Medical-grade Ultra-high Molecular Weight Polyethylene: Past, Current, and Future.

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Ultra-high molecular weight polyethylene is a semi-crystalline polymer (45%-60%) with six decades of orthopaedic applications. This polymer has a high fracture toughness (30 kJ/m^2) which comes from the molecular weight and the chain entanglements. Adverse alteration of the properties may lead to the part's pre-mature failure. This paper reviews the current manufacturing methods, and their effect on the properties of the polymer. The review also focused on the attempts of enhancing the polymer properties. The main cause of failure is implant loosing due to the polymeric wear particles. Many manufacturers have attempted to enhance the wear and oxidation properties of the polymer, the outcome of the new technologies is critically reviewed. Finally, the review explores the potential for future developments.

Keywords: Ultra-high molecular weight polyethylene; Vitamin E; Radiopaque; Packaging; Sterilisation; Crystallinity; Cross-linking.

Subject classification codes: Review paper.

Introduction

Ultra-high Molecular weight polyethylene (UHMWPE) has a low friction, high resistance to wear, high toughness [1] and the polymer is bio-inert. Information with regards to the polymer wear and friction behaviour are summarised in Table 1. The linear wear rate of the acetabular cup is about 0.2 mm/year and the friction coefficient of the polymer is lower than the other commonly used polymer such as poly amides, polytetrafluoroethylene and poly esters, polyether ether ketone (ranged between 0.25-0.6, against steel, dry condition) [2]. In average the friction coefficient of UHWMPE/metal is half of the PEAK/metal. Therefore, UHMWPE is an ideal material

to use for long-term implants. However, many retrieval studies have shown evidence of severe oxidation and wear in UHMWPE implants. Oxidative stability and properties of UHMWPE are linked to the chemical structure, molecular weight, crystalline organization, and thermal history of the polymer [3]. It is crucial that any changes made to UHMWPE implants, do not detrimentally affect their wear properties, oxidation resistance or fatigue strength.

Table 1. Physical and mechanical properties of UHMWPE(GUR 1050)

Properties	UHMWPE	references
Molecular weight (g/mol)	36 million	Product data sheet
Density (g/cm^3)	0.930.935	Product data sheet
Yield strength at 37 °C (MPa)	21	Product data sheet
Elastic modulus at 37 °C (GPa)	0.67	Product data sheet
Friction coefficient (Dry condition) $^{+}$	0.12-0.15	(Ruggiero et al., 2016)
Friction coefficient (Saline solution) $^{+}$	0.05	(Ruggiero et al., 2016)
Volumetric wear (Dry) $^{+}$	5×10^{-5}	(Ruggiero et al., 2016)
Fracture toughness kJ/m^2	30.18	
Linear wear rate	0.174 mm/year	(Geringer et al., 2011)
Shore D hardness (21°C)	60-65	(Geringer et al., 2011)
Surface roughness (μm, before wear testing)	0.01	(Derbyshire et al., 1994)
Surface roughness (μm, after wear testing)	0.032	(Derbyshire et al., 1994)

* Data gathered from the product data sheets and ISO 11542, ISO 527, ASTM790,* MPa megapascal $^{+}$ against CoCrMo * TiAl6V4 (for Standardization, 2005)

From 2003 to 2016 About 796,636 total hip, 871,472 knee are implanted in England and Wales and the most common articulation used was polyethylene [4]. With the ageing population, it is crucial to improve the longevity of the parts. Despite the successful clinical outcome of the most orthopaedic replacement; the longevity of the prosthesis is limited to approximately 15 years [5], and any modification can jeopardize the longevity of the part. Researchers are always trying to enhance the polymer properties and there have been a significant new developments in this field. This review attempts to cover the new technologies. As the polymer changes the body might react to the new polymer differently which needs to be understood to imply the alteration in the implant design. The current data regarding on the mechanical and material properties of the polymer, method of manufacturing, sterilisation and packaging of UHMWPE

components, as well as examining common mechanisms of failures, new technologies as vitamin E UHMWPE and contemplating the future of the polymer.

Clinical Uses of UHMWPE

This polymer was introduced clinically in November 1962 as an articulating surface for hip replacement implants and in the late 1960s, it was first used for knee replacement [6,7]. In a total knee arthroplasty, UHMWPE provides articulating surfaces between the femur and tibia as well as between the femur and the patella [7]. Depending on the pathology of the disease, surgeons might prefer to use unicondylar knee arthroplasty [7]. There are 300 different designs of knee prostheses available around the world, and UHMWPE is used as the bearing materials in almost all of them [7].

The bearings are also used in other types of orthopaedic joints including shoulder, ankle and elbow replacement [8–11]. Although these procedures are performed much less frequently than hip and knee replacements [12], the performance of these prostheses also rely on the polymer for motion and load bearing [8–11]. UHMWPE is also be used in finger joint replacement [13]. The surgical considerations for small joint replacement are different to other joint arthroplasties [14]. In finger joint replacement the implant acts as an internal splint allowing the soft tissues to rebalance [14]. In some designs of these prostheses, UHMWPE bearings have been used [14,15].

UHMWPE has also been used in spinal applications [16]. Chronic back pain can be treated by spinal fusion or disc arthroplasty. In both cases, UHMWPE may play an important role. UHMWPE fibre can be used for spinal fusion and UHMWPE bearings in disc replacement [17–19].

