

## Differences in Viscoelasticity of Ophthalmic Polymer Solution after Sterilization

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### Abstract

Polymer solution has been used for increasing viscosity of ophthalmic solution in order to prolong the retention of active drug in the eye. The ophthalmic solution must be sterilized, which may affect the rheology properties of viscosity-inducing polymers. The aim of this study was to investigate the effect of sterilization treatment on viscosity-inducing agents (i.e., poloxamer, polyvinyl alcohol; (PVA), methyl cellulose (MC), polyvinylpyrrolidone (PVP) and carbomer). The effect of membrane filtration and steam sterilization or autoclaving (121 °C, 15 lb/inch<sup>2</sup>, 15 min) were determined. A rheometer was used to investigate the viscosity and viscoelastic properties between treated and untreated polymer solutions. The power law model, consistency index (k), and power law index (n) of polymer solution viscosity were compared. For viscoelastic properties, storage modulus and loss modulus were examined. The results demonstrated that, viscosity of carbomer and MC solution (1 and 2 %) were changed after steam sterilization. No difference in viscosity was observed for PVP, PVA and poloxamer solution, between untreated and treated samples. The storage and loss moduli of PVA solution after autoclaving were not different when comparing with the untreated polymer solution. From this study, it could be concluded that the sterilization treatment influenced the viscosity behavior and viscoelastic properties of polymer solution used as viscosity-inducing agent in ophthalmic solution. Therefore, the selection of polymer and sterilization method should be carefully considered.

**Keywords:** Viscosity, Viscoelastic, Ophthalmic drug, Polymer, Sterilization

### Introduction

Ophthalmic preparations are available in many forms, such as solutions, ointments, gels, and polymeric inserts. Blurred vision and lack of patient compliance have often been noticed in patients using ointments and polymer inserts [1]. Among the ophthalmic preparations, solutions are mostly used and are also the most compliant. Ophthalmic solutions contain active ingredient and excipients, which regulate osmotic pressure, the pH, and viscosity of the preparations. Antimicrobial agents, antioxidants, and chelating agents may also be added. Due to the limited ability of the eyes to store liquid, ophthalmic solutions generally have a low bioavailability because of fast elimination via nasolacrimal tract [2-4]. Most diseases (> 90 %) are found at the corneal area, but only 5 % of drugs can be absorbed from this site [5]. The effectiveness of treatment depends on the concentration of the drug, the dose of the drug, the duration of contact with the eye, and the frequency of administration. Prolonging the time period of contact with the cornea and improving drug bioavailability may be obtained by increasing the viscosity of

formulations. Viscosity-inducing agents, which have such an effect, include hydrophilic polymers of high molecular weight that do not diffuse through biological membrane and form three-dimensional networks in water [1]; for example, polyvinyl alcohol (PVA), poloxamer, carbomer, hyaluronic acid, and polysaccharides (that is, cellulose derivatives, gellan gum, and xanthan gum).

Before 1955, medication for the eyes was pharmaceutically prepared in a conventional form without sterilization. In 1955, the United States Pharmacopeia [6] defined the sterilization for ophthalmic preparations, i.e., steam sterilization and aseptic technique process [7]. Sterilization processes affected the stability of the formulation, both the active ingredient and, in particular, excipients. Physicochemical properties, viscosity, and viscoelastic properties might be changed under pressure and high temperature. Interestingly, only a few reports in the literature have explained the effect of sterilization treatments on the viscosity and rheology of polymer solutions [8]. The information in these reports regarded the effect of sterilization on the viscosity of polymer solution as structure fragmentation.

In this study, polymers (carbomer, polyvinylpyrrolidone, polyvinyl alcohol, methylcellulose, and poloxamer) at concentrations of 0.5, 1.0, and 2 % w/w were chosen, because these are commonly used in ophthalmic solutions [9,10]. The viscosity and viscoelastic of polymer solutions were investigated and compared based on the concentration of viscosity-inducing agent used in ophthalmic solutions. The rheology properties before and after the sterilization process (filtration or steam sterilization) were compared. The results from this research would be fulfilled in pre-formulation knowledge for selecting suitable formulations of ophthalmic solutions.

## Materials and methods

### Materials

Carbomer (Carbopol 934P NF, crosslinked polyacrylic acid homopolymers, lot no. L600191A-13-06) was purchased from Lubrizol Advanced Materials, Inc, USA. Polyvinylpyrrolidone (PVP, lot no. YK001S160526A1P) K90 was purchased from Nam Siang Co., Ltd., Thailand. Polyvinyl alcohol (PVA, lot no. 12123PD) and Methylcellulose (MC, lot no. 73H0365), 4000 cP were purchased from Sigma-Aldrich, USA. Poloxamer 407 (Lutrol<sup>®</sup> F-127, lot no. WPHYF562C) was donated by BASF Thailand.

### Preparation of polymer solutions

Polymers (carbomer, PVP, PVA and poloxamer) were dissolved in distilled water at concentrations of 0.5, 1.0, and 2 % w/w, and kept stirring until clear solution appeared. MC solution was prepared by dispersing in hot water (80 °C), then adding cold water and mixing until homogenous solution was obtained. The polymer solutions were poured into tight bottles for sterilization, either by autoclaving or membrane filtration.

