Rheological Characterization of Chitosan Matrices: Influence of Biopolymer Concentration

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ABSTRACT: Viscoelastic properties of chitosan (CH), chitosan-poly(ethylene glycol) 400 (CH-PEG), and chitosan-poly(ethylene glycol) 400 with glyoxal as crosslinking agent (CH-PEG-Gly) systems were studied to analyze the effect of chitosan concentration (from 0.83 to 1.67%). Dynamic moduli increase as chitosan concentration increases for all systems. For CH and CH-PEG systems the loss modulus (G'') is greater than the storage modulus (G') with predominance of the viscous over the elastic behavior. This corresponds to the characteristic behavior of solutions (nonstructured systems). The presence of PEG 400 induces a complementary reinforcement of the mechanical properties of the system. Except for the lowest chitosan concentration, when glyoxal was added to the CH-PEG systems, a gelled matrix was obtained. In this case, G' is greater than G'', and practically independent of frequency. This behavior is typical of three-dimensional networks and indicates true gel formation, showing clear elastic behavior (tan $\delta < 1$). In creep and recovery analysis, CH-PEG-Gly systems exhibited distinct regions that were mathematically modeled using Burger's model. This analysis shows that the CH-PEG-Gly matrices (from 1.25 to 1.67%) recover almost totally (100%). Therefore, these matrices could be useful as systems for the development of films for topical hydrophilic drug delivery, and the levels of the residual viscosity (η_0) or the complex viscosity (η^*) could be used to control drug release. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 105: 2121–2128, 2007

Key words: viscoelasticity; creep analysis; oscillatory rheometry; chitosan; crosslinking agent

INTRODUCTION

In recent years, much attention has been focused on biopolymer gels because of their biocompatibility and biological functions, and consequently their potential applications in the biomedical and pharmaceutical fields. The natural polysaccharide chitosan possesses some interesting properties such as nontoxicity, high biocompatibility, and nonantigenicity, which offer advantages for possible clinical use. Chitosan matrix systems are potential vehicles for the controlled release of hydrophilic drugs. Chitosan is a copolymer of β-(1→-linked 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose. This polycationic biopolymer is generally obtained by alkaline deacetylation from chitin, which is the main component of the exoskeleton of crustaceans such as shrimps.[1]The main reason for this growing interest is clearly its promising intrinsic properties.[2] Indeed, chitosan is known to be biocompatible, and thereby, its use is allowed in various medical applications.[3,4] Because of its positive charges at physiological pH, chitosan is also bioadhesive, which means that it leads to an increase in time retention at the site of application.[5,6] Moreover, these physicochemical properties of chitosan are interesting for the production of controlled drug delivery systems [7–9] Chitosan also promotes wound healing[10,11] and it has bacteriostatic effects.[12]

On the other hand, covalent crosslinking leads to chitosan systems with a permanent network structure because of the formation of irreversible chemical links. This systems preparation requires chitosan and a crosslinker in an appropriate solvent, usually water.[2] Crosslinkers are molecules with at least two reactive functional groups that allow the formation of bridges between polymer chains. The most common crosslinkers used with chitosan are dialdehydes such as glyoxal[13] and glutaraldehyde.[14] This reaction of glyoxal with chitosan is well documented.[2,15] The aldehyde groups form covalent imine bonds with the amino groups of chitosan because of the resonance established with adjacent double ethylenic bonds via a Schiff reaction. It should be noted that the crosslinking reaction can induce a conformational change of chitosan, as observed by NMR with 1,1,3,3,-tetramethoxypropane[16] and glutaraldehyde.[17] Other components can be added, such as additional polymers to

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form a hybrid polymer network or semi- or fully-interpenetrating polymer networks: chitosan-poly(*N*-isopropylacrylamide)[18] and chitosan-poly(ethyleneglycol).[19] However, the influence of poly(ethyleneglycol) 400 (PEG 400) and the crosslinking agent upon the properties of vehicles is not clearly understood and requires further research for the optimization of these systems, improved knowledge, and prediction of their properties.

The main objective of this work was the development of chitosan matrix systems with a fixed quantity of crosslinking agent (glyoxal) and PEG 400, as potential vehicles for the controlled release of hydrophilic drugs. To achieve this, in this preliminary study, the effect of chitosan concentration on viscoelastic properties of formulations without and with glyoxal was studied.

EXPERIMENTAL

Chitosan (CH) medium molecular weight (M_W 750,000; 75–85% deacetylated) (lot 01518AD) and Glyoxal (Gly) commercial solution (40%) (lot 50649) were purchased from Sigma Chemical (Madrid, Spain). The poly(ethylene glycol) 400 (PEG 400) (lot 1185145) was supplied by Fluka (Madrid, Spain), with an average molecular weight of 400,000 g/mol. Purified water by reverse osmosis (MilliQ®, Millipore Spain) with a resistivity more than 18.2 MΩ cm was used.