In the last few years, the polymer has been used for anterior cruciate ligament reconstruction [20,21]. In fibre form, it can be used for braided sutures [22]. The modulus of polyethylene fibre is as high as 222GPa and the strength of the fibre is 8GPa

[23]. Porous polyethylene (pore diameter between 100-250μm) can be used for facial reconstruction [24] and bone defect replacement [25–27]. Porous PE (Medpor®) (Medpor Biomaterial; Porex Surgical, Newman, GA) has an application in craniofacial reconstruction [25,28,29], because it can closely mimic porous cancellous bone tissue [26]. This type of polyethylene has the same hardness as cancellous bone tissue and it can be trimmed and modified during the surgery. The polymer makes up 54% volume of the implant and rest of the implant are filled with air. The pores structure allows the bone to ingrowth through the implant with collagen deposition. Therefore, the implant is resistance to infection. Porous polyethylene is able to deform by surrounding tissue [29]. The tensile strength of porous polyethylene is as highs as 4.1GPa, hence polymer is able to resist stress and fatigue [30].

Resin Manufacturing

The formation of resin is the first step toward the manufacturing of an UHMWPE component. The resin can be polymerised by the Ziegler-Natta process using ethylene and hydrogen gases and titanium tetra-chloride (a catalyst) [31]. A solvent is required for heat and mass transfer [31]. The polymerisation of the resin requires a specialised production plant capable of handling dangerous chemicals. Hence, there are only two companies capable of making resins. Medical grade UHMWPE is free of calcium stearate and has a higher purity requirement as set by ISO 5834-1 [32].

Type 1 and 2 resins (GUR 1050, GUR 1020) are produced by a German company called Celanese, and Basell used to produce type 3 resin (1900). Although the manufacturing method is identical, a slight variation in the molecular weight of the

different resins was reported [33]. This variation can be associated with the catalyst package and the polymerisation condition. Table 2 summarises the differences between the resins. Furthermore, a slight variation between the resin morphology was reported. Type 1,2 reins appeared to be more lamellar while type 3 resin has a spherulitic morphology. Type 3 resin is no longer on the market.

Table 2, Physical properties of medical grade UHMWPE resins.

Properties	Type 1	Type 2	Type 3
Average Molecular Weight ($\times 10^6$, $\frac{gr}{mol}$)	3.5	5-6	>4
Particle size μm	140	140	300
Tensile modulus(MPa*)	720	680	750
Impact strength(KJ/m^2)	>210	>130	>65
Yield stress(MPa)	>17	>17	19

* MPa megapascal

The molecular weight of the resin effects on their mechanical properties and their wear abrasion resistance. Clinical data showed that 1900 has a superior resistance to wear and oxidation but the lowest mechanical properties among the three resins. While, as Table 2 the experimental data showed no statistically significant difference between the oxidation resistance of the resins [34]. The wear resistance of 1050 is slightly better than GUR 1020 while GUR 1020 has a better impact strength and toughness.

Manufacture of UHMWPE Components

The second stage towards making a component is the consolidation of the resin under elevated temperature and pressure. Due to its high molecular weight, the polymer has a high melt viscosity and it is not able to flow like lower molecule weight polyethylene [33]; UHMWPE has zero melt flow index. Hence, ram extrusion and compression moulding are two typically used methods to produce semi-finished or finished components [3,33].

The machining temperature needs to be closely monitored as the UHMWPE can be easily damaged by excessive heat [35]. Figure 1 shows the manufacturing steps. Machining is able to change the surface and subsurface properties of the polymer. A higher machining speed leads to a greater mechanical degradation and a lower wear resistance. However, no significant correlations have been found between the machining parameters and the wear coefficient[36,37].

The difference between parts made from extrusion and compression is insignificant, and in both cases, the mechanical properties exceed the ASTM F648 requirement} [38]. The main difference between the ram extruded and compression moulded parts is in the morphology of the segments [3]. TEM images showed that ram extruded polymer lamellae are aligned along the extrusion direction while compression moulded samples showed random orientation of the crystalline lamellae. Lack of preferred orientation in lamellae enhance the fatigue resistance and crack propagation of the polymer which are summarised in table 3.

Table 3Fatigue and crack propagation of ram extruded and compression moulded polymer. Adopted from ref [39].

Properties	Ram Extrusion	Compression moulding
$\Delta K_{th}(\mathrm{MPa}\sqrt{m})$ +	1.3-1.7	1.2-1.8
$\Delta\delta_t$ (mm) *	62.8	70.4

GUR 415 resin which no longer has a medical application, + Crack opening displacement * The fatigue threshold

Some manufacturers prefer to consolidate the resin into semi-finished parts using an individual mould, avoiding intermediate machining steps. Direct compression moulding leads to a smooth surface finish with no machining marks [3]. Tensile properties of DCM parts are suggested to be higher than other methods [40–42]. This is because compression moulding can be performed under a very high pressure (300 MPa), hence there are few/no fusion defects which leads to up to a 40% increase in the yield strength without decreasing the impact strength or toughness of the polymer [3,35]. Another possible reason for the better tensile properties is the greater percentage of crystallinity of directly moulded parts which is nearly 72% percent. This can be associated with lower risk of oxidation in the component and a better resistance to post-irradiation ageing. Microscopic images from the surface of the component also support that direct compression moulded parts have an ability to resist oxidation. The ultimate tensile strength of the samples can drops by 60% over a range of oxidation [39].

This can be because spatial variations in the degree of consolidation of ram extruded the bars along the radius which can be indicated by the presence of inter-particle regions and fusion defects [39,41].

A study by Bankston et al, investigated the wear properties of samples manufactured using direct compression or another form of machining (either ram extrusion or compression moulded part). Clinical studies on two groups of patients, assigning 54 patients to each group with no significant difference between in the average age, weight (average weight =161 pounds and age =66 years old) for average

followup of 6.7 years showed the average linear wear rate per year was 0.05 mm for direct compression moulding and 0.11 mm for machined polyethylene [43]. Retrieved implants show that direct compression moulded samples have a higher chemical stability and little to no oxidative damage and no evidence of delamination or discolouration, in retrievals after four years [43–45]. However, the number un-fatigued parts dropped sharply as the implantation time increased (32% for moulded components and 36% of the machined component)

Direct Compression Moulded is also capable of producing unique designs, but it is a time consuming and expensive method[45].

