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Synthesis and characterization of tribologically enhanced hydrogels

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Synthesis and Characterization of Tribologically Enhanced Hydrogels

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Abstract

Hydrogels are a biomaterial that have potential for a variety of different biomedical applications. However, these hydrogels often have poor friction and wear properties. This document investigates the stability of a proposed method to resolve this limitation. The proposed solution is a blend of a biocompatible polymer, poly(vinyl alcohol) (PVA) with different concentrations of the zwitterionic polymer, polymer Poly([2-(methacryloyloxy) ethyl] dimethyl-(3-sulfopropyl) ammonium hydroxide) p(MEDSAH). Previous analysis has shown that the pMEDSAH acted as a boundary lubricant, resulting in a reduction of the coefficient of friction. The pMEDSAH was successfully synthesized at three different molecular weights and a significantly higher contact modulus was seen at the lower molecular weight. As well, a hydration dehydration study and a degradation study were performed. Both of these studies resulted in an increase in the coefficient of friction, indicating that the pMEDSAH was diffusing out of the hydrogel. If this simple processing method is used in biomedical devices, a packaging method will need to be developed to prevent this. However, this approach provides a promising platform for further increasing the boundary lubricant properties of hydrogels.

Executive Summary

The zwitterionic polymer, polymer Poly([2-(methacryloyloxy) ethyl] dimethyl-(3-sulfopropyl) ammonium hydroxide) p(MEDSAH) was blended with the biocompatible polymer, poly(vinyl alcohol) (PVA) and exposed so a series of freeze- thaw cycles. Mechanical and tribological analyses were performed. As well, degradation and hydration- rehydration studies were conducted on the hydrogels. An increase in the contact modulus was observed by the addition of pMEDSAH. The results also showed an increase in the coefficient of friction after four months in incubation and after three hydration- dehydration cycles. If this simple processing method is used in biomedical devices, a packaging method will need to be developed to prevent this reduction in the hydrogel properties.

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Acknowledgements

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Introduction

Articular cartilage is the thin, smooth white tissue that is found on the articulating ends of joints in the human body. Articular cartilage performs a mechanical function and acts as a bearing surface, supporting the motion between the joints. This cartilage distributes stresses and facilitates the transmission of loads, allowing our bones to glide over one another with little friction [1]. The loads that are supported by articular cartilage can range from 1.5 to 10 times a person's body weight [2]. Articular cartilage is mainly composed of water, with no blood vessels, nerves, or lymph nodes. The cell components that do make up the cartilage have limited mitotic ability. Due to the unique and complex structure of articular cartilage, there is limited capacity for intrinsic healing, resulting in challenging repair or restoration of the defects [3]. Defects that are larger than 2-4 mm rarely heal [4]. These defects can be either induced traumatically or can develop from a degenerative disease, such as osteoarthritis.

Although lots of research has gone into the repair of cartilaginous lesions, the issue is still unresolved and an important clinical concern [5]. A surgical strategy that is currently implemented by many surgeons is the stimulation of bone marrow. The goal of this technique is to expose the defected cartilaginous tissue to the bone marrow, creating a spontaneous repair response. However, the problem with this method is that the repaired tissue from the bone-marrow-derived cells is only effective for a short time and the success is variable. The spontaneous repair response is dependent on various parameter such as the severity of the lesion, the age of the patient, and the activity level of the patient [5].

Another strategy that has been extensively researched for articular cartilage defects is implanting chondral or osteochondral tissues. This technique is used in clinical strategies involving allografts and autografts. The drawback with autografts is that when transferring

tissue, the surgeon is creating an additional lesion that is unlikely to heal in an already damaged tissue. The set back with allografts is the scarcity of fresh donor tissue [5].

The use of synthetic implants for treating articular cartilage defects are also limited due to the tribological and wear properties of articular cartilage, resulting in the need to investigate other methods [6]. An attractive candidate for use in articular cartilage repair is polyvinyl alcohol (PVA). PVA is a synethic polymer that is frequently used in medical devices due to its biocompatibility, high water solubility, chemical resistance, swelling properties, bioadhesive characteristics, and low protein adsorption characteristics. The high water solubility of the PVA allows the polymer to be crosslinked forming hydrogels. The hydrogels are able to swell in the presence of liquid, however are insoluble because of their cross-linked structure. Based on this degree of crosslinking, the amount of fluid uptake will vary, effecting the physical, chemical, diffusional, and biological properties [7].