Samples of polymer solution were autoclaved at 121 °C for 15 min (WiseClave WAC-100, Daihan, South Korea). The autoclaved samples were referred to by the symbol 'AC'. The samples were kept at 25 °C for 24 h before further investigation. Filtration of solution, which is an aseptic technique process, was prepared without heat. The solution clear polymer (0.5, 1.0, and 2 %) was passed through a nylon membrane filter (45-mm diameter, 0.22- $\mu$ m pore size, Sartorius, Germany) using a negative pressure filtration set. The filtrated samples were referred to by the symbol 'F'.

### Characterization of polymer solution

The rheology properties of polymers were observed using a rheometer (Kinexus Pro+, Malvern Instrument Ltd, UK). The samples were tested by rotational and oscillation modes using cone and plated (CP1/50SR 1233 ss) geometry. The varied shear rates in the range of 0.1 to 100 s<sup>-1</sup> at 25 $\pm$ 0.1 °C were used in the rotational mode. The samples were placed directly on the holding plate. The viscosity ( $\eta$ ) of polymer solutions was investigated [11].

The non-Newtonian behavior was determined by power law with the equation as follows (1);

$$\sigma = K\dot{\gamma}^n \quad (1)$$

where  $\sigma$ : is shear stress (Pa),  $K$  is consistency index (k (Pa s<sup>n</sup>)),  $\dot{\gamma}$  is shear rate (s<sup>-1</sup>), and  $n$  is power law index (dimensionless). The rheology behavior of a solution is shown by linear line in log-log shear rate/shear-stress plot, and then shearing properties are obtained. For instance, the power law models for Newtonian, shear thinning (pseudoplastic), and shear-thickening (dilatant) fluid sample give  $n = 1$ ,  $< 1$  and  $> 1$ , respectively. The coefficient of determination ( $r^2$ ) was used to evaluate if it fitted into the power law model using the experimentally obtained flow curves.

The oscillation modes with frequency and amplitude sweep were evaluated for dynamic rheology. The sample was poured into the plate. The stain of amplitude sweep was investigated using a cone and plate at fixed frequency of 1 Hz and at 25 °C under isothermal conditions. The stain of swept amplitude from 0.1 to 100 was given as the increment of a logarithmic scale. During the test, elastic modulus ( $G'$ ) and viscosity modulus ( $G''$ ) were measured. The structure of polymers was studied by a means of frequency sweep. The shear stain of swept frequency from 10 to 0.1 Hz (with the increment of a logarithmic scale) was given not more than LVER (linear viscoelastic region) of samples. During the test,  $G'$ ,  $G''$ , and  $\tan \delta$  were measured.