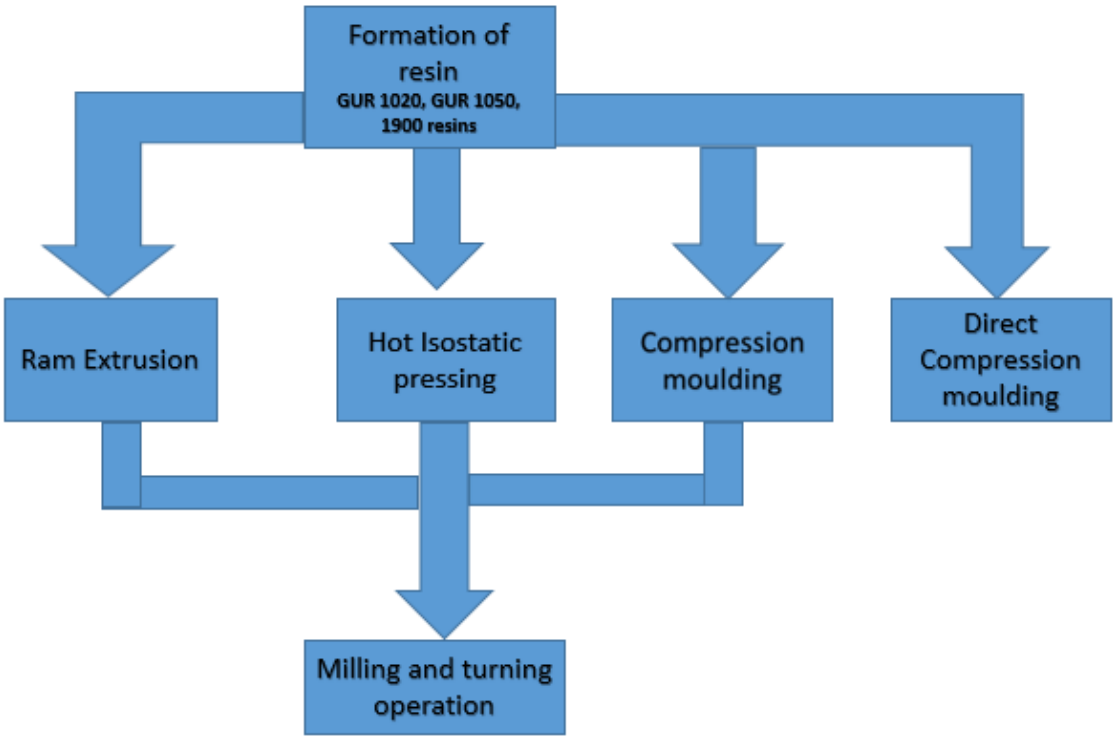

Figure 1. The processing steps involved in making an UHMWPE part.

Cross-linking

The most common failure mechanisms are aseptic loosening and dislocation (82% of cases) which are associated with wear resistance of polyethylene. To improve the wear resistance of UHMWPE, manufacturers have attempted to increase the cross-linking density of the polymer [46]. The conventional form is not cross-linked [47]. Cross-linking significantly increases the wear abrasion resistance, and reduces the mobility of the free radicals [48]. As Table 4 shows the wear rate of conventional polyethylene is 6 times more than the highly cross-linked polymer. Experimental data showed that cross-linking improves the wear properties of the polymer up to 90\% \citep{dum2006, jac2017} (Table \ref{xl}). Furthermore, a higher abrasion resistance in cross-linked polyethylene enables surgeons to use thinner components, which can have clinical advantages. For instance, in hip replacement, this allows for the use of a larger femoral head; which reduces the risk of dislocation \citep{mur2001}.

There are three ways of cross-linking polyethylene: radiation, organic peroxide chemistry or using saline chemistry \citep{mur2001}. However, only the two first methods are clinically approved as saline chemistry is involved the use of harsh chemical.

Table 4. Physical properties of conventional and highly cross-linked UHMWPE

[129,130]

Properties	Conventional	Cross-linked at 30 kGy	Cross-linked at 50 kGy	Cross-linked at 75 kGy	Cross-linked at 100 kGy
Crosslink density ($\times 10^{-4}$ mol/dl)		105.1	158.7	180.8	197.6
Molecular weight between cross-links (gr/Mol)		9500	6300	5800	5060
Crystallinity	53.3±0.9	47.5±1.2	48.5±0.7	47.7±0.5	47.9±7
Oxidation Index*	0	0.013	0.015	0.017	0.030
Oxidation Index *(after 10 weeks ageing)	1.2	1.25	0.1.4	2.40	2.9
Fracture toughness (K_c, (MPa $\sqrt{m}$))	4.0 ±0.5	4.5±0.02	3.0 ±0.6		
Elastic Modulus (MPa)	648	737	570		
Yield strength (MPa)	22±0.4	19.6±0.5	19.6±0.5	19.9±0.1	20.2±0.1
Ultimate tensile strength	50 ± 1.6	47.1 ± 4.2	37.1 ±3.2		
Wear rate (mg/million cycles)	9.8 ±0.7	9.1 ±0.3	4.8 ±0.7	2.5 ±0.4	1.6 ±0.3

*Keton oxidation

In the first two methods, cross-linking is achieved by the formation of active sites at the end of the chains. The active sites (free radicals) can recombine to form trans-vinylene bonds[49]. Gamma irradiation is the most common way to cross-link UHMWPE; however, it also is possible to use electron beam irradiation [48]. Gamma irradiation can also be used to sterilise components [50] as discussed in Section 2.8.; the peroxide method involves its decomposes by a free radical reaction that leads to the formation of cross-links between chains at the elevated temperatures associated with the manufacturing process [3].

