

# Interaction of Pluronic F-127 with serum proteins and its feasibility as a lubricant additive for CoCrMo/UHMWPE interface

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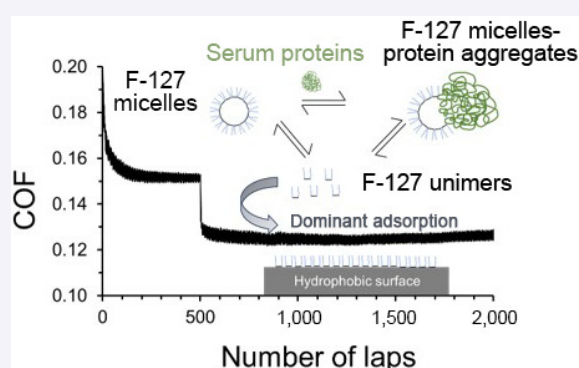
**ABSTRACT:** In this study, we report the feasibility of Pluronic “F-127” as a lubricant for CoCrMo/ultrahigh molecular weight polyethylene (UHMWPE) interface in serum as a synovial fluid (SyF) model. While adsorption and lubrication properties of amphiphilic copolymers such as F-127 at a hydrophobic surface in aqueous media have been well established, its efficacy in serum can be more complicated due to potential interaction of F-127 with serum proteins or competitive adsorption onto UHMWPE surface. When an aliquot of F-127 solution (in concentration range of F-127 from 0.1% to 20% dissolved in 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES)) was added into serum where a CoCrMo pin is sliding against a UHMWPE disk, an immediate decrease in the coefficient of friction (COF) (ca. 20%) was observed. A spectroscopy study employing dynamic light scattering (DLS), circular dichroism (CD) spectroscopy, and ultraviolet (UV) absorbance spectroscopy has shown that serum associatively interacts with F-127 when the F-127 concentration is above critical micelle concentration (CMC), leading to an increase in hydrodynamic size and alteration of tertiary structure of proteins in serum. Mixing of F-127 with the solutions of selected single component biomolecules of serum showed that  $\gamma$ -globulin is the primary molecule that interacts with F-127 above CMC, followed by albumin. Meanwhile, no indication of interaction was observed when the F-127 concentration was below CMC. It is thus proposed that the observed lubricating effect of F-127 in serum is primarily due to the faster surface adsorption kinetics for its smaller molecular weight compared to serum proteins. Further, comparable % reduction in COF over a wide range of F-127 concentration indicates that unimeric F-127 molecules are dominant in contribution to friction-lowering effect even at above CMC at CoCrMo/UHMWPE interface in serum.

**KEYWORDS:** F-127; micelle; lubricant; serum; ultrahigh molecular weight polyethylene (UHMWPE)

## 1 Introduction

It has been known that wear debris of joint replacement implant materials, such as those used in total hip arthroplasty (THA) or total knee arthroplasty (TKA), may trigger a cascade of adverse immune responses, leading to osteolysis, aseptic loosening, and failure of the implants in the long run [1–6]. More than half of implants failure is known to be associated with aseptic loosening [1, 7], and the survival rate of articular joint implants becomes concerning after 15–20 years [1, 8]. This lifespan is considered somewhat short for young patients as they may need revision surgery, which is riskier and more costly [9, 10]. To date, efforts to mitigate this problem have been directed mainly toward the development and/or application of new bearing materials with superior tribological properties. Improvement of wear resistance

of ultrahigh molecular weight polyethylene (UHMWPE) by crosslinking, and then addition of vitamin E or other additives is a representative example [5]. Surface coating of UHMWPE with brush-like, hydrophilic polymer chains at a high surface-grafting density, such as phospholipid polymer 2-methacryloyloxyethyl phosphorylcholine (MPC) [11], polyethylene glycol (PEG) [12], or acrylic acid (AA) [13] is another example to improve anti-friction and anti-wear properties. This idea was inspired by or associated with a progress in aqueous lubrication in recent years, in which hydrophilic and surface-adsorbing, brush-forming polymer chains provide an excellent lubricating effect based on the formation of hydrating layer at the tribological interface [14–16]. Given that water is employed as base stock, this approach could be readily extended to lubricate biomaterials in biological environment. Despite the successful demonstration of lowering effects of friction



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## Nomenclature

AA	Acrylic acid	NCS	Newborn calf serum
CD	Circular dichroism	PEG	Poly(ethylene glycol)
CMC	Critical micelle concentration	PEO-PPO-PEO	Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide)
COF	Coefficient of friction	SyF	Synovial fluid
DLS	Dynamic light scattering	THA	Total hip arthroplasty
FBS	Fetal bovine serum	TKA	Total knee arthroplasty
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethane-sulfonic acid	UHMWPE	Ultrahigh molecular weight polyethylene
MPC	2-Methacryloyloxyethyl phosphorylcholine		

and wear by grafting brush-like, hydrophilic polymer chains on UHMWPE surfaces in initial stages [11–13], we raise a question on how long the coatings can indeed serve as effective lubricating layers when they are irreversibly immobilized on the surface via chemical bonding; the polymer chain layers may be removed eventually from accumulated tribostress and cannot be recovered without retrieval of the implants. To ensure a sufficiently long lubricating performance so that the lifetime of implants can be substantially extended, a viable solution to supply polymer chains, i.e., lubricant additives, to joint implants, repeatedly and periodically, similarly with the lubrication of engineering machinery in general, needs to be devised.

To be able to replenish polymer chains over a long term, polymer chain grafting approach should be “grafting-to”, rather than “grafting-from” [17, 18]. In “grafting-to” approach, ready-made polymers are added to a target substrate surface, and the grafting is achieved via spontaneous adsorption onto the surface. As the target substrate surface in this study is hydrophobic UHMWPE, amphiphilic copolymers, i.e., those composed of hydrophobic-hydrophilic blocks, can be readily employed. In particular, “Pluronic”, polyethylene oxide-polypropylene oxide-polyethylene oxide (PEO-PPO-PEO) triblock copolymers, are cheap and easy-to-access candidates. Furthermore, some of Pluronic, such as F-127 and F-68, have been Food and Drug Administration (FDA)-approved as biocompatible and used in living organisms [19–21]. Amphiphilic block copolymers are known to spontaneously adsorb onto hydrophobic surfaces via hydrophobic interaction between hydrophobic block and hydrophobic substrate surfaces in aqueous media, leaving the hydrophilic blocks as dangling, buoyant chains [22, 23]. Thus, they can effectively hydrophilize hydrophobic surfaces and improve their lubricating properties.

