The effect of hyaluronic acid concentration on the rheological and tribological properties of artificial synovial fluid base solutions

Monika Izabela Grykin[1), *)] (ORCID ID: 0000-0002-2808-1274), **Marcin Klekotka**[1)] (0000-0002-9751-2939), **Jan Ryszard Dąbrowski**[1)] (0000-0002-0175-0669)

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Abstract: Synovial joints are a basic part of the human body. Lack of proper lubrication of joints can lead to significant wear of their surfaces. The tribological and rheological properties of artificial synovial fluid solutions based on hyaluronic acid were studied. It was found that the concentration of selected hyaluronic acid solutions significantly affects the investigated parameters. The most promising results were obtained for 8 wt% hyaluronic acid solution, which showed the highest viscosity and wettability, and the lowest wear.

Keywords: artificial synovial fluid, hyaluronic acid, viscosity, friction, wear.

Wpływ stężenia kwasu hialuronowego na właściwości reologiczne i tribologiczne roztworów bazowych sztucznej mazi stawowej

Streszczenie: Stawy maziowe stanowią podstawową część organizmu człowieka. Brak odpowiedniego smarowania stawów może prowadzić do znacznego zużycia ich powierzchni. W pracy zbadano właściwości tribologiczne i reologiczne roztworów sztucznej cieczy synowialnej na bazie kwasu hialuronowego. Stwierdzono, że stężenie wybranych roztworów kwasu hialuronowego znacząco wpływa na badane parametry. Najlepsze wyniki uzyskano dla 8% mas. roztworu kwasu hialuronowego, który charakteryzował się największą lepkością, zwilżalnością, a także najmniejszym zużyciem.

Słowa kluczowe: sztuczna ciecz synowialna, kwas hialuronowy, lepkość, tarcie, zużycie.

The synovial joint consists primarily of the synovial membrane, articular cartilage, and the joint cavity, which mainly contains joint fluid [1]. In natural joints, the friction is very low because biological frictional systems can self-maintain and self- repair. The synovial fluid is crucial in adequately hydrating and nourishing the elements entering the biotribological system [2–4]. Lubrication occurring in the joint is possible when water molecules penetrate the structures of the joint cartilage during load transfer. At the same time, places with an increased concentration of moisturizing macromolecules in the synovial fluid are created. They come in the form of lubricant, hyaluronic acid, or phospholipids. Such accumulations increase the production of lubricating gel between adjacent tissues, which provides better lubrication and thus reduces movement resistance [5]. Synovial fluid is a complex solution in synovial joints ranging from 0.5 mL to 4 mL [6]. It is a two-phase fluid that exhibits non-Newtonian rheological properties. The synovial fluid has viscous and elastic properties, and the dominance of one over the other depends on the shear force. Elastic properties indicate the ability to store mechanical energy. However, the viscous properties are responsible for the dissipation of mechanical energy, most often in the form of heat. It should also be mentioned that synovial fluid has pseudoplastic features that act as a shock absorber, especially when performing fast and intense movements [7, 8]. Determining a specific lubrication model is not so obvious. Many mechanisms can occur simultaneously or constantly change depending on the conditions present. The main lubrication models can include boundary lubrication and liquid lubrication [9–11]. Liquid lubrication considers the presence of the fluid itself between the cartilage structures. However, over time, it was noticed that it did not create the correct conditions for small sliding movements. Fluid friction occurs at high speeds in the joints and at low load values. There are two types of fluid friction, including hydrodynamic and elastohydrodynamic lubrication, differing in the conditions of the applied load [12–14]. In the case of elastohydrodynamic lubrication, the cartilage structure deforms elastically. This is caused by an increase in pressure in the biotribo-

