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Research Article

Rheological Characterization of Cataplasm Bases Composed of Cross-Linked Partially Neutralized Polyacrylate Hydrogel

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Abstract. Viscoelasticity is a useful parameter for characterizing the intrinsic properties of the cross-linked polyacrylate hydrogel used in cataplasm bases. The aim of this study was to investigate the effects of various formulation parameters on the rheological characteristics of polyacrylate hydrogel. The hydrogel layers were formed using a partially neutralized polyacrylate (Viscomate™), which contained acrylic acid and sodium acrylate in different copolymerization ratios, as the cross-linked gel framework. Dihydroxyaluminum aminoacetate (DAAA), which produces aluminum ions, was used as the cross-linking agent. Rheological analyses were performed using a "stress amplitude sweep" and a "frequency sweep". The results showed that greater amounts of acrylic acid in the structure of Viscomate as well as higher concentrations of DAAA and Viscomate led to an increase in the elastic modulus (G'). However, greater amounts of acrylic acid in the structure of Viscomate and higher concentrations of DAAA had an opposite on the viscous modulus (G''); this might be owing to higher steric hindrance. The results of this study can serve as guidelines for the optimization of formulations for cataplasms.

KEY WORDS: cataplasm; hardness; rheology; viscoelasticity.

INTRODUCTION

Cataplasms, which were first used in Japan, are also employed in the field of traditional Chinese medicine to transform traditional dosage forms such as plaster into modern topical ones. Cataplasms have a number of advantages over other topical dosage forms. They allow for a high degree of drug loading, exhibit good skin compliance, and do not require organic solvents. In particular, their high moisture content helps keep the skin moisturized and irritation free. Modern cataplasms consist of adhesive polymers, that is, a hydrogel layer containing the drug, a piece of unwoven cloth as the backing material, and a release liner. The hydrogel layer plays an important part in determining the adhesion of the cataplasm as well as its drug release and transdermal characteristics. In the past, the hydrogel layer had mainly consisted of non-cross-linked hydrophilic polymers. Lately, cross-linked bases are finding wide application in cataplasms owing to their simple formulation and ease of preparation.

Partially neutralized polyacrylates containing acrylic acid and sodium acrylate in varying copolymerization ratios (Fig. 1) are the most commonly used hydrogel materials. Their cross-linking mechanism involves two steps. First, the aluminum ion provider (usually in the form of dihydroxyaluminum aminoacetate (DAAA)) is dissolved slowly by adding tartaric acid (TA). Then, the released aluminum ions cross-link with the sodium acrylate in the structure of the partially neutralized polyacrylate (1). A scheme of the cross-linking process is shown in Fig. 2. The apparent adhesion and hardness are the parameters most commonly used to characterize the performance of cataplasms. However, there have been few studies on the rheological properties of cataplasms. Viscoelasticity is a fundamental characteristic of cross-linked hydrogels. The viscoelasticity of hydrogels affects their ability to mix with other materials and the extent to which they can be stirred or used as coatings, as well as their ability to release drugs *in vitro* (2). In particular, viscoelasticity has a significant effect on the adhesion, both in terms of strength and duration, of cross-linked gels with respect to skin. Rheological characterization methods have many advantages over other testing techniques, such as simple sample preparation, short testing times, and the ability to study polymer behavior directly during formulation processing, product storage, or use (3).