## Results and discussion

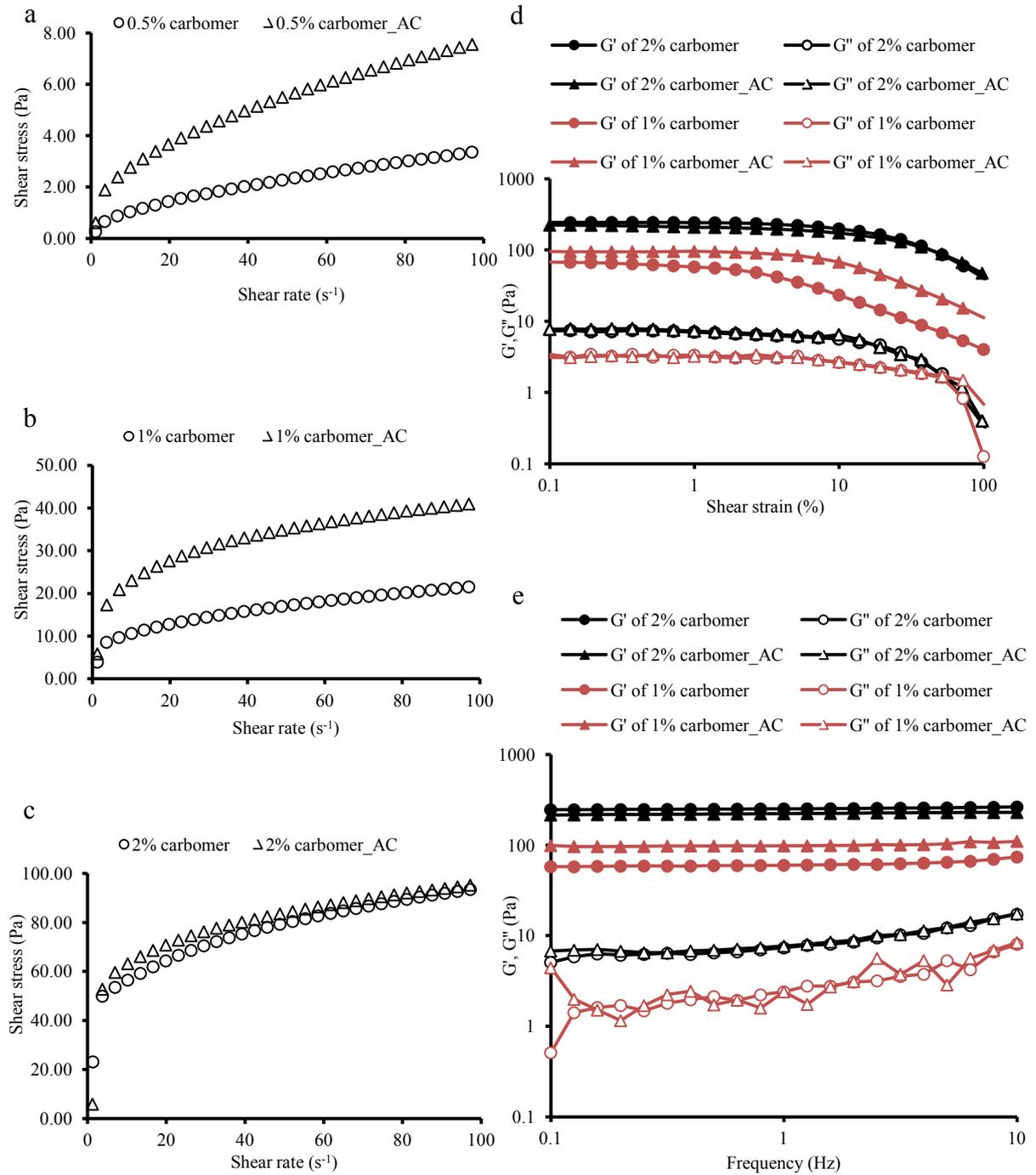
By using aseptic technique in preparation for polymers solution, MC and carbomer solution for all concentrations were not able to pass through filtration membrane filter by negative pressure in this study. This may be due to the fact that the solution has high viscosity and/or high concentration. The viscosity of polymer which fitted into power law equation resulted in  $r^2$  ranging from 0.97 to 0.99 for all solutions (**Table 1**). The lowest  $n$  values (0.2) from were shown from carbomer 2 % w/w, and MC as well as PVP 0.5 % w/w displayed the highest  $n$  value (0.8). Given the effect of polymer concentration, different concentrations of carbomer showed considerable variations in  $n$  values. The  $n$  values of carbomer solution 2, 1, and 0.5 % w/w were 0.20, 0.24, and 0.43, respectively. For other polymer solutions, the same trends were found. The decrease in flow behavior index ( $n$ ) was obtained after the increment of polymer concentration. However, pseudoplastic behaviors were found in all polymer solutions. The same results were found in previous reports [12-14]. The addition of carboxymethylcellulose (CMC), sodium salt, gum arabic, and guar gum to the formulation exhibited pseudoplastic solution behavior. After sterilization, the  $n$  values were changed as in the samples, i.e., carbomer 2 %\_AC, carbomer 1 %\_AC, carbomer 0.5 %\_AC, MC 2 %\_AC, MC 1 %\_AC and MC 0.5 %\_AC solutions. The value of  $k$  was higher by increasing the concentration of carbomer and MC in solution (**Table 1**). The findings revealed that there was some increment of thickening effect and rigidity of polymer solution when increasing the concentration. After treatment, the  $k$  values were changed as in the samples, i.e., carbomer 2%\_AC, carbomer 1 %\_AC, carbomer 0.5 %\_AC, MC 2 %\_AC, MC 1 %\_AC, MC 0.5 %\_AC and 2 % PVP\_F, 1 % PVP\_F and 0.5 % PVP\_F solutions.

Flow curves of carbomer solutions in various concentrations are shown in **Figures 1a, 1b, and 1c**. At same shear rate, shear stress of 0.5 % carbomer\_AC and 1 % carbomer\_AC were much higher than the shear stress of 0.5 % carbomer and 1 % carbomer, respectively. Furthermore, shear stress of 2 % carbomer\_AC was slightly higher than the shear stress of 2 % carbomer. The storage modulus ( $G'$ ) and loss modulus ( $G''$ ) as a function of shear strain for the different carbomer concentrations is presented in **Figure 1d**. No linearity was found as in samples 0.5 % carbomer and 0.5 % carbomer AC (data not show). **Figure 1e** shows the values of  $G'$  and  $G''$  with frequency. When compared with untreated sample, both values of  $G'$  and  $G''$  were reduced as in sample 1 % carbomer and 2 % carbomer. These results suggested that the structures of carbomer were destructed by autoclaving [15]. In solution preparations, metals in water can catalytically degrade carbomer structure and heat can accelerate the reaction [16]. However, carbomer is a substance which reacts with oxygen, which causes a permanent reduction viscosity [17], the changes of viscoelastic properties were also confirmed by this study. The results of