The FDA has approved PVA hydrogels for various biomedical applications such as for contact lenses, as membranes, as drug delivery systems and for orthopedic devices [7]. These hydrogels are specifically attractive for articular cartilage repair due to their high water content, high mechanical properties, and high elastic properties. The method for creating the hydrogels is an extremely important contributor to these properties. The properties will vary based on factors such as the number of freeze-thaw cycles the hydrogels experience during preparation, the freeze-thaw time, the PVA molecular weight, and the concentration of aqueous solution [8,9]. A greater number of freeze-thaw cycles will reinforce crystals, thus increasing the mechanical stability in the hydrogels. As well, a moderate or low molecular weight of PVA is desirable to prevent the potential rearrangement of the structure over time [8].

There are four main regimes of lubrication: fluid film lubrication, elastohydrodynamic lubrication, boundary lubrication, and mixed lubrication. Articular cartilage is made up of a mixture of these lubrication regimes [10] and is a biological hydrogel that is made up of approximately 60-80% water [7]. Unlike organic solvents and oils, which become solid-like when confined between two surfaces down to a thickness of one monolayer, water remains a bulk-like fluid. The large electric dipole that water possesses results in the water molecules surrounding charges in aqueous media such as ions and zwitterions, forming a thin film. This thin water film that forms about the charges is referred to as a hydration layer and has remarkable lubrication properties. A combination of these molecules surrounding a charge can be strongly attached, yet rapidly relaxing. When these hydrated charges are present between sliding surfaces, they are able to support a large normal load while responding in a fluid manner under shear. This phenomenon is referred to as hydration lubrication and leads to a reduction in friction between surfaces exposed to such hydrated layers [11].

Although hydrogels have well-established biocompatibility, adaptability, and biomimetic properties, their friction and wear properties have been shown to limit their use in tribologically demanding situations and to damage natural opposing tissues [12, 13]. The focus of this research is on enhancing boundary lubrication so that hydrogels perform more like natural cartilage. In the boundary lubrication regime, there is a large amount of solid surface contact because the contacting normal surface loads are not supported by the lubricating fluid. However, the pressure is supported by a film on the surface, also referred to as the boundary lubricant [14,15] Zwitterionic polymers have been shown to act as an efficient lubricant in friction and wear processes and act as an effective boundary lubricant [14]. This behavior is due to the formation

of hydration shells around the charged parts of the zwitterionic chains, promoting the hydration lubrication mechanism, similar to in natural cartilage [16].

This concept led to the hypothesis that the presence of the zwitterionic polymer Poly([2-(methacryloyloxy) ethyl] dimethyl-(3-sulfopropyl) ammonium hydroxide) poly(MEDSAH) (hereafter pMEDSAH) within the PVA hydrogel matrix will result in an enhanced lubrication system and more reflective properties of natural cartilage. The primary purpose of this study is to investigate how this approach influences the tribological, mechanical, and physical properties of the resulting hydrogel.

Methods

Materials:

Polyvinyl alcohol (PVA) were purchases from Sigma- Aldrich (St. Louis, MO) with a molecular weight of 130,000 g/mol. The zwitterionic polymer pMEDSAH was synthesized by Allen Osaheni in Syracuse Biomaterials Institute via free radical polymerization of MEDSAH initiated by 2,2'-Azobisisobutyronitrile (AIBN).

Sample Fabrication:

The hydrogel blends were first fabricated by the mixing of 40 wt% PVA to deionized (DI) water. Using a scale, 2 grams of PVA was weight out and mixed with .5 mL of DI water for each sample. Five different wt% of pMEDSAH relative to PVA were then added to the solution: 0 wt%, 3 wt%, 5 wt%, 10 wt%, and 25 wt%. The mixtures were dispersed within an oven and heated for 6 hours at 90ºC. After being heated, the samples were exposed to three freeze/ thaw cycles. A mixture of acetone and dry ice was prepared at -80ºC for each freeze cycle. The samples were frozen for 30 minutes and then thawed at room temperature for 30 minutes, and the process was repeated three times. After the completion of the three freeze/ thaw cycles, the samples were submerged in DI water for 48 hours before any testing could occur, so equilibrium swelling could be reached. The complete hydrogel sample fabrication process is shown in Fig. 1.

