Sodium Alginate–Magnesium Aluminum Silicate Composite Gels: Characterization of Flow Behavior, Microviscosity, and Drug Diffusivity

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ABSTRACT

The aims of the present study were to characterize the flow behavior and thixotropic properties of sodium alginate–magnesium aluminum silicate (SA-MAS) composite gels with various ratios of SA and MAS, and to investigate the drug diffusivity and microviscosity of the composite gels. Moreover, interaction of SA and MAS in the form of dry composite was examined by using Fourier Transform Infrared (FTIR), and a possible structure model of SA-MAS composite gel was illustrated. Incorporating MAS into the SA gels provided higher viscosity and changed the flow behavior from Newtonian to pseudoplastic with thixotropy. This was due to the formation of electrostatic force and intermolecular hydrogen bonding between SA and MAS, leading to a denser matrix structure of the composite gels. Increasing the content of MAS decreased the drug diffusivity but increased the microviscosity of the composite gels. The denser matrix structure of the composite gels had a higher tortuosity, resulting in slower drug diffusion through water-filled channels in the gels. This finding suggested that incorporating MAS into the SA gels could improve the flow behavior and sustain drug release from the gels because of the formation of a matrix structure between SA and MAS in the gels.

KEYWORDS: Alginate, magnesium aluminum silicate, flow behavior, microviscosity.

INTRODUCTION

In pharmaceutics, gelling agents can be divided into inorganic and organic substances. Clay, an inorganic gelling agent, possesses a lamellar structure that can be extensively hydrated. The flat surfaces of particles are negatively charged, while the edges are positively charged. The attraction of face to edge of these colloidal lamellae creates throughout the gel a 3-dimensional network of particles that exhibits a thixotropic property. Organic gelling agents typically contain polymers obtained from nature or synthesis. The long chains of polymer are extended in water because of hydrogen bond formation between the water and hydroxyl groups of the polymers, leading to high viscosity and gel formation.[1]

Magnesium aluminum silicate (MAS) is a mixture of natural smectite clays, in particular montmorillonites and saponites. Smectite clays have a layered structure. Each layer is constructed from tetrahedrally coordinated silica atoms fused into an edge-shared octrahedral plane of either aluminum hydroxide or magnesium hydroxide.[2,3] The charges on the layers of MAS lead to an interaction with anionic polymers, such as xanthan gum[4] and carbomer,[5] which results in viscosity synergism. Thus, MAS has been widely employed in oral and topical formulations as a suspending and stabilizing agent, either alone or in combination with other suspending agents.[6]

Sodium alginate (SA) is a sodium salt of alginic acid, a naturally occurring nontoxic polysaccharide found in brown algae. Alginate has been widely used as a food and pharmaceutical additive, for instance as a tablet disintegrant and gelling agent.[6] It contains 2 uronic acids, α–L-guluronic and β–D-mannuronic acids, and is composed of homopolymeric blocks and blocks with an alternating sequence.[7] Gelation occurs by cross-linking of the uronic acids with divalent cations, such as calcium ions. Moreover, SA also could form a complex with the cationic polymers chitosan[8] and chondroitin sulfate,[9] the non-ionic polymer konjac glucomannan,[10] and the anionic polymer sodium starch glycolate.[11] Recently, it has been demonstrated that the viscosity of SA dispersions could be enhanced by adding MAS. This suggested a viscosity synergism of SA and MAS.[12]

The aims of the present study were to characterize the flow behavior and thixotropic properties of SA-MAS composite gel with various ratios of SA and MAS and to investigate the diffusivity of diclofenac sodium (DS), the model drug, in the composite gels using the square root of time model. The microviscosity of the composite gels was estimated using the Stokes-Einstein equation. Moreover, the interaction of SA and MAS in the form of dry composite was examined by using FTIR spectroscopy. The bond formation in the dry state between SA and MAS could be used to predict the

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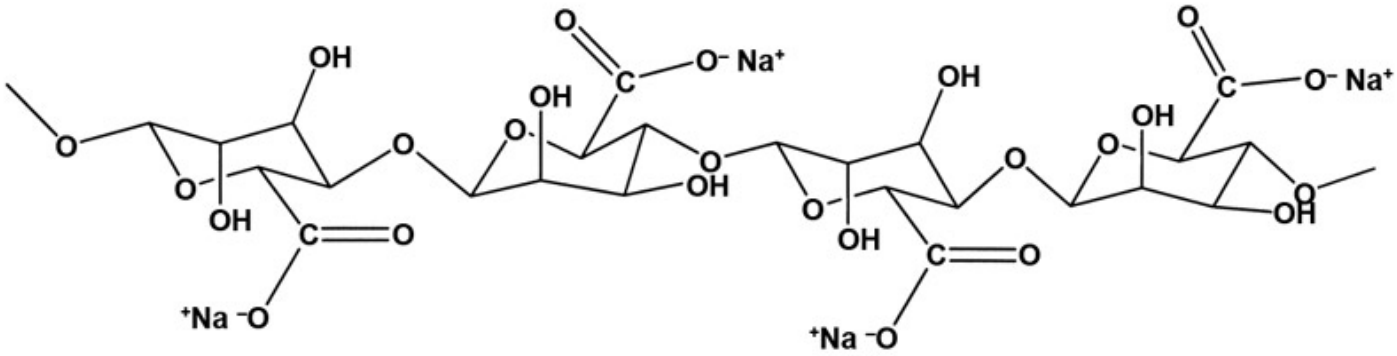

Figure 1. Chemical structure of mannuronic acid–rich type of sodium alginate.

matrix structure of SA-MAS composite gel. A possible structure model of the composite gels was proposed as well.