Preparation of formulation

Chitosan systems were prepared as follows:

- *CH*: Chitosan solutions with different concentrations (1%, 1.25%, 1.5%, 1.75%, and 2%, w/w) were prepared by dissolving the proper amount of chitosan in 0.1 mol/L acetic acid solution. The solution was homogenized (Teflon pestle, 1000 rpm) and filtered to remove debris. The system was left to stand for 24 h at room temperature for complete hydration of the polymer and removal of the bubbles. The pH of all formulations was adjusted to 5.5.
- *CH-PEG*: Chitosan-PEG 400 solutions were prepared adding 1 g of PEG 400 dissolved in distilled water (70%, w/w) to 5 g of above chitosan solutions. The final concentrations of chitosan in these systems were 0.83%, 1.04%, 1.25%, 1.46%, and 1.67% (w/w), respectively.
- *CH-PEG-Gly*: Chitosan-PEG 400-Glyoxal systems were prepared crosslinking 2.5 g of each Chitosan-PEG 400 solution with glyoxal (5 μL, commercial dialdehyde) in a polycarbonate Petri dish (cross-sectional area = 10.99 cm^2.). Therefore the chitosan concentration can be considered practically the same than in CH-PEG formulation.

Rheological characterization

A Haake Rheostress 1 rheometer (Thermo Haake, Germany) with data acquisition software (RheoWin 2.94) and a circulator for sample temperature control was used. The oscillatory tests for CH and CH-PEG systems were carried out using a cone-plate (2°, 60 mm diameter); while CH-PEG-Gly were measured with serrated parallel plates (35 mm diameter, 1 mm gap) to avoid slippage during oscillation. The oscillatory rheological parameters used to compare the viscoelastic properties for all the systems were the storage modulus (G'), the loss modulus (G''), the loss tangent ($\tan \delta = G''/G'$), and the complex viscosity (η^*).

Samples were allowed to rest for at least 600 s prior to analysis. In all cases, the exposed edges of the sample were covered with silicone oil (Dimethicone RFE/Ph. Eur.) to prevent evaporation of water during measurement. All measurements were made in triplicate at 25°C. To determine the linear viscoelastic range, stress sweeps at 25°C and at a frequency of 1 Hz were performed for all systems studied.

Gelation time

First, the gelation time was determined. The crosslinking process with glyoxal was followed by analyzing the storage and loss moduli as a function of time (at 1 Hz). This procedure does not alter the structure of the growing network and can provide a direct measurement of the gelation process.[20] The time at which G' and G'' crossover ($\tan \delta = 1$) was considered as the gelation time (t_{gel}).[21]

Oscillatory test

Frequency sweep tests were performed from 0.01 to 10 Hz, at 1 Pa for CH and CH-PEG systems and for CH-PEG-Gly systems, at 1 Pa samples containing lower concentration of chitosan (0.83%) and at 200 Pa for the higher concentrations (from 1.04 to 1.67%, w/w).

Creep and recovery

Creep and recovery analysis for the CH-PEG-Gly formulations were also carried out under the same experimental conditions mentioned above. A constant stress in the linear region (1 Pa for 0.83% chitosan and 200 Pa for the remaining concentrations) was applied instantly and maintained for a period of 300 s (creep) and the compliance was measured. After removing the stress, compliance values were also measured during 300 s (recovery).

The creep data were analyzed according to the Burger's model [eq. (1)], consisting of one Maxwell unit and one Kelvin-Voigt unit in series (Fig. 1).[22,23]

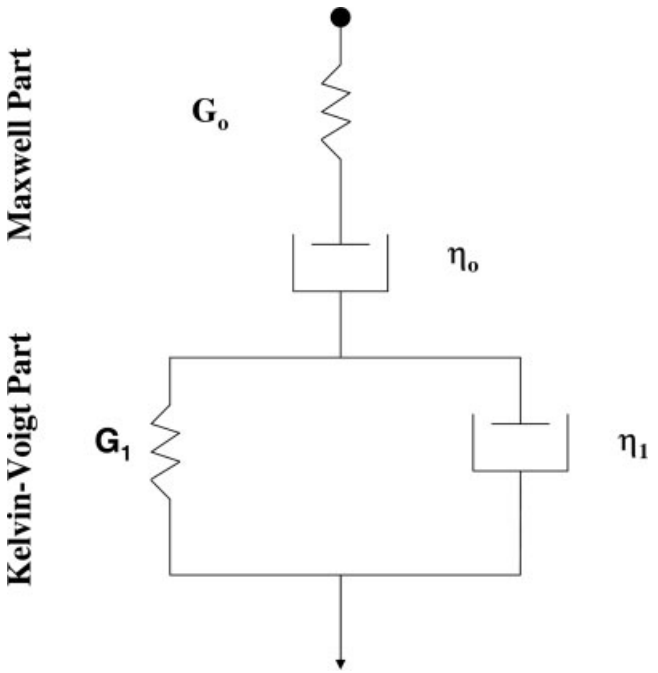

Figure 1 The mechanical model of Burger which simulates the rheological behavior of chitosan gels, consisting of one Maxwell unit and one Kelvin-Voigt unit in series.

