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Mechanical and Swelling Properties of Poly (vinyl alcohol) and Hyaluronic Acid Gels used in Biomaterial Systems - a Comparative Study

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ABSTRACT

There is an increasing demand for designing controlled drug delivery systems with materials which are more biocompatible, economical and materials which can be processed easily. Poly (vinyl alcohol) (PVA) and hyaluronic acid (HA) are promising polymers for applications in drug delivery. PVA forms gel based on the acetal bridges when crosslinked with glutaraldehyde (GA). On the other hand, HA a natural polymer, forms gel with divinyl sulfone (DVS) as a crosslinker. PVA and HA blends upon crosslinking PVA with GA or HA with DVS, in the presence of the other polymer, form gels that are more adaptable to the drug delivery systems. In this work, the mechanical properties and swelling behaviour of PVAHA gels were characterized. The effect of composition on viscoelastic moduli and degree of swelling was determined. The storage modulus (G″) of various gels made of PVA, HA and PVAHA blends were measured using rheology and compared with the values available in the literature. Swelling properties were measured and compared among various PVA and HA gels. Collagen is added to PVA solution and the rheological properties were measured in the gel state. Based on the values of storage modulus, gels of various compositions of PVA, HA and collagen might be selected as potential biomaterials for drug delivery system depending on careful understanding the type of application.

Keywords: Poly (vinyl alcohol), hyaluronic acid, biomaterial, rheology, gel

1. INTRODUCTION

Hydrogels consist of crosslinked polymer networks made with water soluble polymers. These crosslinks might be due to the physical interactions or chemical reactions that lead to a three dimensional network. By tuning the network density, the gel can be designed to accommodate appropriate high water content. This is important as the increased aqueous nature of the gel is highly bio-compatible. One advantage of these hydrogels is that because, they conform to the shape of the surface after the application[1]. The application or the administration of the gels is usually achieved by injection process. The drugs, proteins and cells can be incorporated directly into the polymer solution before gel is formed, and injected at the target. There are several review articles that summarize research activities related to injectable biodegradable hydrogels[2-5].

Poly (vinyl alcohol) is a synthetic polymer endowed with interesting properties and has wide scope applications[6-8]. Hydrogels made of poly vinyl alcohol (PVA) have gained attention because they are biocompatible, sterile, harmless and transparent. PVA hydrogels are often used in the wound healing systems[9]. Baino in a review on 'Towards an ideal biomaterial for vitreous replacement: Historical overview and future trends' gave his concluding remarks that PVA is the most ideal biomaterial for long term vitreous substitutes and needs to be investigated further[9]. According to the author, PVA was considered as vitreous substitute based on the optical properties and the use of PVA solution as vitreous substitute showed that the retinal activity can be attained. In the year 2010, Leone, *et al*. showed the use of PVA hydrogels with different amounts of crosslinking agents can be a potential substitute for vitreous replacement[11].

Hyaluronic acid (HA), a natural polymer, has multiple biological functions and is being studied for vitreous biomedical applications. HA is a linear poly saccharide that contains the repeating disaccharide group, N-acetyl glucosamine and D-glucuronic acid. It is highly biocompatible and it is present in every part of the body, from vitreous of eye to extracellular matrix. Hydro gels made with HA are very attractive for the wound healing as HA is a signalling agent for cell migration and proliferation[9]. Drugs in conjugation with polymer solution form a pro-drug, by covalently bonding the drug to HA. Upon drug delivery, the covalent bond is broken at the target site[10]. Modified HA as adipic dihydrazide derivative when crosslinked with poly (ethylene glycol)-propiondialdehyde yields a hydrogel that can be made in minutes and the dried films of this can be swollen in seconds. Luo, *et al*. claim that such materials can be used at wound sites for controlled release of therapeutics[14].