Hip simulator study demonstrated approximately 98% reduction in wear at 30 million cycles when comparing Longevity HXPE with CPE and a 96% reduction in the rate of steady-state wear at 2-year follow-up when comparing Longevity HXPE to CPE in vivo.

There are some concerns with both the methods. UHMWPE is semi-crystalline and free radicals trapped in crystalline regions are not mobile enough to react with each other[49]. However, over time, the free radicals diffuse slowly to the amorphous regions and can lead to degenerative oxidation [49]. Similarly, there are concerns about the oxidative instability of the peroxide cross-linked version[49].

Even though increasing cross-linking density increase the abrasion resistance of the polymer, however, the cross-linked polymer is less tolerant to severe clinical conditions and less resistance to crack propagation [51,52] . Table 4 shows the mechanical properties of conventional and cross-linked polymer, elastic modulus, ultimate tensile strength yield strength and ductility of the polymer will be reduced as cross-linking density increases. The cross-linking density is increases with radiation and 100kGy is the saturation point.

Any alteration in the microstructure of the polymer changes the mechanical properties. Cross-linking reduces the plasticity of the polymer which leads to a 32% reduction in fracture toughness (K_c). Fracture toughness determined the fatigue crack propagation of the polymer.

Retrieval analysis on 4 highly cross-linked acetabular cups showed that there is no significant sign of oxidation however brittle fracture failure was the main cause of failure in all the samples [52].

Histological studies have shown cross-linking reduce the biological response to the wear particles and a lower amount of multinucleated has been found [49,53]. Fisher has shown that cross-linking generates a larger amount of small particles [54]. Larger particles cannot be ingested by the macrophages so they will be surrounded multinucleated foreign body giant cells, which are the hallmark of a chronic inflammatory process. however, the finer particles induce more macrophage and inflammatory mediator, resulting in more osteolysis (bone resorption means more bone resorption [54].

Overall, there is a lower ductility and fatigue resistance associated with extensive cross-linking [55]. Furthermore, highly cross-linked UHMWPE has a lower toughness and mechanical strength. Therefore, it is desirable to limit the degree of cross-linking and keep it local to the surface of the polymer to retain the bulk mechanical properties [56]. Oxidation is the main concern with cross-linking. Failure analysis of retrieved UHMWPE implants regularly shows signs of surface cracking, abrasion, scratching and pitting marks, which can be due to oxidative degradation [51,57]. Hence, different methods have been developed to increase the oxidative stability of cross linked UHMWPE, this is covered in next section.

Thermal treatment

As mentioned, free-radicals will be formed during cross-linking or sterilisation of UHMWPE, reducing the oxidative stability of the polymer [58,59]. One method used to reduce the amount of free radicals is post-irradiation thermal treatment which at the same time releases residual stress due the thermal history induced by ram extrusion or compression moulding [58]. Two common thermal treatments are re-melting and annealing. Re-melting is when the temperature is elevated above the melting point (approximately 150° C) leads to complete melting of the polymer crystallites, allowing the free radicals trapped in the crystalline phase to diffuse out [3]. Usually, re-melting reduces the amount of residual radicals to undetectable levels. Annealing is when the temperature rise does not exceed the melting point, hence, it leaves a measurable amount of free radicals in the polymer [60].Free radicals can be detected from using a type of spectroscopy (Electron spin resonance) which is able to detect the unpaired electron. There are three types of free radicals alkyl, allyl and polyenyl [61].

The main concern with any thermal treatment is the possibility of reducing crystallinity during the cooling process as there is no pressure applied [62]. With current processing technologies applying pressure is not feasible [49,63]. The crystallinity of UHMWPE is associated with the fatigue crack propagation resistance [64]. Crystallinity can enhance the oxidative resistance of the polymer. This is because the oxygen is only able to diffuse into the amorphous region. Oxidised polymer is more brittle and less resistance to fatigue crack propagation [65]. Remelting has been shown to significantly reduce the degree of crystallinity [66–69], the crystallinity reduction can be as high as 10% [69]. While re-melting determinately effects mechanical properties of the polymer, annealing showed no statistically significant decrease in the crystallinity

($p>0.005$) and many of the mechanical properties of the polymer including yield, ultimate strength and fatigue properties remain unchanged[3,63].

However, results obtained from ageing studies are controversial. Muratoglu and co-workers investigated the wear and oxidation properties of remelted and annealed cross-linked UHMWPE [61] . As was expected, initially the thermally treated UHMWPE had better wear properties than the untreated samples. However, after artificial ageing, residual free radicals in annealed samples were detected by Electron Spin Resonance (ESR) but not in the remelted samples[61]. Free radicals cause oxidation and reduce the ductility and wear resistance of the polymer. A study of real-time aged samples also showed a reduction in oxidative stability of annealed UHMWPE after ageing [70]. In both studies, a significant oxidation was observed on the surface of the UHMWPE test samples.

Many different studies have calculated the linear wear rate of the polymer after thermal treatment using hip simulators. There is a broad distribution in wear rates of different studies [71–73] , which is likely to be due to variations in design, metallic materials and the size of the femoral head. Nevertheless, all studies demonstrated a high reduction in wear rate for the highly cross-linked and annealed UHMWPE, compare to untreated UHMWPE.

The clinical data has detected a measurable amount of oxidation of remelted retrieved parts which was significantly higher than *in vitro* studies. A possible explanation could be the test lubricant and the loading conditions of *in vitro* studies [74–77]. It has been proved that UHMWPE is able to absorb the lipid with synovial fluid which alters its mechanical properties[74,78,79].