$$J(t) = \frac{1}{G_0} + \frac{1}{G_1}\left[1 - \exp\left(\frac{-tG_1}{\eta_1}\right)\right] + \frac{t}{\eta_0} \quad (1)$$

$J(t)$ represents the overall compliance at any time t, G_0 is the instantaneous elastic modulus of the Maxwell unit, and G_1 is the elastic modulus of the Kelvin-Voigt unit. The latter represents the contributions of the retarded elastic region to the total compliance. The dashpot of the Maxwell element represents the residual viscosity, η_0, and the dashpot associated with Kelvin-Voigt is called the internal viscosity, η_1.[24]

On the other hand, the experimental values of the compliance J (Pa^{-1}) in the recovery process were fitted with the following empirical equation [eq. (2)]

$$J(t) = J_\infty + J_{KV}\exp(-Bt^c) \quad (2)$$

where B and C are parameters which define the recovery rate of the system, J_∞ is the residual compliance, J_{KV} is the maximum compliance of the Kelvin-Voigt element, and t is the time.

The empirical equation proposed [eq. (2)] to analyze the recovery process complies with defined limiting conditions:

For $t \to 0$, J is equal to $(J_\infty + J_{KV})$, which corresponds to the maximum deformation of the dashpots in Burger's model (Fig. 1), being the recovery of the spring instantaneous.

For $t \to \infty$, $J(t)$ is equal to J_∞, which provides the residual deformation of the system corresponding to the irreversible sliding of the Maxwell's dashpot.

Additionally, the Maxwell's spring deformation, or initial shear compliance J_0, was obtained by using eq. (3), where J_{MAX} is the maximum deformation corresponding to the experimental compliance value for the longest time (300 s) in the creep transient analysis.

$$J_0 = J_{MAX} - (J_\infty + J_{KV}) \quad (3)$$

The percentage of deformation (S%) of each element of Burger's model can be obtained by means of eq. (4).

$$S = \left[\frac{J_{element}}{J_{MAX}}\right] \times 100 \quad (4)$$

Finally, from J_{MAX} and J_∞ values it is possible to obtain the total recovery (R%) using the following expression:

$$R = \left[\frac{(J_{MAX} - J_\infty)}{J_{MAX}}\right] \times 100 \quad (5)$$

The fitting procedure was carried out by means of KaleidaGraph nonlinear regression (Synergy Software© KaleidaGraph, version 3.51).

Statistical analysis

Homogeneity was confirmed by Barlett test. One-way ANOVA, followed by the Tukey multiple comparison test was performed on the representative values of the storage modulus (G'), the loss modulus (G'') and complex viscosity (η^*), to establish differences between the calculated means (SPSS 12.0).

RESULTS AND DISCUSSION

Gelation time

Initially, the crosslinking process with glyoxal was analyzed to establish the influence of the biopolymer concentration on the gelation time. When glyoxal solution was added to the CH-PEG solutions, G' increased faster than G'' over time in all cases, and reached finally a plateau region (Fig. 2). The gelation time (in seconds), at which the crossover of G' and G'' take place, was 2600 ± 100, 1650 ± 100, 285 ± 15, and 3 ± 1, for 1.04%, 1.25%, 1.46%, and 1.67% (w/w), respectively. The gelation time decreased dramatically with increasing chitosan concentration, and was practically zero for the highest concentration of chitosan (1.67%). The gelation time (t_g) dependency on chitosan concentration (C%) is well described (correlation coefficient $r > 0.91$) by a power law:

$$t_g = (3.2 \pm 0.6) \times 10^3 C^{-(4.6 \pm 1.5)} \quad (6)$$

It is important to note that the amount of crosslinking agent (glyoxal) was the same in all the formula-