The main objective of blending natural and synthetic polymers is to get the blends that have unique structural

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and mechanical properties of base polymers. PVA, because of its attractive mechanical properties[15], HA because of its gel elastiness[16], also as these two materials possess similar characteristics for drug delivery applications, blend systems with both PVA and HA are promising with improved material properties. Hydrogels of PVA and HA blends, crosslinking one polymer in the presence of other, are gaining attention because of their distinct physio-chemical properties. Kim, *et al*. studied the state of water in the interpenetrating polymer networks (IPN) for their bound and free water content. They have also studied the drying reaction rate constant of these IPN systems with change in temperatures[17]. Electrically sensitive hydrogels of PVAHA as IPNs were made and the swelling properties were measured at various salt concentrations and in various pH buffer solutions. As the swollen membrane bends in response to the electrical field, these biomaterial systems can be used in making sensors[18,19]. Physical hydrogels based on PVA and HA by freeze thawing was studied by Agostino, *et al*. To study the strength of hydrogen bonding of various poly saccharides embedded in the gel network were compared in their work[20]. Kim, *et al*. investigated the blends of PVA and HA at various compositions and suggested that PVAHA blend system is a potential candidate for the drug delivery systems, which need to be investigated further[21].

In addition to crosslinking and blending, hydrogels are also prepared by adding a fibrous filler such as collagen, cellulose chitin, etc.[22,23]. The fillers enhance the mechanical properties of the hydrogel, and may also improve other functionalities[24]. Various biomaterial used in drug delivery systems composed of PVA, HA and collagen in the literature is as shown in Table 1.

Hydrogels are often characterized in rheological terms. The storage modulus is an indication of gel strength during the frequency sweep[25]. Also, the modulus becomes independent of frequency over a range, which is the rheological signature of gel[26-28]. The loss modulus and tanδ are usually measured to determine the dissipative nature of the hydrogels, while the storage modulus describes the energy storing capacity of the hydrogels. Therefore, rheological characteristics of hydrogels are important for drug delivery and other biomedical applications. Transport of various species through the hydrogels is strongly dependent on the amount of water present in these systems. Therefore, swelling characteristics of hydrogel systems are also important.

In the present work, various gels made of PVA, HA solutions and PVAHA blends were characterized in terms of rheological parameters. Specifically a blend system of PVAHA, a hydrogel composite of PVA and collagen and crosslinked HA hydrogel were investigated. The swelling properties were also measured and compared among the different material systems.

2. EXPERIMENT

A summary of the materials investigated in this work is given in Fig. 1. In this section, the preparation procedures are described followed by methods of rheological and swelling characteristics.

2.1 Materials

Poly (vinyl alcohol) with an average molecular weight of 146-186 kDa (99% hydrolyzed) and divinyl sulfone (97%

Table 1. Various materials systems used in combination with poly (vinyl alcohol) and hyaluronic acid for making gels, their type of gel and their applications

Material system	Method of making the gel	Applications
Poly vinyl alcohol crosslinking with alginic acid – HA crosslinking with EX-810 (a mixture of diepoxy compounds)	Crosslinked hydrogel films	Grafted hydrogel for tissue regeneration[37]
Poly vinyl alcohol blended with hyaluronic acid/ chondroitin sulfate	Physical hydrogel films made by freeze thawing	Biomedical[20]
Poly vinyl alcohol / Hyaluronic acid blend	Crosslinked hydrogel film	Bio-sensors[18]
Silk fibron / Hyaluronic acid	Poly electrolyte complex films	Electro responsive drug release systems[38]
Oxidized hyaluronic acid / adipic acid dihydrazide	Crosslinked gel	Nucleus pulposes regeneration[39]
Hyaluronic acid / carboxy methyl cellulose sodium	Crosslinked gel	Dermal filler or tissue augmentation[40]
Acrelated hyaluronic acid / cell adhesion peptides	Crosslinked gel	Tissue defect regeneration and remodeling[41]
Hyaluronic acid / Tyramine conjugate	Crosslinked gel	Drug delivery and tissue regeneration[25]
Poly (N-isopropylacrelamide) / hyaluronic acid	Polymerization of isopropylacrelamide	Mimicking cartilage tissue[42]
Oligosaccharides / hyaluronic acid	Crosslinked gel	Crosslinking of drugs to the HA molecule[43]
Hyaluronic acid hydrogels	Crosslinked gel	Pyrogenicity test / dermal filler[44]
Hyaluronic acid / hydrophobic C12 chains (1-brom-de-decan)	Physical gel /Crosslinked gel	Cartilage repair[45]
Collagen / hyaluronic acid	Crosslinked gel	Tissue regeneration[46]
Hydroxy apatite / collagen /hyaluronic acid	Physical gel	Composite biomaterial[47]
Collagen / hyaluronic acid	Photo crosslinking	Tissue engineering and cell culture[48]