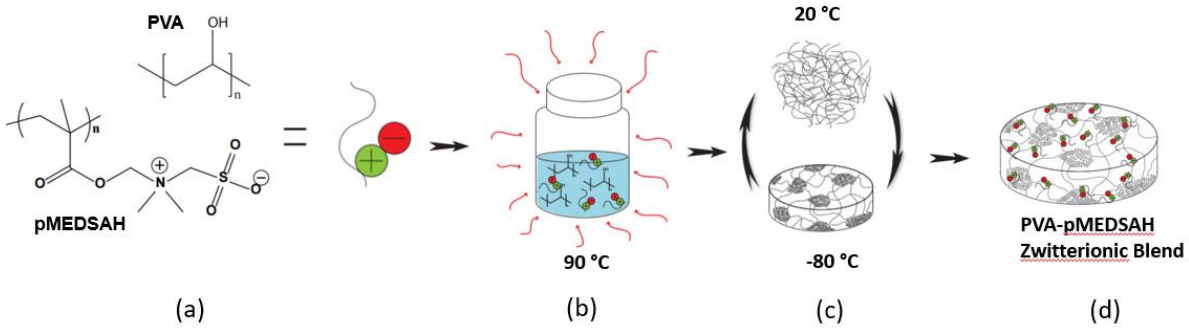


Fig. 1: Schematic of hydrogel fabrication procedure: (a) Structure of PVA and pMEDSAH (b) Representation of the heating of the PVA-pMEDSAH solution (c) Hydrogel crosslinking process (d) Final hydrogel.

Characterization

Tribological Characterization:

An AR-G2 rheometer (TA Instruments, New Castle, DE) was used for the tribological characterization of the samples. A shaft connected to a stainless steel beam coupling was used for the upper plate, allowing the geometry to be able to bend as a result of irregularities in the surface profile. The coupling also attached to a sample holder with a cut out for the hydrogel sample. During the initial tribological testing, the samples were not positioned as centrally on the sample holder, leading to visible vibrations during testing. A new sample holder was manufactured to reduce this effect. A glass petri dish filled with 80 mL of DI water was used as the bottom contacting surface during testing to ensure repeatability and minimal surface roughness. Fig 2 shows a visual representation of the experimental set up.

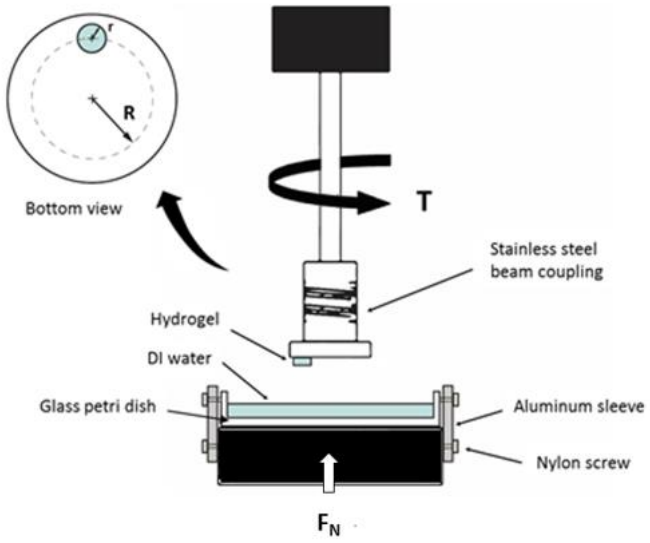


Fig 2: Tribo-rheometer experimental setup.

Testing was run at a constant angular velocity of 0.065 rad/s and the samples were subject to an average pressure of 0.2 MPa. Samples were preloaded to a force of 23 N and the data was collected every one second for a duration of five minutes. In order to calculate the coefficient of friction (COF) of the samples, a uniform normal pressure *P* was assumed. Based off this assumption, the normal force F_N is calculated using the following equation:

$$F_N = P \cdot \pi r^2 \qquad (1)$$

where, *r* is the radius of the sample. The torque *T* that develops the frictional force F_f on the sample is calculated using the following equation:

$$T = F_f \cdot R \qquad (2)$$

where, *R* is the distance between the rotational axis and the point that the force is being applied on the hydrogel. The COF was then be found using the following equation relating the frictional shear force to the normal force:

$$COF = \frac{F_f}{F_N} = \frac{T}{P\pi r^2 R} \qquad (3)$$

In equation 3 above, the values for the torque and the pressure were measured experimentally and were analyzed using Rheology Advantage Data Analysis (TA Instruments, New Castle, DE).

Mechanical Characterization:

Confined compression experiments using an AR- G2 rheometer (TA Instruments, New Castle, DE) and an 8 mm diameter rigid flat punch were performed to measure the elastic compression modulus of the hydrogel samples. In order to perform testing, the samples were placed in a holder of equal diameter (Fig. 3).

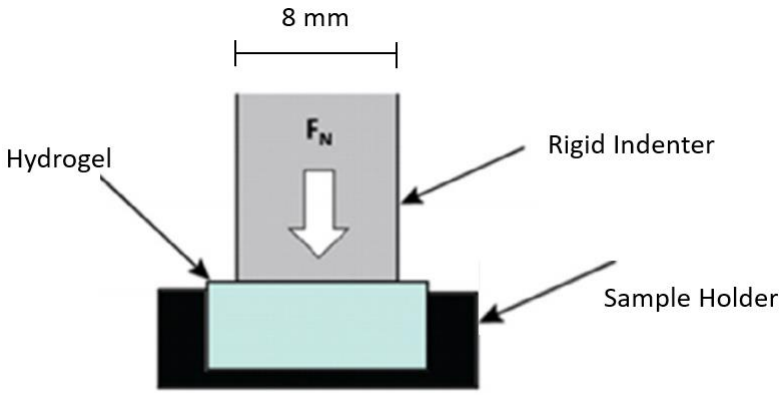


Fig. 3: Illustration of confined compression test set up.

