A Study of the Sol-Gel Transformation of Gelatin Solutions

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Gelatin has been universally used in such pharmaceutical preparations as capsules, tablets and injections. The physical properties of gelatin are important in the production of these pharmaceutical preparations. In recent years, the physical properties of gelatin solutions have been extensively investigated in the field of rheology[1,2], but reports of the sol-gel transformation have been limited to its lower concentrations. Since the productions of pharmaceutical preparations is carried out with gelatin solutions of the higher concentrations, data on the lower concentrations are not useful. Therefore, that sol-gel transformation which is considered to determine the physical nature of the pharmaceutical preparations produced was investigated.

In the study of this transformation, Bourgoin[3] has examined the viscosity and the double refraction of gelatin solutions of the lower concentrations. On the other hand, the method of measuring the solution with a 10% concentration has been described in JIS[4]. In the JIS method for measuring the sol-gel transformation, an apparatus (shown in Fig. 1) is used in which 50 cc. of a hot, 10% gelatin solution is put into an inside vessel. Immediately, the sample is gently stirred with a thermometer, and the flowing behavior of gelatin solution is observed with the naked eye; of the phenomena which the solution shows before the appearance of resistance, some rigidity is called the transformation temperature. The JIS method, however, based as it is on the observation of the human eye, is essentially

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[1] N. Hirata et al., *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zassi*), 74, 347, 441, 810 (1953).

[2] K. Nakamura, presented at the 15th Annual Meeting of the Chemical Society of Japan, Kyoto, April, 1962.

[3] D. Bourgoin et al., "Gelatin and Glue Research". London Pergamon Press (1958).

[4] JIS, K 6503.

inaccurate and is not applicable to solutions of the higher concentrations.

A new measuring method with a Macmichael viscometer is proposed for application to the solutions of necessarily higher concentrations in order to determine their transformation points. On the other hand, a co-axially oscillating rheometer is used for studying the behavior of the sol-gel transformation through the transformation temperature.

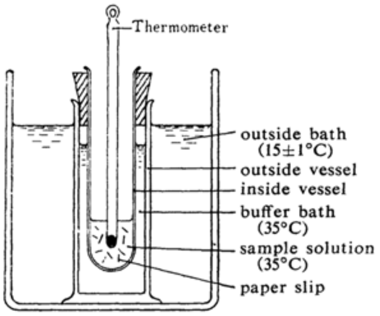

Fig. 1. The apparatus for measuring the transformation temperature. (JIS method).

Experimental

A Macmichael viscometer (I) was used for the observation of viscosity change at the sol-gel transformation, and a co-axially oscillating rheometer (II) was employed to follow the change of viscoelastic behavior through the sol-gel transformation.

Rheometer (I).—The sample was put into the gap between the co-axial internal and external cylinders. The diameters of the internal cylinder, d_1, and of the external cylinder, d_2, were 2.00 and 3.00 cm. respectively. The depth of the immersion of the internal cylinder was 4.00 cm., which was equal to the height of the cylinder. The viscosity is calculated from the following equation:

$$\eta_{\text{I}}=C\cdot(\theta/r) \tag{1}$$

where η_{I} is the apparent viscosity, θ is the angle of deflection of the internal cylinder in radian, r is the number of revolutions of the external cylinder (5 r. p. m.), and C is an instrumental constant, which is either 29.0 or 1.79. Both cylinders ware heated previously by circulating water at 52∼55°C and by putting the sample into the gap between the cylinders, where it was heated for about five minutes at 52∼55°C. Then, the sample was gradually cooled at the rate of 1°C per 5 min. and the viscosity was measured at various temperatures at 5 r. p. m.