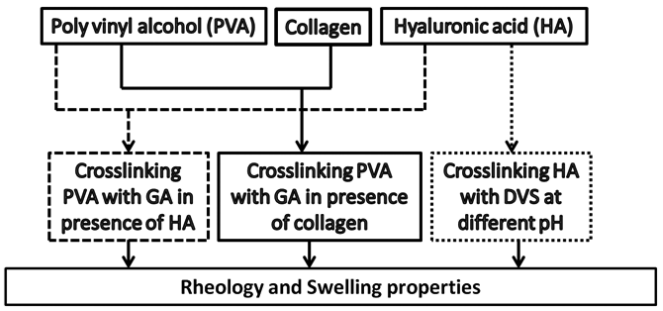
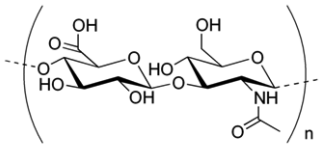


Figure 1. Schematic representing the preparation of gels and evaluated properties.

assay) was procured from Sigma Aldrich. Hyaluronic acid with an average molecular weight of 1270 kDa (44.2% glucuronic acid) and collagen fiber protein derived from animal sources (protein content upto 90%) was purchased from Linyi Taihao International Trading Company Limited, Shandong, China. Glutaraldehyde solution 25% with a molecular weight of 100.12 was supplied by FINAR Chemicals Limited, Ahmedabad. All other chemicals that were used are laboratory reagent grade and used as purchased. For the preparation of solutions Millipore® deionized water was used.

2.2 Preparation of Poly (Vinyl Alcohol) and Hyaluronic Acid (HA) Gels

5% (w/w) of PVA solution was prepared by dissolving 5 grams of PVA in 95 g of water, and stirred on magnetic stirrer at a temperature of 80 °C for 8 h to get a homogeneous solution. 1% HA solution was prepared by dissolving 1 g of HA in 99 g of water and stirring at room temperature for about 1 hour. These two solutions are mixed in different proportions on volume basis to get the PVAHA solutions. When 7 mL of PVA solution and 1 mL of HA solution are mixed, this blend is designated as PVAHA 71. Various compositions used in the present work are shown in Table 2. Similarly other formulations are also designated depending on the volume ratios to prepare ranging from PVAHA 71 to PVAHA 35. A crosslinker solution (XGA) was prepared with glutaraldehyde and other constituents as mentioned elsewhere[29,30]. To 10 ml of the PVA solution, 2.8 ml of the XGA solution was added such that the polymer to crosslinker molar ratio is maintained at 0.35. This ratio was maintained for all the formulations of PVAHA solutions.



Hyaluronic acid

2.3 Preparation of PVA Collagen Gels

5 g of PVA is dissolved in 100 mL of water to make 5% (w/v) PVA solution. To this calculated amount of collagen was added such that weight of PVA in the solution to the weight of collagen has a ratio. For example, in 10 mL of PVA solution, the weight of PVA is 0.5 g. To this 10 ml PVA solution, if 0.056 g of collagen is added, then the weight ratio of PVA to collagen is 9:1. Such a sample is designated as PVAC 91. Other formulations based on the weight ratios that were prepared are PVAC 82, PVAC 73 and PVAC 64, which are shown in Table 3. These samples are stirred well for one day on a magnetic stirrer. Before making the gel, the solutions were sonicated for 30 minutes to get homogeneity. These solutions were crosslinked as explained earlier, with XGA solution by maintaining the polymer to crosslinker ratio of 0.35.