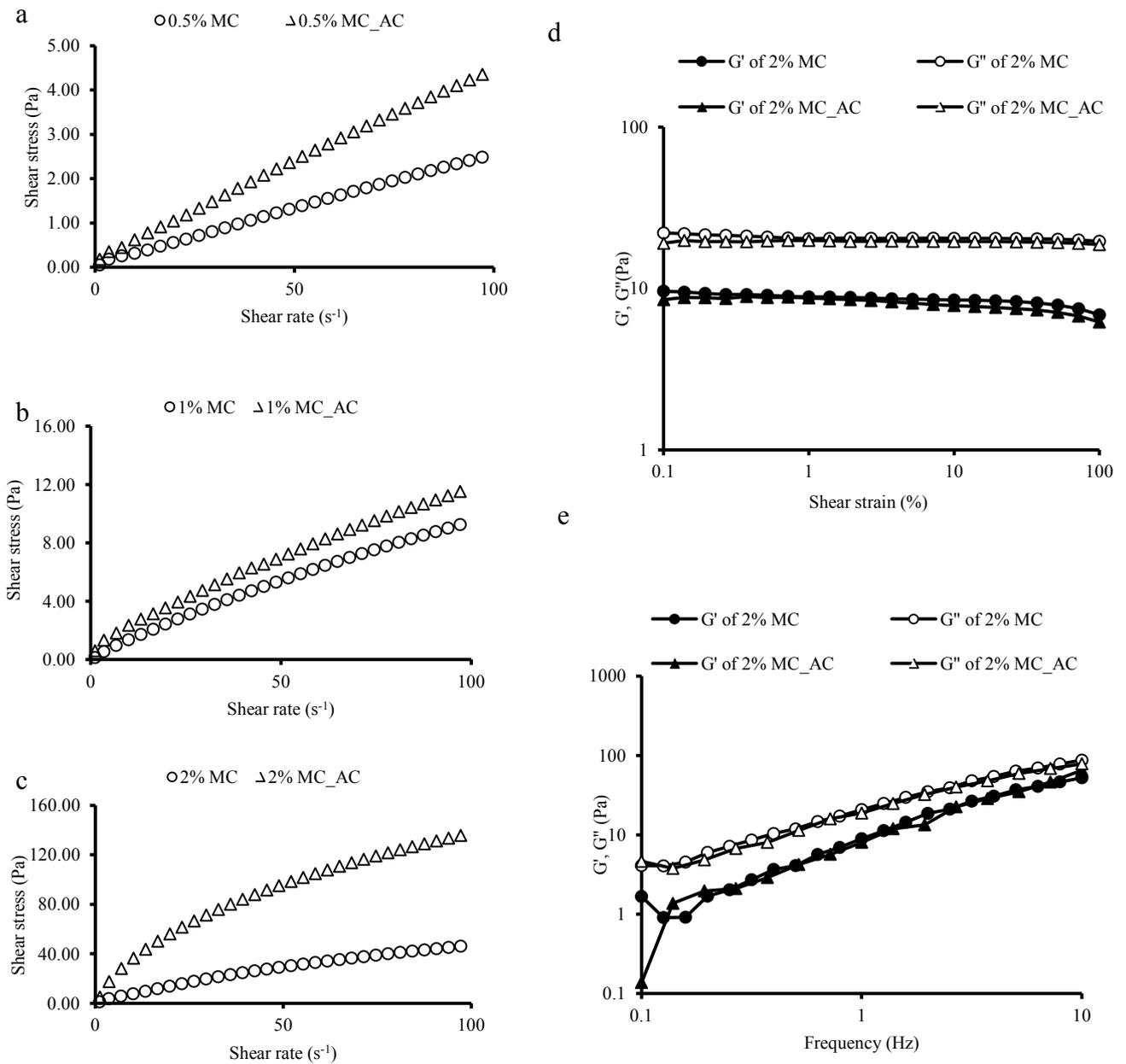
carbomer viscosity contrasted with the previous report [18]. The carbopol 940P solution did not change apparent viscosity after steam sterilization; thus, the difference of viscosity and grade material may affect the results.

