Afyon Kocatepe Üniversitesi Fen ve Mühendislik Bilimleri Dergisi

Afyon Kocatepe University Journal of Science and Engineering

AKÜ FEMÜBİD **22** (2022) 015903 (252-261) AKU J. Sci. Eng. **22** (2022) 015903 (252-261)

DOI: 10.35414/akufemubid.1015110

Araştırma Makalesi / Research Article

Mechanical and Tribological Analysis of Polyacrylamide/Alginate Hybrid Hydrogels for Potential Cartilage Treatment

Yusuf KANCA[1]*, Emir AVCIOĞLU[2], Lynne HOPKINS[3], Ercan BİLGE[4]

[1,2,4]Hitit Üniversitesi, Mühendislik Fakültesi, Makina Mühendisliği Bölümü, Çorum.

[3]APREM Danışmanlık ve Makine İmalat, Çorum.

**Sorumlu yazar e-posta: yusufkanca@hitit.edu.tr ORCID ID: http://orcid.org/0000-0002-8769-0774*

e-posta: emiravcioglu@hitit.edu.tr ORCID ID: http://orcid.org/0000-0002-6560-2921

e-posta: lynnehopkins@gmail.com ORCID ID: http://orcid.org/0000-0003-4244-4796

e-posta: ercanbilge55@gmail.com ORCID ID: http://orcid.org/0000-0003-20263839

Geliş Tarihi: 27.10.2021 Kabul Tarihi: 16.02.2022

Abstract

In this study, polyacrylamide/alginate (PAAm/Alg) based hydrogels have been synthesized and investigated. The four different hydrogels produced contained different concentrations of single- or double- network polymer: 15 wt.% single-network (SN-15), 30 wt.% single-network (SN-30), 15 wt.% double-network (DN-15), and 30 wt.% double-network (DN-30). The tribological performance of these synthesized hydrogels was investigated by using a custom pin-on-disc tribometer in phosphate buffered saline (PBS), where samples were reciprocated against a CoCrMo femoral head under an applied load of 5 or 10 N, at an average sliding speed of 20 mms^{-1}, and body temperature (37±1 °C). The compressive tangent modulus was also determined by compressing samples at a strain rate of 1 min^{-1}, while submerged in PBS, at both ambient and body temperatures. The results showed that a higher polymer concentration or a double-network type of structure led to improved friction (lower friction co-efficient) and wear (lower wear track area) properties. Samples also performed better when a lower applied load used. Sample DN-30 exhibited the highest compressive modulus. These outcomes have contributed to the understanding of the mechanical and tribological performance of PAAm/Alg blend hydrogels when performing under certain physiological conditions.

Keywords
Polyacrylamide;
Alginate;
Cartilage treatment;
Tribology;
Compressive behaviour

Potansiyel Kıkırdak Tedavisi için Poliakrilamid/Aljinat Hibrit Hidrojellerin Mekanik ve Tribolojik Analizi

Öz

Bu çalışmada sentezlenen poliakrilamid/aljinat (PAAm/Alg) bazlı hidrojellerin mekanik ve tribolojik özellikleri incelenmiştir. Üretilen dört farklı hidrojel farklı konsantrasyonlarda tek veya çift ağ yapılı polimerlerden oluşmaktadır: ağırlıkça %15 tek ağ yapılı (SN-15), %30 tek ağ yapılı (SN-30), %15 çift ağ yapılı (DN-15) ve %30 çift ağ yapılı (DN-30). Sentezlenmiş hidrojellerin tribolojik performansı, özel olarak tasarlanmış pin-on-disk tribometre ile, 37±1 °C sıcaklıkta fosfat tamponlu salin (PBS) içerisinde, ortalama kayma hızı 20 mms^{-1} olan CoCrMo femur kafasının altında 5 veya 10 N'luk yükler uygulanıp lineer git-gel hareketi ile incelenmiştir. Hidrojellerin sıkıştırma tanjant modülü, PBS'ye daldırılmış numunelerin hem ortam hem de vücut sıcaklarında 1 dak^{-1} gerinim hızında sıkıştırılmasıyla belirlenmiştir. Test sonuçları daha yüksek polimer konsantrasyonu veya çift ağ tipi bir yapıya sahip olmanın hidrojellerin gelişmiş sürtünme (düşük sürtünme katsayısı) ve aşınma (düşük aşınma izi alanı) özelliklerine sahip olmasına yol açtığını göstermiştir. Hidrojellerin daha düşük yük altında daha iyi performans gösterdiği gözlemlenmiştir. DN-30 olarak kodlanan numune en yüksek sıkıştırma modülü davranışını sergilemiştir. Bu sonuçlar, fizyolojik koşullar altında PAAm/Alg karışımı hidrojellerin mekanik ve tribolojik performansının anlaşılmasına katkıda bulunmuştur.