2.4 Preparation of Hyaluronic Acid (HA) Gels

Various molarities of NaOH solutions of 10 mL each were prepared by dissolving calculated quantities of NaOH in water. To these 10 mL NaOH solutions, 0.5 g of hyaluronic acid (HA) was added to make 5% (w/V) HA solutions and stirred at room temperature for about 1 h on a magnetic stirrer. A homogeneous mixture of HA in NaOH solution was prepared with NaOH molarities of 0.075, 0.1, 0.125, 0.15 and 0.2. pH of all these solutions was measured at room temperature. 46.3 µL of divinyl sulfone (DVS) was added to these solutions to maintain a crosslinker to polymer ratio of 0.35 to make the gels. HA gels made of 0.075 molar NaOH solution is designated as HA 0.075M and so on. The compositions and designation of these samples are as shown in Table 4.

2.5 Rheological Analysis

After preparing the sample solutions, 2 mL of the samples were placed in 20 mL glass vial. To this calculated amount of crosslinker was added and the samples were stirred for 30 seconds on vortex mixer. These samples were immediately transferred on to the rheometer peltier and allowed to gel, after placing the geometry in position. Antonpaar physica 301 stress controlled rheometer was used with cone and plate geometry, with a cone angle of 1° and 25 mm diameter. All the samples are subjected to amplitude sweep to find the linear limit by varying the strain % at a frequency of 10 rad/s. Upon fixing the linear regime the samples were subjected to a frequency sweep by keeping the strain% at a constant value by measuring the storage and loss modulus.

2.6 Swelling

For swelling analysis, films of PVAHA were made by casting the gels in petridishes. These films were dried in ambient conditions and the weight loss was monitored. The

Figure 2. G′, G″ and tanδ for (a) PVAHA 62 (b) PVAC 91 and (c) HA0.1M gels.

Sample	Pure PVA	PVAHA 71	PVAHA 62	PVAHA 53	PVAHA 44	PVAHA 35
PVA solution (Vol %)	100	87.50	75	62.50	50	37.50
HA solution (Vol %)	0	12.5	25	37.5	50	62.5
Swelling ratio	7.24	11.50	10.25	15.37	78.06	108.20
Storage modulus	7280	786	955.33	1995	1886.66	384.50

Table 3. Composition of PVA collagen gels and storage modulus

Sample	HA 0.075M	HA 0.1M	HA 0.125M	HA 0.15M	HA 0.2M
Molarity of NaOH solution	0.075	0.100	0.125	0.150	0.200
pH	12.08	12.18	12.29	12.39	12.45
Swelling ratio	311	891.36	346.72	203.31	270.95
Storage modulus (Pa)	1530	792	1030	572	784

Table 4. Composition of HA gels, swelling ratios and their storage modulus

Sample	Pure PVA	PVAC 91	PVAC 82	PVAC 73	PVAC 64
Weight % PVA	100	90	80	70	60
Weight% Collagen	0	10	20	30	40
Swelling ratio	7.24	21.95	23.48	32.72	36.49
Storage modulus (Pa)	7280	2240	1150	501	83

time when there is no loss in weight of the films, considered to be dry films, are subjected to swelling in water. Similarly for the HA and PVA collagen films, the gels made of HA and PVA collagen were also cast to petridishes to obtain dry films of HA, but by drying them in vacuum oven for overnight at 60 °C. Swelling ratio is calculated as the percentage increase weight times the original weight of the dry film. (At particular instances the swelling ratio of weight of the sample at each drying time to that of completely dried sample was taken to compare the values in the literature).

3. RESULTS AND DISCUSSION

In this section the rheological and swelling characteristics of various hydrogels are described. An attempt has been made to compare them with reported result on similar system, while describing each property, an initial description about the literature results is provided followed by a description of the results of present study.

