

## ABSTRACT

In natural synovial joints under physiological conditions, fluid thin-film lubrication by the hydrated intermediate layer of cartilage is known to be essential for the smooth motion of the joints. In artificial joints with considerably less efficient lubrication as compared to that of synovial joints, polyethylene (PE) wear leading to osteolysis and aseptic loosening is considered to be a common factor limiting the longevity of total hip arthroplasty (THA). A nanometer-scale layer of poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC) with cartilage-mimicking brush-like structures on a cross-linked PE (CLPE) surface, which may realize ideal hydrophilicity and lubricity resembling the physiological joint surface, has been developed for reducing PE wear. In this study, we investigated the effect of photo-irradiation time during graft polymerization and the resultant characteristics of the PMPC brush-like layer. The density of the PMPC layer increased with the photo-irradiation time. The hip joint simulator wear test confirmed that PMPC-graft CLPE with a high density of PMPC layer cups exhibited minimal wear as compared to untreated CLPE cups. Thus, high-density PMPC grafting is essential for maintaining the high wear-resistance of PMPC-grafted CLPE. In order to obtain a PMPC layer with high density, the photo-irradiation time must be greater than 45 min (approximately 90 min). The cartilage-mimicking, density brush-like structure of the PMPC-grafted CLPE could confer high durability to acetabular cups in THA.

*Key words:* joint replacement; polyethylene; phosphorylcholine; graft polymerization; wear mechanism

## Introduction

The number of artificial hip joints used for primary and revised hip replacement is increasing substantially every year all over the world [18]. This indicates that the quality of artificial hip joints has become increasingly important. The most popular artificial hip joint system is a bearing couple composed of polyethylene (PE) and a cobalt-chromium-molybdenum (Co-Cr-Mo) alloy. However, osteolysis has emerged as a serious issue [6, 35]. Osteolysis is triggered by host inflammatory responses to PE wear particles originating from the interface [5, 12, 31], which induces their phagocytosis by macrophages and the ensuing secretion of bone resorptive cytokines [3]. Hence, different combinations of bearing surfaces and improvements in bearing materials have been studied with the aim of reducing the number of PE wear particles and extending the longevity of artificial hip joint [19, 20, 26, 30, 32].

Surface modification is important for the improvement of bearing materials. Recently, we developed an artificial hip joint based on a new concept by using poly(2-methacryloyloxyethyl phosphorylcholine (MPC)) (PMPC) grafted onto the surface of cross-linked PE (CLPE; PMPC-grafted CLPE); this device was designed to reduce wear and suppress bone resorption [21-24, 27-29]. MPC, a methacrylate monomer, is a novel biomaterial designed and developed by Ishihara et al., and it mimics the neutral phospholipids of cell membranes [8]. MPC polymers are one of the most common biocompatible and hydrophilic polymers studied thus far, which have potential application in a variety of fields including biology, biomedical science, and surface chemistry [9, 16, 17, 33, 34, 36]. Surface modifications of MPC polymers for other medical devices have already been shown to suppress biological reactions even when they are in contact with living organisms and are now clinically used on the surfaces of intravascular stents, soft contact lenses, and artificial lungs and hearts under the authorization of the Food and Drug Administration (FDA) of the United States [10, 13, 39]. Hence, there may be no theoretical drawback or risk of applying this technology to clinical use.

The grafting of polymeric molecules onto the substrate through covalent bonding is well known as a method for modifying the polymer surface [38]. Grafting polymerization is mostly performed using

either of the following methods: (1) surface-initiated graft polymerization, termed the “grafting from” method, in which monomers are polymerized from initiators or comonomers and (2) adsorption of the polymer to the substrate, termed the “grafting to” method (i.e., dipping, cross-linking, and ready-made polymers reacting with the substrate) [11, 37]. The former method has an advantage over the latter method in that it synthesizes a high-density polymer brush. The nanometer-scale surface modification of the novel artificial joint developed in this study was accomplished using a photo-induced radical polymerization technique that was similar to that used in the “grafting from” method. However, in this technique, controlling the density of the grafted PMPC was difficult [9].