Anahtar kelimeler
Poliakrilamid;
Aljinat;
Kıkırdak tedavisi;
Triboloji;
Basma davranışı

1. Introduction

Researchers are developing biomaterials for cartilage treatment that can mimic the structure of the cartilage biologically, biochemically and mechanically. These biomaterials are generally categorized into three main groups: natural, synthetic or a combination of natural/synthetic materials. The natural materials are alginate, collagen chitosan, agarose, hyaluronan and fibrin, while the synthetic ones are poly (vinyl alcohol) (PVA), polylactide acid (PLA), poly (ethylene glycol) (PEG), polyurethane (PU), polyacrylamide (PAM) and their derivatives. These natural and synthetic materials can be used together in order to improve the properties of the replacement material and obtain a similar structure to the real cartilage (Duarte Campos *et al*. 2012). Such biomaterials are called hydrogels and that can be defined as three-dimensional networks of hydrophilic polymers that are ionically or covalently cross-linked. Due to the chemical structure of hydrogels, they can absorb large amounts of biological fluids and water without losing their shapes. However, since hydrogels are not water soluble materials, they are subjected to swelling during absorption (Dragan 2014,Hoffman 2002, Peppas *et al*. 2000). Hydrogels can be used as a biomaterial due to their unique features, most notably; similarity to living tissue, biocompatibility, biodegradability, flexibility, softness, versatility, and stimuli-responsivity. Moreover, despite their relative softness, they possess good mechanical and tribological properties (Aswathy *et al.* 2020, Hoffman 2002). These prominent features allow hydrogels to not only be used for cartilage treatment but also contact lenses (Carnt *et al.* 2010), wound dressing (Basu *et al.* 2017), drug delivery (Craciun *et al*. 2018), cosmetic applications (Parente *et al*. 2015), and tissue engineering (Al-sabah *et al*. 2019).

There are 2 common diseases, called osteoarthritis (OA) and rheumatoid arthritis (RA), which require cartilage treatment. OA is caused by aging, obesity and traumatic injury that cause the cartilage to thin, which in turn causes the contact surfaces of the joint to become rougher and increasingly worn out, leading to cartilage loss. On the other hand, RA is brought about by a disorder of the autoimmune system, where healthy cells are attacked by the immune system which causes inflammation of the joint and thickening of the synovial fluid, resulting in cartilage loss (Tamer 2013).

In cartilage treatment applications within tissue engineering area, hydrogels are expected to regenerate damaged tissues (Li *et al.* 2019, Li *et al.* 2012, Xiao *et al.* 2013) and/or replace the damaged tissue. Hip joint is a ball-and-socket synovial joint that helps to dissipate the load and enable angular rotational motion with low friction. The joint contains articular cartilage which separates the femoral head and the acetabulum. Moreover, hip joint is encapsulated by a synovial membrane which produces synovial fluid. The fluid is stored in the cartilage while the joint is not in motion, however during motion, the viscous substance is squeezed out to lubricate the contact area, reducing the friction and circulating nutrients in the joint (Tamer 2013). The cartilage tissue is composed of abundant extracellular matrix (ECM) consisting primarily of collagen type II which provides tensile strength, and highly sulphated proteoglycans that contribute resistance to the load (Goldring & Goldring 2007).