3.1 Viscoelastic Characteristics

Nguyen, *et al*. in their review of injectable biodegradable hydrogels showed that the gels made of polyethylene glycol and polycaprolactone triblock co-polymers form gels which are temperature sensitive and exhibit the modulus ranging from 500 Pa to 2000 Pa depending on their concentrations[2]. Kim, *et al*. in their work in making the MMP sensitive hyaluronic acid hydrogels, evaluated the rheological properties which lie between 300 Pa to 1400 Pa for various concentrations[31]. Gels made of various compositions of poly (vinyl alcohol) (PVA), collagen and hyaluronic acid (HA) were subjected to frequency sweep, at appropriate values of linear limits of strain. The storage modulus (G′) and loss modulus (G″) were followed with change in frequency ranging from 1 rad/s to 100 rad/s. As example variation of moduli and tanδ which is the ratio of G″ to G′ for PVAHA 62, PVAC 91 and HA0.1M gels is shown in Fig. 2(a), 2(b), and 2(c). For all the gels G′ is greater than the G″ and the moduli are independent of frequency, indicating the true gel behaviour. The gels reported in this work were found to be of different storage modulus values and these results are given in Table 2 to Table 4. Therefore, the range of mechanical performance can be expected from these hydrogels depending on their compositions.

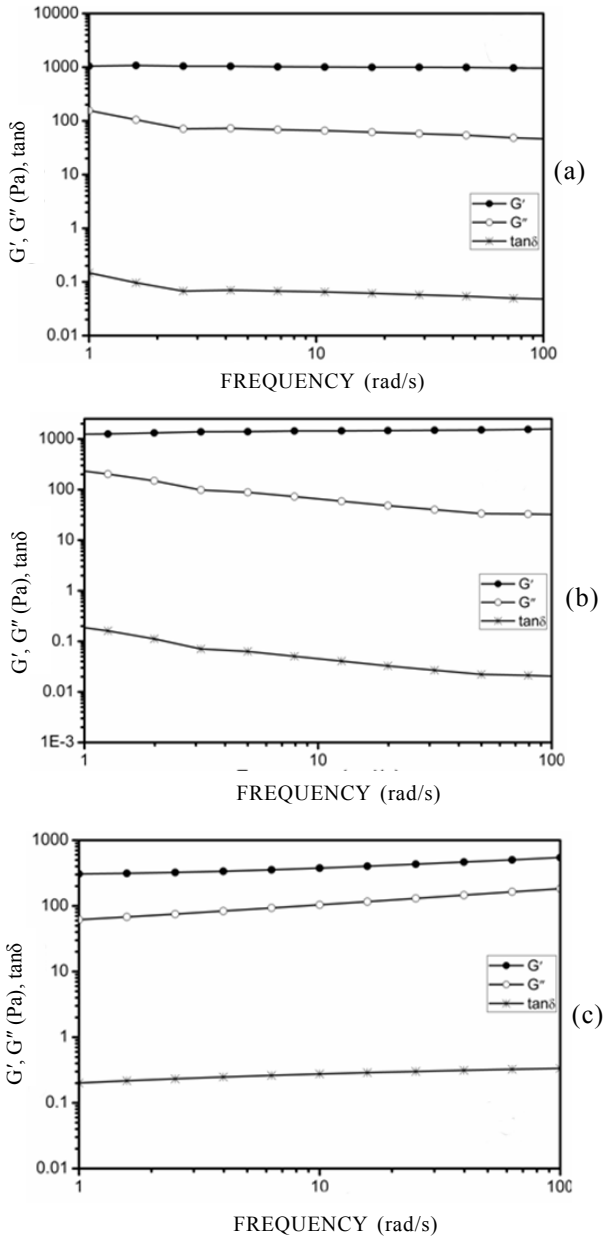


Table 2. Composition of PVAHA gels, swelling ratios and storage modulus

The G′ values of PVAHA gels at 1% strain are shown in Table 2. The gels made of PVA and HA are robust because of the crosslinking network in the gel. These gels show good viscoelastic properties as the elastically effective chains present in the gel network resist the applied shear. The G′ values of PVA and collagen gels at 1% strain are shown in Table 3. The gels made of PVA and collagen showed a decrease in G′ with increased contents of collagen. This is evident as the crosslinking of PVA molecules are much influenced by the presence of collagen fiber. The G′ values of the HA gels are as shown in Table 4. The gels made of HA crosslinked with DVS were more elastic. HA being a larger molecule, can be present everywhere in the gel network, might result the elasticity of these gels.