Rheometer (II).—A top-drive co-axial rheometer which has previously been described by Nakagawa and Seno⁵⁾ was used. The sample was put into the gap between the cylinders. The radius of the internal cylinder, r_1, was 0.6 cm. and that of the external cylinder, r_2, was 0.9 cm. The depth, h, of the immersion of the internal cylinder was about 10 cm. The moment of inertia, I, of the internal cylinder and the wire chuck were 38.07 g. cm. The torsional constants of two wires determined from the period of the free torsional oscillation, $\bar{k}$, were 587.8 and 1313 dyn. cm. To the top of the wire a torsional oscillation was applied, and the oscillation of the internal cylinder was recorded on a paper. A Lissajous figure was obtained by combining perpendicularly the oscillation of the top of the wire and that of the internal cylinder. Since the Lissajous figure thus obtained was an ellipse, the dynamic viscosity, η_{II}, and the dynamic modulus, G, were calculated by the following equations:

$$\begin{aligned}\eta_{\text{II}}&=(R/4h)\cdot(1/r^2{}_1-1/r^2{}_2)\ \text{(poise)}\\ G&=(K/4h)\cdot(1/r^2{}_1-1/r^2{}_2)\ \text{(dyn./cm}^2\text{)}\end{aligned} \tag{2}$$

where R and K were the quantities to be determined experimentally by using the following equations:

$$R=\bar{k}\ T\ \sin\phi/2m \text{ and } K=\bar{k}\ (\cos\ \phi/m-1) + (4\pi^2{}_1/T^2) \tag{3}$$

Here, the lag angle, ϕ, and the amplitude ratio, m, were obtained by an analysis of the Lissajous' figure, and the period of oscillation, T, was 0.0286 cycl./sec.

Preparation of the Gelatin Solution.—The preparation of the gelatin solution has been generally described in JIS. but here the water content of the gelatin was changed to 16%. The gelatin was then dried for 5 hr. at 105∼115°C; after it (X) had been weighed accurately, the amount to be needed was calculated from "$X\times84/(100-y)$", with y indicating the water concent (%) of gelatin. After water had been added to the gelatin, the solution was kept at room temperature for half an hour in order for the gelatin to be completely swollen and then on a water bath at 55∼60°C for 1 hr. for the gelatin to be dissolved. This solution was used for the measurements.

Results and Discussion

The dependnce of the apparent viscosity on the temperature has been shown in Fig. 1. In this figure the sol-gel transformation is shown by a sudden increase in the apparent viscosity. The transformation temperatures obtained by this method are shown in Table I in comparison with the values obtained by the JIS method⁴⁾.

The transformation temperature obtained is higher by 1∼5°C than that of the JIS method, and the temperature rose with the concentration. The rates of the sol-gel transformation seemed to become slower with the increase in the concentration.

Differences in the behavior of various gelatins could not be observed definitely through the data of the sol-gel transformation. Therefore, the transformation was investigated by rheometer II. From the results of viscoelastic measurement, the dynamic viscosity, η_{II}, and

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5) T. Nakagawa and M. Seno, This Bulletin, **29**, 471 (1956).

TABLE I. APPARENT VISCOSITY AND SOL-GEL TRANSFORMATION TEMPERATURES OF GELATIN SOLUTION AT VARIOUS CONCENTRATIONS

Sample No.	Viscosity c. p.	JIS method	Sol-gel transformation temp. The present method			
		at 10%	10%	20%	30%	40%
1	22.5	26.4	27.6	30.0	33.3	37.9
2	20.5	24.9	26.8	28.8	32.0	36.5
3	15.4	22.0	25.3	28.2	31.4	34.9
4	21.7	24.2	25.0	28.1	31.4	34.5
5	19.3	22.3	24.6	27.1	30.3	32.8
6	13.4	20.9	24.2	26.9	30.5	33.8
7	19.7	23.8	24.0	27.8	31.3	35.8
8	23.7	23.3	22.4	25.6	28.2	30.4
9	10.7	18.8	19.4	23.1	25.6	28.3
10	23.0	25.7	27.2	29.7	32.5	37.8
11	22.4	25.3	26.4	29.5	32.2	37.3
12	17.5	23.6	24.5	29.0	31.4	35.0
13	15.0	22.0	24.1	26.4	29.1	32.0

the dynamic modulus, *G*, were calculated by Eq. 2; they are show in Figs. 3—6, where the change of η_{II} or *G* with time is plotted at several temperatures. Both η_{II} and *G* at the higher concentration rose rapidly in a shorter time than at the lower concentration at the same temperature.