Hydrogels are promising substitute materials because their toughness and strength values are close to the corresponding values of cartilage, and they have a lubricating mechanism that transmits the biological fluid to the joint under load conditions (Beddoes *et al*. 2016). There are several hydrogels can be used for treatment and regeneration by transplant into a damaged cartilage or replacement of the whole cartilage. The polymers developed for use in cartilage tissue engineering applications can be listed as follows: polyethylene glycol (PEG) (Mehrali *et al*. 2017), polyvinyl alcohol (PVA) (Dashtdar *et al*. 2013), hyaluronic acid (HA) (Zhu *et al*. 2017), alginate (Park *et al*. 2017), acrylamide (Beddoes *et al*. 2016). Although these given hydrogels were investigated as cartilage substitution materials on their own, it was observed that they are brittle, non-stretchable and possess low mechanical properties. For this reason, research focused on reinforcement materials, crosslinks and hybrid structures additions that were introduced, and indeed found to improve the mechanical properties of the hydrogels to be used for cartilage treatment. For instance, it was found that the PEG hydrogels' strength and compression modulus can approach those of the real cartilage structure when it is in hybrid form – i.e. when it constitutes of a mix of natural and synthetic materials (Liu *et al*. 2010, Scholz *et al*. 2010). On the other hand, PVA hydrogels require reinforcement materials to improve their tensile modulus (Grad *et al.* 2003). Similarly, Alginate also requires additional materials or crosslinking for an adequate compressive strength and stiffness (Scholten *et al*. 2011). The elastic and compressive moduli of Acyrlamide hydrogels can also be improved significantly with the addition of reinforcing materials and crosslinkers (Zaragoza *et al.* 2016). Different type of reinforcement materials and methods such as nanoparticle reinforcement (Yue *et al*. 2019), nano fiber reinforcement (Jang *et al*. 2013), multi-functional crosslinking (Bialik-Was *et al.* 2021) double network applications and hybrid structures (Pourjavadi *et al*. 2020), hybrid hydrogels such as polyacrylamide/alginate (Sun *et al*. 2012) have been studied.

The aim of this study was to synthesize polymer hydrogels with mechanical and tribological properties approximating those of articular cartilage under certain physiologically relevant conditions. This was done by synthesizing single- and double-network PAAm/Alg hybrid hydrogels at concentrations of 15 wt.% and 30 wt.%. Due to articular cartilages contains fluid between %65 and %80, the given concentrations were selected *(Mow et al.* 1992). These hydrogels were subsequently assessed for wear and friction properties, under various loads and while in-vitro. The compressive and swelling behaviours were also investigated.

2. Material and Method

2.1 Acrylamide/Alginate blend hydrogel synthesis

Acrylamide (AAm), N'N-methylenebisacrylamide (NMBA) and ammonium persulfate (APS) were bought from Sigma-Aldrich (Germany), while Alginate (Alg) and $CaCl_2$ were purchased from Merck (Germany). Single-network (SN) and double-network (DN) PAAm/Alg blend hydrogels were prepared using the method described by Sun *et al.* (Sun *et al*. 2012) with modifications. After dissolving Acrylamide monomer (15 and 30 w/v%) in deionized water at room temperature, alginate monomer (1.6 and 3.2 w/v%) was added to the aqueous solution. This was followed by the addition of 0.05 w/w% of NMBA solution and subsequently, 0.1 w/w% of APS solution, which acted as an acrylamide crosslinker and solution initiator, respectively. The solution was stirred continuously using a magnetic stirrer at a constant speed until all the substances were fully dissolved. After pouring the solution into petri dishes, the polymerization process was conducted by exposing the solution to a 254 nm light source in a UV cabinet for 2 h, thus allowing all chemical reactions to be fully completed. Finally, the samples were soaked in 10 w/v% $CaCl_2$ solution for 24 h to enable the ionic crosslinking of alginate and therefore DN hydrogels (Darnell *et al.* 2013, Guo *et al.* 2014, Sun *et al.* 2012, Yang *et al.* 2013). At the end of the process, the samples were washed with deionized water to remove any unreacted chemicals. The hydrogels synthesized at different conditions are summarized in Table 1.