1) Faculty of Mechanical Engineering, Bialystok University of Technology, Wiejska 45C, 15-351 Bialystok, Poland.
*) Author for correspondence: monika.grykin@sd.pb.edu.pl

logical system, which is synonymous with an increase in viscosity [15]. In hydrodynamic lubrication, articular cartilage is lubricated by creating a compression effect and forming a wedge in the narrow gap between the cartilage surfaces where the fluid is located. Selected and specialized molecules in the synovial fluid are responsible for boundary lubrication. Lubricin, hyaluronic acid, and surface-active phospholipids actively participate in this mechanism. Boundary lubrication is mainly determined by the adsorption of individual components in the synovial fluid on the articulating surfaces. This means that it depends on the presence of particles that can bind to the surface. Boundary lubrication is essential for maintaining a low coefficient of friction when two cartilage structures are in contact. However, there is no specific lubrication model that would fully explain the processes occurring in the biotribological system. Therefore, the mixed friction hypotheses seem to be the most likely [14, 16, 17]. Many studies have uncovered other potential lubrication mechanisms. These include lubrication by film extrusion and lubrication of protein aggregation [18–20].

The synovial fluid is primarily composed of surfactant proteins and hyaluronic acid. Also, lipids, enzymes, salts, and other components of the joint capsule or immune system elements can be distinguished [21]. Globulin and albumin, as representatives of proteins, are responsible for reducing wear by adequately lubricating the borders along the joint cartilage. Hyaluronic acid, a linear unbranched polysaccharide, is one of the most abundant polymeric components in the synovial fluid [1, 22, 23]. It is regarded as a significant determinant of viscosity and elasticity [24, 25]. In natural synovial fluid, the concentration of hyaluronic acid is in the range of 2–3%, with a molecular weight of 10^3-10^4 kDa [21]. In a healthy human joint, the concentration of hyaluronic acid is between 1–4 mg/mL. In the case of joint diseases, such as degenerative arthritis or exudative damage, the concentration of hyaluronic acid drops to as low as 0.1–1.3 mg/mL [10].

Among the most common diseases is degenerative arthritis. This affliction mainly reaches the older people but not only. Initial pathological changes begin to appear on a molecular scale, which continuously spread until there is a degradation of the articular cartilage and changes in its composition and structure [26, 27]. In the affected knee joint, narrowing of the joint spaces can be observed, also described as the approximation of the opposing bones of the joint. This indicates wear and tear of articular cartilage and interstitial fluid effusion. In the presence of rheumatic diseases and degenerative arthritis, the viscosity of synovial fluid is reduced [2, 6]. Losing these functions may lead to increased stress forces acting on the knee joint. Excessive forces distort the collagen network, which is responsible for the integrity of the joint surface. Damage to it causes difficulties in the availability of nutrients and problems with removing wear products from the joint cartilage. In degenerative diseases, hyaluronic acid is depolymerized, contributing to the deterioration of rheological properties (viscosity and elasticity) [28]. When the biomolecules of the synovial fluid are degraded, joint dysfunction occurs because of disease or injury. In such cases, medical treatments are most often used, which involve administering a series of injections to deliver the biolubricant into the joint space. Preparations that are substitutes for synovial fluid should be characterized by high biocompatibility as well as appropriate rheological and tribological properties. That is why it is essential to develop an artificial synovial fluid preparation to make the treatment methods more effective. Visco supplementation is one of the most frequently used therapy. Joint alloplastic is used in more severe cases [29].

Because of its high biocompatibility and presence in nature, hyaluronic acid is commonly used in visco supplementation [28, 30]. This therapy involves directly injecting hyaluronic acid or another therapeutic agent into the joint cavity. Such preparations are designed to restore the correct viscosity and lubrication of human joints [1]. In addition, they can reduce pain and inflammation during the disease and restore joint functionality [6, 28, 31, 32]. The administration of hyaluronic acid in the form of injections can also promote anabolic processes, i.e., accelerate the adhesion process. As confirmed by the research of Smith and Gosh [33], when the appropriate dose of hyaluronic acid is injected, a stimulus may occur that will re-stimulate its production in the synovial joint.