**Table 1** Power law model parameters.

Samples	Power law index, n	Consistency index, k (Pa s <sup>n</sup> )	r <sup>2</sup>
2 % carbomer	0.2038±0.0063	37.4133±2.0014	0.9942
2 % carbomer_AC	0.1946±0.0128	32.7600±4.6801	0.9993
1 % carbomer	0.3089±0.0179	12.4033±0.4706	0.9959
1 % carbomer_AC	0.2441±0.0130	5.3620±0.2795	0.9993
0.5 % carbomer	0.5071±0.0818	1.0810±0.0579	0.9914
0.5 % carbomer_AC	0.4267±0.0152	0.3361±0.1216	0.9983
2 % MC	0.6196±0.0142	7.7117±1.0808	0.9973
2 % MC_AC	0.6847±0.0270	5.7280±1.0072	0.9976
1 % MC	0.6854±0.0060	0.5945±0.1172	0.9986
1 % MC_AC	0.8063±0.0227	0.1901±0.0291	0.9949
0.5 % MC	0.7062±0.0284	0.0752±0.0579	0.9899
0.5 % MC_AC	0.7942±0.0223	0.1438±0.0594	0.9122
2 % PVP	0.5294±0.0041	8.7980±0.0845	0.9775
2 % PVP_AC	0.5405±0.0047	8.7107±0.1116	0.9760
2 % PVP_F	0.5544±0.0677	5.2368±1.5269	0.9782
1 % PVP	0.5458±0.0027	8.8537±0.1491	0.9714
1 % PVP_AC	0.5575±0.0046	9.1997±0.1447	0.9703
1 % PVP_F	0.5778±0.0049	7.3077±0.1157	0.9687
0.5 % PVP	0.6250±0.0053	8.9913±0.1491	0.9689
0.5 % PVP_AC	0.6145±0.0020	9.1997±0.1447	0.9660
0.5 % PVP_F	0.6211±0.0055	7.4453±0.1760	0.9646
2 % poloxamer	0.5331±0.0010	8.9137±0.1609	0.9759
2 % poloxamer_AC	0.5384±0.0025	9.0513±0.0378	0.9754
2 % poloxamer_F	0.5450±0.0021	9.0233±0.0687	0.9756
1 % poloxamer	0.5560±0.0030	9.4057±0.2520	0.9733
1 % poloxamer_AC	0.5645±0.0016	9.1290±0.1226	0.9702
1 % poloxamer_F	0.5660±0.0007	8.9993±0.0646	0.9729
0.5 % poloxamer	0.5987±0.0006	9.5753±0.1283	0.9672
0.5 % poloxamer_AC	0.6006±0.0018	9.1857±0.2546	0.9370
0.5 % poloxamer_F	0.6071±0.0018	9.0993±0.1581	0.9697
