al., 1987; Latif et al., 2008; Petillo et al., 1994), rabbits (Williams et al., 1987; Rivard et al., 2002; Jockisch et al., 1992; Cunningham et al., 2013; Grupp et al., 2014), mice (Lorber et al., 2014; Utzschneider et al., 2010), sheep (Toth et al., 2006; Nieminen et al., 2008), dogs (Jockisch et al., 1992; Cook and Rust-Dawicki, 1995), baboons (Bao et al., 2007) or via clinical trials in humans (Pace et al., 2004; Khonsari et al., 2014; Pace et al., 2008, 2005a,b). Another classification for *in-vivo* biocompatibility tests arises from whether the material being evaluated was used directly as a bulk implant/ fixation device at the specific site (Jockisch et al., 1992; Cook and Rust-Dawicki, 1995; Bao et al., 2007; Pace et al., 2004, 2008) or through the use of a subcutaneous implantation such as a pouch inside an animal's body (Latif et al., 2008; Williams et al., 1987), in which wear is not taken into consideration.

The most pertinent classification for biocompatibility is based on the length scale, i.e. biocompatibility in bulk form vs at the particulate level. As mentioned previously, PEEK and PEEK composites have long been established as biocompatible in the bulk form (Williams et al., 1987; Scotchford et al., 2003; Wenz et al., 1990; Jockisch et al., 1992; Morrison et al., 1995; Cook and Rust-Dawicki, 1995; Toth et al., 2006; Nieminen et al., 2008; Petillo et al., 1994). Therefore, their presence in the macro-form inside the human body is less likely to cause adverse effects than in the sub-micron form. More recently, studies have delved deeper into the micron and sub-micron length scales (Hallab et al., 2012; Grupp et al., 2014; Cunningham et al., 2013; Lorber et al., 2014; Utzschneider et al., 2010; Rivard et al., 2002). The biocompatibility literature for PEEK suggests a lack of research devoted exclusively towards particles at the nano-scale. Since PEEK and PEEK composites are often modeled as a substitute for other polymeric materials of interest such as UHMWPE, results from PEEK's biocompatibility tests are often reported in relative terms. In this regard, parameters like cytotoxicity (Howling et al., 2003; Morrison et al., 1995), cellular (Jockisch et al., 1992) and macrophage responses (Hallab et al., 2012), histopathological responses (Cunningham et al., 2013), cytokine expression (Lorber et al., 2014; Hallab et al., 2012), inflammation (Latif et al., 2008; Utzschneider et al., 2010), growth of osteoblasts and fibroblasts (Morrison et al., 1995), histological parameters (Jockisch et al., 1992; Utzschneider et al., 2010; Grupp et al., 2014), alkaline phosphate activity (Scotchford et al., 2003), percent LDH activity per unit surface area (Wenz et al., 1990), number of secreted cells (Petillo et al., 1994), bone contact and interface shear strength (Cook and Rust-Dawicki, 1995), immunocytochemical characteristics (Cunningham et al., 2013) are compared between PEEK and the current standard polymer, Ultra High Molecular Weight Polyethylene (UHMWPE).

Any material that is used in TJR applications will invariably produce wear particles in the long run. Therefore, to find a suitable substitute for UHMWPE, the material must outperform or at the very least, be at par with the current gold standard on the biocompatibility front. PEEK and PEEK composites have demonstrated that they are on par or better than UHMWPE in a majority of studies (Hallab et al., 2012; Jockisch et al., 1992; Howling et al., 2003; Cunningham et al., 2013; Utzschneider et al., 2010; Latif et al., 2008; Grupp et al., 2014). Comparative biocompatibility tests have not been limited to only PEEK vs UHMWPE, but rather include PEEK's biocompatibility being juxtaposed against that of Ti6Al4V (Scotchford et al., 2003), polysulfone composite (Wenz et al., 1990), epoxy resin polymer (Morrison et al., 1995), Ti-coated PEEK (Cook and Rust-Dawicki, 1995), carbon–carbon composites (Howling et al., 2003), and polyetherurethane ureas (PEUU), polydimethylsiloxane (PDMS) and polyetherimide (PEI) (Petillo et al., 1994) with mixed results.