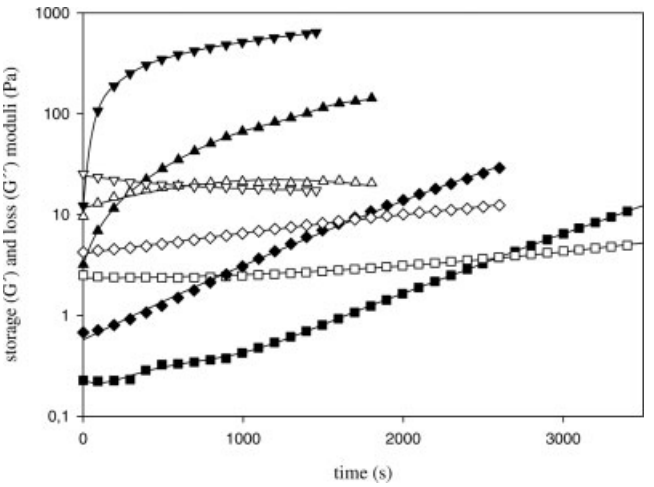

Figure 2 Time dependence of storage modulus (G', filled symbols) and loss modulus (G'', open symbols) for different chitosan concentrations: 1.04% (-■-; -□-), 1.25% (-◆-, -◇-), 1.46% (-▲-, -△-) and 1.67% (-▼-;-▽-).

tions assayed, and was sufficient to obtain the network structure in the range of chitosan concentration used. The lowest concentration of chitosan (0.83%, w/w) does not reach the structure of gel and was not included in the graph (Fig. 2).

Oscillatory test

The viscoelastic properties of chitosan (CH), chitosan-poly(ethylene glycol) 400 (CH-PEG), and chitosan-poly(ethylene glycol) Glyoxal (CH-PEG-Gly) formulations were also studied to analyze the effect of concentration of chitosan and the presence of the crosslinking agent on the gelation process. As an example, Figures 3(a,b) shows storage modulus, G', and loss modulus, G'', as a function of the angular frequency (ω, rad s^{-1}) for CH, CH-PEG, CH-PEG-Gly systems at the indicated concentrations. In all systems the dynamic moduli increase as chitosan concentration increases.

The statistical analysis of dynamic moduli for CH and CH-PEG shows that there are statistical differences ($P < 0.05$). However, the addition of PEG 400 to the chitosan solutions do not change the viscoelastic behavior of the vehicle, regardless of the chitosan concentration used [Fig. 3(a)]. The tendency of both G' and G'' moduli for the solutions formulated with and without PEG 400 was similar. In these systems G'' is greater than G', and both increase as frequency increases, G' having a greater slope than G'' in a log–log plot. This characteristic behavior corresponds to nonstructured systems, with a predominance of viscous over elastic behavior.[25]

When a crosslinking agent (glyoxal) was added to the CH-PEG solutions a gelled matrix [Fig. 3(b)] was obtained, except for the lowest chitosan concentration [Fig. 3(a)]. The storage modulus is larger than the loss modulus, and practically independent of frequency. This behavior is typical of a three-dimensional network.[26]

To compare all the systems the loss tangent (tan $\delta = G''/G'$) was also analyzed. In Figure 4 it is easy to see the difference between non gelled systems with tan $\delta > 1$ and gelled matrix systems, with tan $\delta < 1$.

For CH and CH-PEG solutions the loss tangent tan δ is always greater than 1, which means the viscous behavior prevalence, as previously indicated. The loss tangent tan δ decreases with increasing frequency, reaching values close to 1 for the highest frequencies. Otherwise, the systems with a crosslinking agent show a clear elastic behavior (tan $\delta < 1$) except for the lowest chitosan concentration (0.83%, w/w). Seemingly, a critical number of crosslinks per chain is