Nevertheless, while the lubricating effect of amphiphilic copolymers for nonpolar surfaces mentioned above has been well established in water or aqueous buffer [24–26], whether its efficacy can be extended in biological environment, as in synovial fluid (SyF) is yet to be verified. For instance, amphiphilic copolymers may interact with some components of synovial fluid and affect the surface adsorption and lubricating properties. Even in the absence of such interactions, some components in synovial fluid may compete against amphiphilic copolymers to adsorb and lubricate substrate surfaces. Thus, it is necessary to first characterize and understand the interaction behavior between these copolymers and synovial fluid.

The aim of the present study is thus to run a feasibility test of Pluronic to lubricate UHMWPE surface in biological fluids and understand the results in terms of interaction between Pluronic and biomacromolecules. F-127 was selected as the lubricating copolymer among Pluronic for its proven lubricating capabilities at a hydrophobic interface in aqueous media [27, 28]. In this study, bovine synovial fluid is employed as a control, but a majority of studies were conducted with serum, as it is the most

widely used model of synovial fluid. For a systematic study, different serum models with controlled composition are also employed.

## 2 Materials and methods

### 2.1 Materials

The copolymer used in this work was Pluronic F-127 purchased from Sigma Aldrich, Denmark. F-127 is known to be a linear triblock copolymer with a central block of 65 monomers of propylene oxide (PO) between two blocks of 100 monomers of ethylene oxide (EO) and a total molecular weight of ca. 12,600 Da on average. The polymer was dissolved at different concentrations between 20 and 0.1 wt% in 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffer (1 mM) (VWR Prolabo, Denmark), which was prepared with Milli Q water and the pH was adjusted to a value of 7.4 with NaOH 0.1 M (VWR Prolabo, Denmark).

Different types and batches of serum were employed, including fetal bovine serum (FBS) from Sigma Aldrich, Denmark, and newborn calf serum (NCS) from Serana, Germany, and Pan-biotech, Germany. Bovine SyF was purchased from Lampire Biological labs, USA. Some simpler serum models were also prepared in HEPES (1 mM) at pH 7.4 with single components, including albumin from bovine serum (Sigma Aldrich, Denmark),  $\gamma$ -globulin from bovine blood (99%, Sigma Aldrich, Denmark), D-(+)-glucose (99.5%, Sigma Aldrich, Denmark), cholesterol from lanolin (99%, Sigma Aldrich, Denmark), or L- $\alpha$ -phosphatidylcholine from egg yolk (60%, Sigma Aldrich, Denmark). In addition, mixtures of those single-component model serums were prepared at different concentrations.

CoCrMo alloy was purchased from Zapp Precision Metals GmbH, Germany. CoCrMo alloy was fabricated into a cylindrical pin with a flat end (the diameter was ca. 7 mm in the stem yet was reduced to ca. 3.4 mm at the end). The flat end was further ground sequentially with a series of sandpapers from 120 to 400 grit, following rinsing with EtOH and blow drying with nitrogen. UHMWPE was purchased from Orthoplastics Ltd., UK, and was fabricated to a disk (30 mm in diameter and 5 mm in thickness).

### 2.2 Pin-on-disk tribometry

Friction measurements for sliding contacts of CoCrMo/UHMWPE pair in FBS as model synovial fluid or in FBS + F-127 solution were carried out with a pin-on-disk tribometer (CMS Instruments SA, Switzerland). The contact configuration was flat-on-flat, employing a flat-ended, cylindrical CoCrMo pin and UHMWPE disk as described above. The applied load and sliding speed were set at 10 N and 10 mm/s, respectively, for all measurements. The coefficient of friction (COF) was recorded over the entire sliding contact experiments.

## 2.3 Particle size distribution: Dynamic light scattering (DLS)

DLS measurements were carried out with a ZetaSize NANO (ZSP-Malvern) based on phase analysis light scattering via ZetaPALS particle sizing software. For each measurement, 1 mL of the solution was placed in a disposable plastic cuvette. Statistical results were obtained with the average of three different batches of the samples and 10 measurements for each batch. All the solutions were homogenized by stirring before the measurement of the particle size distributions.

## 2.4 Circular dichroism (CD) and ultraviolet (UV) absorbance spectroscopies

CD and UV-absorbance spectroscopies were carried out with a Chirascan spectrophotometer (Applied Photophysics Ltd., UK). A quartz cuvette with a path length of 1 mm was used for far-UV CD spectroscopy, while a quartz cuvette with a path length of 10 mm was used for near-UV CD and UV absorbance spectroscopies. The far-UV CD spectra were recorded between 190 and 260 nm with a step of 0.5 nm, and the near-UV CD spectra were recorded between 250 and 400 nm with a step of 1 nm. The UV-absorbance spectra were recorded between 250 and 320 nm with a step of 1 nm. An average of three measurements were obtained for each sample. Temperature was set at 20 °C for all measurements.

## 3 Results

### 3.1 Pin-on-disk tribometry

Figure 1(a) presents a representative plot of COF vs. the number of laps from the sliding contacts between CoCrMo pin on UHMWPE disk, representing the most common materials pair in THA or TKA [5], and the influence of adding F-127 solution, as characterized with pin-on-disk tribometry.

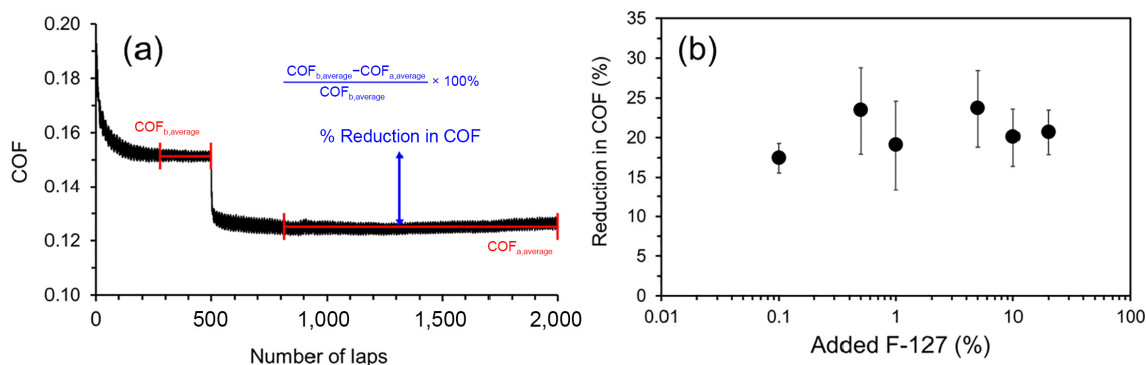
The sliding contact of CoCrMo/UHMWPE pair initially started in FBS. After the COF reached a constant value (after ca. 500 laps), an aliquot of F-127 solution (0.1% in HEPES) was added into the tribocup where a sliding contact was being taken place. The standard volume for the initial serum was 2 mL, and the added F-127 solution was 1 mL. Thus, the concentration of F-127 solution was diluted to 1/3 of the initial value. Upon addition of F-127 solution, the COF dropped immediately, as shown in Fig. 1. The magnitude of reduction in friction forces was assessed in terms of % reduction in COF upon injection of F-127 into serum (i.e.,  $\frac{\text{COF}_{b,\text{average}} - \text{COF}_{a,\text{average}}}{\text{COF}_{b,\text{average}}} \times 100\%$ , where  $\text{COF}_{b,\text{average}}$  is the