Materials and Methods

Materials

DS, a low-viscosity grade of SA (LVSA, viscosity of 2% solution at 25°C: 250 cps), and a high-viscosity grade of SA (HVSA, viscosity of 2% solution at 25°C: 14 000 cps) were purchased from Sigma Chemical Co (St. Louis, MO). Both grades of SA were of the mannuronic acid–rich type because their ratios of mannuronic acid to guluronic acid were 1:6[13]; the chemical structure is shown in Figure 1. MAS (Veegum HV) was obtained from R.T. Vanderbilt Co, Inc (Norwalk, CT). Other reagents used were of analytical grade and used as received.

Preparation of Gels

SA was dispersed in distilled water with agitation to obtain homogeneous gels. MAS was prehydrated with hot water for 15 minutes and then added to the SA gel. The composite gels were adjusted to their final weight (100 g) by using distilled water. The gels were mixed with a homogenizer for 5 minutes and kept for full hydration at room temperature overnight before use. To incorporate DS into the gels, DS was dissolved completely in distilled water before the SA was dispersed and the preparation process continued as described above.

Flow Behavior Studies

The flow characteristics of SA and composite gels with or without DS were investigated using a small sample adapter of a Brookfield digital rheometer (Model DV-III, Brookfield Engineering Labs Inc, Stoughton, MA). The sample temperature was kept at 32°C ± 1°C. A flow curve of the samples was obtained by plotting between shear rate and shear stress for various revolution rates when a spindle (No 31 or 34) was used. An area of hysteresis loop of flow curve can be obtained from the difference of the area under the curve between the up-curve and the down-curve; this area was calculated using the trapezoidal rule. Moreover, the flow type of the SA gels with MAS can be characterized using the following exponential formula[14]:

$$F^N = \eta G \tag{1}$$

$$\mathrm{Log}\, G = N\, \mathrm{Log}\, F - \mathrm{Log}\ \eta \tag{2}$$

where F is shear stress, G is shear rate, N is an exponential constant, and η is a viscosity coefficient, respectively.

Determination of Molecular Interaction of SA and MAS

The molecular interaction of SA and MAS was investigated using an FTIR spectrophotometer (Spectrum One, Perkin-Elmer, Norwalk, CT). The SA gels and SA-MAS composite gels were poured into a plastic plate and dried at 50°C for 24 hours. The composite solids were ground with a mortar and pestle. The fine particles of the sample were gently triturated with KBr powder in a weight ratio of 1:100 and then pressed using a hydrostatic press at a pressure of 10 tons for 5 minutes. The disc was placed in the sample holder and scanned from 4000 to 1200 cm^{-1} at a resolution of 4 cm^{-1}.

In Vitro Drug Release Studies

A 1-diameter vertical diffusion cell (Crown Glass Co, Inc, Somerville, NJ) was used. The receptor medium was 6 mL of distilled water at 37°C, which was stirred at 600 rpm. A piece of 0.45-μm cellulose acetate (Schleicher and Schuell, Dassel, Germany) was used as a membrane. The membrane was soaked in distilled water overnight and then mounted on a diffusion cell. The SA and composite gels containing 1% wt/wt DS (0.5 g) were placed in the donor compartment and the cells were then fixed and tightly fastened by a clamp. At appropriate intervals, 0.4-mL aliquots of the receptor

medium were withdrawn and immediately replaced by fresh medium. The concentration of DS was analyzed by high-performance liquid chromatography (HPLC).

The release rate of the DS from the gels can be estimated using linear regression analysis of the relationship between the amount of DS released per area and the square root of time. This relationship can be described by the following equation[15]:

$$\frac{M}{t^{1/2}} = 2C_0\left(\frac{D}{\pi}\right)^{0.5} \quad (3)$$

where M is the amount of DS released from the gels, which is not much greater than 50% of the drug content in the donor compartment, $t^{0.5}$ is the square root of time, C_0 is the initial concentration of DS in the gels, and D is the diffusivity of DS in the gels.