Nowadays, synovial fluid substitutes are widely used. However, there are many reports that they are not entirely effective. Their operation time is relatively short, which results in results-articular injections having to be repeated frequently. This is associated with tremendous pain and discomfort during the procedure. For this reason, this work undertakes research on potential bases for artificial synovial fluid.

EXPERIMENTAL PART

Materials and methods

Artificial synovial fluid compositions using hyaluronic acid sodium salt (HA) average molecular weight 30–50 kDa (Product number CM61910C, Chemat, Poland) were prepared (Table 1).

T a b l e 1. Chemical composition of hyaluronic acid solutions

Solution	HA content wt%	Solvent
HA 4%	4	PBS 8 g/L NaCl; 0.2 g/L KCl; 1.44 g/L; Na_2HPO_4; 0.24 g/L KH_2PO_4
HA 6%	6	
HA 8%	8	

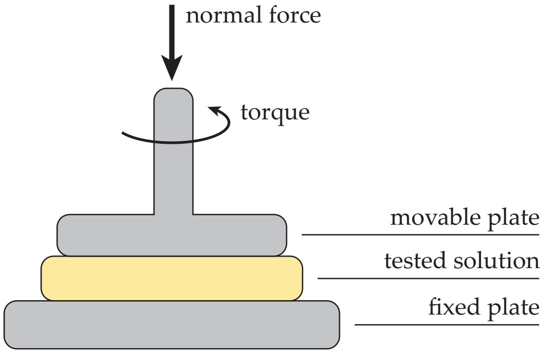

Fig. 1. Scheme of rheological measurement system

For comparative purposes, Hyalgan, one of the most popular commercial preparations used in visco supplementation, was also tested. The molecular weight of sodium hyaluronate (10 mg/mL) used in Hyalgan is 500–730 kDa. It is obtained from rooster combs and is highly purified [34–38]. The other ingredients are sodium chloride, sodium dihydrogen phosphate dihydrate, disodium phosphate dodecahydrate and water. Commercially available syringes from Fidia Farmaceutici S.P.A. (Bologna, Italy) contain 2 mL of solution. All prepared substitutes were placed in a laboratory incubator at 37°C for 24 hours before the test.

Rheological properties

Rheological tests were performed using Rheostress 6000 (Thermo Fisher Scientific, Waltham, MA, USA). The measurement of viscosity and storage modulus was carried out in a plate-plate system (Fig. 1) at a temperature of 37°C.

During the viscosity test, the diameter of the upper movable plate was 35 mm. Meanwhile, the gap between the plates was set to 0.8 mm wide. Viscosity was tested in the shear rate range of 0.01–100 s^{-1}. For measuring the storage modulus G′, the diameter of the upper movable plate was 20 mm. Meanwhile, the gap between the plates was set to a width of 0.5 mm. The storage modulus *G*′ was tested at a constant shear strain value $\gamma = 0.01$, in the frequency range of 0.1–10 Hz.

Tribological properties

Tribological tests were carried out using UMT TriboLab device (Bruker, Billerica, MA, USA) with a ball-disc system (Fig. 2).

The tribological system used CoCrMo cylindrical samples of 5 mm thickness and 8 mm diameter and alumina balls (Al_2O_3) of 6 mm diameter. The metal samples were pre-sanded with 2000, 2500, and 5000 grit sandpaper and then polished with an Al_2O_3 slurry to a mirror-like shine. Each sample was washed in an ultrasonic cleaner in ethanol and deionized water before tribological measurements. The friction tests were performed at a room