To summaries, free radicals were generated during cross-linking and so thermal treatment was applied with the intention of reducing the amount of free radicals and increasing the oxidative stability of the polymer. The first highly cross-linked UHMWPE was irradiated with a high dose followed by melting or annealing. However, the material properties of the polymer underwent a significant change after re-melting [58]; and annealing did not eliminate all the free radicals [80]. In the second generation, high cross-linking levels were achieved by repeating the irradiation and annealing steps to allow the free radicals to recombine completely [81]. This method reduced the amount of free radical to an undetectable level and ageing studies also showed a very low amount of free radicals. However, clinical studies on knee retrievals showed pitting and subsurface white banding and cracking [82,83]. Studies hypothesised this was the result of lower a crystallinity and fatigue strength. This unsatisfactory result led to a search for an alternative to reduce the influence of free radicals, the next section reviews use of anti-oxidants to prevent oxidative degradation.

Anti-oxidants

Vitamin E is a natural anti-oxidant, which is able to suppress the free radicals which cause oxidation by reducing both alkyl and peroxy radicals, and consequently improve the wear resistance of the polymer [84,85]. The addition of vitamin E does not require any post-irradiation thermal treatment [86].

There are two methods of incorporating vitamin E within UHMWPE Figure 2. In the first method, vitamin E is blended with UHMWPE prior to consolidations, a process that does not affect consolidation, [87], as a free radical scavenger and it can

inhibit the formation of cross-links. Hence, the vitamin E concentration in the blend should be limited to less than 0.3 wt% [88]. The alternative method is diffusion of the vitamin into UHMWPE after cross-linking [86], and so cross-linking efficiency is not affected. On the other hand, UHMWPE goes through irradiation without any anti-oxidant protection and an extra homogenisation step is required to obtain an adequate concentration of vitamin E throughout the part. Diffusion and homogenisation require an elevated temperature to facilitate the diffusion of vitamin E, though the temperature is kept below the melting point so it does not effect on the crysrallinity of the polymer [87].

Overall, *in vivo* studies have confirmed that vitamin E increases the oxidative stability of irradiated UHMWPE so, components are now used clinically [64,86,89–91].

Knee simulator studies have suggested that vitamin E containing UHMWPE (GUR 1050) parts have a lower wear volume compared to the conventional polymer parts, suggesting that anti-oxidants improves the wear resistance. The volumetric wear of conventional polymer is 41.3 mm^3 and 27 $mm^{\wedge 3}$ for vitamin E added polymer (max load 2600 N, 5 million cycles) [92].

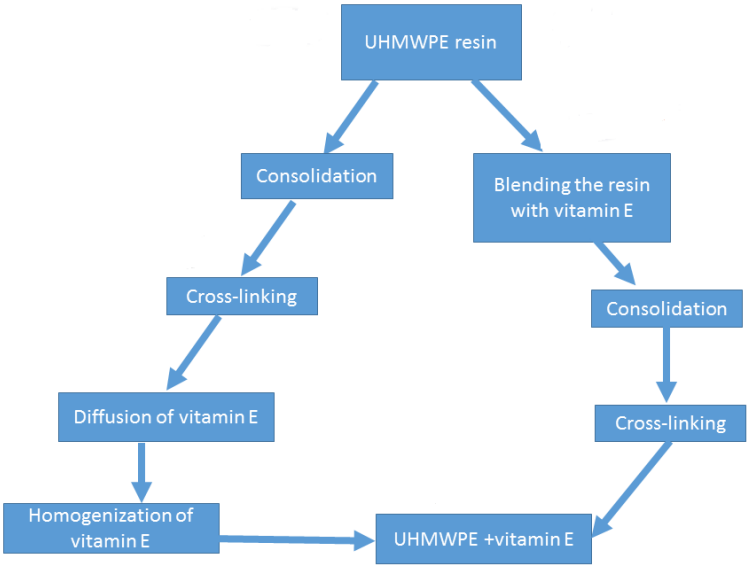

Figure 2 Schematic illustration of the two different methods used to incorporate Vitamin E. The first method involvs the diffusion of vitamin E into consolidated and cross-linked UHMWPE parts, the second is blending of the vitamin E with the UHMWPE resin prior to consolidation.

Vitamin E may have an effect on the re-alignment and recrystallisation of the polymer chains. The individual polymeric chain stems are able to rotate respect to each other, leading to a change in the lamellar structure and also crystals can grow to a larger extent [93]. Okubo *et al*. have shown that stress induced crystallisation of UHMWPE is hindered by the addition of vitamin E. X-ray diffraction results suggested the realignment of the molecular chains within the amorphous phase was the cause of these changes [94].

The tensile properties of the vitamin E infused polyethylene changed, 10% increase in yield strength and 12% drops in ultimate tensile strength of the polymer [95]. There was a 25% increase in fatigue crack propagation of the polymer [95]. A possible explanation is that Vitamin E can be a plasticising agent and lead to an increase in the chain mobility which can be the reason for the improved fatigue strength [93].

The mechanical and fatigue strength of vitamin E infused polyethylene is greater than the highly cross-linked UHMWPE [89], and there was no significant difference

between the mechanical properties of vitamin E treated and untreated samples. vitamin E diffused UHMWPE led to no significant alteration in the stress intensity factor of the polymer after artificial ageing, equivalent to 5 years of natural ageing [64,96]. Stress intensity factor indicates the fatigue crack propagation of the polymer. This can be because one method that materials decrease the localised stress at the crack tip is by plastic deformation. Vitamin E can act as a plasticizing agent and increase the ductility and chain mobility of the polymer. Furthermore as there is no thermal treatment (re-melting or annealing) after adding vitamin E hence the crystallinity of the polymer is going to be intact preserving the mechanical properties of the polymer.