Estimation of Microviscosity of Gels

The Stokes-Einstein equation was applied to compute the microviscosity of the gels. This equation showed a relationship between the viscosity of the solvent and the diffusion coefficient of solutes. The viscosity in this equation was the microviscosity, which represented the viscosity of the entrapped aqueous phase in the polymer network that drug molecules diffused through. The microviscosity of the gels (η') was calculated using the following equation[14]:

$$\eta' = \frac{RT}{6\pi DrN} \quad (4)$$

where D is the diffusivity value obtained from the release studies, R is the molar gas constant, T is the absolute temperature, N is Avogadro's number, and r is the radius of DS (0.427 nm), which had been previously reported by Maitani et al.[16]

HPLC Analysis of DS

The concentration of DS was determined using HPLC (Perkin-Elmer). Reversed-phase HPLC using a C-18 column (HiQ Sil C18V, 4.6 × 250 mm) connected with a guard column was employed. The mobile phase was aqueous 0.033 M potassium dihydrogen phosphate:methanol:acetonitrile (30:45:25 vol/vol), and the pH was adjusted to 6.7 with 5% wt/vol dipotassium hydrogen phosphate. The flow rate of the mobile phase was 1 mL min^{-1}, and the detector was a UV-visible detector at a wavelength of 280 nm. The retention time of DS was ~6.5 minutes. Under these conditions, good linearity and reproducibility were shown over the range of 0.1 to 400.0 μg mL^{-1} DS.

Results and Discussion

Flow Behavior and Matrix Structure of Gels

The flow curve of the HVSA gel and the composite gels at various ratios of HVSA and MAS is shown in Figure 2. Incorporating MAS caused an obvious change in the flow curve of the HVSA gels. The flow parameters of the SA gels and the composite gels are listed in Tables 1 and 2. The N values of the LVSA and HVSA gels increased with increasing concentrations of SA. The LVSA gels could not provide an N value greater than unity, indicating that the flow type was Newtonian. In contrast, the N value of 1.5% HVSA gel was found to be 1.29, resulting in pseudoplastic flow, while the lower concentration (0.38%-1.12%) of HVSA showed Newtonian flow with an N value in the range of 1.04 to 0.78. In the case of the viscosity coefficient, the higher the concentration of SA in the gels, the greater the viscosity coefficient. Incorporation of MAS into the SA gels so that the total weight of SA and MAS was 1.5 g in 100 g of gels resulted in a remarkable increase in the viscosity coefficient when compared with the SA gel alone. Moreover, the N values of the HVSA-MAS composite gels were more than unity, suggesting that MAS could shift the flow of the HVSA gels from Newtonian to pseudoplastic. However, the flow type of LVSA gels did not change despite incorporating MAS. Furthermore, increasing the amount of MAS in the composite gels did not obviously affect the N value, and the viscosity coefficients decreased with increasing ratios of MAS to SA.

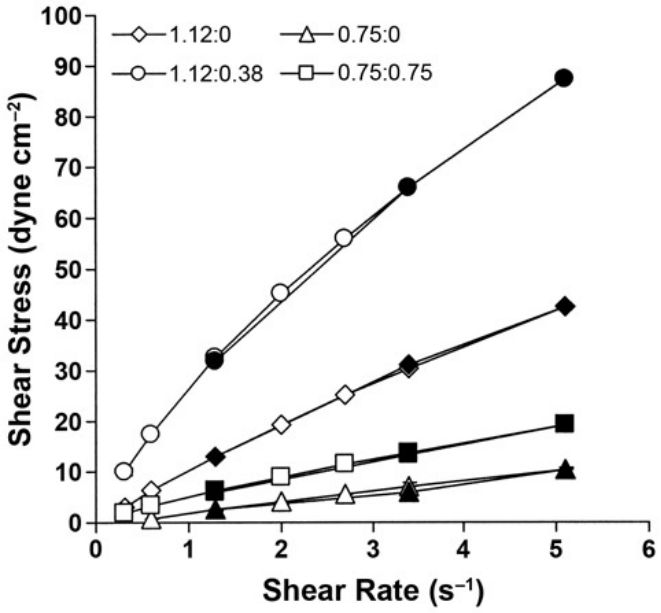

Figure 2. Flow curve of HVSA gel and HVSA–magnesium aluminum silicate composite gels. Open symbols represent the up-curve, and closed symbols represent the down-curve. Each point is the mean ± SD, n = 3. HVSA indicates high-viscosity sodium alginate.

Table 1. Flow Parameters of HVSA and HVSA-MAS Composite Gels*

HVSA Gel			Composite Gel		
Concentration (% wt/wt)	N	Viscosity Coefficient ([dyne cm^{-2}]^N s)	HVSA:MAS (g:g)	N	Viscosity Coefficient ([dyne cm^{-2}]^N s)
1.50	1.29 ± 0.02	129.2 ± 10.1	1.5:0	1.29 ± 0.02	129.2 ± 10.1
1.12	1.04 ± 0.01	10.52 ± 0.42	1.12:0.38	1.29 ± 0.04	67.21 ± 11.41
0.75	0.94 ± 0.01	1.81 ± 0.05	0.75:0.75	1.22 ± 0.08	7.37 ± 1.56
0.38	0.78 ± 0.12	0.31 ± 0.01	0.38:1.12	1.13 ± 0.08	1.15 ± 0.11
			0:1.5	—	—

*HVSA indicates high-viscosity sodium alginate; MAS, magnesium aluminum silicate; —, not determined. Data are mean ± SD, n = 3.

