OsteoFab® Technology

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OPM's OsteoFab® technology platform uses OXPEKK® polymer – a proprietary formulation of polyetherketoneketone (PEKK) – to laser sinter patient-specific and series implantable medical devices. The chemical, mechanical, and biological properties of OXPEKK polymer enable its use in medical implants, and OsteoFab devices have passed extensive ISO 10993 biocompatibility testing as specified for permanent orthopedic devices. The additive manufacturing process of laser sintering allows for patient-specific implants to be designed and produced from CT scan images, or for series devices to be manufactured from a preset design file. OPM's OsteoFab devices have been shown through *in vivo* studies to participate in bony fusion and they possess inherent antibacterial characteristics as a result of an optimized material chemistry and manufacturing process. These devices currently provide world-class solutions in the arenas of neurology, spine, and orthopedic sports medicine and deliver a superior alternative to conventional PEEK and titanium devices.

Introduction

OsteoFab® technology was developed by OPM and is based on the polymer polyetherketoneketone (PEKK) – a member of the polyaryletherketone (PAEK) family of polymers. The OsteoFab process refers to the laser sintering of OXPEKK® powder into implantable medical devices. The technology allows for both the production of patient-specific implants, designed precisely for each patient, and series implants, as in the instance of standard-size spinal interbody fusion cages or suture anchors.

PEKK is a thermoplastic polymer that exhibits comprehensive thermal and mechanical properties. The polymer possesses a combination of characteristics that separates it from the rest of the PAEK family: PEKK retains its mechanical properties at very high temperatures, it is tough, abrasion resistant, has a low coefficient of friction, and has the ability to resist attack by a wide range of chemicals and solvents.[1] The biocompatibility of OsteoFab PEKK has been established on a broad and device-specific basis according to ISO 10993 testing standards.

OsteoFab implants are currently indicated for load bearing and non-load bearing indications. OPM has received six FDA 510(k) clearances for its devices, including single and two-stage patient-specific cranial implants, patient-specific facial implants, standard series vertebral body replacement devices, and suture anchors. Additionally, OPM customers have received a number of 510(k) clearances for interbody fusion devices manufactured using the OsteoFab process.[2]

This article will review OXPEKK polymer, the analytical and mechanical characteristics of PEKK, the additive manufacturing process, material biocompatibility, and the osseointegrative and antibacterial properties of OsteoFab PEKK. This article will also review OsteoFab PEKK in the context of current issues facing the conventional material options of PEEK and titanium.

OXPEKK® Polymer

OXPEKK polymer is composed of monomers diphenyl ether, terephthaloyl chloride, and isophthaloyl chloride. Adjusting the ratio of terephthaloyl chloride monomer to isophthaloyl chloride monomer allows for a variety of OXPEKK grades with differing material properties.

Three grades of OXPEKK polymer (IG100, IG200, and IG300) are synthesized and used in different applications. IG200 is a semi-crystalline, injection molding grade and IG300, while also semi-crystalline, is more suited for use in extruded products. OXPEKK IG300 is available in rod form for medical device companies that perform secondary processing operations to produce spinal implants.

OXPEKK IG100 is used to manufacture OsteoFab products. IG100 has a terephthaloyl chloride to isophthaloyl chloride ratio of 60/40 which results in a PEKK polymer with a glass transition temperature averaging 161°C. Figure 1 shows the structure of the repeating unit.

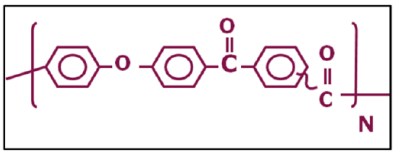

Figure 1: PEKK structural repeat unit.

Analytical and Mechanical Characteristics

The ratio and sequence of ketone (K) and ether (E) moieties affect the physical properties of PAEKs. A higher ketone to ether ratio will produce a polymer chain that allows for stronger molecular interaction, which is therefore more rigid. It has also been shown experimentally that a higher K/E ratio leads to an increase in oxidative stability, even under high temperatures. PEKK's 2:1 K/E ratio is the highest within the commercially available polymers of the PAEK family and produces rigidity in the polymer chain that results in exceptional thermal and mechanical performance.