The rheological characteristics of a material can be accessed on the basis of a variety of parameters such as the complex modulus (G^*), the elastic modulus (G'), the viscous modulus (G''), and the phase angle (δ). The elastic modulus, which is also called the storage modulus, represents the elastic storage of energy and describes the "solid-like" character of the material. A higher G' value would enable the cataplasm base to exhibit greater cohesion, allowing it to be peeled off with ease without leaving a residue, thus preventing clothing from becoming contaminated. The elastic modulus can also

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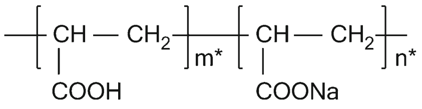

$$-\!\!\left[\underset{\text{COOH}}{\text{CH}}-\text{CH}_2\right]_{m^*}\!\!\left[\underset{\text{COONa}}{\text{CH}}-\text{CH}_2\right]_{n^*}\!\!-$$

* Copolymerization ratio (m/n) = 65/35 to 30/70 (mole ratio)

Fig. 1. Chemical structure of Viscomate

explain the phenomenon of “cold flow”, which is often noticed during the storage of cataplasms. The viscous modulus, which is also called the loss modulus, represents the loss or dissipation of viscous energy and describes the “liquid-like” character of the material. It is associated with the tack of the material; a high G'' value would enable the base to flow to a sufficient degree to promote close contact between itself and the skin. Finally, the complex modulus and phase angle are used to determine the degree of elasticity of a cataplasm.

Given the importance of the rheological characteristics of cataplasm bases, a comprehensive study of these characteristics was necessary. For illustrative purposes, we also considered the hardness, which is a commonly used parameter for testing gel strength. In addition, it is important to determine the relationship between the hardness and rheological parameters. Thus, the overall aim of the study was to investigate the effects that the basic formulation parameters have on the rheological characteristics of cataplasm bases, including those of the different grades and concentrations of Viscomate as well as the different concentrations of DAAA. We also aimed to determine the factors that would result in the optimal cataplasm formulation.

MATERIALS AND METHODS

Materials

Three grades of partially neutralized polyacrylates, marketed under the Viscomat ™ brand name, namely, NP 800, NP 700, and NP 600, were used in the study. The compounds were obtained from Showa Denko KK (Kawasaki, Japan). As shown in Table I, the acrylic acid/sodium acrylate copolymerization ratios for NP 800, NP 700, and NP 600 were 65:35, 50:50, and 30:70, respectively. Purified water was obtained from a Milli-Q ultrapure water system (Millipore Corp., Billerica, MA, USA). DAAA, TA, and glycerin were purchased from Sinopharm Chemical Reagent Co., Ltd (Shanghai, China).

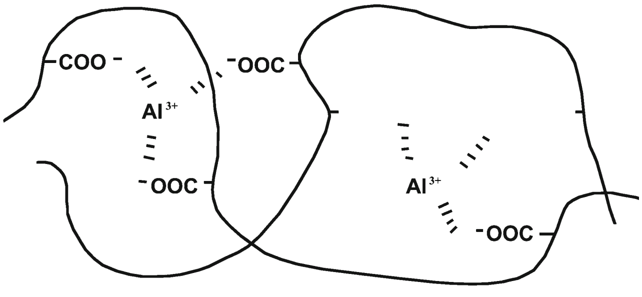

Fig. 2. Cross-linking of Viscomate and Al^{3+} ions (each Al^{3+} ion cross-links with 3 ROO^- groups)

Preparation of Formulations

Through a trial experiment, we found that, when the Viscomate concentration was less than 6% (*w*/*w*), the base formed was too soft for rheological testing. On the other hand, when it was greater than 10% (*w*/*w*), the base agglomerated and was not fit for use as a coating. Thus, we chose a Viscomate concentration in the range of 6 to 10% (*w*/*w*) for the study. For the same reason, the DAAA concentration was limited to 0.2 to 0.4% (*w*/*w*). TA and DAAA were used in the same concentrations in all the formulations. To prepare the formulations, first, TA was dissolved in purified water to form aqueous tartaric acid solutions. Then, Viscomate and DAAA were dispersed uniformly in glycerin, and the aqueous tartaric acid solution was added to the mixture while it was stirred gently. The mixture was stirred for approximately 5 min until the hydrogel base was formed. Finally, a portion of the base was coated between two polypropylene release liners (Wen Zhou Hui Cheng Plastics Film Factory, Zhejiang, China) using a laboratory coater (TB-0612B, Shanghai KaiKai Science and Technology Company, Shanghai, China). The sample was then cut and sealed for use in the rheological measurements. The remaining base sample was placed in a 50 ml clear plastic bottle and used for the hardness test. All the test samples were stored at room temperature for 3 days prior to the tests.