The literature overwhelmingly supports the biocompatibility claim for PEEK and PEEK composites, both in the bulk (or direct implant) form as well as in the particulate form (refer to Table A.4 in the Appendix) while clearly pointing to the need for more targeted studies aimed at ascertaining their biocompatibility at the nano-level. This paves the way for future researchers to explore the biocompatibility of nano-particles produced by PEEK and PEEK composites.

5. Conclusions

This review highlights the numerous limitations, and a deep divide between, clinical studies and mechanical testing of PEEK and PEEK composites. A major limitation to bringing PEEK and PEEK composites for orthopedic applications is the lack of retrieval studies. Further, the lack of mechanical testing standard and inability to replicate *in-vivo* conditions, makes it challenging to definitively recommend as a replacement to current TJR materials. While simulating *in-vivo* conditions could improve development time of implants, a few challenges arise: matching the behavior of bodily fluids to dynamically react to changes in loads, pH, viscosity, and temperature. Hence, making it difficult to replicate the dynamic lubrication regime observed in a human body within a laboratory without the use of a test subject. This reveals a gap in the existing literature pertaining to the complex parameters impacting the lubrication regime.

This is especially critical for assessing wear as conflicting literature complicates design decisions. While there are conflicting results from different testing methodologies, the fiber content does affect the wear rate. Additionally, vast majority of the literature has shown that CFR-PEEK has a higher wear rate than UHMWPE under high-stress nonconforming contact conditions as is the case of the knee joint. On the other hand, although a reduction of wear rate of the polymeric material is desirable, even more problems arise when the metallic couplings are worn. This can lead to a whole different type of biological reaction, hence a final decision on PEEK composite suitability also depends on the study of material coupling combination.

This review aggregates the expansive number of studies that assess the biocompatibility of PEEK and PEEK composites, both in the bulk and particulate form (micron and sub-micron ranges). Simultaneously, this review identifies the need for more detailed investigations into the biocompatibility of PEEK and its composites at the nano-level, which remains rather unexplored. It can also be observed that there are innumerable variables impacting biocompatibility test conditions such as testing environment (*in-vivo* vs *in-vitro*), the use of animals vs humans studies, the site of implantation, the potential application, and the biological parameters that are being used to assess the biocompatibility of the said materials.

A majority of experiments indicate that PEEK composites are more appropriate for hip rather than knee implants. But the lack of research regarding clinical trials or retrieval analysis, make it challenging to definitively state that PEEK composites will be the new go-to material in the future. Based on the limitations presented (Li et al., 2015), the authors of the present paper cannot present a final recommendation for PEEK or PEEK composite knee implants. While research findings and studies remain inconclusive, PEEK and PEEK composites warrant further exploration as candidate biomaterials for enhanced longevity in orthopedic devices.

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.

Data availability

No data was used for the research described in the article.

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Appendix

A.1. Review articles on PEEK

See Table A.1.

A.2. Tribological experiments references

See Tables A.2 and A.3.

Table A.1
Table highlighting the relevant review articles discussing Poly-ether-ether-ketone (PEEK) for use in medical applications.

Reference	Year	Aim
Li et al. (2015)	2015	Assesses the performance of carbon fiber reinforced-PEEK, specifically as an implant material for arthroplasty systems.
Abdullah et al. (2015)	2015	The review discusses the biomechanical and bioactivity challenges for utilizing PEEK and PEEK composites in orthopedic implants.
Monich et al. (2016)	2016	Reviews the mechanical and biological behavior of PEEK composites for biomedical applications.
Lvhua et al. (2017)	2017	Reviews the research progress and status in the aspects of preparation, mechanical properties, and biological performance of these PEEK matrix with bio-active ceramics for hard tissue implant, and predicts its future development.
Liao et al. (2020)	2020	Reviews recent advances in the development, preparation, bio-compatibility, and mechanical properties of polyetheretherketone (PEEK) and its composites for hard and soft tissue engineering.
Verma et al. (2021)	2021	Documents the development of PEEK as a biomaterial and highlights the major advancement and breakthroughs.
Ma et al. (2021)	2021	Reviews research progress of performance requirements, material development, and material surface modification of PEEK as an orthopedic implant, and discusses future advancement of medical PEEK materials.

Table A.2
A compilation of tribological experiments regarding PEEK and PEEK composites for use in orthopedic applications.