The OsteoFab® process uses the amorphous OXPEKK® polymer with a terephthaloyl chloride to isophthaloyl chloride ratio of 60/40 (IG100). Melting temperature for IG100 is generally about 300°C. For finished OsteoFab devices, the mean glass transition temperature is ~161°C and the average specific gravity is 1.29 g/cm^3. Mechanical properties are shown below in Table 1.[3] All analytical and mechanical property data are statistical averages of values determined from laser sintering builds using qualified OXPEKK IG100 powder.

Mechanical Property	English Unit	Metric Unit
Tensile Strength	13.0 ksi	89.6 MPa
Elongation at Break	3.0 %	3.0 %
Young's Modulus	534 ksi	3.7 GPa
Compressive Strength	24.0 ksi	165 MPa

Table 1: Typical mechanical properties of OsteoFab products.

Test specimens are fabricated with each build so that the thermal and mechanical properties of finished OsteoFab parts can be verified. Specimens are evaluated for tensile strength, percent elongation, Young's modulus, specific gravity, glass transition temperature, and percent FTIR match to an accepted PEKK standard.

Additive Manufacturing Process (3D Printing)

OsteoFab® finished devices are manufactured from OXPEKK® IG100 powder via a proprietary laser sintering process.[4] Only laser light and IG100 powder are involved in the process; no additives, solvents, or other materials are used. Purified compressed air is passed through a nitrogen generator that extracts nitrogen and uses it to blanket the build chamber during the lasing process.

The laser sintering machine (EOS EOSINT P 800) uses STL files to build a part. For OsteoFab implants, the development of the STL files begins with a Computed Tomography (CT) scan of the defect area in a patient in the instance of patient-specific craniomaxillofacial implants or as a CAD file for standard series parts. When a part or implant is ready to be built, OXPEKK powder is loaded into the laser sintering machine and successive layers of part geometries are lased to produce a solid part.

Upon completion of the building process, parts are excavated from the powder bed. Tools manufactured by OPM from OXPEKK powder are used for coarse removal of parts from the bed. The parts are then blasted to remove any excess powder. Figures 2, 3, and 4 show examples of, respectively, a craniomaxillofacial implant, Fortilink® spinal interbody fusion devices,[2] and OPM's latest suture anchor product offering.

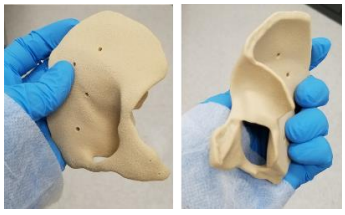

Figure 2: Patient-specific craniomaxillofacial implant.

Figure 3: Fortilink® interbody fusion devices.[2]

Figure 4: OsteoFab® Suture Anchors and instrumentation.

Biocompatibility

OsteoFab® PEKK samples have been extensively tested per the ISO 10993 standard set for implant devices with tissue/bone contact and a permanent implant duration. This testing includes cytotoxicity, sensitization, irritation and intracutaneous reactivity, acute systemic toxicity, material-mediated pyrogenicity, subchronic/subacute toxicity, genotoxicity, implantation, and chronic toxicity. All tests have yielded passing results and have been used successfully to support the safety and effectiveness claims of OPM's numerous orthopedic devices.

The extensive amount of biocompatibility testing performed on PEKK devices demonstrates its ability to exist *in vivo* without causing an adverse tissue response or immune response, substantiating its suitability for use as an implant in the human body. In fact, OPM's OsteoFab devices have shown a highly desirable bone response.

OsteoFab® Surface Technology

In addition to a biocompatible device, an important factor resulting from the additive manufacturing process is the inherent rough surface topography of OsteoFab devices. OsteoFab PEKK has an average surface roughness (Rq) of 26 µm (1022 µ in.) that creates a peak-and-pit surface topography much rougher compared to conventional PEEK material.[5] Figure 5, below, illustrates this difference in surface roughness via CLSM.