2 % PVA	0.6010±0.0030	9.8180±0.1179	0.9918
2 % PVA_AC	0.5854±0.0028	9.1413±0.4893	0.9921
2 % PVA_F	0.5956±0.0036	9.5000±0.1249	0.9913
1 % PVA	0.6833±0.0036	9.0447±0.1336	0.9833
1 % PVA_AC	0.7164±0.0133	9.1413±0.1893	0.9837
1 % PVA_F	0.6853±0.0032	9.0356±0.1012	0.9836
0.5 % PVA	0.7751±0.0043	9.6390±0.2000	0.9782
0.5 % PVA_AC	0.7993±0.0283	9.1407±0.1670	0.9752
0.5 % PVA_F	0.7928±0.0015	9.1438±0.1509	0.9734



**Figure 1** (a, b and c) Flow curves of the different carbomer concentrations; (d) the storage modulus ( $G'$ ) and loss modulus ( $G''$ ) as a function of shear strain for the different carbomer concentrations; (e) the storage modulus ( $G'$ ) and loss modulus ( $G''$ ) as a function of frequency for the different carbomer concentrations.



**Figure 2** (a, b and c) Flow curves of the different MC concentrations; (d) the storage modulus ( $G'$ ) and loss modulus ( $G''$ ) as a function of shear strain for the different MC concentrations; (e) the storage modulus ( $G'$ ) and loss modulus ( $G''$ ) as a function of frequency for the different MC concentrations.

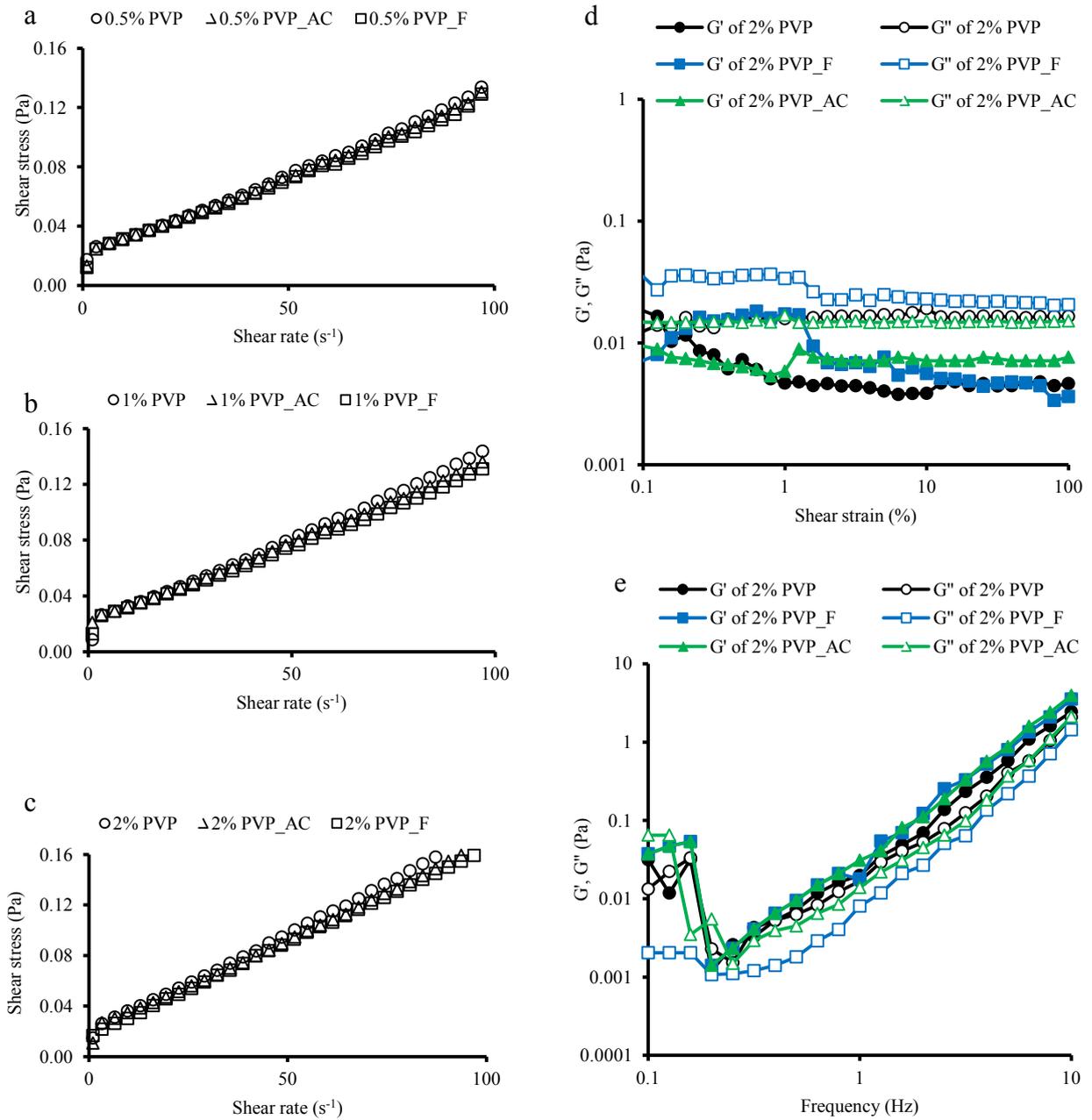
For MC solutions (**Figures 2a, 2b and 2c**), the values of shear stress responses at same shear rate of 2 % MC<sub>AC</sub>, 1 % MC<sub>AC</sub> and 0.5 % MC<sub>AC</sub> were dramatically higher than 2 % MC, 1 % MC, and 0.5 % MC, respectively.  $G'$  and  $G''$  as functions of shear strain for the 2 % MC and 2 % MC<sub>AC</sub> solutions saw large linearity, in **Figure 2d**. **Figure 2e**, autoclaved 2 % MC solution changed  $G'$  and  $G''$  values