To resolve this issue, we investigated the effect of photo-irradiation time on photo-induced graft polymerization. The results revealed that it was possible to control PMPC graft chains in order to reduce wear of PMPC-grafted CLPE and extend the longevity of artificial hip joints.

## **Materials and methods**

### **MPC graft polymerization**

A compression-molded UHMWPE (GUR1020 resin; Poly Hi Solidur Inc., IN, USA) sheet stock was irradiated with a gamma-ray of 50 kGy in N<sub>2</sub> gas and annealed at 120°C for 7.5 h in N<sub>2</sub> gas in order to attain cross-linking. The CLPE specimens were machined from this sheet stock after cooling.

The CLPE specimens were immersed in an acetone solution containing 10 mg/mL benzophenone for 30 s and then dried at room temperature in order to remove the acetone. MPC (NOF Corp., Tokyo, Japan) [8] was dissolved in degassed pure water to obtain 0.50-mol/L MPC aqueous solution, and the CLPE specimens coated with benzophenone were immersed in this solution. Photo-induced graft polymerization on the CLPE surface was performed using UV irradiation (UVL-400HA ultra-high pressure mercury lamp; Riko-Kagaku Sangyo Co., Ltd., Funabashi, Japan) with an intensity of 5 mW/cm<sup>2</sup> at 60°C for 11 to 180 min; a filter (Model D-35; Toshiba Corp., Tokyo, Japan) was used restrict the passage of UV light to wavelengths of 350 ± 50 nm. After polymerization, the PMPC-grafted CLPE specimens

were removed, washed with pure water and ethanol, and dried at room temperature. These specimens were then sterilized by 25 kGy gamma-ray under N<sub>2</sub> gas.

### **Surface analysis of PMPC-grafted CLPE**

The surface elemental contents of obtained PMPC-grafted CLPE were analyzed using X-ray photoelectron spectroscopy (XPS). The XPS spectra were obtained using an XPS spectrophotometer (AXIS-HSi165; Kratos/Shimadzu Co., Kyoto, Japan) equipped with an Mg-K $\alpha$  radiation source by applying a voltage of 15 kV at the anode. The take-off angle of the photoelectrons was maintained at 90°. Each measurement was scanned five times, and five replicate measurements were performed on each sample. The average values were taken as the surface elemental contents.

Functional group vibrations of the PMPC-grafted CLPE surface were examined using attenuated total reflection (ATR) by Fourier-transform infrared (FT-IR) spectroscopy. FT-IR/ATR spectra were obtained in 100 scans over a range of 800 to 2000 cm<sup>-1</sup> by using an FT-IR analyzer (Perkin-Elmer FT-IR 1650; Perkin-Elmer Corp., MA, USA) at a resolution of 4.0 cm<sup>-1</sup>. The relative amount of PMPC units grafted on the CLPE surface was evaluated by quantifying of the phosphate (P–O) groups contained within the structure of an MPC unit. The relative amount of phosphate groups was defined as the P–O group index, and was calculated as follows [21].

$$\text{P–O group index} = (1080 \text{ cm}^{-1} \text{ peak intensity}) / (1460 \text{ cm}^{-1} \text{ peak intensity}) \quad (1)$$

### **Cross-sectional observation by transmission electron microscopy**

A cross-section of the PMPC layer on the PMPC-grafted CLPE surface was observed using a transmission electron microscope (TEM; JEM-1010; JEOL, Ltd., Tokyo, Japan). The specimens were first embedded in epoxy resin, stained with ruthenium oxide vapor at room temperature, and then sliced into ultra-thin films (approximately 100-nm thick) by using a Leica Ultra Cut UC microtome (Leica

Microsystems, Ltd., Wetzlar, Germany). The thickness of the PMPC layer was determined by averaging twenty points on the cross-sectional TEM image.

### **Static water-contact angle measurement and friction test**

The static water-contact angles of PMPC-grafted CLPE were measured with an optical bench-type contact angle goniometer (Model DM300; Kyowa Interface Science Co., Ltd., Saitama, Japan) using the sessile drop method according to the ISO standard 15989. Subsequently, fifteen replicate measurements were performed on each sample, and the average values were taken as the contact angles.