2.2 Friction and wear studies

Friction and wear experiments employing linear reciprocating motion were conducted using a custom pin-on-disk tribometer (Figure 1). Prior to clamping into the testing equipment, PAAm/Alg specimens (nominal diameter 39 mm, thickness 4.5±0.3 mm) were fully hydrated in PBS for at least 48 h, and subsequently glued onto stainless steel discs (thickness 3 mm). The femoral head (Ø28 mm; average surface roughness, R_a<0.050 µm), against which the samples were tested was made of CoCrMo. With a stroke length of 10 mm at 1 Hz, the average sliding speed was 20 mm s^{-1}, thus simulating that experienced by the articular cartilage during walking activities. The loads applied were 5 and 10 N, which, according to the Hertzian contact theory, yielded average contact pressures of 0.02 -0.05 MPa, respectively. Tests were run for 1 h in PBS (Sigma–Aldrich), and throughout the tests, the lubricant temperature was kept constant at 37±1 °C. The test conditions are shown in Table 2. Following the tests, the hydrogel discs were rinsed with distilled water and rehydrated in PBS for a minimum of 48 h. The resulting wear tracks were analyzed visually for signs of surface damage, photographed alongside a ruler to enable measurement of the damaged area and processed using ImageJ software.

Table 1. Composition of the hydrogels prepared using various concentrations and crosslinking agents.

Polymer	Aam[1] (w/v%)	Alg[2]. (w/v%)	NMBA[3] (w/w%)	APS[4] (w/w%)	$CaCl_2$ (w/w%)
15%-SN[5]	15	1.6	0.05	0.1	-
30%-SN	15	1.6	0.05	0.1	-
15%-DN[6]	30	3.2	0.05	0.1	10
30%-DN	30	3.2	0.05	0.1	10

[Note]: The explanation of the abbreviations given in the Table 1 is shown below.

[1] Acrylamide

[2] Alginate

[3] N'N-methylenebisacrylamide

[4] Ammonium persulfate

[5] Single Network

[6] Double Network

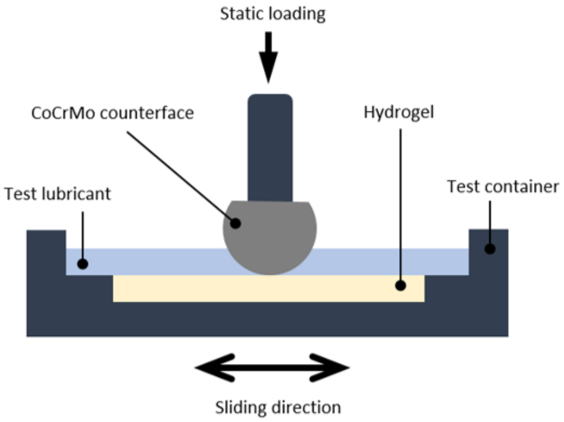


Figure 1. Schematic of tribometer.

Table 2. Test conditions for friction and wear tests

Test Parameters	
Load	5 and 10 N
Sliding speed	20 mm/s
Lubricant	PBS
Test Duration	1 h
Test Temperature	37±1 °C

2.3 Hydrogel compressive properties

The compressive properties of the PAAm/Alg blend hydrogels were tested by uniaxial unconfined compression tests, performed by a mechanical tester (AG-IS, Shimadzu Co., Japan) that was equipped with a 50 N load cell. The tests were conducted at both ambient temperature and body temperature (37 ±1 °C), while submerged in PBS. The hydrogel discs (diameter 11.8±0.3 mm, thickness 6.6±0.8 mm) were pre-loaded as 0.1 N to ensure full contact. The samples were compressed at a strain rate of 1 min^{-1}, to 40% of their original thickness. Following the conversion of the load-displacement data into engineering stress-strain, the compressive modulus was deduced as a first derivative of stress with respect to strain at various strain levels. Stress relaxation tests that assess the time-dependent mechanical characteristics of the hydrogels were conducted by holding the 0.4 compressive strain constant for 300 s, while recording the load-time response that was subsequently converted to compressive stress versus time. The stress relaxation rate (SRR) was quantified by applying the following equation:

$$SRR = [(\sigma_p - \sigma_e)/\sigma_p] * 100\,(\%) \tag{1}$$

Where σ_p is peak compressive stress and σ_e is equilibrium compressive stress. Each test was performed three times and the average values were reported.