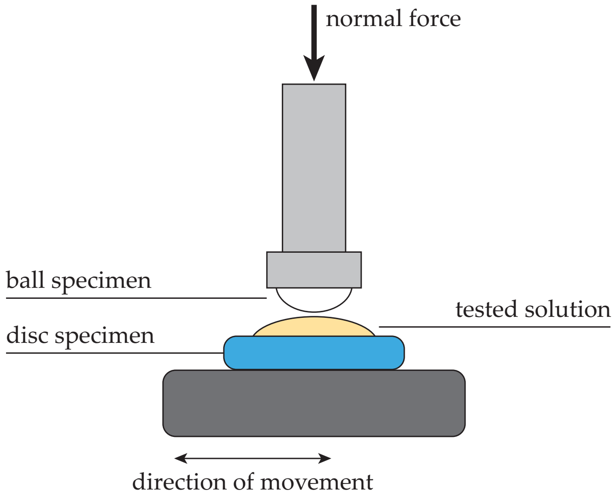

Fig. 2. Ball-on disc tribological system

temperature of 21°C, at a constant frequency of 1 Hz, for 30 minutes. The displacement amplitude was set at 500 μm. The normal contact force was 5 N. For statistical purposes, each measurement was performed three times. The wear traces obtained during the tribological test were evaluated using a LEXT OLS4000 confocal microscope (CLSM, Olympus, Tokyo, Japan). Determination of the volume of friction traces was carried out using specialized computer software compatible with the microscope.

Static contact angle

The static contact angle was determined by the sitting drop method using Ossila goniometer (Ossila, Sheffield, England). Drops of hyaluronic acid sodium salt solutions with a volume of 5 μL were applied to the CoCrMo samples, maintaining the same minimum height of the needle above the tested surface and the same cutting direction of its tip. The droplet was photographed with a goniometer camera 5 s after deposition on the sample surface. The contact angles were determined using the goniometer computer software.

RESULTS AND DISCUSSION

Rheological properties

The viscosity (*h*) and storage modulus (*G*′) of the tested HA solutions are shown in Fig. 3 and 4, respectively.

The study focused on comparing how changing the concentration of the active ingredient affects the viscosity of the preparation. The results obtained for the hyaluronic acid-based composition were compared with a commercial formulation, which is one of the most frequently used for the treatment of osteoarthritis. Tested solutions are characterized by the fact that as the concentration of hyaluronic acid increases, the viscosity of the solution increases. All tested solutions show a decreasing trend in viscosity with an increasing shear rate (Fig. 3).