average COF before addition of F-127, yet after stabilization and  $\text{COF}_{a,\text{average}}$  is the average COF after addition of F-127 to the end of experiments, i.e., 2,000 laps). It is noted that the lubricating effect was assessed in terms of % reduction in COF mainly because the  $\text{COF}_{b,\text{average}}$  values were variant from measurement to measurement. The full data set for COF vs. laps plots (Fig. S1 in the Electronic Supplementary Material (ESM)) and the values of % reduction in COF (Table S1 in the ESM) are provided. As a reference, the lubricating effect of adding F-127 solution into HEPES buffer was also measured. However, the COF values before addition were not stabilized and often continued to increase for an extended interval (> 1,000 laps), even though an instant drop in COF was observed upon addition of F-127 solution. This is presumably because unlike in serum, CoCrMo/UHMWPE interface is not well lubricated in HEPES buffer. It made quantitative analysis difficult and thus is not included in this study. One case that showed a relatively stable COF value in HEPES buffer is presented in Fig. S2 in the ESM.

Further experiments were performed with increasing concentrations of F-127, namely 0.5%, 1.0%, 5.0%, 10%, and 20% prior to addition. CoCrMo/UHMWPE pair and serum were replaced with new settings for each measurement. The reduction in COF as a function of F-127 concentration is plotted in Fig. 1(b). The reduction in COF was 17.5% on average for 0.1% F-127 but was overlapped in error bars that were obtained from the ranges of reduction in COF as stated above, with other cases with higher F-127 concentrations, which were ca. 20%. These results indicate that F-127 can serve as an effective lubricant additive for CoCrMo/UHMWPE interface in serum. It is most notable that the reduction in COF in serum is virtually similar over a wide range of F-127 concentration, i.e., from 0.1% to 20%, despite the significantly different concentrations up to 200 times.

### 3.2 DLS

In order to understand whether/how F-127 molecules may interact with biomolecules in serum, a number of spectroscopic approaches have been employed. Firstly, the size distribution of F-127, various serums, and their mixtures were characterized with DLS. Prior to mixing with serum and any possible interaction with biomolecules that may occur therein, the size distribution of F-127 alone was characterized in HEPES in a variation of F-127 concentration. In Fig. 2, DLS data from F-127 solution as a function of concentration between 20 and 0.1 wt% are presented. The data presented in Fig. 2 are the averages over 10 measurements for each concentration, and the error for each measurement was between 1.6% and 4.2% (not shown for clarity). It should also be noted that the size distribution in Fig. 2 is presented in volume mode. In this mode, it is easier to probe the



**Fig. 1** (a) An immediate decrease of COF was observed when 1 mL of F-127 solution (0.1%) was injected into FBS (2 mL) at ~500 laps (arrow), and it persisted to the end of tests (2,000 laps). (b) Reduction in COF (%) as a function of added F-127 (concentration in %, prior to addition).

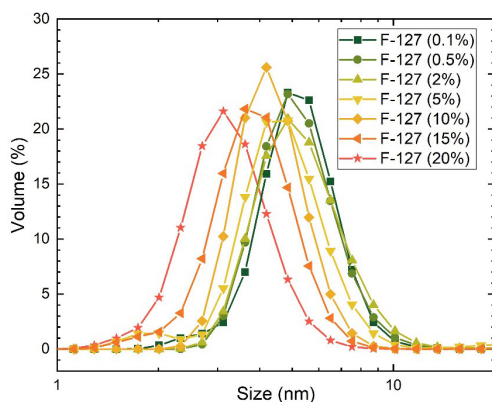


changes in size distribution with increasing F-127 concentration. More accurate values of the average particle size can be assessed from “Z-averages” presented in Fig. S3 in the ESM.

A clear tendency shown in Fig. 2 is that the particle size distribution is gradually decreasing with increasing F-127 concentration. When the concentration is higher than the critical micelle concentration (CMC) (Please note that the CMC of F-127 is around 1% in water at this temperature [29], but salts are known to decrease CMC [30], i.e., the CMC of F-127 in HEPES buffer is possibly lower than 1%), the polymer coils can self-associate to produce self-assembled structure complexes. These complexes are similar to the micelles found in surfactant systems. The results in Fig. 2 thus suggest that the F-127 micelles have a more compact structure than single coil counterparts in HEPES. The more compact conformation of concentrated polymer solutions has been reported earlier using other polymeric systems [31].

Mixtures of FBS with the F-127 solutions were prepared at a volume ratio of 2:1, giving new solutions with a concentration of F-127 at one-third of that of the initial F-127 solutions. In addition, a solution of FBS with HEPES at the same ratio (2:1) was prepared as a control. Figure 3 shows the DLS data of mixture solutions where the final F-127 concentration is below the CMC. The concentrations of F-127 in the legend are those before mixing with FBS.