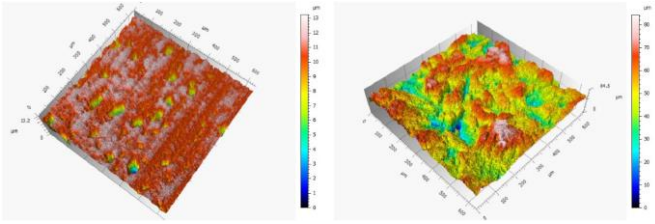

Figure 5: CLSM images of machined PEEK (left) and OsteoFab PEKK (right) depicting the rougher surface topography of PEKK.

Due to the material chemistry and surface energy of PEKK, when OsteoFab parts are laser sintered, successive layers bond strongly to one another to create dense, fully formed shapes. While the surface of printed PEKK devices is rough, the bulk parts are completely solid – lending to many of the mechanical characteristics discussed above. A cross section of a typical cranial implant is shown below in Figure 6 to illustrate the solid-formed device along with the rough surface layer.

Figure 6: Cross section of a typical OsteoFab PEKK cranial implant, sectioned through one of the through holes. Note the fully dense part structure and visibly rough outer surface.

The rough surface topography of OsteoFab PEKK devices leads to a number of performance benefits – namely osseointegration, antibacterial properties, and a fluid wicking capability of the part surface (pictured below in Figure 7). These functional advantages, driven by the right combination of material chemistry and manufacturing process, are able to provide more tailored solutions to meet today's growing clinical needs.

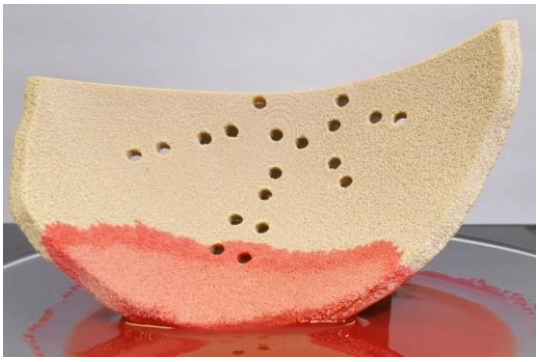

Figure 7: OsteoFab PEKK cranial implant section demonstrating vertical fluid conduction through the rough outer surface.

Osseointegration

Early *in vitro* studies (circa 2010)[6] had indicated a positive cellular response to OsteoFab PEKK and subsequent *in vivo* studies that examined tissue response to OsteoFab PEKK implants in an osseous environment (rabbit model, circa 2013) showed that native PEKK material supported bone apposition.[7] OsteoFab PEKK showed no observable immunological rejection and no increase in inflammatory response cells. Figure 8 in the next column shows the *in vivo* bone response to OsteoFab PEKK compared to machined PEEK in a rabbit femoral model at 8 and 12 weeks: (a,b) Bone (pink) growing onto the surface of a PEKK rod implant and into the peaks and pits of the rough surface; (c) Fibrous tissue (blue) surrounding a PEEK rod implant; and (d) Fibrous tissue (blue) present in the interface of a PEEK rod implant and existing femoral bone.

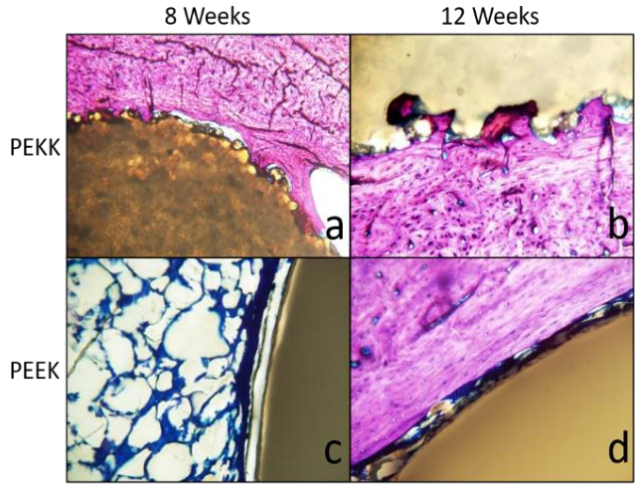

Figure 8: *In vivo* bone response to OsteoFab PEKK versus machined PEEK in a rabbit femoral model at 8 and 12 weeks.