Further, the kinetic procedure was employed in order to investigate what the nature of the transformation was from sol to gel. From the plot of the logarithm of η_{II} or *G* against time,

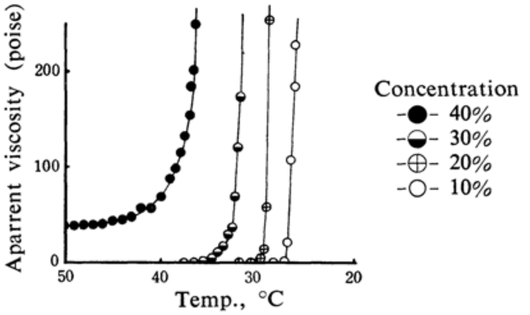

Fig. 2. Dependence of apparent viscosity on temperature.

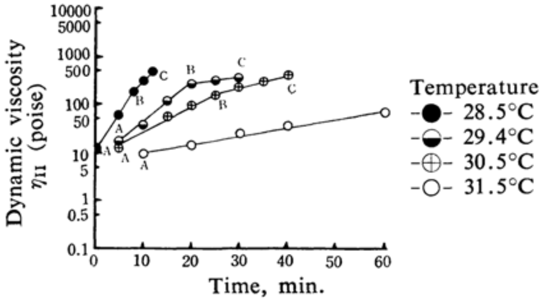

Fig. 3. The change of dynamic viscosity, η_{II}, with time at the concentration of 20%.

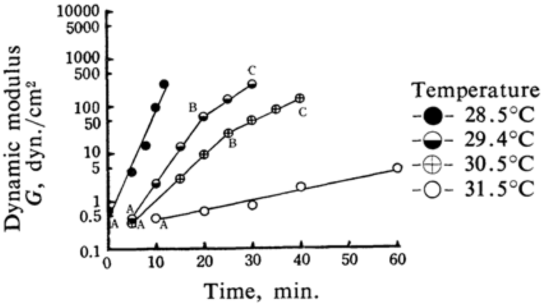

Fig. 4. The change of dynamic modulus, *G*, with time at the concentration of 20%.

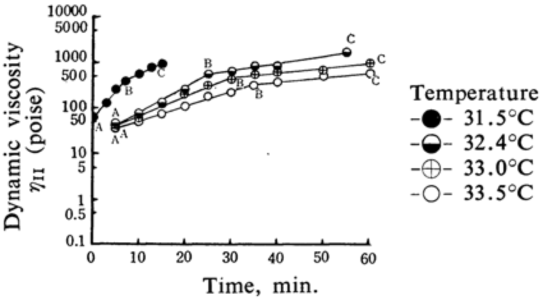

Fig. 5. The change of dynamic viscosity, η_{II}, with time at the concentration of 30%.

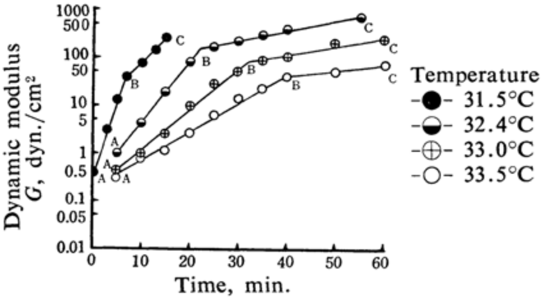

Fig. 6. The change of dynamic modulus, *G*, with time at the concentration of 30%.

two straight lines, AB and BC, crossing at B were obtained as Figs. 3—6 in most cases. The slope, k, of the initial line, AB, $\mathrm{d}\ln\eta_{\mathrm{II}}/\mathrm{d}t$ or $\mathrm{d}\ln G/\mathrm{d}t$, was calculated as shown in Table II. On the other hand, the slope, k', of the second line, BC, of the appearance at the 30% solution was calculated by the same method at the initial line, AB.