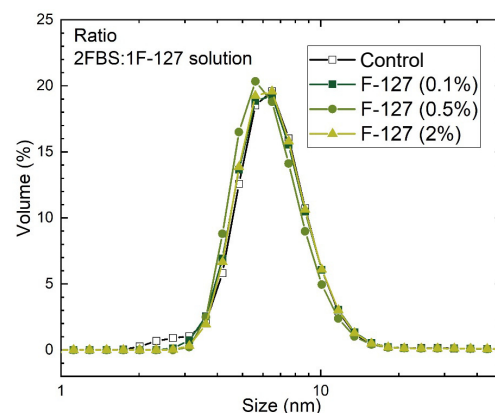
For all cases in Fig. 3, the concentration is below the CMC of F-



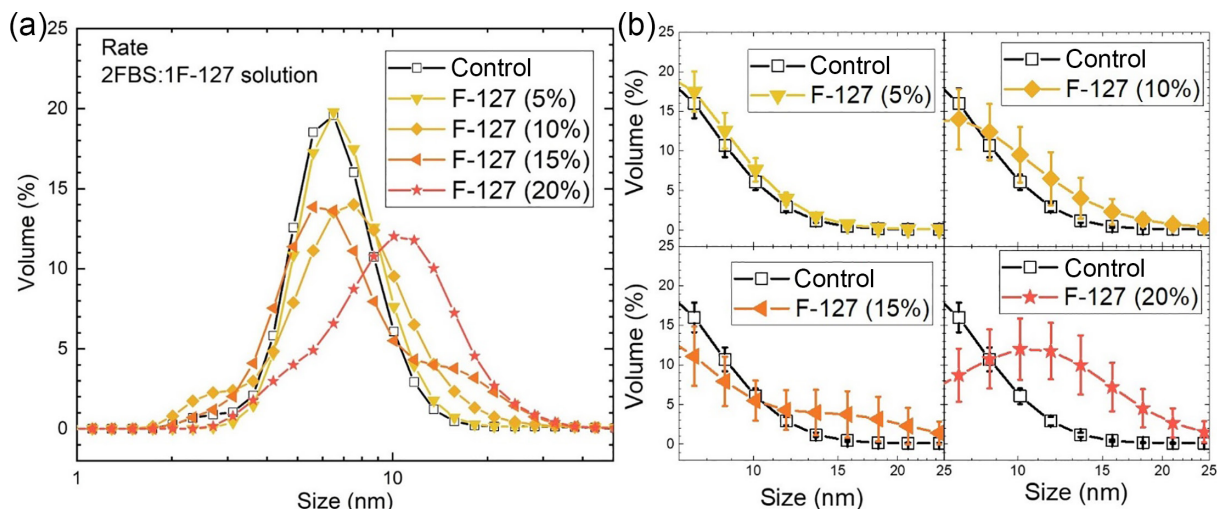
**Fig. 2** Particle size distribution of F-127 in HEPES as a function of concentration as characterized with DLS.

127, and the size distribution peaks are close to those of diluted FBS as well as F-127 solutions at low concentrations ( $< 0.5\%$ ) in Fig. 2.

Figure 4 shows the cases in which the final concentration of F-127 is above the CMC ( $> 1\%$ ) after mixing with FBS. Two features are noticeable in Fig. 4; firstly, the hydrodynamic diameter of the main peak is shifted from that of serum alone upon addition of F-127 solutions. The shifts are not simply a gradual increase or decrease with increasing F-127 concentration, but somewhat complex. For instance, the main peak shifted slightly to the right (i.e., higher hydrodynamic diameter) at 5% and 10%, then shifted to the left at 15%, and finally to the right again at 20% with respect to the main peak of the control. Secondly, regardless of the direction of the main peak shifts, a shoulder peak with a higher hydrodynamic diameter started to emerge with increasing F-127 concentration. At the highest concentration, i.e., the mixture of FBS and 20% F-127 (the final F-127 concentration of 6.7%), the shoulder has become the main peak. The evolution and development of the shoulder peaks with increasing F-127 concentration are better visualized in the magnified plots in Fig. 4(b). Since the distribution of hydrodynamic diameters of F-127 micelles (Fig. 2) and serum (controls in Figs. 3 and 4(a)) are very similar, it is not straightforward to clarify the presence of



**Fig. 3** Particle size distribution of mixtures of FBS with F-127 in HEPES at a volume ratio of 2:1 as characterized with DLS. Total concentration of F-127 is below CMC. Concentrations of F-127 in legend are those before mixing with FBS.



**Fig. 4** Particle size distribution of mixtures of FBS with F-127 in HEPES solutions at the volume ratio of 2:1. The total concentration of F-127 is above the critical micelle concentration. The concentrations of F-127 in the legend are those before mixing with FBS. (a) Display of all the plots (b) magnification of “shoulder” peaks at each concentration of F-127.

interaction between them based on these data in addition to that DLS is generally not a stand-alone experimental approach to unravel the interaction nature between two species in solution. Nevertheless, if the peaks shown in Fig. 4(a) are a simple overlay of those of serum and F-127 micelles without any interaction between them, the resulting peaks should be gradually shifted to the left only with increasing concentration of F-127 micelles because the hydrodynamic diameters of F-127 micelles are gradually decreasing with increasing concentration (Fig. 2). The occurrence of shoulder peaks with larger diameters with increasing F-127 concentration indicates that an associative interaction may occur between FBS and F-127 micelles when the final concentration of F-127 is higher than the CMC. The mixture of F-127 solutions with other batches of FBS or NCS showed the same trend. Furthermore, the mixture of F-127 and SyF also showed the same behavior, which indicates that serum can be a good model for synovial fluid in view of the interaction with macromolecules such as F-127. The results are presented in Fig. S4 in the ESM.

While FBS, NCS, and SyF have many components, major components are known to be similar. Lowering the concentration to one-third of full FBS has the effect of further resembling synovial fluid in terms of albumin concentration [32]. In order to characterize the interaction of F-127 with single components in these biological fluids, model synovial fluids with each major component, namely (a) albumin, (b)  $\gamma$ -globulin, (c) glucose, and (d) cholesterol and phospholipids, have been prepared. Figure 5 shows the size distribution of F-127 (20% in HEPES, prior to mixing) with either albumin (45 mg/mL) or  $\gamma$ -globulin (10 mg/mL) solutions at the ratio of 2:1. The selection of concentrations for albumin and  $\gamma$ -globulin was based on the average values in serum [33].