Shifting from studying the implant material response to implant structure and morphology, latticed OsteoFab PEKK scaffolds were similarly examined in *in vitro* and *in vivo* experiments.

- In 2014, a research study demonstrated the successful growth of bone marrow cells on 3D printed PEKK scaffolds and since then, a number of publications have examined the use of mesenchymal stem cells (autologous, adipose-derived, and human synovial fluid-derived) on PEKK scaffolds in critical size defects.[8]
- In 2016, Adamzyk et al. studied the use of PEKK scaffolds with autologous mesenchymal stem cells in a sheep calvarial defect model and found that 3D printed PEKK scaffolds allowed for the adherence, growth, and osteogenic differentiation of human and ovine stem cells, with considerable amounts of newly formed bone in all PEKK groups.[9]
- In 2017, Roskies et al. similarly studied 3D printed PEKK scaffolds with adipose-derived stem cells for the reconstruction of critical size mandibular defects.[10] This group determined that the PEKK scaffolds presented a promising solution to improve bone-implant interfaces and biomechanical attributes of implanted materials.

This work culminated into a 2019 publication in *Nature* that established a definitive link between OPM's OsteoFab PEKK and bone regeneration.[11] *In vitro* results of the study demonstrated the ability of human synovial fluid mesenchymal stem cells to attach, proliferate, and differentiate on PEKK scaffolds, and *in vivo* results showed strong evidence of new bone formation. Regardless of stem cell seeding or defect model, native OsteoFab PEKK test groups have demonstrated bone apposition, bone ongrowth, and improved biomechanical properties, making OsteoFab PEKK a more desirable and functional implant material.

Antibacterial Properties of OsteoFab® PEKK

In 2017, a study was initiated to examine the antibacterial potential of OsteoFab PEKK due to its material chemistry and inherent rough surface (26 µm average Rq). The results showed that OsteoFab PEKK provides an inherent, antibacterial environment and demonstrated decreased bacterial adhesion and growth when compared to PEEK (Invibio PEEK-OPTIMA®).[12] In this study, OsteoFab PEKK showed a 40-55% higher antibacterial effect when examined using a Live/Dead assay, just on the native surface of printed PEKK. Culminating in a publication in the *International Journal of Nanomedicine*, these results highlight the unique properties attainable when the right material and manufacturing method are combined to produce more robust medical devices.

In order to better understand the mechanisms of this observed antibacterial property, a follow-up study was initiated in 2020 to extend the results of the 2017 publication. The follow-up study showed a greater adsorption of the proteins casein, mucin, and lubricin to OsteoFab PEKK when compared to PEEK (Invibio PEEK-OPTIMA®) and titanium surfaces.[13] This finding is important because the proteins tested are endogenous and known to decrease bacterial attachment and growth. With the greater adsorption of these proteins, attributed to the similarity in surface energy between them and PEKK, there was a clear correlation of this increased adsorption to significantly decreased bacterial colonization on OsteoFab PEKK compared to PEEK and titanium. This result was consistent across all bacteria tested, which included *S. epidermidis, P. aeruginosa,* and MRSA. The Live/Dead assay results also illustrated fewer viable bacterial colonies on PEKK when compared to PEEK and titanium surfaces, which was consistent with the study published in 2017.

Additional Differences between OsteoFab® PEKK versus PEEK and Titanium

Conventionally, PEEK, Ti-coated PEEK, and titanium have been used as standard biomaterials for implants like spinal interbody cages, but recent shortcomings in these materials have led to the adoption of newer, more innovative technologies. Although PEEK shows an elastic modulus comparable to that of cortical bone, literature has illustrated that it consistently prompts a fibrotic and inflammatory tissue response, preventing it from integrating with host tissue.[14,15] And while titanium may exhibit stronger osseointegrative properties when compared to PEEK, it is radiopaque, which makes bone fusion assessments difficult as the bone/implant interface is often obscured in post-operative imaging. Furthermore, with titanium implants, there is a risk of stress shielding and tissue resorption as the metal material is much stiffer than surrounding bone in orthopedic applications. This can lead to implant failure and result in the need for revision surgery. Recent workarounds include coating PEEK with titanium, resulting in similar drawbacks but with the added risks of delamination of the titanium coating, subsidence, and the generation of wear debris.