2.4 Swelling studies

Synthesized hydrogel was weighed (W_S) and subsequently immersed in PBS (Sigma–Aldrich) at 37.0±0.1 °C until equilibrium was reached. The swollen hydrogel sample was then blotted with filter paper to remove excess water and weighed again (W_s). Swelling degree (SD) was determined using the following formula;

$$SD = (W_S - W_D)/W_D \qquad (2)$$

3. Results and Discussion

3.1 Coefficient of friction

Figure 2 gives the coefficient of friction (COF) with sliding time for the articulation of PAAm/Alg hydrogels against a CoCrMo femoral head. The figure also illustrates how the COF behavior alters with a change in polymer concentration (Fig 2a), polymer network (Fig 2b) and applied load (Fig 3c). The 30%-DN hydrogel that was worn at an applied load of 5N exhibited a low and stable COF behavior throughout the test. This behavior can be explained by the formation of biphasic lubrication (Sakai *et al*. 2018). In all the other experiments, which involved either at a lower polymer concentration (15 wt%), a higher applied load (10 N) or a different polymer chain structure (SN), the COF was observed to increase for the first 10 min and then settle to a steady-state condition. A lower applied load led to a shorter transition to steady-state for SN hydrogels. This increase in COF has been attributed to a loss of interstitial fluid support with time (Mostakhdemin *et al.* 2021).

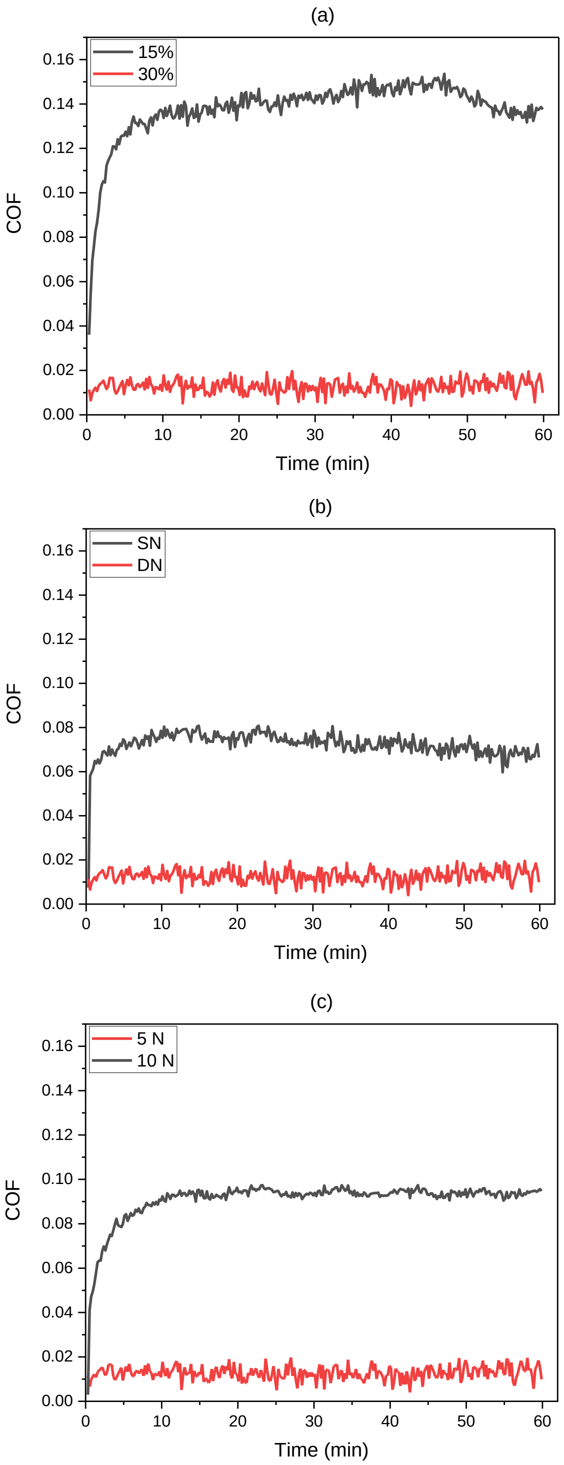


Figure 2. Coefficient of friction versus time; (a) concentration comparison for DN hydrogel tested at 5 N, (b) network comparison for 30% hydrogel tested at 5 N, and (c) test load comparison for 30%-DN hydrogel.