Samples were compressed to 10% strain at a rate of 10 $\mu m/s$, held at 10% strain for one minute, and then released at a strain rate of 10 $\mu m/s$. The elastic compressive modulus was calculated by finding the average slope of the linear portion of the stress- strain curve that was produced during the unloading portion of the test. This relationship is shown using the following equation, relating the stress (σ) and strain (ε):

$$E = \frac{\sigma}{\epsilon} \qquad (4)$$

Viscosity Average Molecular Weight:

Molecular weight of a polymer is analogous to chain length. The intrinsic viscosity $[\eta]$ can be used to calculate molecular weight given the Mark-Hauwink parameters a and k which depend on polymer solvent and temperature. This molecular weight is referred to as the viscosity average molecular weight (M_v) as seen in Equation 5 with constant *k* equal to $2.06 \cdot 10^{-3}$ and constant *a* equal to 0.4071 [17]:

$$[\eta] = k \cdot {M_v}^a \qquad (5)$$

For experimentation, 0.2 M aqueous NaCl solutions were prepared with pMEDSAH concentration at five levels ranging from 3.5 – 1.4 g/dL. Viscosity was then measured by flowing solution through m-VROC^{TM} viscometer (Fig 4).

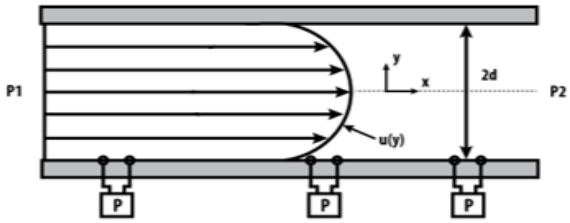


Fig 4: Illustration of the viscosity measurement method.

Using Navier Stoke's momentum balance equation, the following equation is obtained and used to calculate the solutions viscosity:

$$\eta = \frac{2wd^3}{3Q}\left(\frac{-dP}{dx}\right) \qquad (6)$$

where μ is the viscosity of the solution, *d* is the half channel height, *w* is the width of channel, *Q* is the volumetric flow rate, and $\frac{-dP}{dx}$ is the pressure drop.

Effective Contact Modulus:

Indentation is a useful method for contact mechanics. The effective contact modulus (E_c) can be found by the indentation of a half space of a rigid substrate with a radius *R*. This approach is referred to as Hertzian biphasic theory (HBT) and requires that the contact diameter *2a* be less than the thickness of the half space [18]. Using the recent analytical solution developed for biphasic materials by HBT, the effective contact modulus is estimated from the slope of the linear region of the normal force (F_N) and displacement (δ) curve [19]. The following equation is curve fit to find the value of the effective contact modulus:

$$F_N = \frac{4}{3} E_c R^{0.5} \delta^{1.5} \qquad (7)$$

where, R is the radius of the indenter tip. The samples were compressed to 10% strain and indented at a rate of 100, 50, 10, 5, 1, 0.5, and 0.1 $\mu m/s$ in a random order. In equation 7 above, the values for the normal force and displacement were measured experimentally.

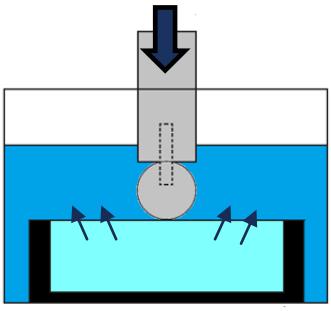


Fig 5: Illustration of Indentation Test Configuration.

Dehydration/ Rehydration Study:

To access whether or not repeated hydration/ dehydration cycles (HDC) influenced the tribological, mechanical, and physical properties of the samples, a hydration/ dehydration study was conducted. Hydrogels were exposed to up to three HDC and characterization occurred upon their completion. Samples were dehydrated in a vacuum oven (Isotemp Vacuum Oven, Thermo Fisher Scientific, Waltham, MA) until equilibrium was reached and the equilibrium dehydrated mass (m_d) was recorded. Samples were then submerged in DI water until equilibrium conditions were reached and the equilibrium rehydrated mass $(m_w)$was calculated. The equilibrium water content (EWC) was calculated by the percent different between the hydrated and dehydrated masses of the samples:

$$EWC = \frac{m_w - m_d}{m_w} \qquad (8)$$

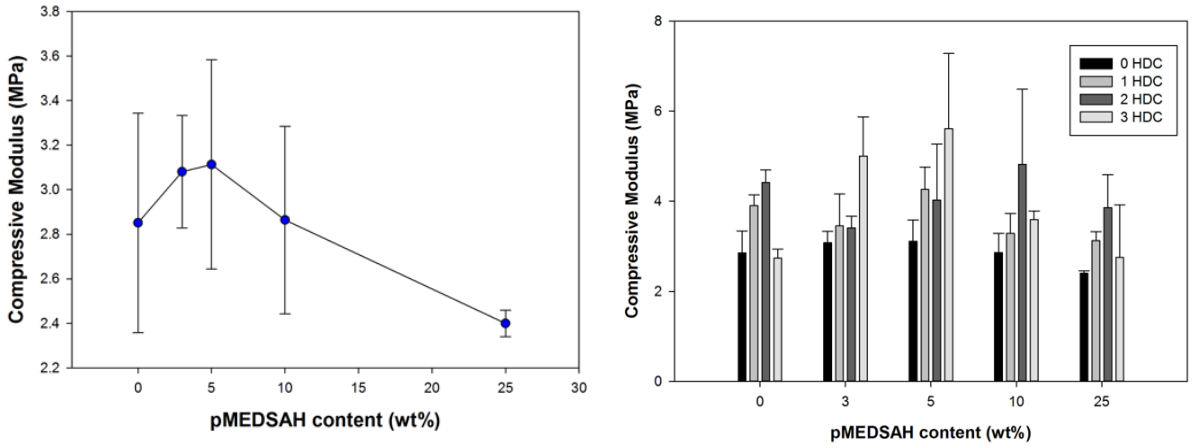
Degradation Study:

In order to evaluate the long term stability of the hydrogels, a degradation study was performed. The purpose of this study was to investigate the storage capacity of the hydrogels for potential use as bio- implants. Neat PVA hydrogels and hydrogels with 3 wt%, 5 wt%, 10 wt%, and 25 wt% pMEDSAH in sets of three were placed in incubation for 4 months. After incubation, samples were thoroughly tested as previously described.

Results

Mechanical Characterization:

The confined compression experiments showed that increasing the pMEDSAH content resulted in a peak average compressive modulus of $3.11 \pm .47$ MPa at concentration of 5 wt % pMEDSAH followed by a steady decrease (Fig 6a). The average compressive modulus ranged from $2.40 \pm .06$ MPa to $3.11 \pm .47$ MPa.



(a) (b)

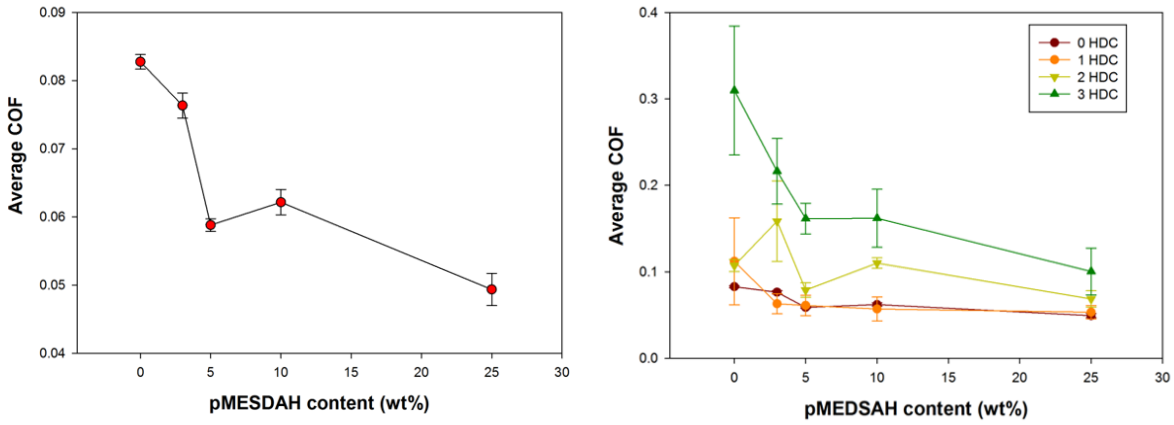
Fig. 6: Characterization of compressive modulus of the neat and blended hydrogels for three samples at each concentration (a) Fully hydrated samples with no hydration dehydration cycles (b) Samples with 0 to 3 hydration dehydration cycles

A series of three HDC were performed for the samples. A similar trend was seen after each of the cycles between samples containing pMEDSAH concentrations of 3 wt % and 5 wt% and samples containing pMEDSAH concentrations of 10 wt% and 25 wt%. For samples containing 3 wt% and 5 wt% pMEDSAH, a maximum compressive modulus was seen after 3

HDC. A peak was seen after 2 HDC for samples containing 10 wt% pMEDSAH and 25 wt% pMEDSAH.