Reference	Test	Objectives and results
Wang et al. (1998b)	Hip simulator	• The objective of this research was two-fold (1) identifying the tribological performance of CFR-PEEK composite as a bearing surface for total hip replacement and (2) developing a CFR-PEEK composite acetabular cup that outperformed, in terms of wear resistance, the gold standard couples UHMWPE/Metal and UHMWPE/ceramic. • A suitable wear couple was identified as a 30 wt% pitch-based carbon fiber reinforced PEEK composite acetabular insert articulating against zirconia ceramic head.

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Table A.2 (*continued*).

Reference	Test	Objectives and results
Wang et al. (1999)	Hip Simulator and Reciprocating wear test	• The CFR-PEEK composites exhibited a poor wear performance in high stress non-conforming contact situation. • The CFR-PEEK composites exhibited improved wear performance (over UHMWPE against metal or ceramic) in a conforming ball-in-socket arrangement. • Pitch-based carbon fibers outperformed PAN-based carbon fibers. Further, it was observed that ceramic heads were superior to metal heads (under a conforming system).
Flöck et al. (1999)	Pin-on-disc	• Pitch-based carbon fibers exhibited lower mechanical properties in comparison to PAN-based carbon fibers. • It was observed that pitch-based carbon fibers had a different friction and wear property profile, in comparison to PAN-based carbon fibers.
Scholes and Unsworth (2007)	Pin-on-plate	• The motive behind this study was to assess the tribological suitability of different articulating material combinations for use in joint couplings. • It was seen that CFR-PEEK Optima articulating against ceramic yields lower wear factors in comparison to metal-on-metal couplings. • Key takeaway was that PEEK-on-ceramic may perform well in joint applications.
Scholes and Unsworth (2009)	Pin-on-plate	• This research was aimed at identifying which material combination(s) do well in joint applications. • The material combination of CFR-PEEK articulating against ceramic yielded lower wear debris, in comparison to a metal-on-metal coupling, when tested under the same tribological conditions.
Grupp et al. (2010)	Knee wear simulator	• This research endeavor evaluated the suitability of two types of CFR-PEEK for potential use in fixed bearing unicompartmental knee articulations. • CFR-PEEK was found to be unsuitable as a bearing material for fixed bearing knee articulations. • Similarly, pitch-based CFR-PEEK was also not suitable as it did not reduce wear in comparison to polyethylene. • The baseline of CoCr-on-PE was used in all the comparative studies as a reference when evaluating the overall performance of CFR-PEEK and its tribological results.
Brockett et al. (2012)	Hip simulator	• The study explored the wear rate of CFR-PEEK (pitch-based), and observed improved wear resistance when articulating against BioloxDelta ceramic and Co-Cr heads.
Evans et al. (2014)	Pin-on-plate	• The wear performance of CFR-PEEK articulating against Zirconia-Toughened Alumina (ZTA) ceramic was investigated and the key research finding was that the wear behavior is strongly dependent on the applied contact stresses. It was further noted that increasing the stress, resulted in a concomitant increase in the wear rate. • The researchers suggested that CFR-PEEK against ZTA is best suited for low stress situations such as in hip joints, and cautioned against the use of this system in high stress situations like the knee joint replacement.
East et al. (2015)	Pin-on-plate	• The researchers involved in this project addressed the suitability of using CFR-PEEK and HXLPE as a potential joint couple. • Their key takeaway was that the orientation of the carbon fibers substantially influenced the wear factors, obtained through thorough tribological investigations.
Brockett et al. (2017)	Knee wear simulator	• The aim of this experimental investigation was to gauge the wear performance of PEEK and CFR-PEEK composites in a low conformity system simulating the total knee replacement. • CoCr femoral bearings articulating against PEEK and CFR-PEEK inserts were closely studied for achieving the goals of this study. • High wear rates for both materials (PEEK and CFR-PEEK composites), along with evidence of cracking and material failure in the wear region were noticed. • Based on the wear performance, the study concluded that these aforementioned materials may not be suitable alternatives for UHMWPE in low-conformity designs scenarios.
Regis et al. (2018)	Pin-on-flat	• This study considered the lubricant film formation as an important and relevant factor when examining the wear phenomena in PEEK or CFR-PEEK against Al_2O_3 couple. • Their results led them to deduce that wear reduction is larger in unfilled material than for pitch-based CFR-PEEK and PAN-based CFR-PEEK under lubricated conditions (bovine serum lubrication). • Moreover, they noted that annealing treatments negatively affected the wear resistance of all tested PEEK formulations, under dry lubricant conditions. • They inferred that the carbon fiber reinforced material exhibited improved wear resistance, in comparison to unfilled PEEK.
Kandemir et al. (2019)	Pin-on-disc	• Their experiments revealed that CFR-PEEK culminated in lower wear rates vis-a-vis UHMWPE and cross-linked UHMWPE. • Furthermore, the wear rates of the pin did not significantly change across different contact stresses and this turned out to be one of their key conclusions from this tribological evaluation utilizing a pin-on-disk setup.