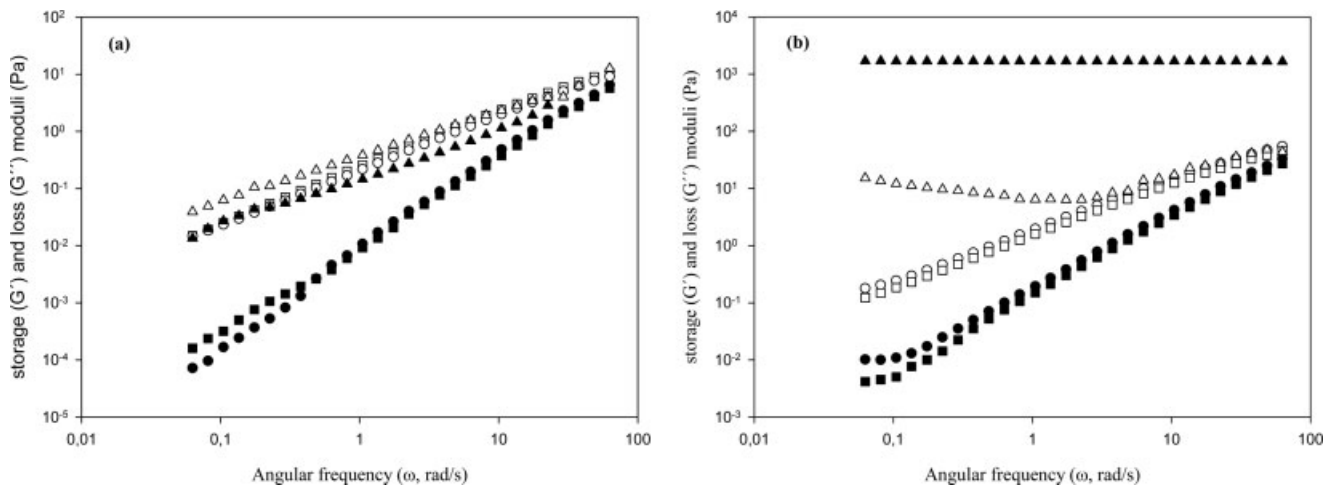

Figure 3 Frequency dependence of storage modulus (G', filled symbols) and loss modulus (G'', open symbols): (a) CH 1% (-●-; -○-), CH-PEG 0.83% (-■-; -□-), CH-PEG-Gly 0.83% (-▲-, -△-) and (b) CH 1.75% (-●-; -○-), CH-PEG 1.46% (-■-; -□-), CH-PEG-Gly 1.46% (-▲-, -△-).

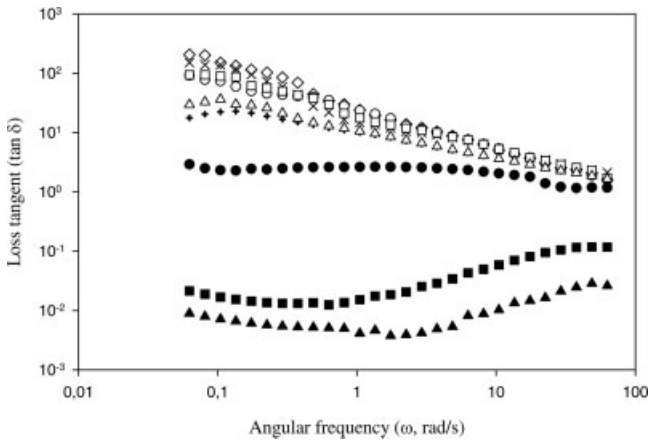

Figure 4 Effect of the chitosan concentration at 25°C on the loss tangent (tan δ) as a function of angular frequency. For CH: 1% (◇); 1,25% (×), 1,75% (+); CH-PEG: 0,83% (○), 1,04% (□), 1,46% (△) and CH-PEG-Gly: 0.83% (●), 1,04% (■), 1,46% (▲).

required to allow the formation of a network structure.[27] Likewise, the loss tangent values decrease with increasing chitosan concentration, indicating that the crosslink density within the matrices increases the system elastic behavior (Fig. 4). The prevalence of elastic over viscous nature in gelled systems could be considered an advantage for the development of bioadhesive systems.[28]

For all systems studied the complex viscosity $\eta^* = f(\omega)$ decreases as the angular frequency increases. Otherwise the complex viscosity η^* increases with increasing chitosan concentration (Fig. 5). On comparing CH and CH-PEG solutions with similar concentration of chitosan, the complex viscosity was larger for systems including PEG 400 [Fig. 5(a)]. In these cases, the statistical analysis of the complex viscosity shows that there are significant differences ($P < 0.01$). This fact suggests the presence of hydrogen bonds between the chitosan and PEG 400 chains[29] that can induce a complementary reinforcement of the mechanical properties of the system.[14] For the CH-PEG-Gly matrices (chitosan concentration from 1.04 to 1.67%, w/w) [Fig. 5(b)] the complex viscosity η^* values are much larger than those of the respective solutions [Fig. 5(a)]. Otherwise, the η^* values for the 0.83% CH-PEG-Gly system are in the same range as those corresponding to systems without a crosslinking agent. For this chitosan concentration (0.83%) a gel structure was not obtained. In this case the presence of PEG400 could act inhibiting the action of the crosslinker, since the ratio CH/PEG decrease as the concentration of chitosan decrease.

The complex viscosity values obtained for gelled systems were fitted to power law functions

$$\eta^* = A\omega^{-B} \tag{7}$$

where the power index, B, is close to 1 [straight lines in Fig. 5(b)]. Since the storage modulus G' is much greater than the loss modulus G'' (therefore η^* is almost G'/ω) the behavior is characteristic of structured systems.[30] This fact confirms that a matrix structure has been formed, as commented above.