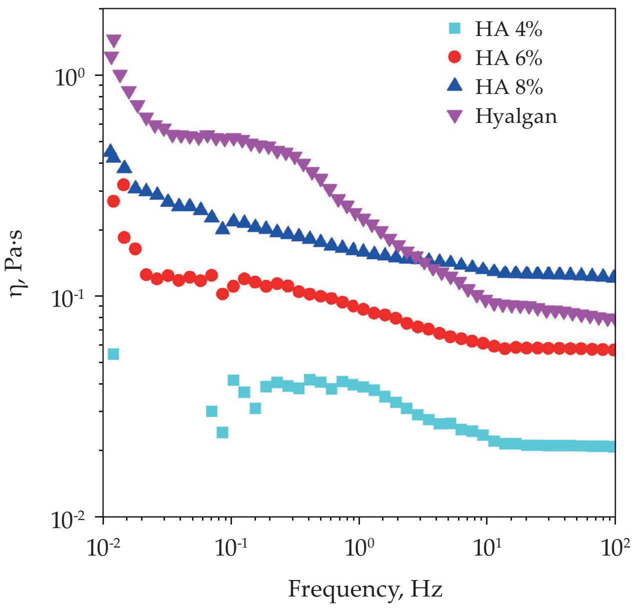

Fig. 3. Viscosity of HA solutions

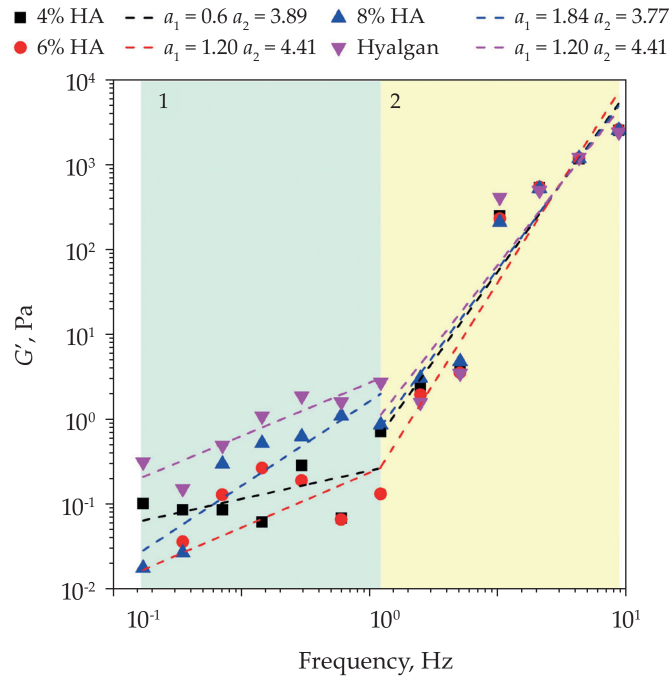

Fig. 4. Storage modules (*G'*) as a function of frequency for HA solutions; a_1 and a_2 – slope parameters

This indicates the demonstration of the non-Newtonian nature of the shear-thinning fluid [39, 40]. Solutions with concentrations of 6 wt% and 8 wt% hyaluronic acid show more similar values to Hyalgan. The viscosity is also close to the once of natural synovial fluid, which is in the range of 1–175 Pa·s [6]. The solution with a concentration of 4 wt% hyaluronic acid shows lower viscosity. In addition, there were high fluctuations at the initial values of the shear rate, which indicates the rather fluid consistency of this solution.

The storage modulus (*G'*) *vs* frequency shown in Figure 4 is divided into two areas. The first area, marked in green, includes frequency values from 0.1 Hz to 1 Hz. The second area marked in yellow covers the frequency ranges from 1 Hz to 10 Hz. Similar results were obtained for all tested solutions. This is especially evident in the higher frequency range. At lower frequencies, there are slight differences, but they are not practically significant. All curves are marked with the slope parameter *a*. In the second area, the increase in modulus is steeper than in the first area, which is also indicated by the higher values of the parameter *a*.

Research on synthetic synovial fluids was conducted by Bortel E. *et al.* [21]. They also tested the viscosity of hyaluronic acid-based solutions and compared it to the viscosity value of the natural synovial fluid. The researchers tested several different formulations, each based on hyaluronic acid and differing in additives. The molecular weight of the hyaluronic acid used was 1,300 kDa. The viscosity was in the range of 12–65 mPa·s and depended on the concentration of hyaluronic acid. The higher the concentration, the higher the viscosity [23, 41, 42]. As in the case of our research, the shear thinning characteristic of non-Newtonian fluids was observed, which means that the viscosity of solutions decreases with increasing shear rate [21]. Similar studies were carried out by Mathieu *et al.* [6], in which the viscosity was also compiled with the concentration of hyaluronic acid. The results also confirm the relationship that the viscosity of the tested preparations increases with increasing concentration [6]. Researchers Prekasan *et al.* [43] and Bhuanantanondh *et al.* [44] also subjected the rheological studies of synovial fluids. The results for viscosity and storage modulus are comparable to those reported in our work.

Tribological properties

Tribological tests allow us to determine the coefficient of friction (COF) for friction pairs in the presence of a hyaluronic acid-based lubricant and a commercial formulation of Hyalgan. The results of the friction tests are shown in Figure 5.

Based on the tribological tests, it can be concluded that all substitutes fulfill their function and reduce the coefficient of friction. The tested solutions based on hyaluronic acid reduce friction comparable to the commercial preparation of Hyalgan. The coefficient of dry friction increases with time and reaches a value of approx. 0.65 at 30 minutes of friction. However, when lubricants are used, these values are in the range of 0.25–0.35. Also, the value of the coefficient of friction is much more stable. According to literature references, an increase in the concentration of hyaluronic acid causes a decrease in the coefficient of friction [10, 20, 45]. This trend was not evident in our studies.

Images of friction marks were compared to evaluate wear. Selected images of wear tracks are shown in Figure 6.