The flow characteristics of 1% wt/wt SA gels incorporating various amounts of MAS and 1% wt/wt DS were also investigated in this study. The relationships between shear rate and apparent viscosity of the composite gels are shown in Figure 3. It can be seen that the apparent viscosity at a low shear rate was higher than that at a high shear rate when a higher content of MAS was incorporated into the SA gels. This indicated pseudoplastic behavior of the composite gels, which was not necessary to calculate the N values in Equation 2 for defining this flow behavior. This result was similar to that found in the previous report.[12] The greater the content of MAS, the higher the apparent viscosity of the composite gels, although MAS dispersion in a concentration of 1.5% wt/wt could not be determined because it had very low viscosity. Furthermore, the area of hysteresis loop between the up-curve and the down-curve of the flow curve of the composite gels is shown in Figure 4. The area of hysteresis loop increased with an increasing content of MAS. This suggested that MAS could improve the thixotropic properties of the SA gels.

The interaction between SA and MAS in dry composite was investigated by using FTIR spectroscopy. FTIR spectra of SA showed the stretching peaks of OH, COO^- (symmetric), and COO^- (asymmetric) at around 3430 to 3432, 1607 to 1610, and 1416 to 1417 cm^{-1}, respectively (Figure 5).[17] Similar spectra were obtained from both types of SA. Incorporation of MAS caused a shift to a higher wavenumber and decreased the intensity of both COO^- stretching peaks of SA, which was similar to that of a previous study.[18] The negative charge of the carboxyl groups may have had an electrostatic interaction with the positively charged sites at the edges of MAS. It can be also observed that the LVSA-MAS composite provided a higher shift of COO^- stretching peaks than the HVSA-MAS composite did, suggesting that a stronger interaction occurred between LVSA and MAS than between HVSA and MAS. Moreover, the OH stretching peak of the silanol group (SiOH) at 3632 cm^{-1} disappeared in the spectra of SA-MAS composites, and the OH stretching peak of SA shifted to a higher wavenumber. Intermolecular hydrogen bonding could be created between silanol groups on the surface of MAS and the hydroxyl or carboxyl groups of SA. The silanol groups have a hydrogen bonding potential with some substances.[19] With these results, the bond formation of SA and MAS in the dry state could be used to predict the matrix structure of SA-MAS composite gels, even though the structure in the dry state may not be a true representation of the hydrated state and the structure of the hydrated gels can change during the drying process. However, intermolecular hydrogen bonding and electrostatic forces between SA and MAS that were confirmed by FTIR studies were obviously created in the hydrated state because of the change of flow properties of SA gels from Newtonian to pseudoplastic with thixotropy when MAS was incorporated.

The possible structure model of the SA-MAS composite gels is in Figure 6. The SA molecules possessed a negative charge due to ionization of the carboxyl groups and could form intermolecular hydrogen bonds with themselves (Figure 6a), whereas the silicate layer of MAS might not have created a

Table 2. Flow Parameters of LVSA and LVSA-MAS Composite Gels*

LVSA Gel			Composite Gel		
Concentration (% wt/wt)	N	Viscosity Coefficient ([dyne cm^{-2}]^N s)	LVSA:MAS (g: g)	N	Viscosity Coefficient ([dyne cm^{-2}]^N s)
1.50	0.90 ± 0.02	0.39 ± 0.02	1.5:0	0.90 ± 0.02	0.39 ± 0.02
1.12	0.78 ± 0.06	0.16 ± 0.02	1.12:0.38	0.93 ± 0.05	0.27 ± 0.02
0.75	0.78 ± 0.02	0.08 ± 0.01	0.75:0.75	1.07 ± 0.08	0.20 ± 0.02
0.38	—	—	0.38:1.12	0.83 ± 0.06	0.08 ± 0.01
			0:1.5	—	—

*LVSA indicates low-viscosity sodium alginate; MAS, magnesium aluminum silicate; —, not determined. Data are mean ± SD, n = 3.