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Table A.2 (*continued*).

Reference	Test	Objectives and results
Brockett et al. (2016)	Pin-on-plate	• The series of tribological studies performed by them investigated the effect of three parameters of interest on the wear factor of PEEK, CFR-PEEK, and UHMWPE, i.e. contact pressure, cross-shear, and counterface material, with the objective of deciphering if PEEK and/or CFR-PEEK could be potentially used as a substitute for UHMWPE in TJR systems. • The wear tests performed in this study ranked the wear factor of PEEK articulating against CoCrMo much higher than that obtained for CFR-PEEK and UHMWPE. • Wear factors attained for PEEK and CFR-PEEK increased concomitantly with increasing contact pressure and reducing contact area. • With regards to the cross-shear influence, PEEK demonstrated dependence on the degree of cross-shear whereas it had a very marginal effect on wear behavior of CFR-PEEK. • On a similar note, counterface arrangement markedly affected PEEK but did not have any influence on the wear characteristics of CFR-PEEK. This can be attributed to the randomly-oriented carbon fibers in CFR-PEEK which precluded any reorientation as seen in PEEK, thereby preventing any cross-shear dependency.

Table A.3
Summary of tribological experiments: tribo-couple, test equipment, and testing conditions.

Bearing material and composition	Counter-bearing material	*In-vitro* test equipment	Type of joint being simulated	Lubricant and test temperature	Ref
CFR-PEEK (10–30 wt% Pitch and 10–30 wt% PAN CFR-PEEK)	100Cr6 steel disc	Pin-on-disk	–	Graphite and PTFE, 150 °C and ambient temperature	Flöck et al. (1999)
CFR-PEEK (CFR-PEEK-OPTIMA PAN and Pitch)	Ceramics BioLox Delta (75% Alumina, 25% Zirconia) and BioLox Forte (100% Alumina)	Four station Multi-directional pin-on-plate using rotational and reciprocation motion	–	Bovine Serum, 37 °C	Scholes and Unsworth (2007)
PEEK (PEEK-OPTIMA) and CFR-PEEK (CFR-PEEK PAN and Pitch)	Low-carbon and High-carbon Co-Cr-Mo alloy	Four station Multi-directional pin-on-plate using rotational and reciprocation motion	–	New born calf serum, 37 °C	Scholes and Unsworth (2009)
CFR-PEEK (30 wt% Pitch CFR-PEEK)	Ceramic BioLox Delta (75% Alumina, 25% Zirconia)	Four station pin-on-plate using rotational and reciprocation motion	Hip and Knee	New born calf serum, 37 °C	Evans et al. (2014)
PEEK (PEEK-OPTIMA)	UHMWPE	Six-station multi-axial pin-on-plate reciprocating rig	Knee	Bovine serum, ambient temperature	Cowie et al. (2020)
PEEK (PEEK-OPTIMA), CFR-PEEK (PAN and Pitch)	PEEK-OPTIMA against itself, CFR-PEEK against itself	Four station Multi-directional pin-on-plate using rotational and reciprocation motion	–	New born calf serum, 37 °C	Scholes and Unsworth (2010)
PEEK (PEEK-OPTIMA) and CFR-PEEK (30 wt% Pitch CFR-PEEK)	Highly Cross-linked Polyethylene	Four-station pin-on-plate machine	Fingers, hips	Newborn calf serum	East et al. (2015)
PEEK (Unfilled PEEK) and CFR-PEEK (30 wt% Pitch CFR-PEEK)	Co-Cr-Mo alloy	Six-station force–displacement controlled knee simulator	Knee	Newborn calf serum	Brockett et al. (2017)
CFR-PEEK (30 wt% Pitch and 30 wt% PAN CFR-PEEK)	$CoCr_{29}Mo_6$	Customized four-station servo-hydraulic knee wear simulator	Knee	Newborn calf serum	Grupp et al. (2010)
PEEK (Unfilled PEEK) and CFR-PEEK (10–30 wt% PAN and 30 wt% Pitch CFR-PEEK)	CoCr, Alumina, and Zirconia	Eight station Multi-directional motion hip simulator system	Hip	Bovine Serum, 33 ± 3 °C	Wang et al. (1998b)
CFR-PEEK (Pitch CFR-PEEK) and UHMWPE	Ceramic BioLox Delta (75% Alumina, 25% Zirconia) and CoCr	10-station Prosim hip wear simulator and single station pendulum friction simulator	Hip	Water and bovine serum	Brockett et al. (2012)
CFR-PEEK (30 wt% Pitch CFR-PEEK) and UHMWPE	Zirconia	Multistation (8-station) hip joint simulator	Hip	Bovine calf serum	Polineni et al. (1998)