Animal and cell studies did not detect any adverse biological response to vitamin E infused part, and clinical data to date support the *in-vitro* results. Hence, it can be concluded, vitamin E-stabilisation is a promising alternative to thermal treatments [97].

Vitamin UHMWPE was clinically introduced in 2007, and short term clinical data (up to 3 years) shows that there is no specific complication with this type of polymer and there is no significant difference in the wear rate of UHMWPE and highly cross-linked polymer [98]. Clinical data to date support there are no negative short term complications with this material and low concentration of free radicals can be indication of long term oxidative stability. However, there is no information available regarding the performance of the parts beyond 10 years.

Packaging and sterilisation

Finished UHMWPE components need to undergo packaging and sterilisation before clinical use. Figure 3 shows the current packing methods used.

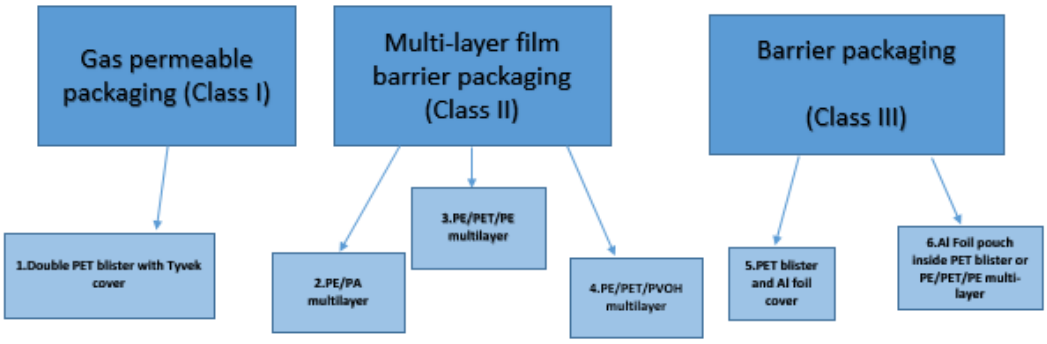

Figure 3 There are three different type of packaging for an UHMWPE part including gas permeable, multi-layer film barrier packaging and barrier packaging.,

The most common way to sterilise UHMWPE is high energy radiation [99]. Typically, a nominal dose of 25 to 40 kGy gamma sterilisation is used [100]. As mentioned previously, cross-linking can be formed using irradiation and the main concern was that a high dose of radiation in air promotes oxidative degradation and loss of desirable properties [101]. To avoid any oxidation, manufacturers perform the irradiation in a vacuum or under an inert gas such as nitrogen or argon [102]. Since there is no oxygen available, the free radicals will recombine and form UHMWPE cross-links rather than oxidise the UHMWPE.

Another method of sterilisation is ethylene oxide sterilisation (EtO). EtO has a high toxicity and is able to neutralise bacteria, spores and viruses. EtO can be used for UHMWPE parts as there are no constituents which are able to react or bind to the toxic gas. Therefore, EtO has no substantial influence on the mechanical, physical and mechanical properties of the polymer [103,104]. Sterilisation of UHMWPE is achieved by diffusion of EtO into near surface regions (up to 2 mm depth), then allowing it to diffuse out [75]. It is important that all ethylene diffuses out of the polymer as it can be toxic for biological tissues. Studies on retrieved implants have shown that EtO

sterilised UHMWPE ex-plants have a less surface damage and delamination compared to those which underwent gamma sterilisation [105].

The third possible method of sterilisation is gas plasma, a surface sterilization method that relies upon ionized gas for deactivation of biological organisms [99]. Either low-temperature peracetic acid gas plasma or low-temperature hydrogen peroxide gas plasma can be used. Many different studies show that gas plasma has no effect on the mechanical, chemical and physical properties of the polymer [106–109]; however, it has been shown that the mechanical properties of porous UHMWPE and UHMWPE fibre can change as it goes through GP. Studies have hypothesised this is because gas plasma reacts with the surface of the polymer, and porous or fibrous UHMWPE have a higher surface area [104]. The main advantage of gas plasma is that it does not leave any toxic residue in the polymer and does not create free radicals.

Different manufacturing procedures tend to use different methods of sterilisation and none of these options can be considered as the preferred method. All these methods have some disadvantages; radiations create free-radicals, while there is a possibility that EtO leave toxic residues within the UHMWPE however to the date of this study there is no case of toxicity. Finally GP might modify the surface chemistry of the polymer [104].

Packaging is important, as the UHMWPE components are usually stored prior to implantation. There are three clinically approved classes of packaging, including gas permeable packaging (class I), multi-layer film barrier packaging (class II) and barrier packaging (class III). All the manufactured at entitled to show an expiration date on the packaging}. {The main difference between the types of packing is the polymers used in the packages. The polymeric materials of each type of packaging has been explained in Figue 3.

A study by Costa *et al* examined the oxidation level of the parts packed using one of the three classes [110]. The oxidation index was calculated based on American society for Testing and Materials (ASTM). According to the standard the oxidation index of the parts should be less than 1 to be suitable for clinical application. Prior to the expiry date the oxidation index of the parts in all three different type of packaging were less than 0.5 and there was no statistically significant difference between the values of the oxidation index of different groups ($p < 0.05$ for Mann-Whitney tests). On the other hand, significant oxidation was associated with class I and II expired packaging but not class III [110].

Overall, all three types of packaging meet ASTM requirements and none of them causes a significant alteration in the chemistry of the polymer unless the packaging is expired.