The friction test was performed using a ball-on-plate machine (Tribostation 32; Shinto Scientific Co., Ltd., Tokyo, Japan), according to the ASTM standard F732. Each of several PMPC-grafted CLPE surfaces with various photo-irradiation times were used to prepare five sample pieces. A Co-Cr-Mo alloy ball with a diameter of 9 mm was prepared. The surface roughness ( $R_a$ ) of the ball was  $<0.01$ , which was comparable to that of femoral head products. The friction tests were performed at  $37^\circ\text{C}$  with a load of 0.98 N, sliding distance of 25 mm, and frequency of 1 Hz for a maximum of 100 cycles. A mixture of 25 vol% bovine serum, 20 mM/L ethylene diamine tetraacetic acid (EDTA), and 0.1 mass% sodium azide was used as the lubricant. The mean dynamic coefficients of friction were determined by averaging five data points from the 100 (96–100) cycle measurements.

### **Hip joint simulator wear test**

A 12-station hip joint simulator (MTS Systems Corp., MN, USA) with CLPE and PMPC-grafted CLPE cups each with inner and outer diameters of 26 and 52 mm, respectively, was used for the hip joint simulator wear test according to the ISO standard 14242-3. For each photo-irradiation time, four sample pieces were prepared. A Co-Cr-Mo alloy ball with a diameter of 26 mm (Japan Medical Materials Corp., Osaka, Japan) was used as the femoral component. A mixture of 25 vol% bovine serum was used as the lubricant, which was replaced every  $0.5 \times 10^6$  cycles. Walks, which simulated a physiological loading

curve (Paul-type) with double peaks at 1793 and 2744 N loads, with a multidirectional (biaxial and orbital) motion of 1 Hz frequency were applied. Gravimetric wear was determined by weighing the cups at intervals of  $0.5 \times 10^6$  cycles. Load-soak controls ( $n = 2$ ) were used to compensate for the fluid absorption by the specimens, according to the ISO standard 14242-2. Testing was continued until a total of  $5.0 \times 10^6$  cycles were completed. After  $5.0 \times 10^6$  cycles of the hip joint simulator test, volumetric wear of the cups was measured using a three-dimensional coordinate measurement machine (BHN-305, Mitsutoyo Corp., Kawasaki, Japan) and reconstructed using 3D modeling software (Imageware, Siemens PLM Software Inc., TX, USA).

Wear particles were defined using the maximum dimensions determined by field emission scanning electron microscope (FE-SEM) analysis. The wear particles were isolated from the bovine serum solution which was used as a lubricant in the hip joint simulator wear test. The solution was sequentially filtered through a 0.1  $\mu\text{m}$  membrane filter, and the membrane was observed directly by FE-SEM (JSM-6330F; JEOL DATUM Ltd., Tokyo, Japan).

## Results

In the  $N_{1s}$  and  $P_{2p}$  spectra of Fig. 1A, clear peaks were observed only for PMPC-grafted CLPE. Peaks at 403 and 134 eV were assigned to the  $-\text{N}^+(\text{CH}_3)_3$  and phosphate groups, respectively; these peaks are characteristic of the phosphorylcholine in the MPC units. In Fig. 1B, a transmittance absorption peak attributed mainly to the methylene ( $\text{CH}_2$ ) chain in the CLPE substrate was observed at  $1460 \text{ cm}^{-1}$  for both CLPE and PMPC-grafted CLPE. However, the peaks ascribed to the phosphate ( $\text{P}-\text{O}$ ) group in the MPC unit at 1240, 1080, and  $970 \text{ cm}^{-1}$  were observed only for PMPC-grafted CLPE. Similarly, the peak at  $1720 \text{ cm}^{-1}$  observed only for PMPC-grafted CLPE corresponds to the ketone ( $\text{C}=\text{O}$ ) group in the MPC unit. The P concentration increased proportionally with photo-irradiation time; the measured content of P in PMPC-grafted CLPE with a 90-min photo-irradiation time was 5.2 (Fig. 1C). This value was almost equivalent to the theoretical value ( $\text{P} = 5.3$ ) of PMPC. In addition, the  $\text{P}-\text{O}$  group index also increased

with the irradiation time (Fig. 1D).