As shown in Fig. 5, the average particle size of albumin model is smaller than F-127 micelles while that of  $\gamma$ -globulin is bigger. Figure 5 also shows the mixtures of these models with F-127 solution at a volume ratio 2:1. For both cases of albumin and  $\gamma$ -globulin, the average particle size distribution is increased. It can be further noted that upon mixing with F-127, while the overall size of albumin increased, the size of  $\gamma$ -globulin split into a smaller portion and a larger one compared to that of  $\gamma$ -globulin alone. This is probably due to the fact that while the sample “albumin” is highly homogeneous, the sample “ $\gamma$ -globulin” is, in fact, a mixture of different types of globulins, and the interaction behavior with F-127 micelles is more complex and the resulting entities are more inhomogeneous. Alternatively, a relatively lower concentration of  $\gamma$ -globulin compared to albumin could lead to an aggregation with F-127 (larger peak) as well as remaining F-127 micelles

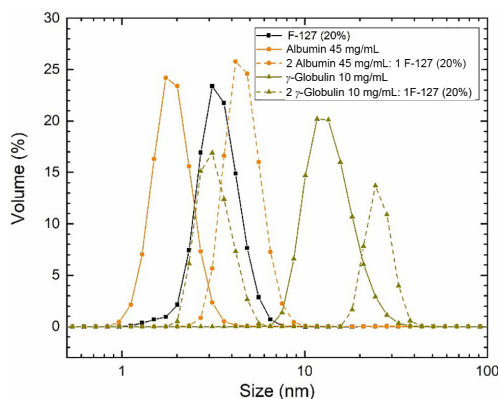


Fig. 5 Particle distribution of some models of serum and their mixtures with F-127 solution at 20% in HEPES as measured with DLS.

(smaller peak). On the other hand, the mixture of F-127 with other single component solutions, including glucose and cholesterol/phospholipids, did not show an increase in the size distribution. This observation suggests that the major components of serum (Fig. 4) or synovial fluid (Fig. S3 in the ESM) that are responsible for the interaction with F-127 micelles are albumin and  $\gamma$ -globulin.

DLS experiments were carried out by employing serum models with more than one component, too, but the reproducibility was poor, and thus, they are not further considered in this study.

### 3.3 CD spectroscopy

Far UV CD spectroscopy was run on FBS and the mixtures with F-127 of 0.1% and 20% (before mixing) at the ratio of 2:1 (serum: F-127 solution), as shown in Fig. S5 in the ESM. No meaningful changes in the far UV CD spectra were observed upon addition of F-127 to FBS compared to FBS alone. These observations suggest that while an associative interaction may occur between F-127 and major components of FBS, such as albumin and  $\gamma$ -globulin, according to DLS data (Fig. 4), the secondary conformations of these proteins remain intact. The addition of F-127 to the serum model made by mixing all the single components (Section 2.1) also showed no meaningful differences in the far UV CD spectrum of FBS compared to the FBS model without F-127 (Fig. S6 in the ESM).

Another use of CD spectroscopy is related to the tertiary structure of proteins, and it is possible to associate changes in the near UV spectra with changes in the structure of the proteins [34]. Figure 6 shows the near UV CD spectra for the mixtures of FBS and F-127 at two different concentrations.

FBS was diluted with HEPES buffer (1:50) to decrease the noise in the signal. Similarly with the DLS results (Fig. 4), a clear change in the spectra was observed when the concentration of F-127 was higher than the CMC (i.e., the case of FBS 1:50 + F-127 6.7% in Fig. 6). This change can also be ascribed to the changes in the tertiary structure of particular component(s) of FBS [35]. Thus, we have measured the near UV CD spectra of the two model solutions with either albumin or  $\gamma$ -globulin upon mixing with F-127. In these experiments, the albumin and  $\gamma$ -globulin solutions were also diluted to decrease the noise level to final concentrations of 5 and 1 mg/mL, respectively, and the two final concentrations of F-127 in the mixed solutions were 0.5% and 6.7%. In Fig. 7(a), the near UV CD spectra with albumin model are plotted, where the mixtures with F-127 do not show any noticeable changes.

Meanwhile, the near UV CD spectra of  $\gamma$ -globulin show a clear change upon mixing with F-127 when its concentration is higher than CMC as shown in Fig. 7(b). This behavior is similar to the

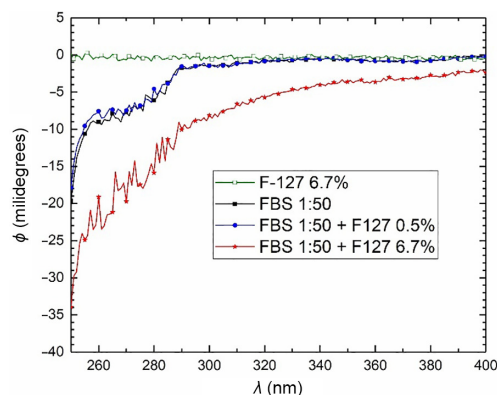


Fig. 6 Near CD spectra of FBS and mixtures with F-127 solutions. Notice that the FBS components are diluted 50 times to reduce the noise signals.

mixtures of FBS with F-127 at different concentrations (Fig. 6). Overall, CD spectroscopy study suggests that while mixing of FBS with F-127 does not induce any noticeable conformational changes in the secondary structure of proteinous components, it leads to a clear change in the tertiary structure as driven mainly by the interaction between  $\gamma$ -globulin and F-127 micelles.

### 3.4 UV absorption spectroscopy

Figure 8 shows the absorption spectra between 250 and 320 nm for solutions of albumin and  $\gamma$ -globulin and F-127 diluted in HEPES at different concentrations.

The spectra for both protein solutions show a maximum of 278 nm, which is related to the presence of tyrosine, tryptophan, and phenylalanine in the protein molecules, and it is a characteristic of each protein. In the case of F-127, it does not show a specific peak, but the presence of F-127 in solutions increases the background of absorbance spectra. The plots of the absorbance vs. the concentration of the proteins, assuming a molecular weight of 67,000 and 150,000 g/mol for albumin and  $\gamma$ -globulin, respectively, let us obtain the molar extinction coefficients through the slopes (the linear regression results are shown in Fig. S7 in ESM). A molar extinction coefficient for F-127 was also calculated at 278 nm (12,600 g/mol), and the results are shown in Table 1.

Absorbance measurements were further carried out on the mixed solutions of the proteins and F-127 at varying concentrations of F-127 (Fig. 9).

As the concentration of the protein was kept constant, the variation in the concentration of F-127 should show the same progressive changes in the spectra as those shown in Fig. 8(c), i.e., those of F-127 alone, if F-127 and the proteins do not interact with each other but simply co-exist in the solutions. Thus, the same molar extinction coefficient should be obtained even though

the overall intensity of the absorbance spectra may be increased due to the presence of the proteins in the solutions. However, the molar extinction coefficients obtained from the mixed solutions (Table 1) were deviated from the values obtained from F-127 alone. Between the two proteins,  $\gamma$ -globulin was found to induce a larger deviation in the molar extinction coefficient of F-127.

In addition, UV absorbance measurements were carried out on the mixed solutions with a fixed concentration of F-127 and varying concentrations of the proteins, as shown in Fig. 10.