when compared to the untreated MC solution. However, a 0.5 - 1 % of MC solution in water is recommended [19]; the cloudy and lumpy solutions may be formed at higher than 1 % of MC. MC solution is thermosensitive; a big chunk of high concentration MC will be formed, maybe because of the rehydration not taking place sufficiently. The viscosity of MC solution is reduced by the aggregation after autoclaving [19], which may cause changes of viscoelastic properties.

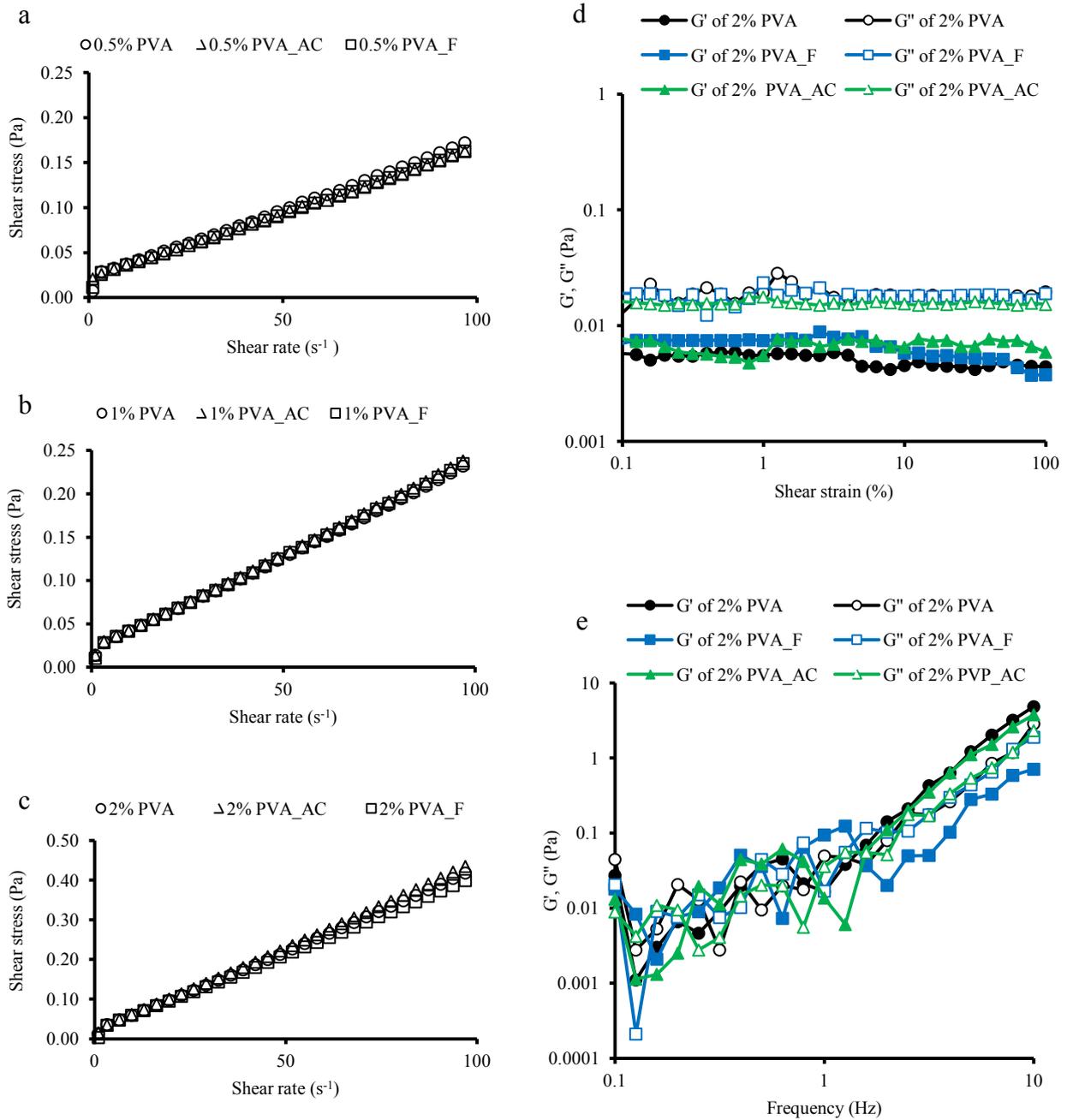
The flow curves of the different PVP concentrations are demonstrated in **Figures 3a, 3b, and 3c**. The shear stress responses with shear rate of PVP solution at 0.5, 1, and 2 % after filtration and autoclaving were intact compared to the untreated PVP solutions.  $G'$  and  $G''$  versus shear strain for the 2 % PVP, 2 % PVP\_AC and 2 % PVP\_F solution saw large linearity, **Figure 3d**.  $G'$  and  $G''$  versus frequency for the 2 % PVP solution are presented in **Figure 3e**.  $G'$  and  $G''$  of 2 % PVP\_AC and  $G'$  of PVP\_F were similar to  $G'$  and  $G''$  of 2 % PVP, but the value of  $G''$  of 2 % PVP\_F was lower than  $G''$  of 2 % PVP. The result of viscosity determination might also support the reduction of loss modulus; the consistent efficiency of PVP was changed after filtration (**Table 1**). Because PVP K90 has high molecular weight (360,000 g/mol) [20], some parts of PVP solution might not pass through the membrane. The swelled PVP molecules were bigger than the pores of the filter.