With photo-irradiation times longer than 45 min, a uniform PMPC layer was clearly observed on the CLPE surface (Fig. 2A); the PMPC-graft layer thicknesses became almost constant at 100 nm (Fig. 2B).

The static water-contact angle of untreated CLPE was 90° and decreased markedly with a reduction in the photo-irradiation time (Fig. 3A). For PMPC-grafted CLPE, the static water-contact angle decreased as photo-irradiation time increased. The coefficients of friction decreased markedly with an increase in photo-irradiation time and were lowest at 90 min; however, they increased at a photo-irradiation time of 180 min (Fig. 3B). The PMPC-grafted CLPE exhibited approximately 80% reduction in its dynamic friction coefficients when compared with untreated CLPE.

PMPC-grafted CLPE cups were found to undergo significantly less gravimetric wear than untreated CLPE cups (Fig. 4). The gravimetric wear of PMPC-grafted CLPE cups subjected to a 23-min photo-irradiation time started to increase after  $2.5 \times 10^6$  cycles. PMPC-grafted CLPE cups showed a slight increase in weight. This was partially attributable to greater fluid absorption in the tested cups than in load-soak controls. When using the gravimetric method, the weight loss of the tested cups is corrected by subtracting the weight gain in the load-soak controls; however, this correction cannot be perfectly achieved because only the tested cups are continuously subjected to motion and load.

Three-dimensional coordinate measurements with PMPC-grafted CLPE cups revealed little or no detectable volumetric wear, while substantial volumetric wear was detected in untreated CLPE (Fig. 5A). The wear particles of untreated CLPE and PMPC-grafted CLPE cups during  $4.5\text{--}5.0 \times 10^6$  cycles of the hip joint simulation test, as characterized by FE-SEM, were predominantly sub-micrometer-sized granules (Fig. 5B). Significantly fewer wear particles were found for PMPC-grafted CLPE cups with photo-irradiation times of 45, 90, and 180-min than for untreated CLPE cups and for PMPC-grafted CLPE cups with a 23-min photo-irradiation time.

## Discussion

In natural synovial joints under physiological conditions, fluid film lubrication by the hydrated intermediate layer is essential for the smooth motion of joints [2, 7], and a nanometer-scaled phospholipid layer which covers the joint cartilage surface provides hydrophilicity and works as an effective boundary lubricant [14]. Hence, grafting a phospholipid-like layer onto the surface may realize ideal hydrophilicity and lubricity which resemble those of the physiological joint surface. The present study revealed that the biocompatible phospholipid polymer PMPC, when grafted onto the acetabular cup surface of a total hip arthroplasty (THA) prosthesis, caused high wear-resistance as shown by the reduced cup weight loss in the simulator test. This suggests that the approach may be promising for extending the longevity of THA by varying the characteristics of the nanometer-scaled PMPC layer formed on the CLPE surface via photo-induced radical graft polymerization using various photo-irradiation times.

After  $5.0 \times 10^6$  cycles of the hip joint simulator test, we confirmed that PMPC-grafted CLPE cups with a P-O group index of 0.32 to 0.48 exhibited a relatively low steady wear rate ( $-0.02$  to  $0.32$  mg/ $10^6$  cycles). This indicates that PMPC-grafted CLPE cups with a P-O group index greater than 0.32 show a  $> 90\%$  reduction in steady wear rate compared with untreated CLPE as well as with PMPC-grafted CLPE cups having a low P-O group index (0.11) and a low density of PMPC graft chains. The steady wear rate of the PMPC-grafted CLPE cups with 23-min photo-irradiation time and that of untreated CLPE are almost the same. The advantage of photo-induced graft polymerization comes from the fact that the grafted PMPC gave a high lubricity only on the surface, and had no effect on the bulk properties of the CLPE substrate. As shown in Fig. 3A, the water wettability of the PMPC-grafted CLPE surface was considerable greater than that of an untreated CLPE surface. Previous studies reported that the water molecules adsorbed on the surface of the highly hydrophilic PMPC brushes act as lubricants and reduce the interaction between the brushes and the counter-bearing face [1, 15]. Therefore, the artificial hip joint bearing with the PMPC-grafted surface exhibited considerably higher lubricity than that without PMPC. The significant reduction in the coefficient of friction of the PMPC-grafted surface resulted in a substantial improvement in wear resistance (Fig. 3B). We assume that the bearing surface of the artificial hip joint