Two concentrations of F-127, namely one over the CMC (6.7%) and the other below the CMC (0.5%) were employed. Table 1 also shows the molar extinction coefficients acquired in the same manner. Again, it is confirmed that there is no meaningful difference in the calculated coefficients for the mixture of albumin and F-127, but a large difference was observed from the mixture of  $\gamma$ -globulin and F-127 at 6.7%.

## 4 Discussion

Due to amphiphilic characteristics, F-127 and other Pluronics, as well as many other copolymers, tend to form micelles in aqueous solutions with increasing concentration [29]. Micelles formulated from amphiphilic copolymers can be a candidate for drug carriers, and thus, the interaction with serum or serum protein-containing media has been a focus of research interest in drug delivery [36–41]. Given that drug-loaded micelle should circulate in blood stream, a premature breakdown of the micelle structure is hardly expected to fulfill the purpose of drug delivery. While the stability of polymeric micelles in serum or serum protein media is known to be variant depending on the type of copolymers (even among nonionic copolymers), proteins, and media conditions [33, 42–44], commonly reported is that micelles tend to break down upon extended exposure to serum, serum proteins, or cell culture media, although they are stable in distilled water or saline buffers

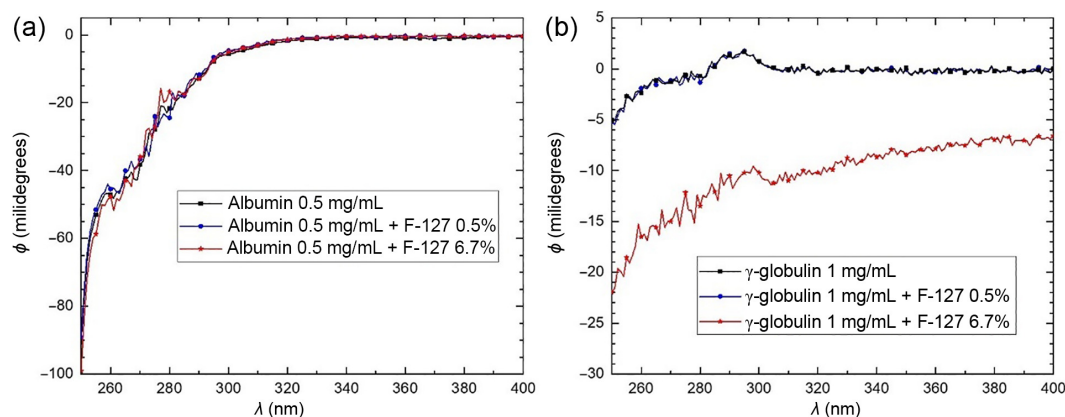


Fig. 7 (a) Near CD spectra of albumin solution and mixtures with F-127 solutions. (b) Near CD spectra of  $\gamma$ -globulin solution and mixtures with F-127 solutions.

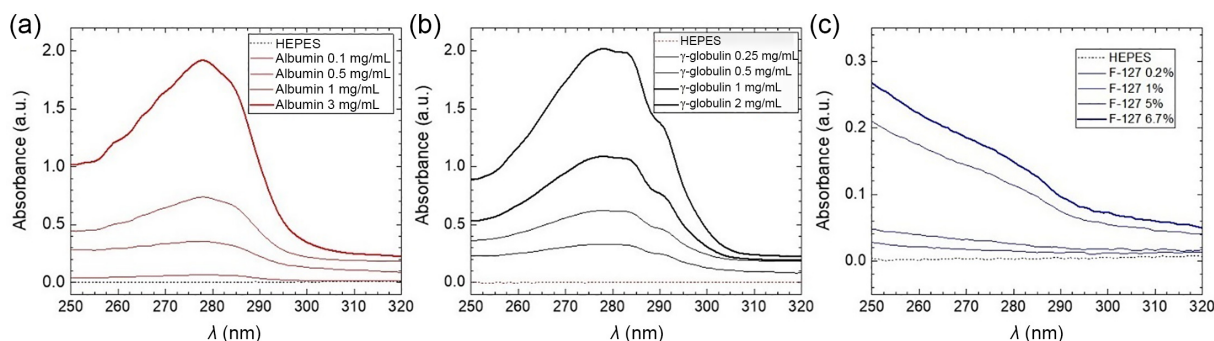


Fig. 8 UV absorbance of (a) albumin, (b)  $\gamma$ -globulin, and (c) F-127 solutions at different concentrations.