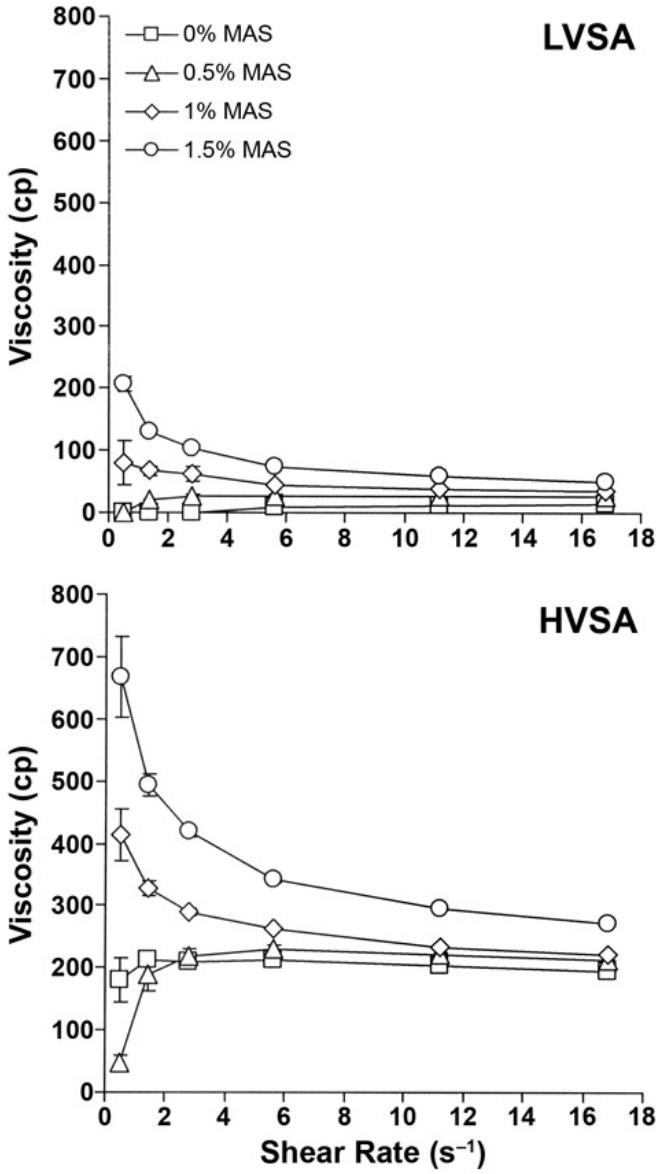

Figure 3. Apparent viscosity of LVSA-MAS and HVSA-MAS composite gels containing diclofenac sodium at various shear rates. Each point is mean ± SD, n = 3. MAS indicates magnesium aluminum silicate; LVSA, low-viscosity sodium alginate; HVSA, high-viscosity sodium alginate.

3-dimensional network because a low concentration of MAS was used (Figure 6b).[20] The structure model of the SA-MAS composite gel is presented in Figure 6c. It can be seen that SA and MAS formed electrostatic and intermolecular hydrogen bonds, which brought about numerous points of contact to create a denser 3-dimensional network, and the composite gel had a more rigid structure. The higher the content of MAS, the denser the gel structure. The structure model presented in Figure 6c was likely that a cross-linking of SA could be formed by silicate layers of MAS. However, SA chains could also serve as a bridge between neighboring silicate layers[20] when a higher content of MAS was incorporated. In addition, the increase in viscosity of the HVSA-

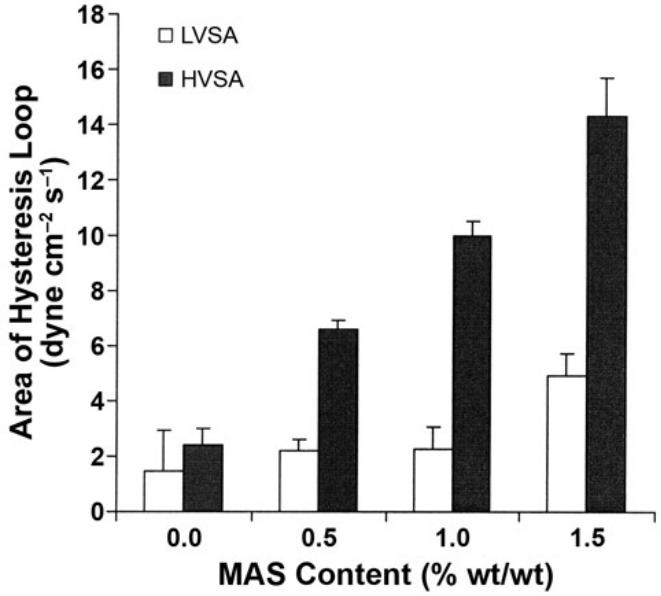

Figure 4. Hysteresis loop area of flow curve of composite gels containing diclofenac sodium. Each point is mean ± SD, n = 3. LVSA indicates low-viscosity sodium alginate; HVSA, high-viscosity sodium alginate; MAS, magnesium aluminum silicate.

MAS composite gels was higher than that of the LVSA-MAS composite gels because longer linear molecules of HVSA could be cross-linked with MAS at several points. This led to a denser gel matrix. However, LVSA gels had a lower