The most significant and most visible wear marks were created during dry friction (Fig. 6e). The rest of the

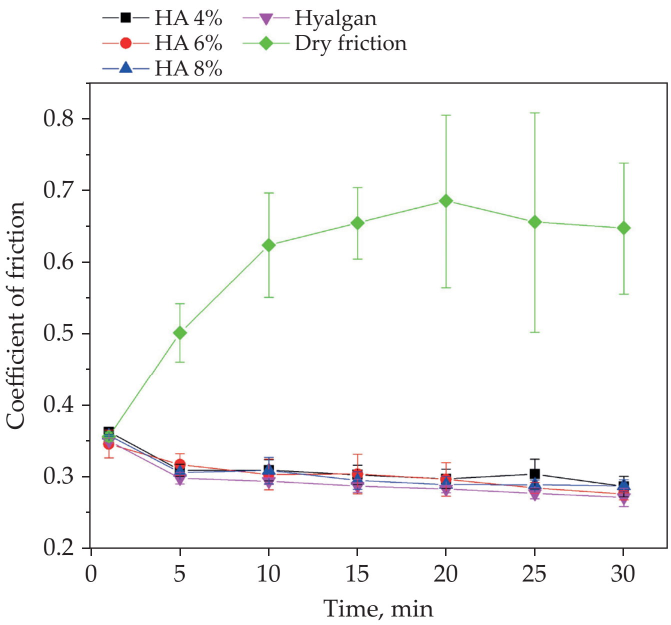

Fig.5 Coefficient of friction as a function of time for HA solutions

wear tracks are similar, which is correlated to the friction coefficient. The differences were not very significant. However, the smallest and the most uniform marks were obtained for HA 8% solution (Fig. 6c). Furthermore, obtained 3D image profiles allowed us to determine the volume of wear marks, which are shown in Figure 7.

Analysis of wear track images (Fig. 6) and volumes (Fig. 7) shows that all tested solutions significantly reduce wear. The solution with 8 wt% hyaluronic acid was the most effective and achieved the lowest wear trace volume. It obtained a more favorable result than the commercial formulation, and it is suitable as a base for further, extended research with additives improving the functionality of the artificial synovial fluid.

Despite slight differences in friction coefficients, they are noticeable in wear. Kienle *et al.* [46] also noticed that hyaluronic acid injected into patients during Visco supplementation therapy does not have a significant impact on the value of movement resistance. Still, it does reduce wear and tear in the joint. This proves that wear does not