In a recent paper published by the FDA (Biological Responses to Metal Implants, September 2019),[16] it is evident that the FDA is no longer grandfathering classic alloys for use in medical devices. Data from this paper highlight the fact that all metals will corrode in the body and that the corrosion products will move through the body. Long term monitoring has revealed varied responses to implantation of metallic devices, largely revealing adverse side effects. These include but are not limited to pseudotumors, infections, and implants loosening via osteolysis. Adverse systemic effects include pro-inflammatory responses, toxic, immunogenic, and auto-immune reactions. Even titanium has been shown to cause both local and systemic effects including headache, fatigue, and hemolytic anemia. Historically, 'well tolerated' is no longer readily equated with 'safe.'

With OsteoFab PEKK, there exists a practical and beneficial material solution that provides all desirable device properties in one product. OsteoFab PEKK delivers the necessary mechanical integrity, radiographic visibility, osseointegration, as well as inherent antibacterial characteristics. In a recent publication in *The Spine Journal*, a study examined the *in vivo* material characteristics of PEEK, titanium-coated PEEK, and OsteoFab PEKK in a sheep model.[14] Overall, the PEKK implants experienced bone ingrowth, no fibrotic tissue formation, and significant increases in bony apposition over time, as well as a significantly higher push-out strength when compared to PEEK. From a histological standpoint within a 2mm radius of the implant, OsteoFab PEKK exhibited the highest bone area percentage when compared to PEEK and Ti-coated PEEK at both the 8- and 16-week endpoints.

By directly comparing three implant materials in an *in vivo* model, there is clear evidence of the performance characteristics at the bone-implant interface. In this instance, OsteoFab PEKK presented a high propensity for bone ingrowth, no radiographic interference, and a material structure that allowed for an increase of integration of cancellous bone into the implant. In a clinical scenario, OsteoFab PEKK implants could improve the effectiveness of spinal fusion procedures by promoting osseointegration and decreasing the chance of complications associated with PEEK, Ti-coated PEEK, and metal implants alike.

Conclusion

Since 2013, OPM has been additively manufacturing patient-specific cranial and facial implant devices. In addition to over 2,700 CMF implants, OPM has manufactured tens of thousands of spinal implants via its OsteoFab® technology and is enthusiastic about the performance of its new suture anchor product line. OsteoFab PEKK continues to be a strong clinical solution with an increasing user base, and as the pendulum swings away from traditional material solutions, OsteoFab PEKK products are providing a robust alternative and a better standard of care.

About Oxford Performance Materials, Inc.

Oxford Performance Materials, Inc. was founded in 2000 to exploit and commercialize the world's highest performing thermoplastic, PEKK (poly-ether-ketone-ketone). OPM's Materials business has developed a range of proprietary, patented technologies for the synthesis and modification of a range of PAEK polymers that are sold under its OXPEKK® brand for biomedical and industrial applications. The Company is a pioneer in 3D printing. OPM Biomedical's OsteoFab® technology is in commercial production in numerous orthopedic implant applications, including cranial, facial, spinal, and sports medicine devices. OPM is the first and only company to receive FDA 510(k) clearance to manufacture 3D printed, patient-specific polymeric implants, and the company has six 510(k) clearances in its portfolio. OPM Industrial produces 3D printed OXFAB® production parts for highly demanding applications in the energy, transportation, and semiconductor markets. OXFAB® structures offer significant weight, cost, and time-to-market reductions that are defined in a set of specified performance attributes in the exhaustive OPM B-Basis database, developed in conjunction with NASA. For more information, please visit: www.oxfordpm.com

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