combined with PMPC exhibited the fluid film lubrication of the hydrated intermediate layer (i.e., hydration lubrication) and suggest that this novel artificial hip joint mimics the cartilage in natural joints.

In order to obtain a PMPC layer with high density, the photo-irradiation time must be controlled [9]. The density of PMPC chains on the surface of the CLPE gradually increased with increasing photo-irradiation time, and the entire surface of the CLPE was coated using photo-irradiation times longer than 45 min. As shown in Fig. 2B, with longer photo-irradiation times, the thickness of the PMPC layer remained the same (100 nm). In PMPC-grafted CLPE cups with a high surface density of PMPC graft chains, the PMPC graft chains are assumed to stand up and exhibit a brush-like structure [1, 4, 25]. Fig. 1D implies that the density of PMPC chains on the CLPE surface was different, even if the water wettability and thickness of the PMPC layer in PMPC-grafted CLPE was constant (15° and 100 nm, respectively); this is because the P–O group index changed remarkably within the range of 0.3 and 0.5. These results indicate that the density of the grafted PMPC can be controlled by polymerization time, since the number of polymer chains produced in a radical polymerization reaction is generally correlated with the photo-irradiation time.

PMPC-grafted CLPE cups decreased the amount of wear particles isolated from the lubricants. Since wear particles from PMPC-grafted CLPE surfaces were hardly observed due to their extremely small amounts, they could not be classified according to size (Fig. 5B) [28]. In contrast, the majority size of the wear particles from untreated CLPE surfaces was 0.1–1.0  $\mu\text{m}$ . In addition to enhancing the wear resistance of the cups, reducing bone resorptive responses to generated wear particles is important for preventing periprosthetic osteolysis. Such responses are dependent not only on the total amount of wear particles, but also on the proportion of particles which are within the most biologically active size range. The CLPE cups release a high number of sub-micrometer and nanometer-sized particles which are known to induce a greater inflammatory response than larger particles. Hence, although CLPE indeed causes a reduction in the total amount of particles, it might not necessarily lead to the prevention of periprosthetic osteolysis. Clinical evidence regarding the longevity of artificial joints with CLPE is anticipated in the

future. A previous study has shown that polymer particles covered with PMPC are biologically inert with respect to phagocytosis by macrophages and subsequent bone resorptive actions [27]. An increasing number of studies address potential pharmacological modifications of the adverse host response to wear particles using agents such as cytokine antagonists, cyclooxygenase-2 inhibitors, and osteoprotegerin, or anti-RANKL (receptor activator of NF- $\kappa$ B ligand) antibody. However, they may cause serious side effects because the agents must be taken for a long period after surgery and because they are not currently targeted to the site of the problem. Because the absence of side effects has already been confirmed clinically by several medical devices, PMPC-grafting is superior to these developing pharmacologic treatments. In addition, clinical trials of THA with PMPC-grafted CLPE acetabular cups are currently underway to evaluate clinical efficiency.

In conclusion, when compared with untreated CLPE and PMPC-grafted CLPE with a low P–O group index, PMPC-grafted CLPE with a high P–O group index (cups with a high density of PMPC graft chains) exhibited a > 90% reduction in steady wear rate. Thus, PMPC grafting at a high density is essential for maintaining the high wear-resistance of PMPC-grafted CLPE acetabular cups in THA over long periods of time. In order to obtain a PMPC layer with high density, the photo-irradiation time must be greater than 45 min (approximately 90 min). The cartilage-mimicking, high-density brush-like structure of PMPC-grafted CLPE could confer a high durability to acetabular cup bearings in THA.