Creep and recovery

Creep and recovery analysis has been carried out, for all these systems, to understand the internal structure for the CH-PEG-Gly formulations. The time dependence of compliance, J, is shown in Figure 6. The CH-PEG-Gly formulation with the lowest chitosan concentration [Fig. 6(a)] presents the typical behavior of a liquid, nonstructured system, with an almost continuous deformation beginning at zero and an almost total

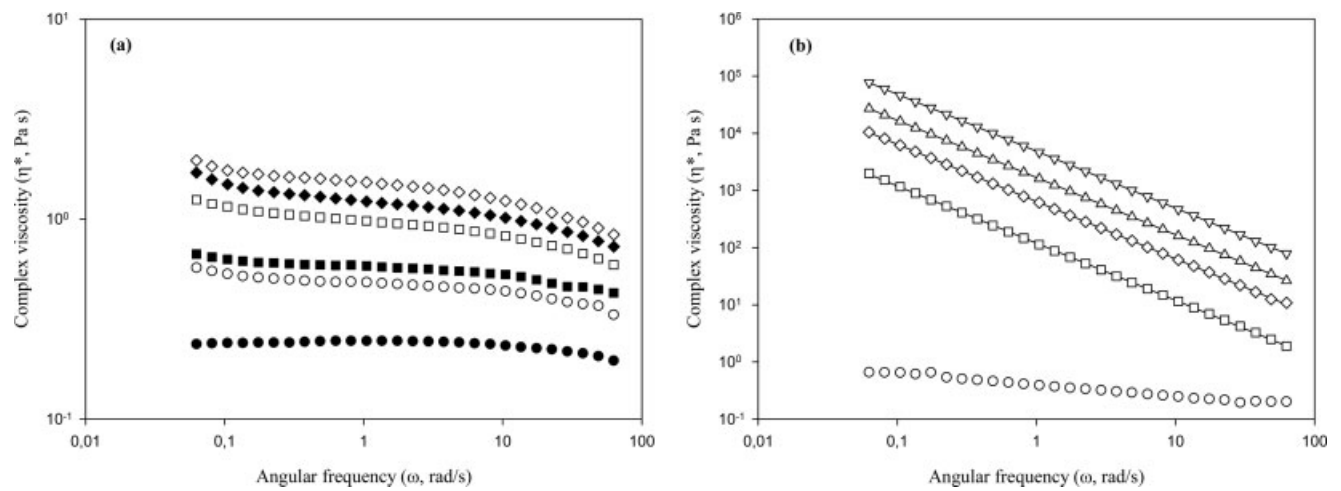

Figure 5 Frequency dependence of complex viscosity (η^*) for CH, CH-PEG 400 and CH-PEG-Gly systems: (a) For CH: 1% (●), 1,25% (■), 1,5% (◆) and CH-PEG: 1,04% (○), 1,25% (□), 1.46% (◇); (b) For CH-PEG-Gly: 0.83% (○), 1.04% (-□-), 1.25% (-◇-), 1.46% (-△-) and 1.67% (-▽-).