Hardness Test

The hardness was evaluated using a TA.XTplus texture analyzer (Stable Micro Systems, Haslemere, UK) in the texture profile analysis (TPA) mode. A measurement probe (diameter of 12.7 mm) was compressed twice into each sample to a depth of 15 mm at a rate of 300 mm s^{-1}; there was a 10-s delay between the compressions.

Rheological Tests

The rheological characteristics of the cataplasm bases were investigated using a Bohlin Gemini™ advanced rheometer (Malvern Instruments, Malvern, UK). A stainless steel parallel plate with a diameter of 20 mm and a gap size of 1,000 μm was used during the tests. All the tests were performed at 25°C in the oscillation mode.

Stress Amplitude Sweep

The linear viscoelastic regions (LVRs) of the test samples were determined using a stress amplitude sweep, wherein a range of incremental shear stresses (0–500 Pa) were applied on the samples at a constant frequency (1 Hz) and temperature (25°C). Within the LVR, the magnitude of G^* is constant with respect to the stress amplitude (4), and the shear stress (σ) is proportional to the shear strain (γ).

Frequency Sweep

The samples were subjected to a monitored shear stress (50 Pa) over a range of frequencies (0.016 to 16 Hz) within their respective LVR at a constant temperature (25°C). The master curves were obtained by recording the dynamic moduli (G' and G'') and δ as functions of the frequency for values

Table I. Properties of Different Grades of Viscomate

	NP 600	NP 700	NP 800
pH (0.2% aq. solution)	7.2	6.5	5.9
Viscosity (0.2% aq. solution)	500–600 mPa s	500–650 mPa s	Approx. 600 mPa s
Acrylic acid (%)	30	50	65
Sodium acrylate (%)	70	50	35

between 0.016 and 16 Hz. The different parameters were used to define the rheological characteristics of the samples and to determine whether their structures corresponded to that of a gel from a rheological viewpoint (5).

Swelling Tests

To determine the cross-linking densities of the cataplasm bases, we performed swelling tests on the bases. Cataplasm bases formed with different DAAA concentrations (0.2, 0.3, and 0.4% (*w*/*w*)) were cut into squares with dimensions of 50× 50 mm. These squares were soaked in purified water at 25°C for 8 h. Next, the squares were removed from the water and hung in the air for 10 min to drain out the excess water. The swelling ratio was calculated as follows.

$$\text{Swelling ratio } (\%) = \frac{m_{\mathrm{f}} - m_{\mathrm{i}}}{m_{\mathrm{i}}}$$

where m_{f} is the mass of the square after it has been soaked in water and the excess water has been removed from it and m_{i} is the initial mass of the square before soaking.

Statistical Analyses

The effects of the different grades and concentrations of Viscomate on the values of the hardness and the measured rheological parameters were statistically evaluated using one-way analysis of variance (ANOVA). The effects of the different DAAA concentrations on the hardness and rheological parameters were also statistically evaluated using one-way analysis of variance (ANOVA). Values of $p<0.05$ were considered significant in all the statistical comparisons.

RESULTS

Hardness Testing

The effects of the different grades and concentrations of Viscomate on the hardness of the cataplasm bases are shown in Table II. A significant difference was observed between all the grades when they were used in the same concentration. The hardness values corresponding to the three grades of Viscomate at the same concentration could be arranged in the following order: NP 600<NP 700<NP 800. For all the grades, the gel hardness increased with an increase in concentration. For instance, in the case of NP 700, the effect of the DAAA concentration on hardness was investigated; the results are shown in Table II. When the NP 700 concentration was kept constant at 8% (*w*/*w*), the gel hardness increased with an increase in the DAAA concentration.