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## Figure captions

Figure 1. XPS and FT-IR/ATR analysis of PMPC-grafted CLPE. (A) XPS spectra of untreated CLPE and PMPC-grafted CLPE surfaces. The peaks in the nitrogen ( $N_{1s}$ ) and phosphorus ( $P_{2p}$ ) atom regions at 403 and 135 eV, respectively, are specific to MPC. (B) Surface elemental concentration ( $n = 5$ ) of PMPC-grafted CLPE as a function of photo-irradiation time. Data are expressed as means  $\pm$  standard deviations. (C) FT-IR/ATR spectra of the surfaces. Absorptions representing the phosphate group (P–O) at 1240, 1080, and 970  $\text{cm}^{-1}$ , and ketone group (C=O) at 1720  $\text{cm}^{-1}$  are specific to MPC, while the methylene group ( $\text{CH}_2$ ) at 1460  $\text{cm}^{-1}$  is common to the untreated CLPE and PMPC-grafted CLPE surfaces. (D) P–O group index ( $n = 1$ ) of PMPC-grafted CLPE surface as a function of photo-irradiation time.

Figure 2. Cross-sectional analysis of PMPC-grafted CLPE. (A) Cross-sectional TEM images of PMPC-grafted CLPE obtained with various photo-irradiation times. Scale bar indicates 100 nm. (B) PMPC-graft layer thickness ( $n = 20$ ) determined by TEM observation. Data are expressed as means  $\pm$  standard deviations.

Figure 3. Surface functional analysis of PMPC-grafted CLPE. (A) Static water-contact angle ( $n = 15$ ) of PMPC-grafted CLPE as a function of photo-irradiation time. Data are expressed as means  $\pm$  standard deviations. (B) Dynamic coefficients of friction ( $n = 5$ ) for PMPC-grafted CLPE as a function of photo-irradiation time. Data are expressed as means  $\pm$  standard deviations.

Figure 4. Gravimetric wear ( $n = 4$ ) of PMPC-grafted CLPE cups with various photo-irradiation times during the hip joint simulator wear test. The P–O group indices are shown in



parentheses of captions. Data are expressed as means  $\pm$  standard deviations.

Figure 5. Analysis of PMPC-grafted CLPE after the hip joint simulator wear test. (A) Three-dimensional coordinate measurements of PMPC-grafted CLPE cups obtained with various photo-irradiation times. (B) SEM images of wear particles isolated from lubricants of the hip joint simulator wear test. Scale bar indicates 5  $\mu\text{m}$ .