Radiopaque UHMWPE

At the time of this study, there was no commercially available bulk radiopaque UHMWPE. However, Bogie *et al*. used bismuth trioxide to develop a novel radiopaque UHMWPE fibres [18] for an application in a growth-guidance system for early-onset scoliosis. In this study 20 wt%, Bi_2O_3 particles were blended into each UHMWPE fibre [18]. This polymer is available on the market under the commercial name of Dyneema.

However, this product is relatively new and there are not many publications examining the effect of Bi_2O_3 on the mechanical properties of the UHMWPE. Bogie *et al* referred to unpublished data which confirmed all the samples containing Bi_2O_3 survived the fatigue test (N=5 million cycles, F=1350 N) [18].

Recently, Roth et al. studied the effect of the addition of Bi_2O_3 on the fatigue and tensile properties of UHMWPE woven cables [111]. Their study suggested that the tensile and fatigue strength of the UHMWPE were not deleteriously affected by the addition of Bi_2O_3 particles. Contrary to expectations, a leaching study did not find a detectable release of Bi_2O_3 in the *in vitro* environment [111]; however, the animal testing detected particles of Bi_2O_3 in different tissues [18]. One possible explanation for this difference is that in this study the samples were not loaded, and furthermore, the saline solution used does not accurately represent the in vivo environment [112].

There are no clinical studies are available with regard to the radiopaque UHMWPE fibre. Histological studies on the surrounding tissues of the animals showed no chronic inflammation to the radio-pacifying agent [18],

In a different study Kozakiewicz *et al.* attempted to make a radiopaque UHMWPE using TiO_2 [113]. Their experimental data suggested that some of the mechanical properties of the polymer including hardness, tensile modulus and strength of modulus of the polymer decreased. Also, even though a slight radiological detection was possible, the radiopacity of this polymer was not comparable with metals.

A few patents have disclosed methods to create radiopaque UHMWPE [114,115]. One of them suggested combining UHMWPE with oil-based fluids containing heavy elements such as iodine [114]. Another patent by US researchers used

an ion plasma deposition coating to make UHMWPE visible in X-ray images [116]. One of the limitations with the use of a coating is its adhesion strength to the main component, though this is an interesting approach which could have potential for further research.

Critique and Research Gaps

UHMWPE is the bearing material for most of the orthopaedic replacements. The polymer has a limited radiopacity wear resistance and antimicrobial properties which if improved, could enhanced the longevity of the implant.

One of the limitations with UHMWPE components is lack of radiopacity. Therefore, early diagnosis of failure can be hard and it is not possible to monitor the implant positioning during the surgery. Currently, there is no clinically approved radiopaque UHMWPE which can be used for bulk surgical implants. The only radiopaque UHMWPE is a fibre and the technology cannot be used manufacture UHMWPE components. Therefore, enhancing the radiopacity of the polymer could have significant clinical benefits. One way to enhance the radiopacity of the polymer is by introducing a group like iodine which has a high radiopacity. As this review covered, vitamin E is an oil-based fluid which has been used to increase the oxidative stability of the polymer. Vitamin E had no detrimental effect on the mechanical properties of the polymer. It can be hypothesised that other oil-based fluids are also able to diffuse into the polymer. Lipiodol is another oil-based fluid with similar properties to vitamin E and the fluid contains iodine, so it is radiopaque. Lipiodol can be diffused into the polymer and enhance the X-ray attenuation of the part [114].

Wear of the UHMWPE bearing is the major cause of failure and a key limitation. Hence, many researchers have attempted to enhance the wear resistance of the polymer to reduce the production of wear particles and enable implants to have greater longevities. Introducing cross-linking and vitamin E to the polymer, using thermal treatment are ways of enhancing the wear resistance. However, wear is still a common cause of failure. A few patents have been disclosed which aim to enhance the wear resistance of UHMWPE parts. One of them suggested the polymer resin can be irradiated prior to consolidation to have a better control on the radiation and achieving a higher degree of cross-linking [117]. A possible complication is that a high degree of cross-linking reduces to the ductility of the part, hence it is preferable to limit the cross-linking to the surface of the polymer not the bulk. Another possible challenge in this method is that radiation may enhance the rate of oxidation due to the formation of free radicals. Although most of the time the part will be stored in a non-oxidative environment, oxidation can occur *in vivo* and is increased by certain macromolecules in the synovial fluid such as Squalene [118]. The feasibility of running the consolidation and manufacturing process in an inert environment is low.

Another patent suggested that the use of sequential irradiation and followed by sequential annealing is able to reduce the oxidation and enhance the wear resistance [119]. This is because each radiation can be low while the total dose of irradiation is sufficient enough to achieve a high degree of cross-linking. A possible limitation of this method is controlling the location of the cross-linking. To retain the mechanical properties of the polymer, cross-linking should be limited to the surface of the polymer. Micro-injection moulding attempted to be used to control physical and chemical

properties of the polymer and enhance the wear resistance [120]. Due to the high molecular weight of the polymer, this method can be very expensive.

Most of the methods that enhance the wear resistance of the polymer may lead to the reduction of some other mechanical properties of the polymer. The fatigue crack propagation resistance of cross-linked UHMWPE is approximately %40 lower than the none cross-linked polymer [55,96]. This is a source of concern, especially where the implant is subjected to a high stress. Hence there should be a way to enhance the fatigue resistance of the polymer without jeopardizing the wear resistance. Currently, manufacturers try to limit cross-linking to the articulating surface, so the mechanical properties of the bulk stay intact. This method is not feasible for curved surfaces. A study by Oral et al. attempted to manipulate the degree of cross-linking by using a spatially variant concentration profile of vitamin E during irradiation [121]. The surface of the polymer has a lower concentration of vitamin E than the bulk and their experimental data was promising. Using materials with a higher fatigue resistance can be very beneficial as it means a thinner part can be used. Using thin parts means surgeons would be able to preserve a higher amount of the bone stock and reduce the chance of dislocation [121].