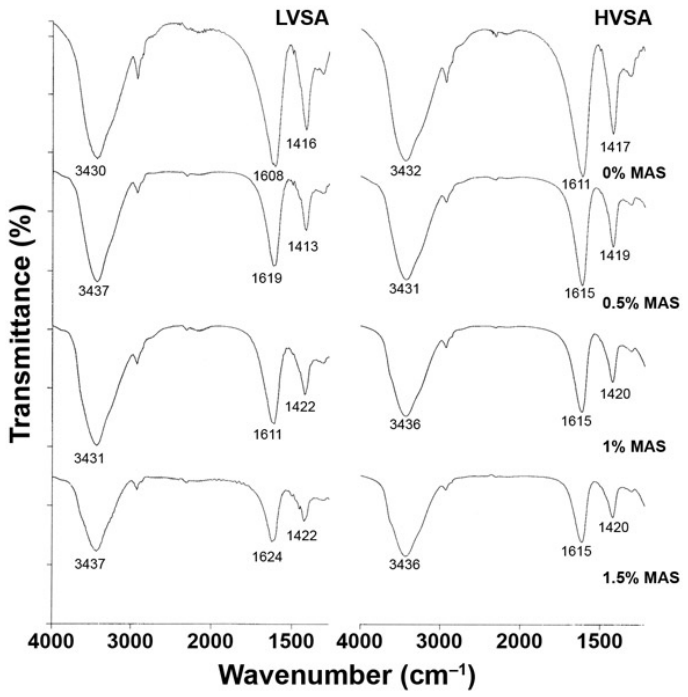

Figure 5. FTIR spectra of LVSA-MAS and HVSA-MAS composites containing various amounts of MAS. LVSA indicates low-viscosity sodium alginate; HVSA, high-viscosity sodium alginate; MAS, magnesium aluminum silicate.

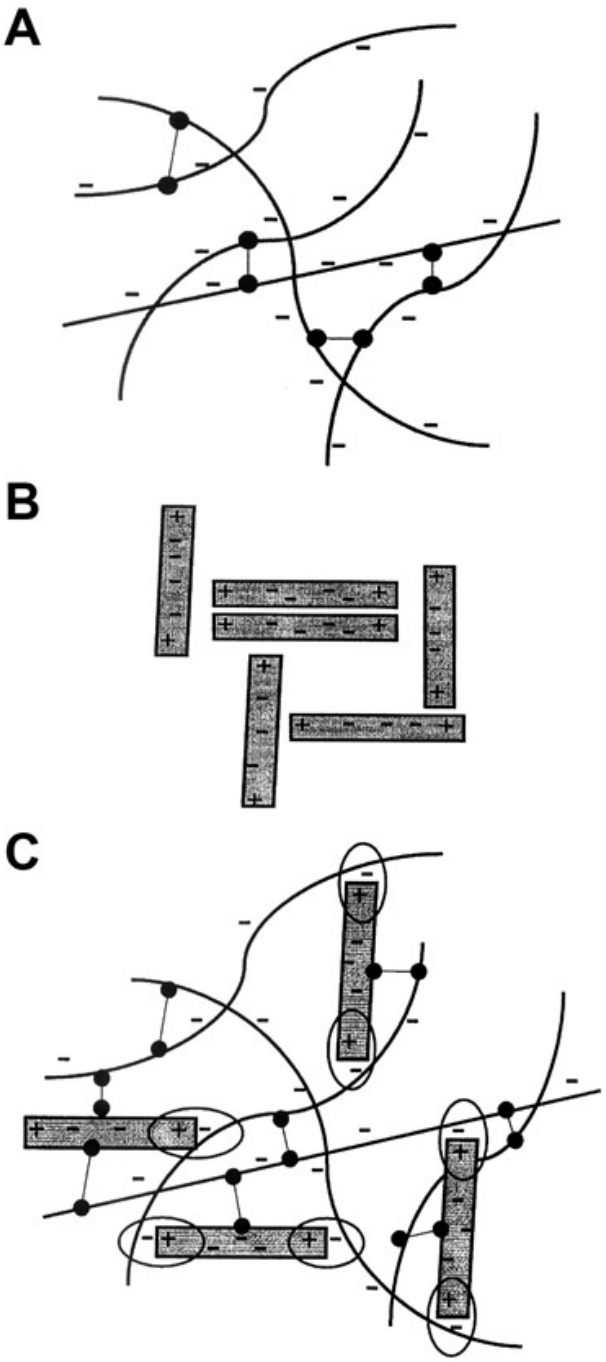

Figure 6. Possible structure model of (A) SA gel, (B) MAS dispersion, and (C) SA-MAS composite gel. •—• indicates intermolecular hydrogen bonding; ⬭, electrostatic interaction. SA indicates sodium alginate; MAS, magnesium aluminum silicate.

tortuosity of matrix structure than HVSA gels did, leading to a higher possibility of interaction between LVSA and MAS. This resulted in a stronger interaction, which caused a higher shift of carboxyl groups of LVSA in FTIR spectra. When shear stress was applied to the gels, some bonding bridges were broken down and then the 3-dimensional network structure was transformed into a sol structure. This characteristic was the pseudoplastic (shear thinning) property of the composite gels. After the shear stress was eventually removed, the structure started to return slowly to the initial state of the gels, which could be observed from the hysteresis loop area of the flow curves. This indicated that the composite gels had thixotropic properties that were dependent upon the content of MAS added.