Tribological Characterization:

Experiments showed a decrease in the average COF by the addition of the zwitterionic polymer pMEDSAH to the hydrogel matrix (Fig 7a). The average COF decreased from $.08 \pm .001$ for the neat hydrogels to $0.05 \pm .001$ at a pMEDSAH concentration of 5 wt%. The largest change in average COF was observed at 25 wt% pMEDSAH with a value of $.049 \pm .002$ and a percent decrease of 40.36%.



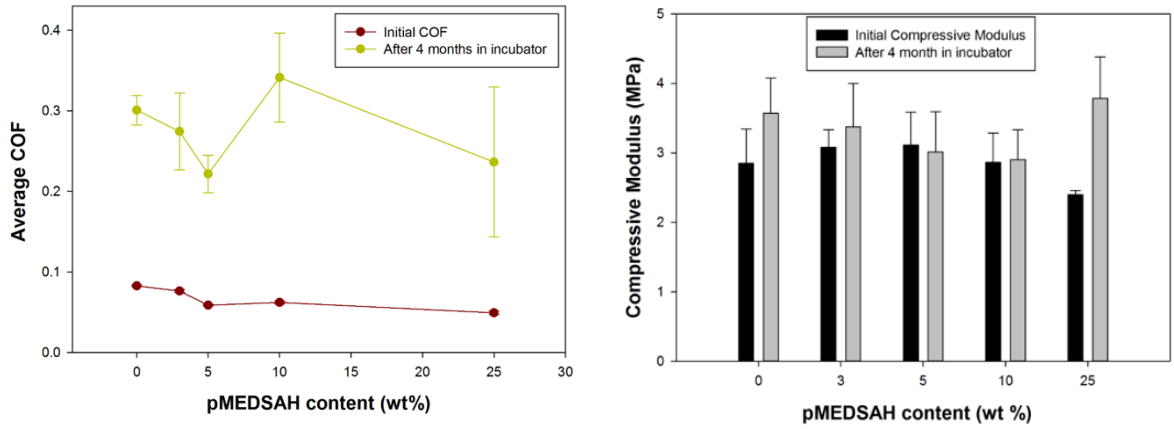
(a) (b)

Fig 7: Friction data for hydrogels will increasing pMEDSAH content (a) Fully hydrated samples with no hydration dehydration cycles (b) Samples with 0 to 3 hydration dehydration cycles

The change in the average COF was also examined after a series of HDC (Fig 7b). A decreasing trend in average COF was seen after no HDC, one HDC, and 3 HDC. No trend was seen for the hydrogels after 2 HDC. The hydrogels experience little change after 1 HDC. However, after 3 HDC, an average percent increase in average COF of 179% was calculated.

Degradation:

Stability of elastic compressive modulus has been quantified over a four-month time period. A large change in compressive modulus was only observed at the 25 wt% level with an increase from 2.40 ± 0.06 MPa to 3.78 ± 0.59 MPa. However, stability was not seen for the average COF after a four- month period, a large increase was seen for the neat hydrogels and at all four pMEDSAH concentrations. The greatest increase was seen at the 10 wt% level where the average COF increased from .06 ± 0.002 to .34 ± 0.6, which is a 449% increase.



(a) (b)

Fig 8: Characterization of hydrogels before and after 4 months in the incubator (a) Friction data for hydrogels with increasing pMEDSAH content (b) Compressive modulus data for hydrogels with increasing pMEDSAH content

Molecular Weight:

The monomer (MEDSAH) concentration was left constant at 0.25 M and three different monomer-indicator ratios were chosen. As well, the solvent volume was left constant at 70 mL. Once the solution viscosity was measured over a range of concentrations, relative viscosity (η_r) and specific viscosity (η_{sp}) were calculated. Using specific viscosity and relative viscosity,

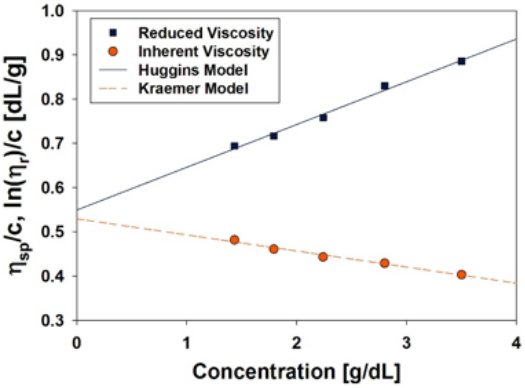
inherent viscosity and reduced viscosity were found (Fig 9a). The Huggins and Kraemer models were then used to determine the intrinsic viscosity [η] (Fig. 9b).