Rheological Testing

The position and length of the LVR indicate the ability of the sample to resist flow as well as its stability over a range of stresses (6). When the stress was greater than the LVR, the G^* values for all the grades decreased significantly, indicating that structures formed had been destroyed, resulting in decreased stability. The LVRs for the different grades of Viscomate are displayed in Fig. 3. The LVRs of NP 800, NP 700, and NP 600

Table II. Effects of Different Grades of Viscomate as well as Different Viscomate and DAAA Concentrations on the Hardness and Viscoelasticity Characteristics of the Cataplasm Bases at 1 Hz

Viscomate grade	Viscomate (%,*w*/*w*)	DAAA (%,*w*/*w*)	Hardness (*N*)	G' (Pa)	G'' (Pa)	δ (°)
NP 600	6	0.3	0.7	384.9	88.7	13.0
	8	0.3	1.2	550.6	114.1	11.7
	10	0.3	2.0	1080.0	156.8	8.3
NP 700	6	0.3	1.2	496.2	62.3	7.2
	8	0.2	1.6	778.8	118.4	8.6
	8	0.3	2.0	894.0	82.4	5.3
	8	0.4	2.3	1214.0	46.1	2.2
	10	0.3	3.8	1844.0	91.9	2.9
NP 800	6	0.3	1.9	815.9	34.8	2.5
	8	0.3	3.2	1457.0	44.1	1.7
	10	0.3	4.1	3326.0	58.9	1.0

The data exhibited a minor standard deviation. Hence, only the mean values are shown (n=4). TA and DAAA were used at the same concentrations in all the formulations

DAAA dihydroxyaluminum aminoacetate, *NP* partially neutralized polyacrylate

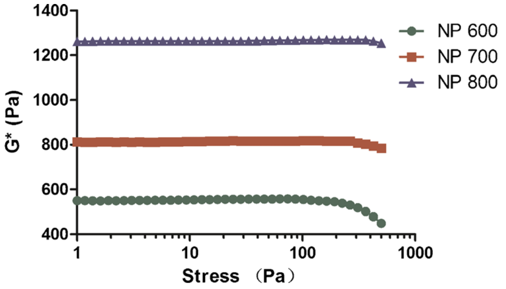

Fig. 3. *G** as a function of stress for the different grades of Viscomate (concentration of 8% (*w*/*w*)). *Each point* represents a mean value (n=4)

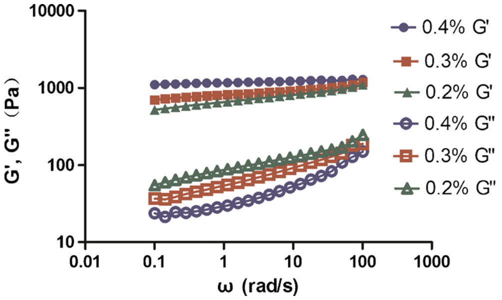

Fig. 5. G' and G'' as a function of frequency for different DAAA concentrations. The grade NP700 (concentration of 8% (*w*/*w*)) was used in this case. *Each point* represents a mean value (n=4)

corresponded to stress ranges of 1 to 430 Pa, 1 to 330 Pa, and 1 to 110 Pa, respectively. The LVRs also could be determined from the fact that the shear stress (σ) is proportional to the shear strain (γ). The stress tolerance range of NP 600 was only approximately one-third of that of NP 700 and a quarter of that of NP 800. The G^* values of the three grades can also be seen in Fig. 3; the G^* values could be arranged in the following order: NP 600<NP 700<NP 800.

The G' and G'' values corresponding to the three grades of Viscomate (8% (*w*/*w*)) are displayed in Fig. 4; the samples were subjected to a stress of 50 Pa. Both the G' and the G'' values increased with an increase in the frequency. This was true for all the three grades. Significant differences were noticed in the G' and G'' values for the three grades. It was found that G' was higher than G'' for the entire range of frequencies investigated; this reflects the intrinsic elastic nature of the cross-linked gels. The G' values for the three grades could be arranged in the following order: NP 600<NP 700<NP 800. However, the G'' values exhibited an opposite trend to that observed in the case of the G' values.