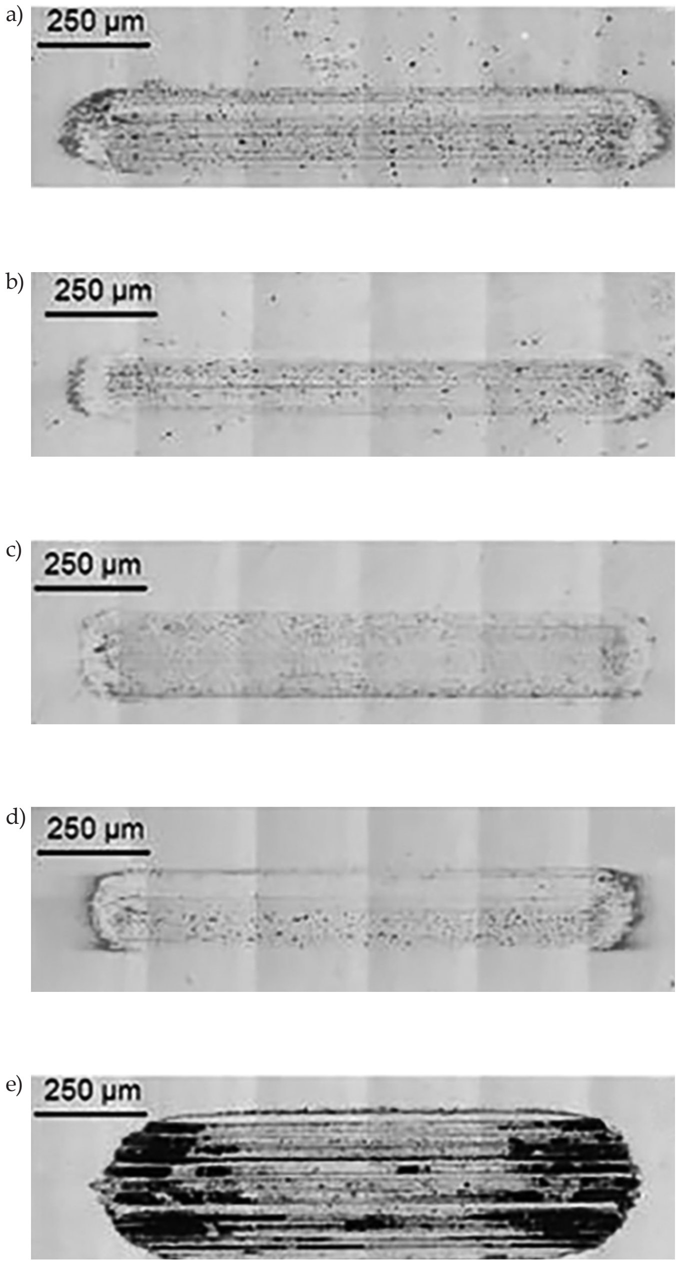

Fig. 6. Wear tracks: a) HA 4%, b) HA 6%, c) HA 8%, d) Hyalgan, e) dry friction

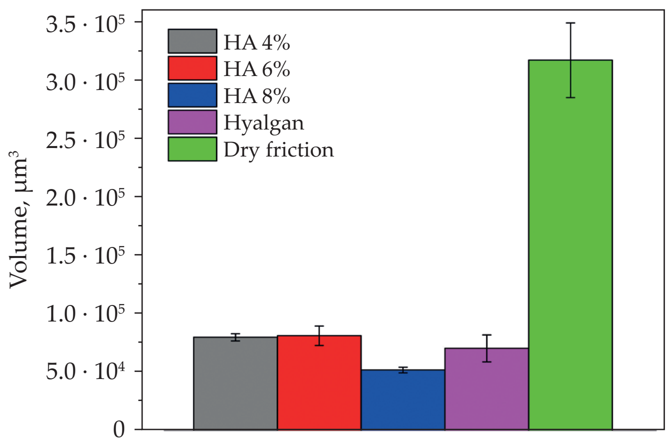

Fig. 7. Wear tracks volume of HA solutions

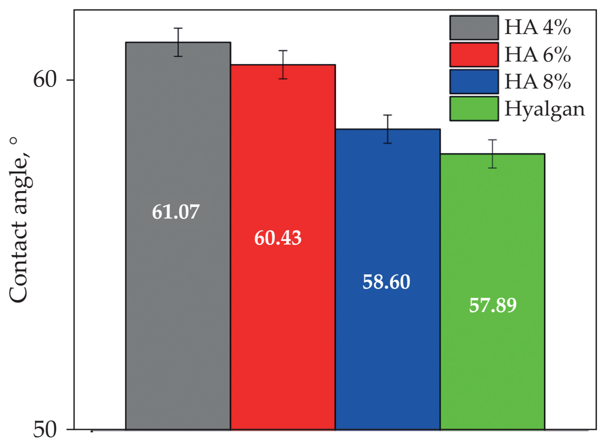

Fig. 8. Contact angle for HA solutions

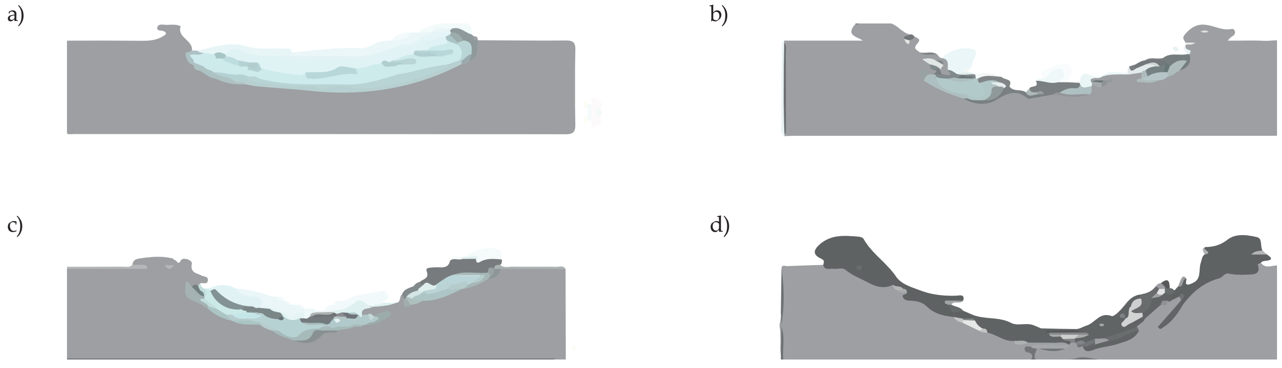

Fig. 9. Lubrication scheme: a) HA 8%, b) HA 6%, c) HA 4%, d) dry friction

always have to be correlated with the value of the friction coefficient [16].

Literature reports confirm the excellent lubricating properties of hyaluronic acid. An example was studies conducted by Bortel *et al*. [21] or Mabuchi *et al*. [47], in which researchers tested the influence of hyaluronic acid on friction coefficient in animal joints. The obtained test results were promising. Furthermore, it is worth noting that density has a significant impact on the lubricating properties of hyaluronic acid solutions, and it grows with the concentration of HA [42].

Wettability

Contact angle measurements were used to determine the effect of hyaluronic acid concentration on wettability. The results are shown in Figure 8. The contact angle decreases with the concentration of HA, which proves better wettability. This property mainly depends on the forces between the particles of the liquid and the forces of adhesion between the surface and the fluid [48–52]. The wear ratio is closely related to the viscosity, wettability, and density of HA solutions. A lubricant that has higher density, wettability, and viscosity allows for better protection of the surface by creating a kind of suspension, resulting in lower resistance to movement and wear. The lubrication scheme is shown in Figure 9.