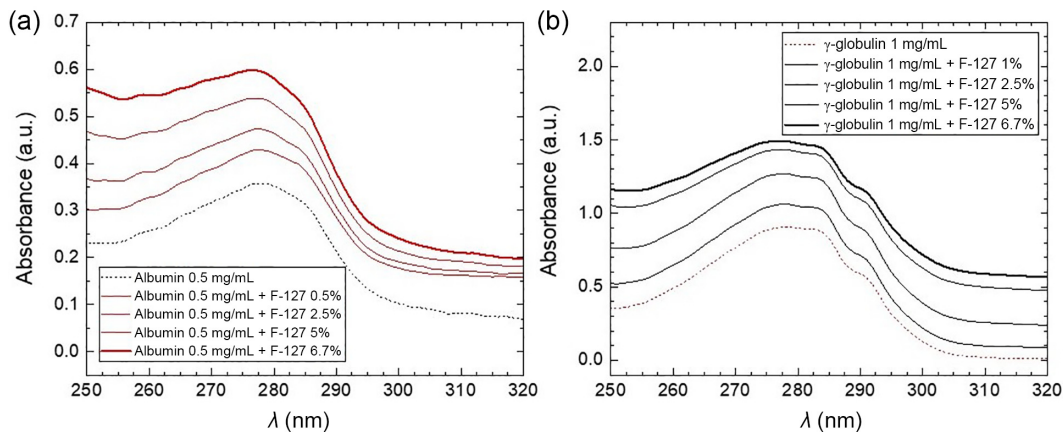
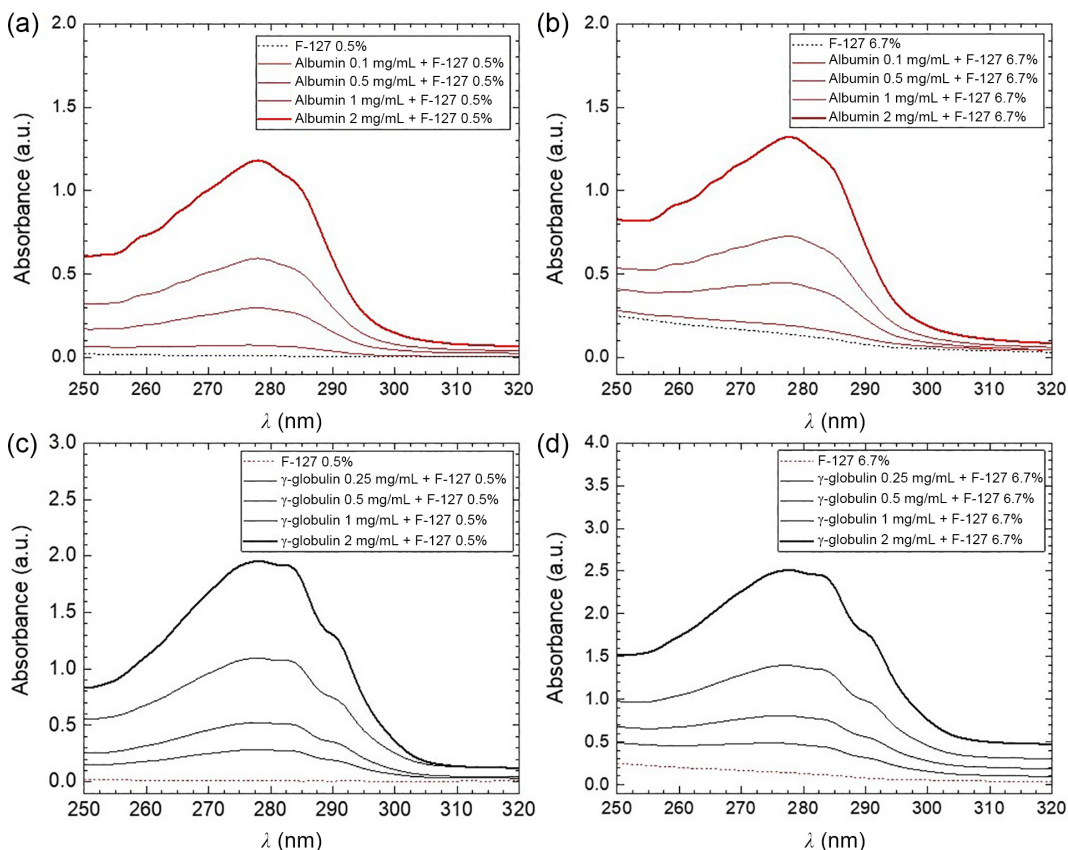
**Table 1** Calculated molar coefficient extinctions at 278 nm

Sample	Molar extinction coefficient at 278 nm ( $M^{-1}\cdot cm^{-1}$ )
Albumin	$42,800 \pm 1,300^{(a)}$
$\gamma$ -Globulin	$149,000 \pm 6,000^{(a)}$
F-127	$28.6 \pm 0.8^{(a)}$
Albumin 0.5mg/mL + F-127	$40 \pm 5^{(b)}$
$\gamma$ -globulin 1mg/mL + F-127	$108 \pm 16^{(b)}$
F-127 0.5% + albumin	$39,000 \pm 200^{(c)}$
F-127 6.7% + albumin	$39,400 \pm 300^{(c)}$
F-127 0.5% + $\gamma$ -globulin	$146,000 \pm 5,000^{(c)}$
F-127 6.7% + $\gamma$ -globulin	$178,000 \pm 4,000^{(c)}$

Note: Calculated from (a) Fig. 8, (b) Fig. 9, and (c) Fig. 10

[42]. In those studies, as the focus of interest is the delivery of embedded drugs, the breakdown of the micelles was mostly deduced from released drugs out of the micelle cores by, for example, fluorescence-based techniques.

The present study distinguishes from those studies in that there are no “drug molecules” to deliver in the core of micelles. Instead, the focus of this study is whether F-127 can display a lubricating effect for CoCrMo/UHMWPE tribological interface in serum as a model for synovial fluid, i.e., even in the presence of various biomacromolecules. Nevertheless, understanding the interaction between F-127 and serum is still important in this study, as biomacromolecules in serum can interfere with the adsorption and lubricating properties of F-127. Proteins in serum can affect the adsorption and lubricating behavior of F-127 mainly in two ways. Firstly, they can compete with F-127 in adsorption onto

**Fig. 9** UV absorbance spectra of the mixed solutions of the proteins with F-127 at varying concentrations of F-127.**Fig. 10** UV absorbance of mixtures of proteins with F-127 with variation of the protein concentration.

UHMWPE surface. This scenario is likely to be dominant when F-127 and serum proteins do not have a significant interaction but are simply co-existent in solution. Secondly, when F-127 and serum do interact with each other and form aggregates, adsorption and lubricating properties of F-127 can certainly be altered compared to those of F-127 alone.

The spectroscopic approaches employed in this study, including DLS, CD spectroscopy, and UV absorbance spectroscopy, collectively indicate that the interaction between F-127 and serum is dependent on the concentration of F-127; at low concentration (below CMC), F-127 exists predominantly as unimer and do not interact with serum. Meanwhile, at high concentrations (above CMC), F-127 starts to form micelles, and they interact with serum associatively. In addition, among the studied individual proteins and other biomolecules,  $\gamma$ -globulin is observed to be the primary player for this interaction, along with albumin, to a certain extent.