For each grade of Viscomate, concentrations of 6, 8, and 10% (*w*/*w*) were used for determining the G' and G'' values; the concentration of DAAA was set at 0.3%. The results corresponding to a frequency of 1 Hz are shown in Table II. It was found that increasing the concentration of Viscomate increased the G' value; the increase was greater for a change in concentration from 8.0 to 10.0% (*w*/*w*) than from 6.0 to 8.0% (*w*/*w*). Similarly, increasing the concentration of Viscomate led to an increase in G'' as well.

The cross-linking agents DAAA and TA are commonly used together because they result in moderately dense, stable cross-links at a desirable rate. Aluminum ions are released from DAAA under the acidic conditions produced by TA. The changes in the viscoelasticity of the three grades of Viscomate were similar for increases in the DAAA concentration. Representative plots of the variations in G' and G'' with the concentration of DAAA for a given NP 700 concentration (8% (*w*/*w*)) are displayed in Fig. 5. The corresponding values are listed in Table II; the frequency used was 1 Hz. Both G' and G'' increased with an increase in the frequency. However, for the same increase in frequency, the increase in G' was always much greater than that in G''. This behavior was similar to that of an ideal gel. The increase in G' was less pronounced for an increase in the DAAA concentration from 0.2 to 0.3% (*w*/*w*) than it was for an increase from 0.3 to 0.4% (*w*/*w*). Further, in contrast to what was noticed in the case of G', increasing the concentration of DAAA reduced G'' (see Fig. 5). The swelling ratios of the cataplasm bases are shown in Fig. 6. It was found that increasing the concentration of DAAA reduced the swelling ratio. Hence, increasing the DAAA concentration increased the cross-linking density, which led to a decrease in the swelling capacity.

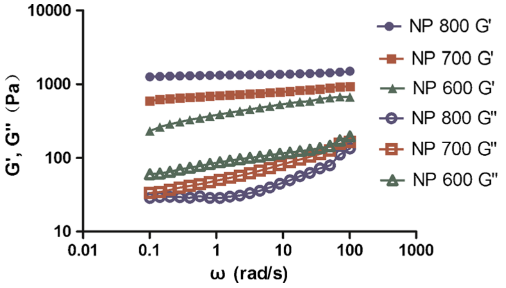

Fig. 4. G' and G'' as a function of frequency for the different grades of Viscomate (concentration of 8% (*w*/*w*)). *Each point* represents a mean value (n=4)

Representative plots of δ for a given Viscomate concentration (8% (*w*/*w*)) and DAAA concentration (0.3% (*w*/*w*)) are displayed in Fig. 7. As can be seen from Table II and Fig. 7, when the concentrations were the same, the values of δ corresponding to the three grades of Viscomate could be arranged in the following order: NP 800<NP 700<NP 600. The loss tangent (tan δ) is described as the ratio of the energy

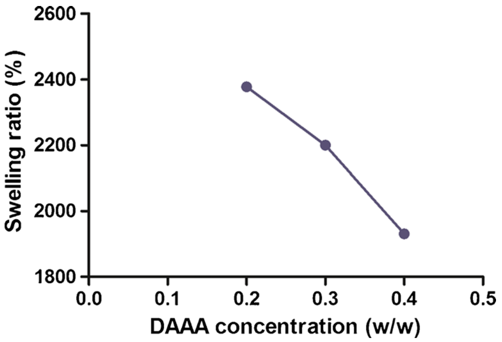

Fig. 6. Swelling ratio as a function of DAAA concentration. The grade NP700 (concentration of 8% (*w*/*w*)) was used in this case. *Each point* represents a mean value (n=4)