The lubrication scheme shows how tested solutions behave depending on the concentration of hyaluronic acid. In the case of the highest concentration (Fig. 9a), the layer of lubricant (light blue) is the most adhesive to the surface, creating a barrier. As a result, the wear trace is smoothest. If the concentration of HA is lower, less of the lubricant adheres to the surface (Fig. 9b and 9c). However, in the case of dry friction (Fig. 9d), there is no adhesive layer. The wear trace is very large and deep. Wear products (dark gray) accumulate in the wear path, which can lead to increased wear and resistance to movement. This trend is maintained regarding the concentration of HA in the solution. With a higher concentration, less wear products are deposited in the friction node, which reduces abrasive wear.

CONCLUSIONS

The study focused on the tribological and rheological properties of prepared HA solutions in comparison to a commercial synovial fluid substitute. The starting point for further research is basic research on the influence of hyaluronic acid concentration on biofunctional properties. The viscosity of the tested HA solutions increases with the hyaluronic acid concentration. The viscoelastic nature of artificial synovial fluid is closely related to deformation. As the frequency increases, the storage modulus also increases. HA solutions reduce wear and movement resistance of kinematic pairs. Higher concentrations of hyaluronic acid can lead to greater surface-liquid adhesion forces, resulting in better wettability. Wear does not always correlate with the friction coefficient. The friction coefficient of the tested solutions was similar. However, a tendency to decrease in wear was observed as the concentration of hyaluronic acid increased. Viscoelastic properties showed that the 8 wt% HA solution has a slightly higher storage modulus, indicating better load capacity. Moreover, this solution had the highest viscosity and the best anti-wear properties. Therefore, it seems to be the best option for further research on improving the functionality of artificial synovial fluid.

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