In the present work, the PVA chains were crosslinked by GA in the presence of collagen fiber to make an IPN and the properties like swelling and modulus were measured. As this method does not involve freezing and thawing, processing the materials and applications are quite simple.

The gel properties reported by Peng, *et al*. include compressive strength and swelling ratio and the properties of G′ reported in our work might be for the first time. It is also very distinct in formulation compared to the work of Peng, *et al*., as we are using the collagen fiber protein directly into the PVA solution, not in the form of a solution. It is to be noted again that the processing of such materials is very easy and the method described above is simple. The G′, which are indication of stiffness of the gels and the swelling ratios are as shown in the Table 3. The strength of the gel decreases with increase in collagen content in the solution. This might be because of the effect of collagen fiber present in the IPN and affecting the effective crosslinking of PVA molecules.

There are instances where researchers compare the damping factor or tanδ (ratio of loss modulus to storage modulus) values of gels to evaluate the degree of crosslinking and gel stiffness[32]. In vitreous materials the analysis is based on the resilience of the material, which is a function of tanδ[33]. A high value of damping indicates viscous behavior and very low value indicates the elasticity. In general, damping close to 1 is the sol-gel transition.

In the present work, an attempt was made to compare the tanδ values of various gels, and is as shown in Fig. 3. It can be seen that, though the tanδ of pure PVA is high, with the addition of HA to PVA in the gel state exhibits low values. It can also be seen that the change in tanδ is non-monotonic, may be due to the pattern of networking and crosslinking of hydrophilic polymers. When collagen is added to PVA, these PVAC gels exhibit less values of tanδ than the pure PVA gel, but also the change in tanδ is non-monotonic, with increase in collagen content, the tanδ decreased, as shown in Fig. 3. For the HA system crosslinked with DVS, it is very clear that the molarity of the NaOH solution used to prepare the HA solution plays key role. Since the molarity changes the pH of the HA solution, by comparing the pH values in Table 4 and the tanδ values in Fig. 3, it can be argued that within the range of pH from 12.08 to 12.45, there is much variation in tanδ value. It is also clear that this tanδ decrease with increase in pH of the HA solution but the change in tanδ is non-monotonic.

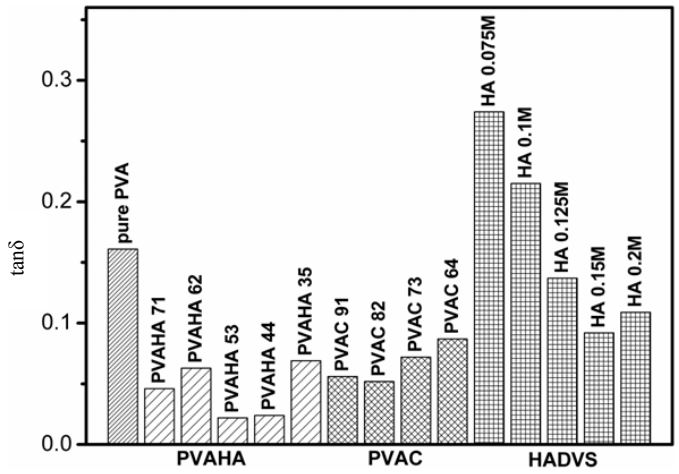


Figure 3. Comparison of damping factor for various gels made of poly vinyl alcohol, collagen and hyaluronic acid.