Bacterial infection is a post-operative complication and one of the main cause of early failure [122,123]. Around 4000 to 8000 infected knee implants requiring surgical revision annually [124]. Due to lack of blood supply around the implant, it can be hard to deliver a drug to the site of surgery. Localised drugs and antibiotics are normally used after the surgery. This means patients will be exposed to a high dose of drugs which can be dangerous [125]. Furthermore, this is not a long term solution. Hence, making an implant with sustained antimicrobial ability can be very beneficial. So a few studies have attempted to use UHMWPE as a drug delivery device [126,127]. A study

by Kumar *et al*. attempt to coat the inner surface of with some drug loaded biodegradable polymer [126] , so as the polymer wear off drugs will be realised to the site of surgery. In this case, retaining the tribological and mechanical properties of the polymer can be very challenging. Muratoglu *et al,* tried to mould UHMWPE with vancomycin which is an antibiotic; their results showed that the present of the drug reduced the ultimate strength and the impact toughness of the polymer. Antimicrobial properties of UHMWPE can also be enhanced using ion implantation. The experimental results showed that the bacterial adhesion reduces up to 90% depending on type of the ion [128]. There is no published information available with regards to alteration in the mechanical properties of this type of resin polymer.

This section attempted to cover the gaps of research and how UHMWPE can be modified to enhance. The mobility and quality of life for the patients. Radiological limitation of UHMWPE led to difficulty in implant positioning and post-operative follow-up. Wear resistance and fatigue propagation of the polymer should be improved and anti-microbial UHMWPE can reduce the risk of revision surgery.

Conclusion

As Figure 4 shows the number orthopaedic procedure increases every year. Therefore, this paper has reviewed and explained the clinical applications of UHMWPE, how polyethylene implants are manufactured and the concerns associated with them in orthopaedic replacement.

Ultra-high molecular polyethylene is the material of choice for the orthopaedics bearing materials. The experimental data showed that the polymer has a friction of approximately 0.5, however, polymer wear properties are limited and the resistance to wear decreases with time. A possible explanation is oxidation caused by free radicals.

Oxygen is able to diffuse through the polymer even very slowly. Oxidation causes breakage of the polymer chains, making the polymer less ductile. Plastic deformation of the polymer is a way that polymer resists the fracture crack propagation. Therefore, as the ductility decreases, the polymer resistance to crack decreases.

Another common cause of failure is wear and researchers have attempted to enhance the wear properties of the polymer, which can be achieved by introducing the cross-linking. Depending on the amount of cross-linking, the wear resistance of the polymer can be enhanced by 90% however cross-linking will reduce the resistance of the polymer to crack propagation and fatigue. The radiation dose of 50-100 kGy is required for cross-linking. Also free radicals are required to form cross-links. If there is a free radical trapped inside the crystalline areas of polymer, over the time it can react with oxygen and cause oxidation.

Thermal treatment was introduced to reduce the amount of the free radicals inside the polymer. Post-irradiation melting leads to the reduction in the crystallinity which reduces the other properties of the polymer.

Alternative approaches have been developed to enhance the polymer oxidation and wear resistance. One them is incorporating vitamin E, experimental and clinical data so far suggested that there is no short term complication. Vitamin E was clinically introduced on 2007 and there is no long term information available.

Even though wear and oxidation reduced significantly since the first generation of bearing, they are still cause major concern. Radiopacity of the polymer can be enhanced to improve the wear analysis of the implants as well as diagnose early failure.

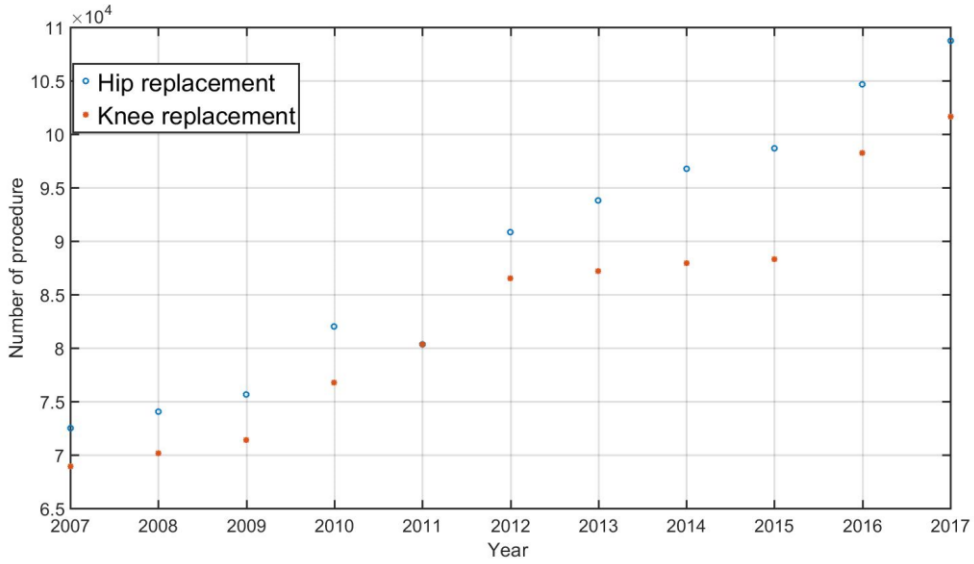

Figure 4. The number of hip and knee replacements in England and Wales

Acknowledgement

I would like to thank to my supervisors Dr Elise Pegg and Professor Richie Gill for their great support and kind advice.

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