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Table A.3 (*continued*).

Bearing material and composition	Counter-bearing material	*In-vitro* test equipment	Type of joint being simulated	Lubricant and test temperature	Ref
CFR-PEEK (30 wt% carbon filled PEEK)	CoCr	50-station pin-on-disc machine	Hip	Newborn calf serum	Kandemir et al. (2019)
PEEK (Unfilled PEEK) and CFR-PEEK (30 wt% Pitch and 30 wt% PAN CFR-PEEK)	Alumina	Pin-on-flat	–	Dry and Bovine Serum, 37 ± 2 °C	Regis et al. (2018)
CFR-PEEK (0–50 wt% Pitch and 0–50 wt% PAN CFR-PEEK)	CoCr, Alumina, and Zirconia	High-stress line-contact reciprocating wear tester and Low-stress ball-in-socket hip simulator	Knee and Hip	Bovine calf serum	Wang et al. (1999)
PEEK (PEEK-OPTIMA)	PEEK against itself and against Stainless Steel 316L	Four station Pin-on-Plate rig with both unidirectional and multi-directional motion	Knee and Hip	Newborn calf serum	Chamberlain et al. (2019)
PEEK (PEEK-OPTIMA), CFR-PEEK (30 wt% Pitch CFR-PEEK), and UHMWPE	CoCrMo	Multidirectional pin-on-plate wear simulator	Knee and Hip	Newborn bovine serum	Brockett et al. (2016)

Table A.4
Biocompatibility literature.

Bulk or particulate	Composite formulation	Type of study	Biocomp-atiliblity	Potential application	Reference
Bulk	PAN (30%)	In-vitro	Yes	Replace metal alloys in orthopedic applications	Wenz et al. (1990)
	30% chopped PAN CFR-PEEK	In-vivo, Animal study (rabbits and dogs)	Yes	Fracture Fixation Plates	Jockisch et al. (1992)
	PEEK	In-vivo, Animal study (sheep)	Yes	Spinal Implants	Toth et al. (2006)
	PEEK	In-vivo and in-vitro, Animal study (sheep)	Yes	Spinal Implants	Nieminen et al. (2008)
	PEEK	In-vivo, Animal study (rats)	Yes	Monolithic Implants	Petillo et al. (1994)
	mix of PEEK, tricalcic phosphate (-TCP) and titanium di-oxide (TiO_2)	In-vivo, Human Study (three cases)	No	Dental Implants	Khonsari et al. (2014)
	PEEK	In-vivo and in-vitro, Animal study (baboons)	Yes	Disc arthroplasty device	Bao et al. (2007)
Particulate	Both 30% Pitch and 30% PAN	In-vivo and in-vitro, Animal study (mice)	No	Knee implants	Lorber et al. (2014)
	PEEK	In-vitro	Yes	metal-on-polymer, bearing surfaces	Hallab et al. (2012)
	PEEK	In-vivo, Animal Study (Rabbits)	Yes	Spinal Implants	Rivard et al. (2002)
	PAN	In-vitro	Yes	Load Bearing Surfaces for Artificial Hip Joints	Howling et al. (2003)
	Both (30% Pitch and 30% PAN CFR-PEEK)	In-vitro, knee simulator and in-vivo, Animal study (mice)	Yes	Load Bearing for Orthopedic Applications	Utzschneider et al. (2010)

A.3. Biocompatibility experiments references

See Table A.4.

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