For **Figures 4a, 4b, and 4c**, the flow curves of various PVA concentrations are shown; all concentrations of PVP curves after treatments and nontreatment were the same.  $G'$  and  $G''$  versus shear strain for the 2 % PVA saw large linearity, **Figure 4d**.  $G'$  and  $G''$  frequency for the 2 % PVA is presented in **Figure 4e**; the clear differentiation curve of 2 % PVP\_AC, 2 % PVP\_F and 2 % PVP was not observed. These results may be used to confirm the stability of PVA solution. The shear viscosity and viscoelastic properties remained stable after treatments. PVA is a viscos-inducing agent; it has been used in topical ocular solution to enhance ocular contact time of ophthalmic medication and as a wetting and coating agent for who use contact lens [21].

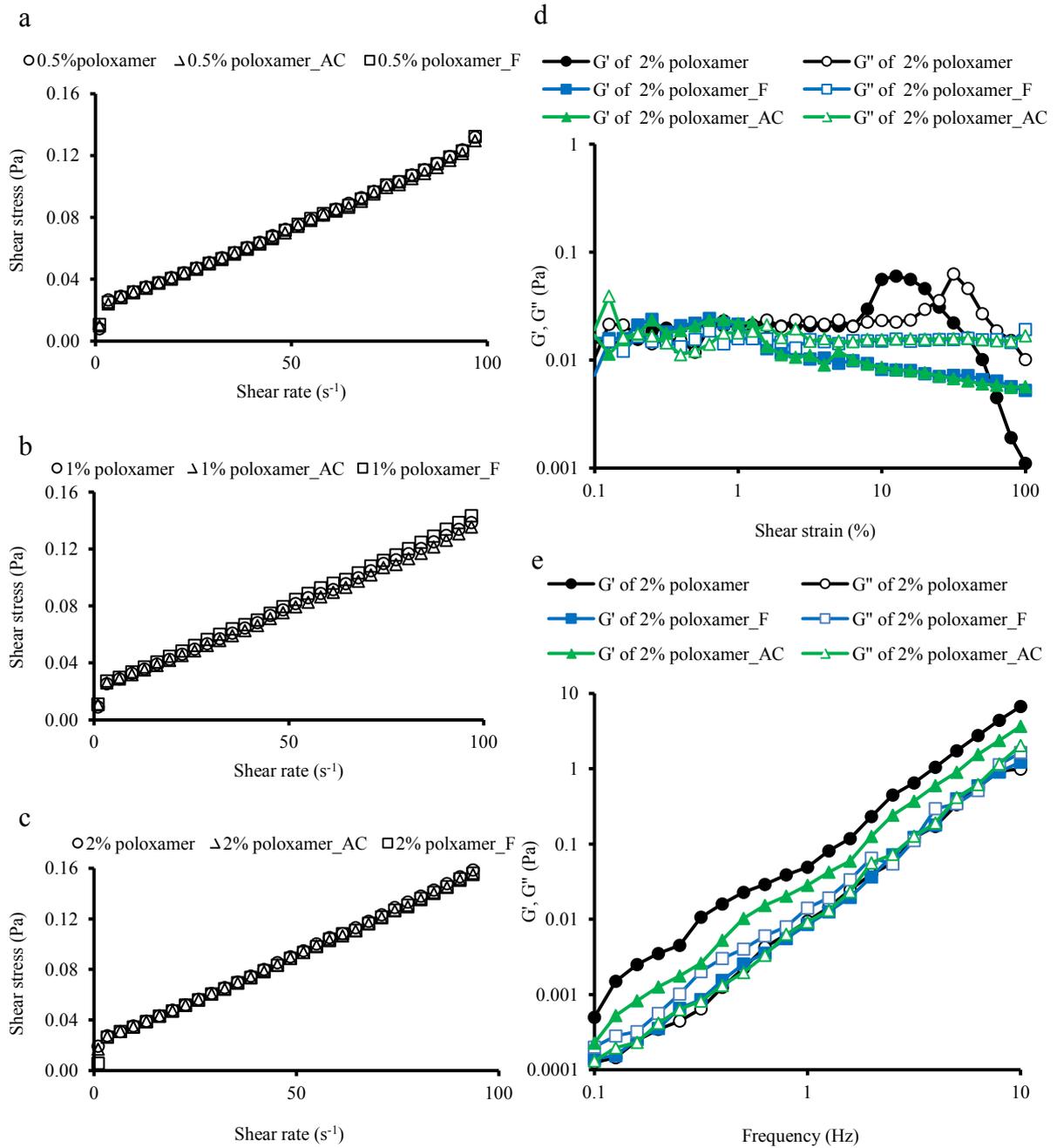
The values of shear stress responses at same shear rate of difference poloxamer concentration are demonstrated in **Figures 5a, 5b, and 5c**. For all concentrations, the curves of poloxamer solutions of treated condition were similar to untreated solution.  $G'$  and  $G''$  versus strain are demonstrated in **Figure 5d**. Nonlinear responses of  $G'$  and  $G''$  were discussed by Hyun *et al.* [22,23]. The types of strain amplitude dependence are classified into the following; type I: strain thinning ( $G'$  and  $G''$  decreasing), type II: strain hardening ( $G'$  and  $G''$  increasing), type III: weak strain overshoot ( $G'$  decreasing,  $G''$  increasing followed by decreasing), and type IV: strong strain overshoot ( $G'$  and  $G''$  increasing followed by decreasing). In **Figure 5d**, the plotting pattern of poloxamer 2 % w/w might correspond with type IV, where the overshoot of  $G'$  and  $G''$  at intermediate strain amplitude was observed. It can be attributed to strong structures responding to intermediate strain, which was hardening strain followed by the response of shear thinning with high strain amplitude [24,25]. The results revealed the middle-level tolerance of intermolecular force towards amplitude strain. The shear thickening behavior at intermediate strain was found [26-28]. After filtration and autoclaving, the overshoot of  $G'$  and  $G''$  at intermediate strain amplitude was not found; large linearities of  $G'$  and  $G''$  from sample 2 % poloxamer\_AC and 2 % poloxamer\_F were observed.  $G'$  and  $G''$  with frequency are presented in **Figure 5e**.  $G''$  of 2 % poloxamer\_AC and 2 % poloxamer\_F were no different to  $G''$  of 2 % poloxamer, but  $G'$  values of 2 % poloxamer\_AC and 2 % poloxamer\_F were lower than  $G'$  values of % poloxamer. These results suggested that viscosity and viscoelastic properties of poloxamer were influenced by the sterilization using autoclaving and filtration. In previous research, the shear viscosity of poloxamer is not altered by autoclaving [29-31] or filtration [32] sterilization. However, these results from oscillatory rheology profiles could have revealed the clear differentiation of samples after sterilization.



**Figure 3** (a, b and c) Flow curves of the different PVP concentrations; (d) the storage modulus ( $G'$ ) and loss modulus ( $G''$ ) as a function of shear strain for the 2 % PVP; (e) the storage modulus ( $G'$ ) and loss modulus ( $G''$ ) as a function of frequency for the 2 % PVP.



**Figure 4** (a, b and c) Flow curves of the different PVA concentrations; (d) the storage modulus ( $G'$ ) and loss modulus ( $G''$ ) as a function of shear strain for the 2 % PVA; (e) the storage modulus ( $G'$ ) and loss modulus ( $G''$ ) as a function of frequency for the 2 % PVA.



**Figure 5** (a, b and c) Flow curves of the different poloxamer concentrations; (d) the storage modulus ( $G'$ ) and loss modulus ( $G''$ ) as a function of shear strain for the 2 % poloxamer; (e) the storage modulus ( $G'$ ) and loss modulus ( $G''$ ) as a function of frequency for the 2 % poloxamer.

## Conclusions

In this study, the viscosity and viscoelastic properties of selected polymer solutions were investigated. The viscosity and viscoelastic properties of carbomer and MC were changed after treatments. The viscosity of PVP and poloxamer was not different, while viscoelastic properties were changed after sterilization. PVA was an optimum polymer; it was not altered in viscosity or viscoelastic properties. From this study, it could be concluded that the sterilization treatment influenced the viscosity behavior and viscoelastic properties of polymer solutions used as viscosity-inducing agents in ophthalmic solutions. The findings from this study suggest that the addition of viscosity-inducing agents should be carefully taken into account.

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