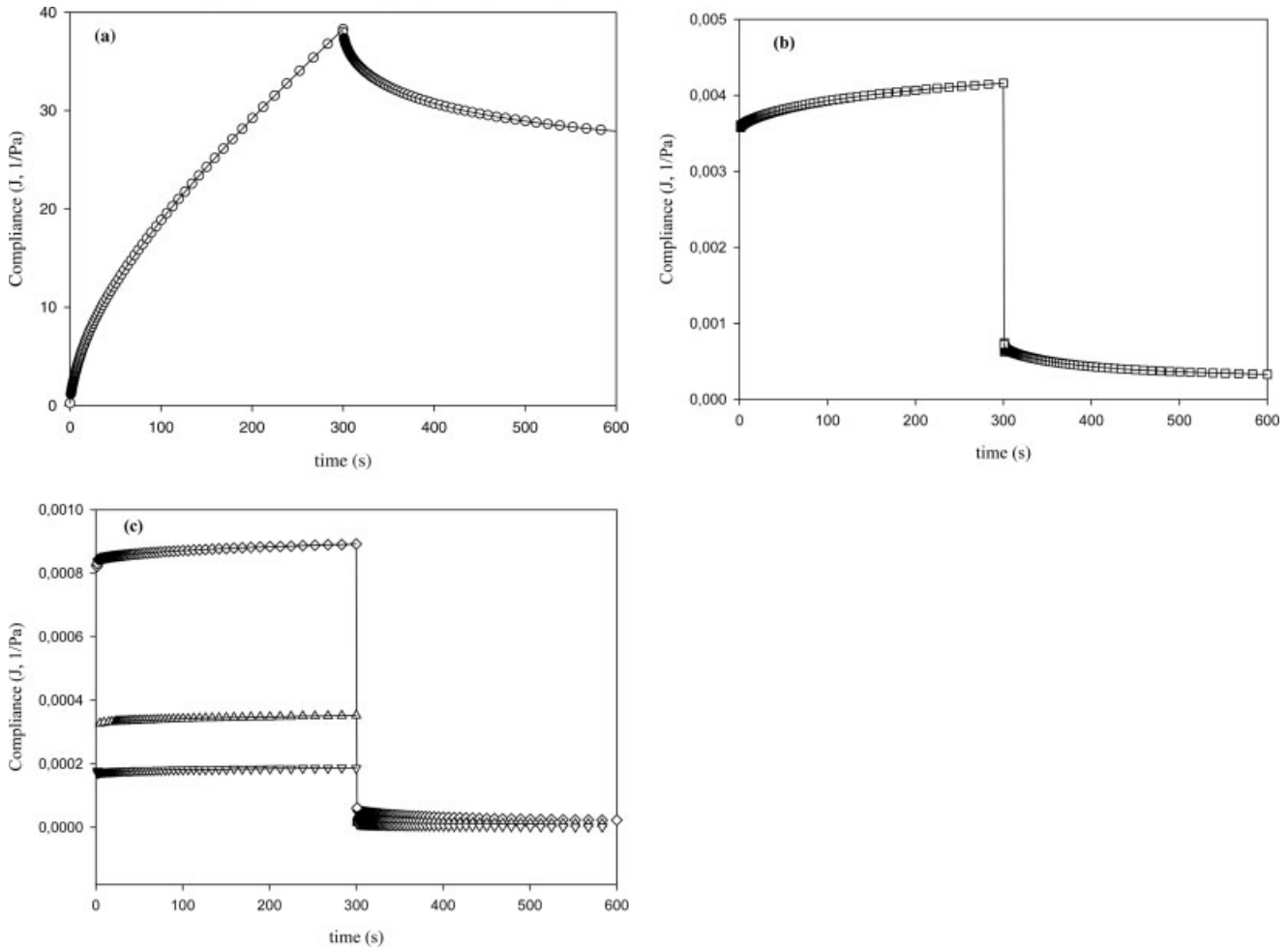

Figure 6 Creep and recovery compliance curves of chitosan-PEG 400-Glyoxal for different concentrations of chitosan: 0.83% (a); 1.04% (b) and concentrations from 1.25 to 1.67% (c): 1.25% (-◇-), 1.46% (-△-) and 1.67% (-▽-).

TABLE I
Kelvin-Voigt Unit Elastic Moduli (G_0, G_1) and Dashpot Viscosities (η_0 and η_1), and Correlation Coefficient (r) Using the Mechanical Burger's Model for Chitosan-PEG 400-Glyoxal Formulations[a]

Chitosan concentration (%, w/w)	G_0 (Pa)	G_1 (Pa)	$\eta_0 \times 10^{-4}$ (Pa s)	$\eta_1 \times 10^{-4}$ (Pa s)	$r >$	$\eta^*_\omega = 0.063_s^{-1}$ (Pa s)
0.83	0.97 ± 0.04	0.124 ± 0.002	0.0011 ± 0.00007	0.00035 ± 0.000017	0.999	0.66 ± 0.03
1.04	27.85 ± 0.1	3900 ± 100	93 ± 3	17.5 ± 1.2	0.999	1999 ± 80
1.25	1186.5 ± 0.2	47,000 ± 1000	1040 ± 20	211 ± 12	0.999	10,460 ± 500
1.46	3045.3 ± 1.6	81,000 ± 4000	2600 ± 180	560 ± 80	0.999	27130 ± 1300
1.67	5770 ± 5	160,000 ± 10,000	4200 ± 400	670 ± 90	0.994	76,880 ± 4000

[a] The complex viscosity (η^*) at the lowest angular frequency (0.063 rad/s) are also included. The uncertainties are based on standard deviation for all the tables.

TABLE II
J_{MAX}, J_∞, J_{KV}, and J_0 Compliance Values for CH-PEG-Gly Formulations at Different Chitosan Concentrations

Concentration (%)	J_{MAX} (10^4 Pa^{-1})	J_∞ (10^4 Pa^{-1})	J_{KV} (10^4 Pa^{-1})	J_0 (10^4 Pa^{-1})
0.83	382,900 ± 100	255,000 ± 1000	127,000 ± 1000	900 ± 30
1.04	41.6 ± 0.1	2.48 ± 0.02	4.7 ± 0.2	34.4 ± 0.2
1.25	8.92 ± 0.01	0.168 ± 0.007	0.380 ± 0.008	8,37 ± 0.02
1.46	3.52 ± 0.01	0.082 ± 0.003	0.189 ± 0.005	3.25 ± 0.008
1.67	1.86 ± 0.01	0.001 ± 0.0007	0.111 ± 0.009	1.75 ± 0.03

TABLE III
Deformation Percentages (*S*%) and Total Recovery Percentage (*R*%) at Different Chitosan Concentrations for CH-PEG-Gly Formulations