Table 3 depicts the mean COF values for various test conditions. Average values for the COF were found to be between 0.01 and 0.14. COF was observed to increase when either a higher load was applied, when the polymer concentration was lower or when the structure was of SN type. Figure 3 gives an illustrative plan view of a wear scar of a PAAm/Alg hydrogel, while the calculated wear track areas are reported in Table 3. The damage area of 30%-DN hydrogel worn at 5 N (16 mm^2) was found to increase when either polymer network changed to SN (24.7 mm^2) or test load increased to 10 N (30.1 mm^2). Conversely, increasing hydrogel concentration from 15 to 30 wt% caused a lower wear track area as the hydrogels became stronger. A good correlation (R^2=0.97) between the COF and the wear track area was found.

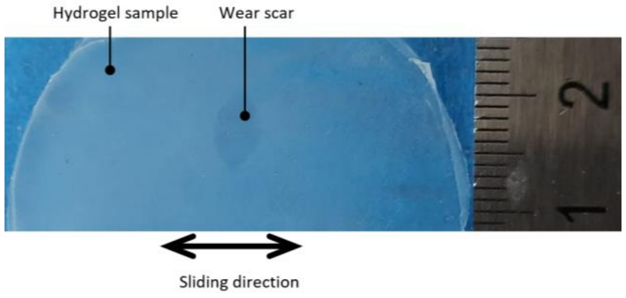


Figure 3. An illustration of wear track for 30%-DN hydrogel under 5 N**.**

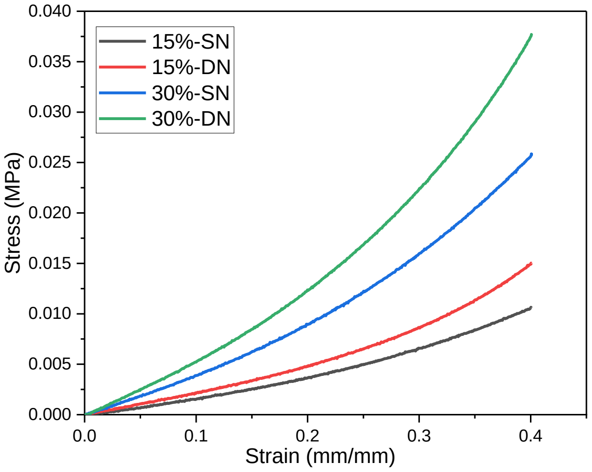
Table 3. Mean COF and wear track area for the hydrogels worn in PBS lubricant.

Hydrogel	Test load (N)	Mean COF	Wear track area (mm^2)
15%-DN	5	0.14	34.5
30%-DN	5	0.01	16.0
30%-SN	5	0.07	24.7
30%-DN	10	0.09	30.1

3.2 Hydrogel compressive behaviour

PAAm/Alg hydrogels were compressed to 0.4 strain at a rate of 1 min^{-1}, at both ambient and body temperatures. A non-linear stress-strain response (Figure 4) was observed for the hydrogels at both of the tested temperatures. The range of compressive modulus observed lied in between 0.016±0.001 and 0.179±0.014 MPa – with the variation being caused by factors such as the hydrogel group, the strain magnitude and the test temperature (Figure 5). As the strain magnitude increased, higher compressive moduli were reported. Similarly, increasing the hydrogel concentration from 15 to 30%, resulted in an increased compressive modulus for all the hydrogel groups tested. DN hydrogels were found to exhibit higher compressive moduli than the corresponding SN group for all strain magnitudes and test temperatures. The highest compressive modulus (0.057±0.006 – 0.179±0.014 MPa) across all the test groups was observed for the %30-DN samples. This result falls within the lower range of the stiffness reported for natural articular cartilage (0.1–1 MPa) (Davis *et al.* 2021). The testing temperature affected the compressive modulus across all the tested hydrogel groups, with a higher testing temperature resulting in a lower compressive modulus. This result was attributed to the tendency of polymer chain damage at higher temperatures (Kabiri *et al.* 2008).