3.2 Swelling Characteristics

Stauffer, *et al*. in their work made gels consisting of PVA by freeze thawing method showed swelling ratios from 7.7 to 8.6 at various freezing and thawing cycles[31]. Lee, *et al*. in their work showed the swelling characteristics of the Interpenetrated network (IPN) hydrogels made of PVA and poly (acrylic acid) produced by applying UV irradiation followed by freeze thawing method[31]. They argued that these IPNs are temperature sensitive and the swelling ratios range from 9 to 17 approximately, at various concentrations of the polymers. They have also shown that the PVA crosslinked gels show a swelling ratio of 14.4 and decreases with increase in temperature. Kim, *et al*. reported the values of swelling ratio as high as 250. In their work, method of drying the samples is by vacuum drying at 60^0C for overnight whereas in our case it is ambient drying conditions.

In the present work, the IPNs made from PVA and HA, the swelling ratios range from 11 to 108 at various concentrations of HA. The swelling ratios of PVAHA gels with various HA content are shown in Table 2. It can be seen that with increase in HA content, the swelling ratio increases. As these IPNs are made with crosslinking networks, by crosslinking PVA with glutaraldehyde (GA), the presence of HA molecules in the network affect the effective crosslinking among the PVA molecules. It can also be argued that this effect alters the network density and improves the swelling behavior. Since these IPNs possess good swelling properties, they may be quite useful in drug delivery systems.

Hydrogel scaffolds composed of PVA and collagen, chemically crosslinked by glutaraldehyde was reported by Peng et al. It was found that the swelling ratio is function of PVA present in the PVA collagen blend and increased with increased PVA content[32]. The swelling ratios were 17 when no PVA was present and 22.5 when 75% by weight PVA was present and it is to be noted that these gels were prepared not by pure chemical crosslinking but by applying freezing and thawing operation.

The swelling ratio of PVA collagen samples varied from 21% to 36% and it was observed that the swelling ratio is increased with increase in collagen content. This is expected

as the numbers of crosslinkings will decrease with increase in collagen content. Unlike the gels reported by Peng, *et al*., these gels are made with crosslinking of PVA molecules and because of the absence of freezing and thawing cycles, the swelling ratio will increase with increase in collagen content.

Collins, *et al*. in their work while evaluating the physical properties of crosslinked hyaluronic acid hydrogels, evaluated the swelling ratios of HA gel crosslinked both with divinyl sulfone (DVS) and GA[36]. According to their work, the gels crosslinked with DVS have higher swelling ratios ranging from 5 to 6.5 for crosslinker to polymer ratio of 0.5 (in this case swelling ratio is weight of swollen sample to that of dry sample, W_s/W_d) and the speed of swelling to their equilibrium water content is a function of crosslinking density and hydrophobicity of the system.

The gels presented in our work follow similar lines and are presented in Fig. 4. The swelling ratios of various HA gels at different pH values are as shown in Table 4. In the present work, the gels made of hyaluronic acid exhibited swelling ratios in the range of 3 to 10 for various concentrations of NaOH solutions (here the swelling ratios are expressed in terms of W_s/W_d). It was also observed that at the given crosslinker to polymer ratio for these gels, the initial rates of swelling is high and are as shown in Fig. 4. As reported by Kim, *et al*. these samples were also swollen rapidly and reached equilibrium swollen conditions within 30 min, which indicated the hydrophilicity of HA molecule. The increase in swelling ratio in this case might not only due to the crosslinking density but also due to the availability of large number of water binding sites in HA.

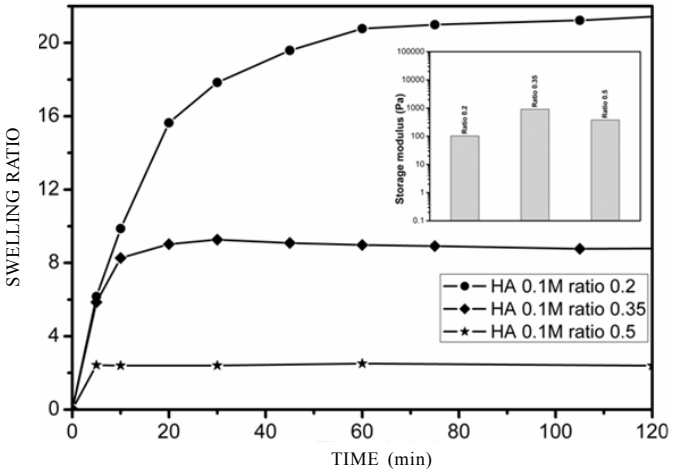


Figure 4. Rate of swelling for HA 0.1M gel at various crosslinker to polymer ratios. Inset shows the storage modulus of these samples at 10 rad/s.