Concentration (%)	*S* (%)			*R* (%)
	J_∞/J_{MAX}	J_{KV}/J_{MAX}	J_0/J_{MAX}	
0.83	66.3 ± 0.3	33.1 ± 0.3	0.60 ± 0.02	33.7 ± 0.3
1.04	6.00 ± 0.06	11.3 ± 0.5	82.7 ± 0.7	94.0 ± 0.5
1.25	1.9 ± 0.1	4.3 ± 0.1	93.8 ± 0.3	98.1 ± 0.3
1.46	2.3 ± 0.1	5.4 ± 0.2	92.3 ± 0.05	97.7 ± 0.6
1.67	0.05 ± 0.4	5.9 ± 0.5	94 ± 2	100 ± 1.5

deformation when stress disappears. Thus, viscous behavior prevails. Otherwise, the CH-PEG-Gly formulations with chitosan concentrations between 1.04 and 1.67% show a solid-like behavior, with a large initial instantaneous deformation and an almost total recovery. That is, they exhibit high elasticity [Figs. 6(b,c)]. These results are consistent with those obtained previously from oscillatory measurements.

All the creep curves were fitted to Burger's model [eq. (1)]. The values of the elastic moduli, G_0 and G_1, and the dashpot viscosities, η_0 and η_1, are shown in Table I. The elastic moduli increase with the chitosan concentration, i.e., the system becomes more difficult to deform with increasing amounts of chitosan. In the same way, increasing the concentration of chitosan gave rise to significantly higher residual viscosities of the CH-PEG-Gly formulations (Table I); thus, the residual viscosity (η_0) is significantly affected by the biopolymer concentration. This behavior could be attributed to an increased polymer chain entanglement density in the presence of the crosslinking agent.

The residual viscosity is usually very large, often reaching 10^6 Pa s,[24] and is many orders of magnitude larger than the complex viscosity (η^*) obtained by the oscillatory test at the lowest rotation speed ($\omega = 0.063\ s^{-1}$, see Table I). The relationship between residual viscosity (η_0) and complex viscosity (η^*) is, however, linear, with an acceptable correlation coefficient ($r > 0.961$):

$$\eta_0 = 3.22 \times 10^6 + 524.9\eta^* \text{ at } \omega = 0.063\ s^{-1} \quad (8)$$

that allows to use any of both parameters to analyze the influence of the viscosity on drug release.[31,32]

The compliance, and, the percentage of deformation (*S*%) and total percentage of recovery (*R*%) obtained for each of the elements of the Burger model by means of eqs. (3), (4), and (5) are shown in Table II and III, respectively. As it is expected, the initial elastic recovery compliance (J_0) in recovery analysis (Table II) is similar to the initial compliance in creep analysis ($1/G_0$) (Table I), which shows the usefulness of the new empirical eq. (3).

It is easy to observe that for the system formulated with the lowest concentration (0.83%) the contribution of the spring of Maxwell is negligible (has a percentage of deformation J_0/J_{MAX} of only 0.6%) and that to the dashpot of Maxwell corresponds the largest percentage of deformation ($J_\infty/J_{MAX} = 66\%$, Table III). Therefore, it will be deformed and will flow easily when constant stress is applied to this system. This gives rise to greater compliance values. The system only recovers the 33.7% of the initial form, since the deformation taking place in the dashpot of Maxwell is irreversible. The liquid-like behavior of this system suggests elongation and orientation of the polymer chains, chitosan and PEG 400, involving the breaking and reforming of secondary bonds (i.e., hydrogen bonds).

For the 1.04% chitosan concentration the percentage of deformation (Table III) corresponding to J_0/J_{MAX} is 82.7%, while the contribution of the ratio J_∞/J_{MAX} is not negligible (6%), i.e., the total recovery of this system is not reached. Otherwise, for the matrices with chitosan concentration between 1.25 and 1.67%), the percentage of deformation (Table III) from J_0/J_{MAX} is close to 94%, whereas the contribution of the ratio J_∞/J_{MAX} is negligible. Therefore, these systems recover almost totally ($R \geq 97.7\%$). This behavior could be attributed to the stretching of molecular bonds (i.e., covalent bonds), which increase with increasing chitosan concentration, and may be visualized as an extension of the spring of Maxwell (G_0) in the mechanical model.

CONCLUSIONS

In view of the results obtained in this study, the CH and CH-PEG are nonstructured systems (solutions) and the presence of poly(ethylene glycol) 400 hardly changes the viscoelastic behavior of the vehicle. However, this polymer induces a complementary reinforcement of the mechanical properties of the system.

However, when a crosslinking agent was added to the CH-PEG solutions, a gelled matrix was obtained, except for the case of the lowest chitosan concentration (0.83%), and these matrices show a clear elastic behavior (loss tangent, $\tan \delta < 1$).

From creep and recovery analysis we obtain that the CH-PEG-Gly matrices with concentrations be-

tween 1.25% and 1.67% recover totally (almost 100%). Hence, these matrices can be useful as a base for the development of films for topical hydrophilic drug delivery, and the residual viscosity (η_0) or the complex viscosity (η^*) can be used on the control of the drug release.

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