Drug Diffusivity and Microviscosity of Gels

The release of DS from the gels through a cellulose acetate membrane showed first-order release kinetics (Figure 7). This suggested that the diffusion of drug through the membrane

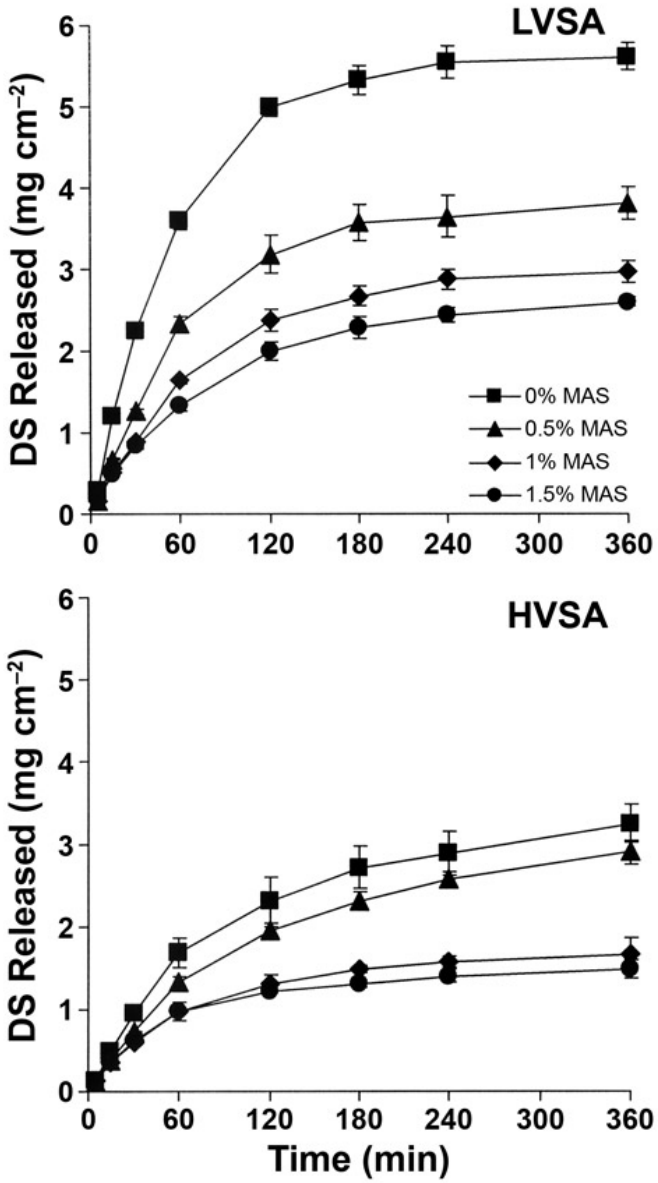

Figure 7. DS release profiles of LVSA-MAS and HVSA-MAS composites gels. Each point is the mean ± SD, n = 3. DS indicates diclofenac sodium; LVSA, low-viscosity sodium alginate; MAS, magnesium aluminum silicate; HVSA, high-viscosity sodium alginate.

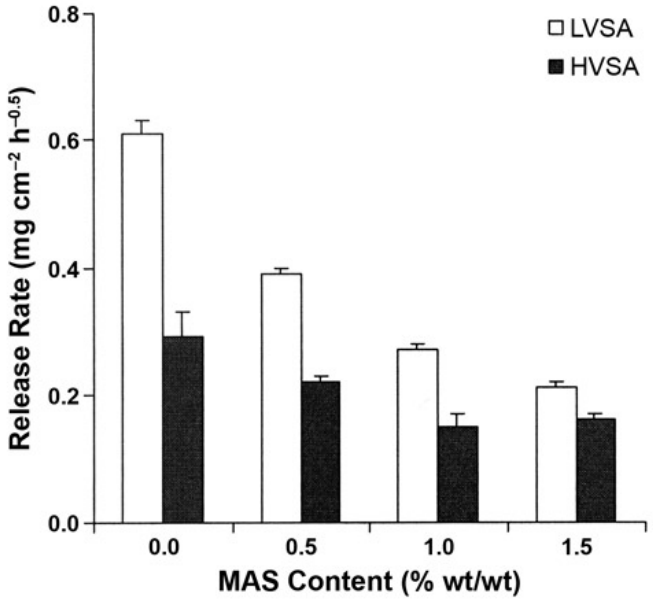

Figure 8. Release rate of diclofenac sodium from LVSA-MAS and HVSA-MAS composite gels. Each bar is mean ± SD, n = 3. LVSA indicates low-viscosity sodium alginate; HVSA, high-viscosity sodium alginate; MAS, magnesium aluminum silicate.

was not a rate-limiting step of the release of DS, but the diffusion in the gel matrix was. The cumulative DS released within 1 hour had a good relationship with the square root of time ($R^2 > 0.99$) when analyzed using linear regression analysis, indicating that the release of DS from the gels could be described using Equation 3. The slope of this relationship was the DS release rate. The LVSA-MAS composite gels had a higher DS release rate than the HVSA-MAS composite gels (Figure 8). The release rate of DS from LVSA-MAS and HVSA-MAS composite gels decreased with increasing content of MAS. Diffusivity (D) of DS in the gels and microviscosity of the gels are shown in Figure 9. Incorporation of MAS into the gels caused both a decrease in the D value of DS and an increase in the microviscosity of the gels. Moreover, the microviscosity calculated was remarkably lower than the apparent viscosity at low shear rate, which was measured using viscometer.