Synthesis parameters used to achieve these pMEDSAH molecular weights.

Symbol	Name	Units
η	Solution Viscosity	cP
η_s	Solvent Viscosity	cP
$\eta_{rl} = \eta / \eta_s$	Relative Viscosity	-
$\eta_{sp} = \eta_{rl} - 1$	Specific Viscosity	-
$\eta_i = \ln \eta_{rl} / c$	Inherent Viscosity	dL/g
$\eta_{rd} = \eta_{sp} / c$	Reduced Viscosity	dL/g

(a)

Intrinsic Viscosity 825 kDA



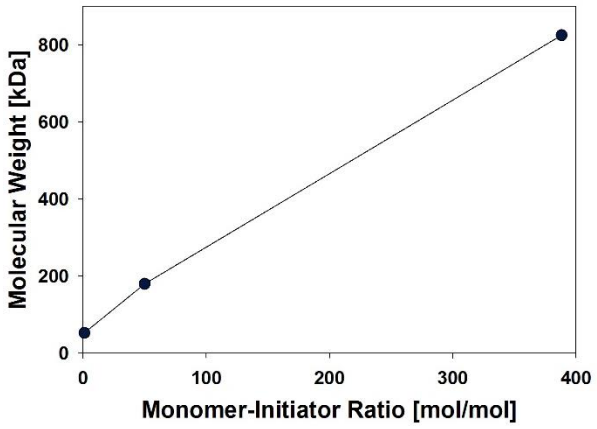
(b)

Fig. 9: (a) Table showing the synthesis parameters used to achieve the three different molecular weights. (b) Visual representation of Higgin and Kraemer models being used to calculate intrinsic viscosity for 825 kDA pMEDSAH

The zwitterion polymer pMEDSAH was successfully synthesized at three molecular weights. Figure 10a shows the monomer- initiator ratios that were used to achieve the different molecular weights. As the monomer- initiator ratio increased, the molecular weight also increased. There was a difference between the lowest molecular weight and the highest molecular weight of 772,539 g/mol.

Monomer-Initiator Ratio [mol/mol]	Molecular Weight [g/mol]
1.19	52,525
50.12	179,641
388.32	825,064

(a)

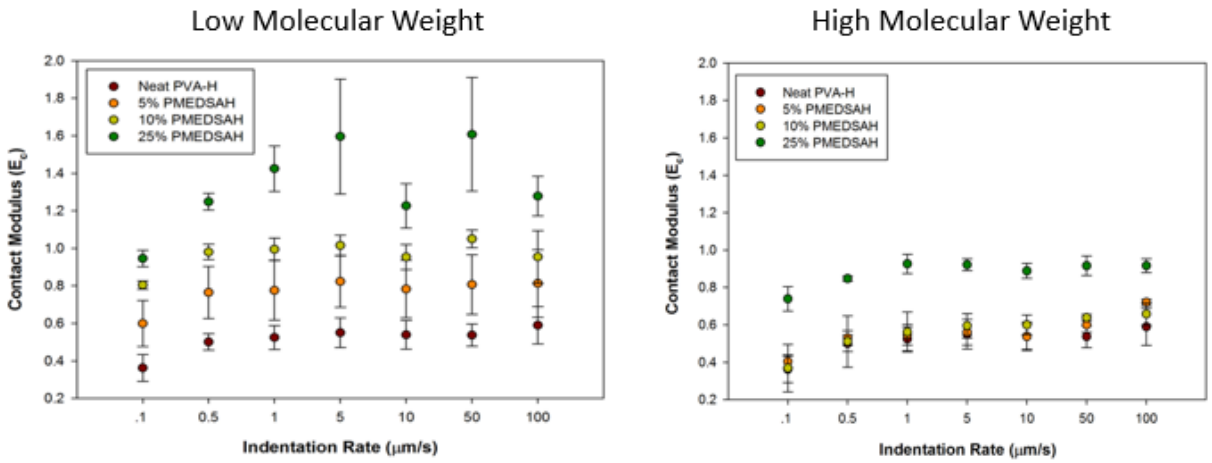


(b)

Fig 10: (a) Table showing the synthesis parameters used to achieve the three different molecular weights. (b) Visual representation of the monomer- initiator ratio versus the molecular weight.

Contact Mechanics:

Characterization of effective contact modulus of neat PVA-H compared to the zwitterionic blends revealed that blending pMEDSAH with PVA resulted in a trending increase in effective contact modulus. The lower molecular weight resulted in a higher contact modulus for all the different concentrations of pMEDSAH. For the lower molecular weight samples, the contact modulus seemed to increase uniformly for the different pMEDSAH concentration. However, for the high molecular weight hydrogels, a large increase in the contact modulus was only seen for the 25 wt% level samples. At both molecular weights and for almost all of the samples, the contact modulus increased with the increasing indentation rate and seems to reach an asymptotic limit [19].