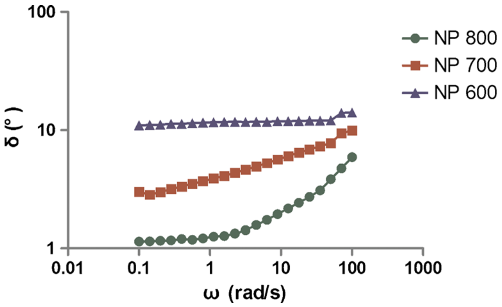

Fig. 7. δ as a function of frequency for the different grades of Viscomate (concentration of 8% (*w*/*w*)). *Each point* represents a mean value (n=4)

lost (G'') to the energy stored (G') during an oscillatory cycle (tan $\delta = G''/G'$) (7). The values of tan δ were less than 1.0 for all the formulations. In addition, with an increase in the concentrations of Viscomate and DAAA, δ decreased.

DISCUSSION

It is necessary to define the LVR in order to be able to make measurements at fixed stress amplitude (that lies within the LVR) for different frequencies (8). The length of the LVR also reflects the stability of the base. In general, the lower the LVR was, the more likely the cataplasm base was to fracture over a range of stresses (4), indicating its internal structure had been destroyed. In the case of the three grades, the length of the LVR for NP 600 was only one-third of that of NP 700 and one-fourth of that of NP 800; this indicated that its structure was especially fragile and would perhaps have an effect on its degree of drug loading. That the stress tolerance of NP 800 was the highest indicated that it had the highest degree of cross-linking and was the best suited for drug loading. Accordingly, the values of G^* could be arranged in the same order as the LVRs: NP 600<NP 700<NP 800. Keeping the LVRs of the three grades of Viscomate in mind, we chose a stress of 50 Pa (a value that lay within the LVRs) for the frequency sweeps.

The results of the ANOVA of the G', G'', and tan δ values revealed that there were significant differences between all the formulations. It can be seen in Fig. 4 that the curve did not obey the Maxwell model, which reflects the viscous nature of polymer solutions at low frequencies. For the entire range of frequencies investigated, G' was much higher than G''. This reflects the intrinsic elasticity of the polyacrylate gels, which had been cross-linked with Al^{3+} ions. The G' value is a measure of the "solid-like" nature of the base. Hardness can be defined as the force necessary to produce a given deformation (9). Thus, both G' and hardness reflect the degree of cross-linking of the base and generally exhibit the same behavior. The G' values of the three grades could be arranged in the following order: NP 600<NP 700<NP 800; this order is the same as that for the hardness values. Generally, differences in the rheological characteristics of hydrogels can be attributed to differences in the molecular structures of the constituent polymers, as these result in differences in the nature and strength of polymer interactions (10). However, the manufacturer of Viscomate provides only limited information related to the properties of the material; this information is listed in Table I. NP 800 contained acrylic acid in the highest copolymerization ratio, which was 65 mol%, and exhibited a pH of 5.9, a value much lower than those of NP 600 (pH of 7.2) and NP 700 (pH of 6.5). As mentioned in the introduction, the cross-linking mechanism relies on the free Al^{3+} ions cross-linking with sodium acrylate in the structure of Viscomate. It is assumed that the OH group provided by an organic acid and the carboxylic acid provided by Viscomate act cooperatively to gradually dissolve the sparingly soluble aluminum salt in the system. NP 800 has a lower pH value, resulting in a low-pH environment, which may cause a greater number of Al^{3+} ions to be released for cross-linking with the carboxylate (1). The same phenomenon also could explain why NP 800 exhibited the highest G^* and hardness values. A base with a high G' value would obviously be able to bear a greater quantity of drugs, such as medicine extracts, while maintaining good cohesion with the skin. It would also not be subjected to the phenomenon of "cold flow", which often occurs during the storage of cataplasms.