TABLE II. RELATIONSHIP OF THE INITIAL SLOPE, k, OF THE AB PERIOD TO THE TEMPERATURE

Concn. of sample %	Temp. °C	k	
		η_{II}	G
20	28.5	0.1336	0.2104
	29.4	0.0788	0.1343
	30.5	0.0567	0.0722
	31.5	0.0201	0.0212
30	31.5	0.1095	0.2769
	32.4	0.0490	0.1373
	33.0	0.0422	0.0890
	33.5	0.0326	0.0613

RELATIONSHIP OF THE SECOND SLOPE, k', OF THE BC PERIOD TO THE TEMPERATURE

Concn. of sample %	Temp. °C	k'	
		η_{II}	G
30	31.5	0.04204	0.09933
	32.4	0.02062	0.04027
	33.0	0.01151	0.01918
	33.5	0.00768	0.01148

The values of η_{II} or G at the point of B were lower at the higher temperature than at the lower temperature. The values of k', were lower than that of k. These results are probably due to the increased difficulty of the arrangement of the colloidal particles at the BC period than at the AB period.

Besides, log k was plotted against the inverse temperature, as in Fig. 7. The straight line was obtained within a narrow range at the lower temperatures. Its range decreased in a 20% solution and deviated from the straight line. At the 30% concentration, the relationship of k' and the inverse temperature was similarly obtained as a straight line.

From the relation between the activation energies of k and k', $\Delta E_{K'}^{\ne}$ and $\Delta E_{K'}^{\ne}$ were calculated by the Arrhenius equation; they are shown in Table III. $\Delta E_{K'}^{\ne}$ higher than $\Delta E_{K}^{\ne}$ was obtained.

TABLE III. ACTIVATION ENERGY, $\Delta E^{\ne}$, OF k AND k'

Concn. of sample %	k		k'	
	η_{II}	G	η_{II}	G
20	77.0	97.3	—	—
30	109	139	159	201

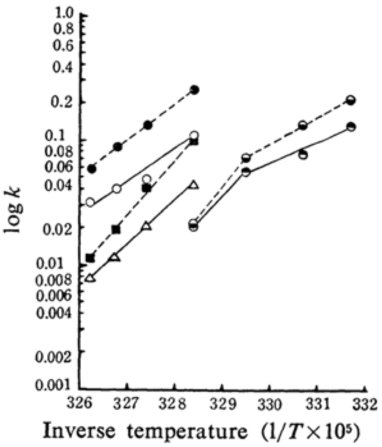

Fig. 7. Relationship of log k of η_{II} or that of G with the inverse temperature.
-◓- η_{II} at the concentration 20% of AB period
-◒- G at the concentration 20% of AB period
-○- η_{II} at the concentration 30% of AB period
-●- G at the concentration 30% of AB period
-△- η_{II} at the concentration 30% of BC period
-■- G at the concentration 30% of BC period

The difference in behavior between the AB and BC periods is probably due to the difference in the interaction of colloidal particles at various temperatures. In other words, the movement of colloidal particles is restricted at the BC period as compared with the AB period.

As has been described above, as the change from sol to gel at the AB period is relatively easy, the aggregation of gelatin particles occurs rapidly in a gelatin solution, but as the gelatin has already started the aggregation at the BC period, it is more difficult for the remaining gelatin particles in sol at the BC period to aggregate than at the AB period, when almost all the gelatin particles are in sol. Accordingly, it is natural that k' should be a smaller quantity than k and that $\Delta E_{K'}^{\ne}$ should be larger than $\Delta E_{K}^{\ne}$. The arrangement of colloidal particles at the higher temperature must be more systematical than that at the lower temperature.

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