(a) (b)

Fig 11: Representative plots of contact modulus vs indentation rates for neat and blended samples. (a) Hydrogel samples with low molecular weight pMEDSAH. (b) Hydrogels samples with high molecular weight pMEDSAH.

Discussion

The zwitterionic polymer pMEDSAH was crosslinked at different wt % levels with PVA. Based on the data that is shown in Fig 7a, the addition of 5 wt% pMEDSAH resulted in a 40.36% decrease in the COF. It is expected that this is due to the hydration shells that form around the charged portions of the pMEDSAH, the positively charge sulfur trioxide group (SO_3^-) and the negatively charged quaternary ammonium group (NR_4^+) [14]. Water molecules are attracted to these charged groups due to their dipole. We expect that there is then a gradual extrusion of the pMEDSAH to the surface of the hydrogel, forming a molecular scale H_2O film. [14, 20]. This film experiences a fluid like response under high pressure, resulting in a reduction of the shear stress between surfaces and a lower coefficient of friction [11].

An increase of the COF was seen after three HDC. We expect that this is a result of a decrease in the water content after the cycles, due to the pMEDSAH diffusing out of the hydrogels over time. Further investigation would include measuring the equilibrium water content and the viscosity of the fluid after each cycle. Our results showed that HDC have an effect on the performance of the samples and need to be taken into account when considering bulk manufacturing of this product for medical use.

The results of the compressive modulus after the HDC showed similar results for the samples with 10 wt% and 25 wt% as the neat PVA hydrogels. This also suggests that for the samples with higher concentration of pMEDSAH, the pMEDSAH is diffusing out. Viscosity measurements can be conducted to measure the rate that the pMEDSAH is coming out of the samples. Both passive diffusion and active diffusion should be investigated.

The increase in the average COF after the samples were in the incubator is expected to be for a similar reason. These results show that the current processing method works well to

produce these tribolically enhanced hydrogels in a laboratory setting, but more investigation will be needed before these hydrogels can be properly packaged and distributed. As well, if the tribological properties of these hydrogels were greatly changed in only four weeks, we also need to investigate how they will react in the human body over longer periods of time.

The results showed that the edition of the zwitterionic polymer pMEDSAH did not compromise the mechanical properties of the neat PVA [14]. Four months in incubation only resulted in an increase in the compressive modulus for the hydrogels with 25 wt% pMEDSAH. This occurred due to the crosslinked nature of the hydrogel. The results showed that the mechanical stiffness did not deteriorate over time, this is because the hydrogel was physically crosslinked by the freeze-thaw cycles. The increase in stiffness is thought to be due to dehydration of the gels over time, which can be confirmed with water content experiments in the future.

The contact modulus is higher for the lower molecular weight samples suggesting that the higher molecular weight of the pMEDSAH prevents the PVA from cross-linking as well. We also expect to see a direct correlation between the molecular weight of the samples and the COF because the larger molecules should be harder to extrude to the surface of the samples, creating the hydration lubrication [20]. Repeat testing on the samples showed that the results were repeatable and not sensitive to the order of the indents [19]. To further investigate the contact mechanics of the hydrogels, stress relaxation testing is being conducted. Based off the data that is collected by compressing the hydrogels until equilibrium is reached, the equilibrium contact modulus can be calculated. Using these values and the contact modulus as a function of strain rate, $\dot{\delta}$, a non-linear least square curve fit algorithm can be used to estimate permeability and tensile modulus [19].

For future work, one question that needs to be addressed is whether or not blending pMEDSAH with PVA affects the wear properties of PVA-H. We have extensively investigated the impact adding pMEDSAH has on the tribological properties of the hydrogels, but little attention has been given to how this affects the wear properties. These wear tests will be conducted using a migrating contact pin on disc method. DSC testing should also be performed to characterize the crystallinity of the different molecular weight hydrogels.

Conclusions

This study showed enhancement of PVA hydrogels by the addition of the zwitterionic polymer pMEDSAH into the hydrogel matrix. The blends were prepared by a solvent casting and freeze- thaw process. Mechanical and tribological analyses were performed. As well, degradation and hydration- rehydration studies were conducted. The results showed an increase in the coefficient of friction after four months in incubation and after three hydration- dehydration cycles. If this simple processing method is used in biomedical devices, a packaging method will need to be developed to prevent this reduction in the hydrogel properties. However, this approach provides a promising platform for further increasing the boundary lubricant properties of hydrogels.

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