(a) ambient temperature



(b) body temperature

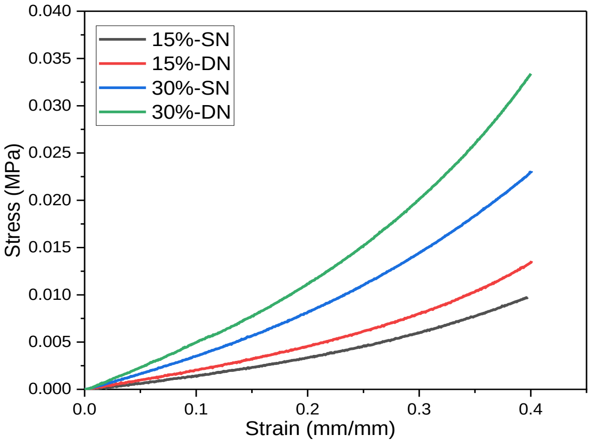
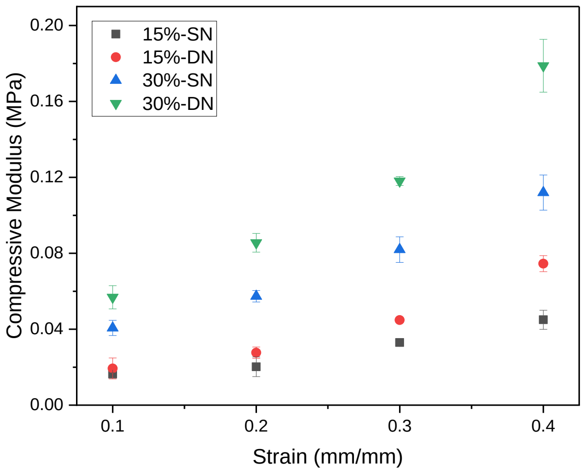


Figure 4. Compressive stress versus strain of PAAm/Alg at (a) ambient and (b) body temperatures.


(a) ambient temperature

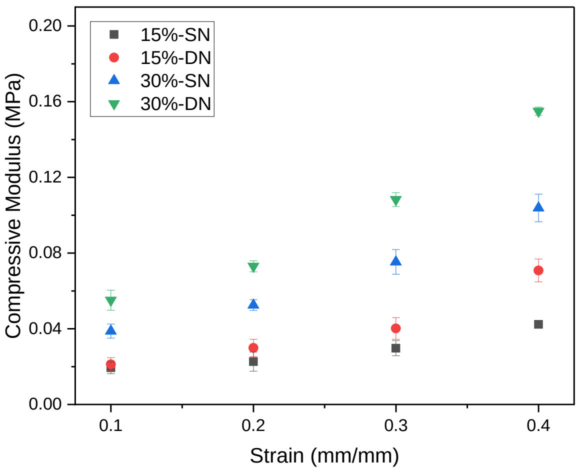
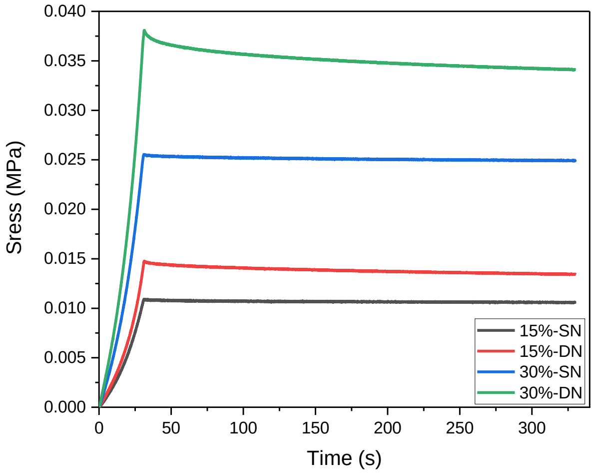

(b) body temperature

Figure 5. Compressive modulus of PAAm/Alg hydrogels at various strains at (a) ambient and (b) body temperatures.

The stress relaxation behavior of the hydrogels was investigated by holding the strain constant at 0.4 for the duration of 300 s. DN hydrogels possessed a higher stress relaxation rate (8.4 – 10.4%) compared to SN hydrogels (2.5 – 4.1%) (Table 4). This behavior has been attributed to the fluid flow and viscoelasticity of the respective matrice (Chaudhuri *et al*. 2020).