Figure 1  
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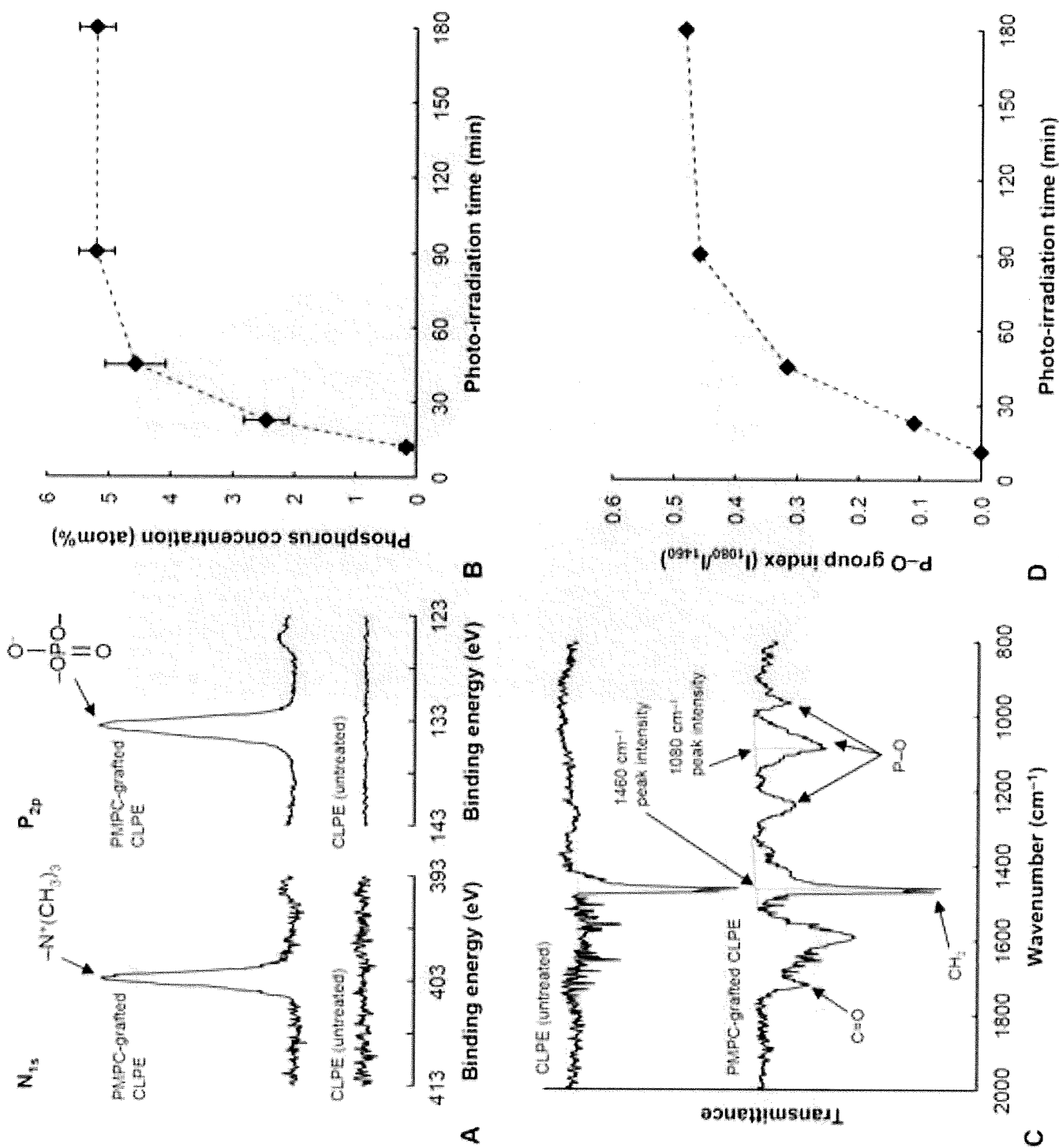