The G'' value is a measure of the "liquid-like" nature of the base. Theoretically, the higher the copolymerization ratio in which acrylic acid is present, the greater should be the affinity of the base with respect to the skin, because the acrylic acid in the polymer structure promotes close contact between itself and the skin (11). NP 800 contained acrylic acid in the highest copolymerization ratio (65 mol%), and exhibited the lowest G'' value of the three grades (as can be seen from Fig. 4). This might be because NP 800 generates a larger cohesive force, resulting in a higher cross-linking density. As a result, there is greater steric hindrance, and the acrylic acid on the "outside" cannot interact readily with the skin (12). Although NP 600 contained acrylic acid in the lowest copolymerization ratio (30 mol%), it had the highest G'' value; this may have been because, in this case, the acrylic acid was fully in contact with the skin, owing to the weak structure of the grade.

As mentioned previously, on the basis of a trial experiment, we chose a Viscomate concentration of 6 to 10% (*w*/*w*) in this study to investigate the effects of the concentration on the G' and G'' values. We found that increasing the concentration of Viscomate increased G' and G''. It is known that cross-linking occurs owing to the formation of ionic bonds between the carboxyl groups of Viscomate and aluminum ions. Thus, it can be concluded that, as the number of Viscomate–aluminum cross-links increased, the density of the three-dimensional network formed also increased, resulting in an increase in the strength of the cataplasm base. The increase in G'' may also result from the presence of a greater amount of acrylic acid with the increase in the concentration of Viscomate.

Increasing the concentration of the cross-linking agent DAAA in the range of 0.2 to 0.4% (*w*/*w*) resulted in an increase in G' and a decrease in G''. Generally, the cross-linker concentration is directly related to the cross-link density of the resultant gel (13). The results of the swelling tests also confirmed that this was indeed the case. We found that, at lower DAAA concentrations, the cataplasm bases exhibited lower cross-linking densities and hence higher swelling capacities, whereas the cataplasm bases formed with higher DAAA concentrations had higher cross-linking densities and lower swelling capacities. It is likely that, as the concentration of

DAAA was increased, the rate and extent of release of aluminum ions also increased. As a result, a greater number of cross-links were formed, and the cross-link density increased, resulting in an increase in G'. However, increasing the concentration of DAAA reduced G''. It is suggested that, as the cross-link density increased with the increase in the concentration of DAAA, the steric hindrance also increased, impeding the acrylic acid on the "outside" from interacting readily with the skin (12).

Tan δ is a measure of the relative contributions of the elasticity and viscosity of a material (14). It is known that a tan δ value close to 1 is indicative of a more "liquid-like" behavior, whereas a value close to 0 means a more "solid-like" behavior (15). The values of tan δ were less than 1.0 for all the formulations. This showed that the resulting bases predominantly exhibited "solid-like" characteristics, with their elastic nature being dominant ($G' > G''$). This indicated that the samples had formed a continuous network-like structure, as is characteristic of a "strong" gel (16). We also performed stress-relaxation tests on the samples. The resulting relaxation modulus-time curves suggested that, after decaying rapidly in the beginning, the time-dependent relaxation modulus, $G(t)$, did not relax to a zero-stress state but reached an equilibrium state after a large period. This indicated that cross-linked polymers had been formed and that they exhibited viscoelastic solids. With regard to the fact that the cataplasm bases exhibited a predominantly "solid-like" character and lacked viscosity, this issue can be resolved by adding different tackifiers to the formulations to increase the G'' values of the resulting bases. This will be the focus of our next study.

CONCLUSION

The hydrogel layers of the cataplasm bases were found to have the characteristics of a "strong" gel. Their G' values increased with an increase in the amount of acrylic acid present in the cross-linked gel framework as well as with the concentration of DAAA and the density of the cross-linked gel framework. Their G'' values also increased with an increase in the density of the cross-linked gel framework. However, their G'' values decreased with an increase in the DAAA concentration as well as with the amount of acrylic acid in the cross-linked gel framework.

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