In a previous study, the DS released from SA and SA-MAS composite gels was analyzed using $T_{20\%}$ (time to achieve release of 20% of the DS content in the donor compartment),[12] whereas the DS release rate computed using the square root of time model was used in this study. The use of both parameters gave similar results about the effect of MAS on DS release. However, the DS diffusivity value could be estimated using the square root of time model, and that was an advantage of using this model. It can be seen that drug diffusivity of the composite gel was affected by the denser matrix structure created by interaction between SA and MAS. Lower drug diffusivity was obtained from the LVSA and HVSA composite gels with a higher content of MAS. The denser matrix structure had higher tortuosity, which resulted in slower drug diffusion through water-filled channels in the gels.

Generally, the apparent viscosity measured by viscometer is a true reflection of the resistance to molecular transport in solution. In dispersion of polymers the apparent viscosity does not necessarily represent the viscosity through which the solute molecules travel because the diffusion of solutes in the polymers normally occurs through the water-filled channels.[21,22] For this reason, a viscosity measured without the mechanical influence of a viscometer was considered. The Stokes-Einstein equation had been previously applied to estimate the microviscosity by using an experimental diffusivity

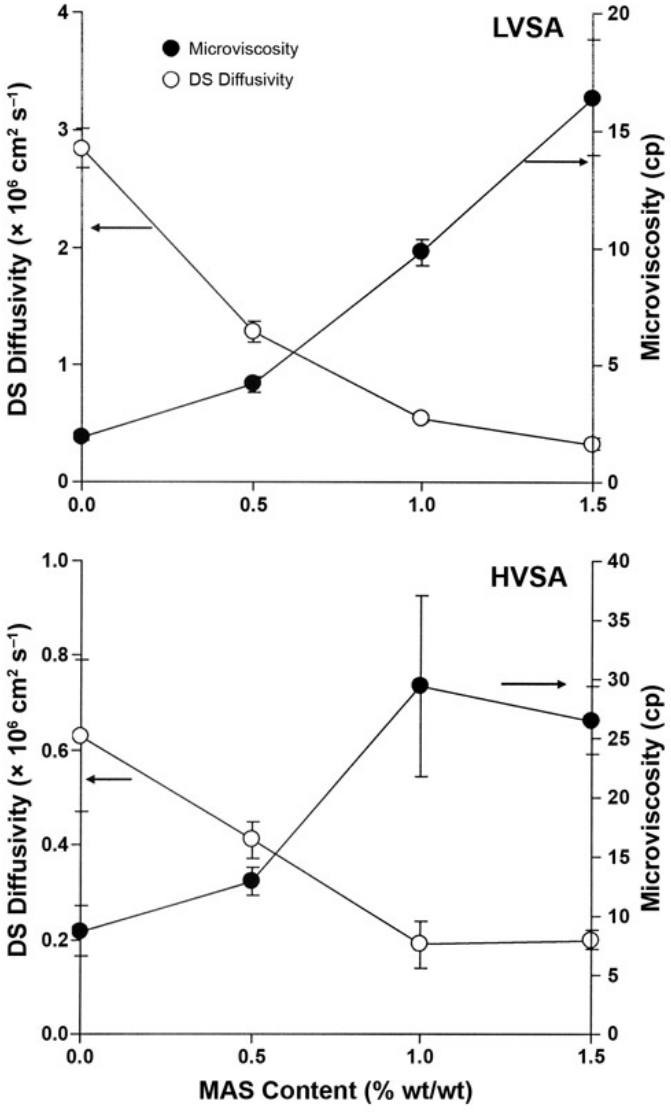

Figure 9. Relationship of apparent DS diffusivity and estimated microviscosity of LVSA-MAS and HVSA-MAS composites gels. Each point is mean ± SD, n = 3. LVSA indicates low-viscosity sodium alginate; HVSA, high-viscosity sodium alginate; MAS, magnesium aluminum silicate.

in polymer dispersions[23] and gels.[24] The microviscosity represented the viscosity of the entrapped aqueous phase in the polymer network that drug molecules diffused through. In this study, the microviscosity of the SA gels obviously increased when MAS was added. This indicated that the denser matrix structure formed by the interaction between SA and MAS could increase the viscosity of the microenvironment aqueous phase of the composite gels, which was likely to provide higher tortuosity of the water-filled channel in the gel matrix.

CONCLUSION

Incorporation of MAS into the SA gels increased the viscosity and shifted the flow behavior from Newtonian to pseudoplastic with thixotropy. This was because of the formation of electrostatic force and intermolecular hydrogen bonding between SA and MAS. The increase of MAS content in the SA gels decreased drug diffusivity in the gels but increased the microviscosity of the water-filled channel of the gels. Thus, incorporating MAS into the SA gels could improve the flow behavior and sustain drug release from the gels.

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