3.3 Overall Comparison

PVA and HA based hydrogels exhibit a range of storage moduli, tanδ and swelling ratios. A general comparison is therefore needed to choose a particular system for any drug delivery application based with due consideration on the mechanical properties, swelling behavior biocompatibility and other properties. As per the results obtained with our systems and related material systems from literature, effort has been made to give a comparison is being presented to highlight the range of material response. Figures 5(a) and 5(b) gives a broad comparison of modulus and swelling ratios of such gels used in various potential drug delivery systems. It is apparent from the data, that depending on the type of drug delivery system being investigated, a suitable composition of PVA and HA based system can be chosen.

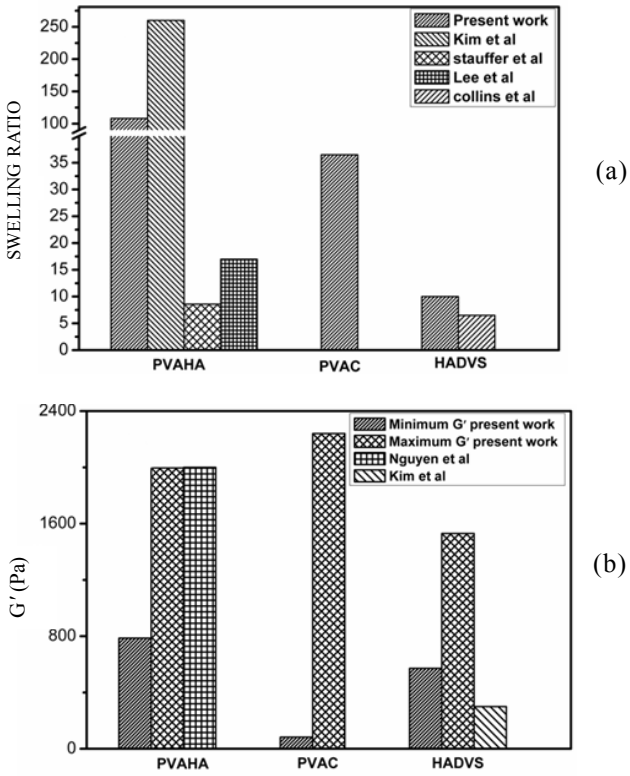


Figure 5. (a) Comparison of Swelling ratio of PVAHA gels with Kim[18,19], *et al*., Stauffer[34], *et al*., Lee[31], *et al*. Also comparing the swelling of HADVS (weight ratio of swollen film to dry film) with Collins[36], *et al*. Swelling ratio of PVAC gel is shown. (b) The storage modulus of the present work with minimum and maximum values are compared with Nguyen[2], *et al*. for PVAHA gels and Kim[18,19], *et al*., the values of PVA collagen is also shown.

4. CONCLUSIONS

We have shown with our results that various drug delivery systems composed of poly (vinyl alcohol) (PVA), collagen and hyaluronic acid (HA) with various combinations of material systems give different swelling and mechanical properties. It is shown for PVAHA samples, the swelling ratio by and large increases with increase in HA content. The reason might be due to the change in network structure and also the hydrophilicity of HA molecule. For PVAC system, it is observed that the gel strength decreases with increase in collagen content. This might be due to the effect of collagen on ineffective crosslinking of PVA molecule in the presence of collagen during the formation of interpenetrating network. Characterization of HA gels, at various molarities of NaOH, revealed reasonable modulus and excellent swelling properties. Based on the results outlined and the comparisons made from the literature, these novel material gel systems can be used as biomaterial for potential drug delivery systems.

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