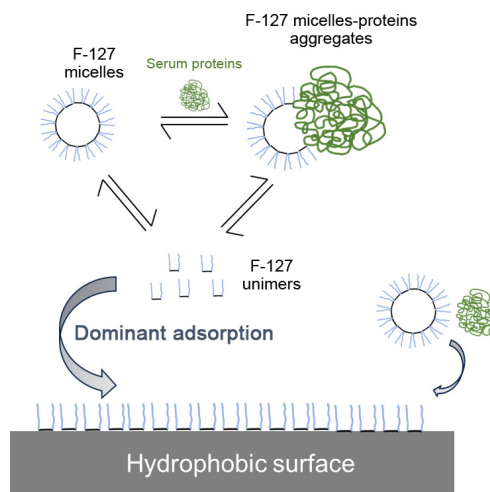
The interaction between F-127 micelles and serum proteins tends to increase the size of nanoparticles at sufficiently high concentrations, as detected by DLS (Figs. 4 and 5). This may appear puzzling, considering that drug-loaded polymeric micelles are known to break down in contact with serum in drug delivery [33, 42–44]. However, “breakdown” here does not necessarily mean a complete disassembly of micelles into copolymer unimers, but rather a disruption of well-defined micelle structure and release of loaded drugs to surrounding media. Thus, it is possible to form a cluster larger than intact micelles as a result of breakdown upon interaction with serum proteins. To date, in-depth studies on this “breakdown” mechanism are very rare, apart from some speculations. For example, the attraction between the loaded drug molecules and serum proteins was suggested as the driving force for disruption of micelle structures [45]. Another possibility suggested is that micelles and protein molecules may form a mixed micelle after disruption of initial micelle structure [42]. The former is most likely driven by the hydrophobic interaction, and the latter can be caused by the amphiphilicity of some proteins and hydrophobic interaction with the hydrophobic blocks of amphiphilic copolymers [46]. Given that associative interaction occurs even in the absence of drug molecules, as shown in this study, the first possibility cannot be an exclusive reason driving the interaction between micelles and serum proteins. The interaction between F-127 micelles and serum proteins can be seen surprising, considering the nonionic characteristics of F-127 and well-known resistance of highly packed PEO chains against nonspecific protein adsorption on surfaces [47–49]. However, such property is most effective when PEO polymer brushes are generated via strong anchoring on planar surfaces, either covalent or electrostatic bonding, and at a high grafting density [47–49]. The capabilities of PEO brushes formed as corona or shells for micelles to resist nonspecific adsorption of proteins are expected to be inferior due to relatively loose packing of PEO chains [50].

To understand the lubricating efficacy of F-127, in addition to the interaction behavior between F-127 and serum, one more factor should be further considered, namely the presence of a hydrophobic substrate, e.g., UHMWPE, in the system. As is well known, the driving force to formulate micelles of amphiphilic molecules at above CMC is to minimize the unfavorable interaction of hydrophobic patches with water molecules [29]. Unlike in bulk solutions without UHMWPE substrate, unimeric F-127 molecules can migrate to adsorb onto UHMWPE surface as another way to minimize the interaction of PPO blocks with water than forming micelles. The source of F-127 can be diverse; (i) at or

below CMC, unimers themselves, (ii) above CMC, unimers in equilibrium with micelles or micelle-serum aggregates. Available species in serum with F-127 molecules at above CMC are shown graphically in Fig. 11.

In addition, not only unimeric F-127 but also F-127 micelles or F-127 micelles-serum protein aggregates can adsorb onto UHMWPE surfaces. However, their contribution to lubricating capabilities is expected to be insignificant, as the anchoring of micelles or micelle-protein aggregates onto UHMWPE surfaces is weak due to the hydrophilic characteristics of their outer surfaces. Rather, the adsorbed micelles onto hydrophobic surfaces are known to go through a rearrangement so that hydrophobic blocks of F-127, i.e., PPO blocks, can be facilitated to interact with UHMWPE surfaces [51]. This process should be, however, much slower than direct adsorption of unimeric F-127 onto UHMWPE surfaces.

It is important to note that prior to the addition of F-127 into serum, CoCrMo/UHMWPE interface is already being lubricated by serum, e.g., for the number of laps up to ca. 500 in Fig. 1(a). Previous studies have reported that albumin is one of the major components contributing to this lubrication in serum, although its lubricating efficacy is not very high [52, 53]. The fact that COF is instantaneously decreased upon addition of F-127 implies a few important points. Firstly, the binding strength of adsorbed serum proteins onto UHMWPE surface is relatively weak and they are readily removed by tribostress in pin-on-disk tribometric setup in a cyclic pattern [54]. Presumably, the binding strength of F-127 onto UHMWPE surface is not substantially higher either, as the adsorption of both serum proteins and F-127 onto UHMWPE surface is achieved via hydrophobic interaction. However, an important point is that while serum proteins pre-occupy the UHMWPE surfaces, “available spots” are repeatedly generated due to tribostress-induced desorption process. Secondly, F-127 favorably competes against serum proteins in adsorption to UHMWPE surfaces. The molecular weight of F-127 (ca. 12.6 kDa) is clearly smaller than those of albumin (67 kDa) and  $\gamma$ -globulin (150 kDa), and thus, F-127 molecules are expected to move faster towards the surface of UHMWPE in competitive adsorption event according to “Vroman effect” [55–57]. Lastly, a comparable reduction percentage in COF from 0.1% to 20% in F-127 concentration (Fig. 2 and Table 1) suggests that the concentration of available unimeric F-127 in bulk solution, or more precisely



**Fig. 11** A schematic illustration displaying the diverse sources of F-127 unimers in serum and the dominant adsorption onto a hydrophobic surface, e.g., UHMWPE, at above CMC of F-127.



that of migrating to UHMWPE surface, is similar over this range of F-127 concentration. Despite the availability of F-127 micelles and F-127 micelle-protein aggregates at concentrations higher than CMC, no further reduction in COF supports the assumption mentioned above that the major contributing species to friction-lowering effect is unimeric F-127, not F-127 micelles or F-127 micelles-serum proteins aggregates.

## 5 Conclusions

With a long-term aim to design replenishable surface-protecting lubricant layer for articulating joint implants, we have investigated the feasibility of lowering friction forces between CoCrMo and ultrahigh molecular weight polyethylene (UHMWPE) interface by addition of F-127 solution into serum where the tribological contact is in progress. A first set of tests in this study showed that addition of F-127 solutions with a wide range of concentration (0.1% to 20% prior to addition) into serum led to an immediate decrease in coefficient of friction (COF) by ca. 20% on average. This observation suggests that F-127 molecules can immediately replace serum proteins pre-adsorbed on UHMWPE surfaces and generate a F-127-dominant lubricating layer upon addition. Spectroscopic studies with dynamic light scattering (DLS), circular dichroism (CD) spectroscopy, and ultraviolet (UV) absorbance, indicate that there is no interaction between unimeric F-127 molecules and serum proteins. In contrast, F-127 micelles associatively interact with serum, in particular  $\gamma$ -globulin and albumin, leading to an increase in the hydrodynamic size of F-127 micelles, alteration of tertiary protein structures of  $\gamma$ -globulin, and an overall disruption of F-127 micelle structure. A similar magnitude of reduction in COF for F-127 from 0.1% to 20% suggests that it is unimeric F-127 molecules that contribute to friction-lowering effect even at the concentrations above critical micelle concentration (CMC), whereas the contribution of F-127 micelles or F-127 micelles-serum proteins is insignificant.

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## Declaration of competing interest

The authors have no competing interests to declare that are relevant to the content of this article.

## Electronic Supplementary Material

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