Figure 2

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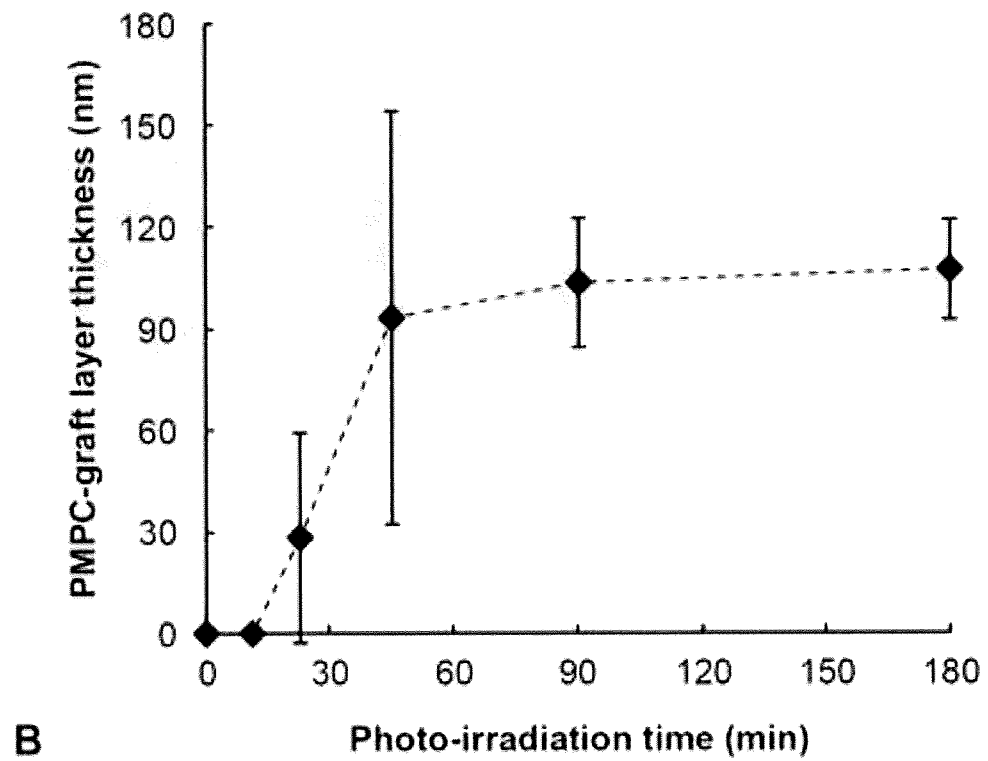
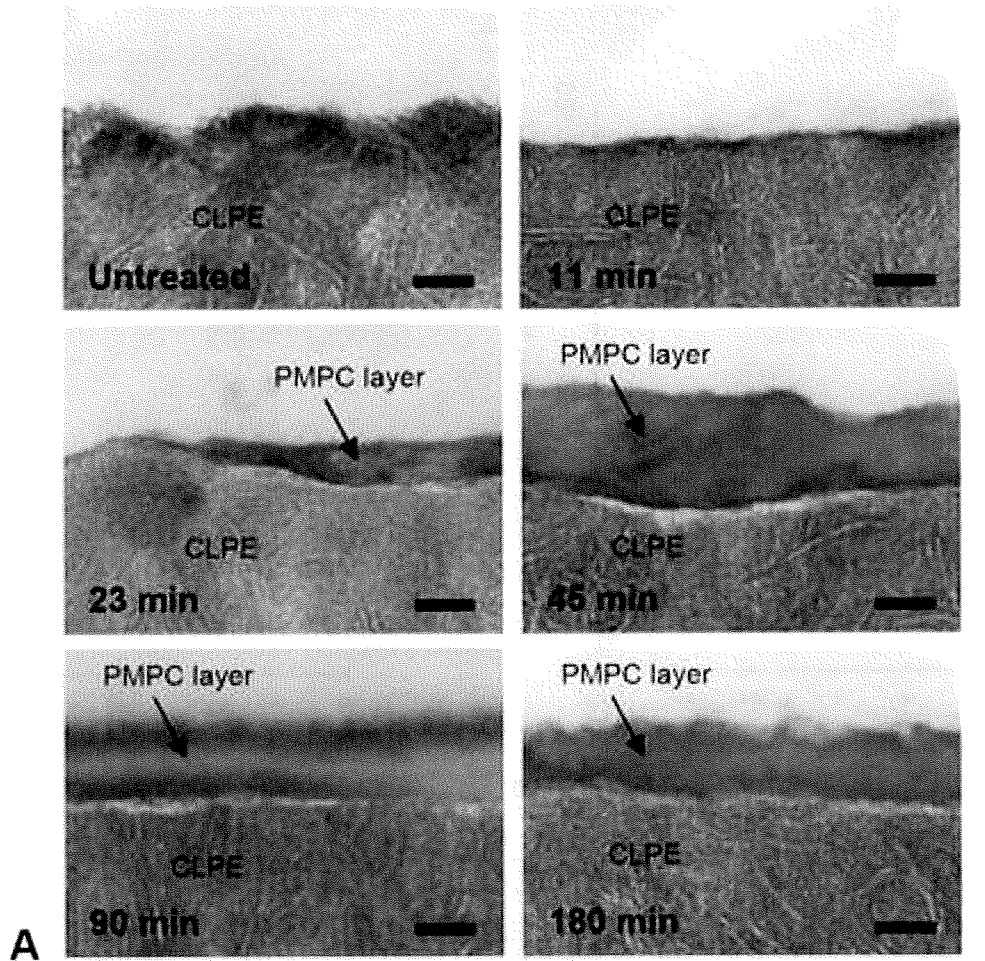


Figure 3  
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