(a) ambient temperature

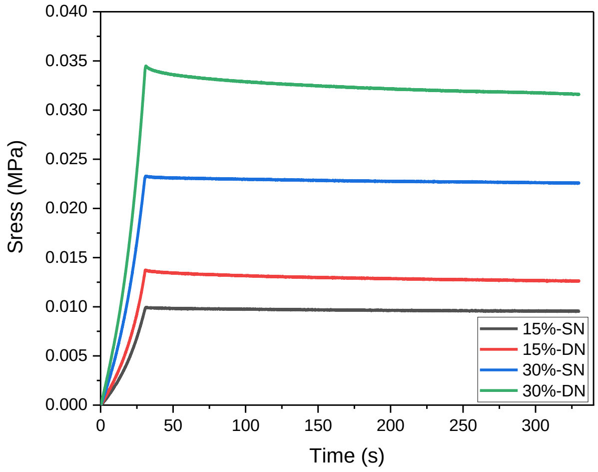

(b) body temperature

Figure 6. Stress relaxation versus time of PAAm/Alg compressed at a strain of 0.4 at (a) ambient and (b) body temperatures.

Table 4. Stress reduction rate of PAAm/Alg hydrogels.

Hydrogel	Test temp.	Peak compress. moduli (MPa)	Equil. compress. moduli (MPa)	Stress reduct. rate (%)
15%-SN	RT	0.0109	0.0106	3.0
	37°C	0.0100	0.0096	4.1
15%-DN	RT	0.0148	0.0134	9.0
	37°C	0.0137	0.0126	8.2
30%-SN	RT	0.0255	0.0249	2.5
	37°C	0.0233	0.0226	3.0
30%-DN	RT	0.0381	0.0341	10.4
	37°C	0.0345	0.0316	8.4

3.3 Hydrogel swelling

The water absorption capacity of the investigated PAAm/Alg hydrogels is revealed in Figure 7. The equilibrium swelling ratio of the hydrogels was determined over a time period of 2 days. 30% SN and 30% DN hydrogels exhibited a swelling degree of about 13 (g/g) whilst 15% SN and 15% DN hydrogels were about of 10 (g/g). This difference in swelling degree could be attributed to the greater pore size found in lower concentration hydrogels, which allows water to diffuse more easily through its structure.

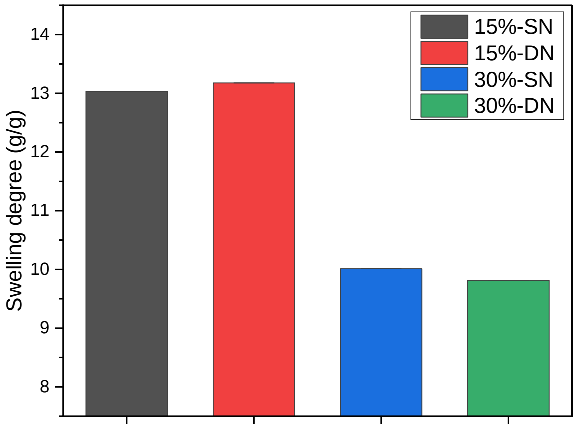


Figure 7. Swelling behavior of PAAm/Alg immersed in PBS (pH 7.4) at 37.0 ± 0.1 °C for 2 days.

4. Conclusion

In this work, various PAAm/Alg blend hydrogels were synthesized and tested for tribological and mechanical properties. The mechanical properties of the hybrid hydrogel synthesized in this study have better mechanical properties than the structure in which each hydrogel is used individually and synthesized (Yang *et al.* 2013). The best performing hydrogel in terms of compressive moduli as well as low friction coefficient and wear track area, was hydrogel 30%-DN –which consisted of an acrylamide concentration of 30% and a double network structure. The elastic properties of the synthesized hydrogels was found to be similar to native articular cartilage (Guo *et al.* 2014). The compression behaviour of the 30 %DN hydrogel was found to be similar to that of the PEG hydrogels (Nguyen *et al.* 2012). The COF obtained for this sample at an applied load of 5 N was 0.01 which is lower than PAAm-Alg included hydrogel (Liao *et al*. 2013) and very comparable to that of the native articular cartilage (Kanca *et al.* 2018). Thus, amongst the synthesized and investigated hydrogels, 30%-DN has the highest potential to be applied as a substitute to articular cartilage, with the aim of restoring the functional properties that are facilitated by the articular cartilage. It is recommended that further in-vitro pre-clinical studies that implant 30%-DN in animal joints are conducted to provide further information about the mechanical and tribological suitability of this synthesized hydrogel.

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