The author is indebted to Prof. H. Nogami of the University of Tokyo for valuable suggestions and encouragements.

Summary

Tablets were compressed during a short period, its weight variation was evaluated as coefficient of variance in percentage, and the effect of four factorials was examined. From the results obtained, following conclusions were drawn :

1) Significant difference was not recongnized among tablet bases A, B, and C.

2) Decrease of diameter of punch increased the weight variation of tablets quadratically.

3) Increase of the granulated sieve mesh decreased weight variation of tablets, and linear relation was proved between them.

4) The degree of decrease was different for each punch.

5) Significant difference was not recognized between two compression rates, 76 and 42 tabs./min.

6) Without considering variation of mean weight for a long-period operation of a tabletting machine, from the OC-curve obtained by Dunnett and Crisafio, and 95% and 99% confidence limits of regression line for each punch, compression of tablets under the conditions listed in Table IV is recommended. The lot manufactured under such conditions may be accepted by U. S. P. test in probability of $0.95 \times 0.95 = 0.90$ and $0.99 \times 0.95 = 0.94$.

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6. **Hisakichi Matsumura, Sadao Iguchi, and Magobei Yamamoto** : Colloid Chemical Researches on Suspension in Pharmacy. II. On Aging of Thixotropy in Vegetable Oil-Aluminum Stearate System.

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In the preceding paper[1], some fundamental rheological studies on the mixture of vegetable oil and aluminum stearate system was reported. Both peanut oil and castor oil were used, since the former, which is now widely used as a base for penicillin injection in oil, has been known to show thixotropic behavior when dispensed with aluminum stearate (Al-St). Castor oil possesses an extremely distinct character, and therefore the corresponding Al-St system was selected for the sake of comparison. The measurements were carried out by employing the "concentric cylinder method" and the results obtained showed some interesting differences in rheological properties between the peanut oil and castor oil systems containing Al-St, whereas the oils themselves behaved as Newtonian flow when they did not contain Al-St. The gel containing more than 2% of Al-St in peanut oil clearly behaved as a Newtonian flow immediately after stirring, whose viscosity was very high compared to that of the oil alone. On the contrary, elastic deformation appeared on standing and its rigidity tended to increase with passage of time (setting time) and turned into a non-Newtonian flow.

On the other hand, the castor oil system always showed Newtonian flow without changing the mode of flow whether it contained Al-St or not. This made a clear contrast to the peanut oil—Al-St system.

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1) H. Matsumura, *et al.* : This Bulletin, **3**, 131(1955).

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The forgoing experimental results were obtained with samples taken immediately after preparation, or after comparatively short storage. Besides these fundamental rheological findings, one of the interesting phenomena already observed in the previous studies was that the peanut oil—Al-St system gradually tended to lose the gelation property when repeated mechanical work was added or stored for a long period. The loss of such characteristics is an important problem for drugs whose thixotropic behavior is utilized for preparation.

Therefore, it was considered necessary to investigate changes in rheological properties of these oil bases when stored under various conditions.

In this paper, effect of repeated mechanical work on the gel of peanut oil—Al-St system and the effect of long storage at various temperatures are reported.

Experimental

Peanut oil (J. P. VI) and aluminum stearate (Kwanto Chemical Co. product), and the preparative method for thixotropic system employed in the present experiment were the same as those described in the preceding papers. The Al-St powder was added to peanut oil with agitation, completely dissolved by heating for 1 hr. at 130° with thorough agitation, and the mixture was rapidly cooled in ice water. The system was kept under cooling for 24 hrs. In these studies all samples contained 2% (W/V) of Al-St in peanut oil. To obtain the flow curves, concentric cylinder method was employed, the principle of which was almost the same as that of Alfrey.[2)]

Measurements were carried out at 25°(in a thermostat) for 1 hr. after filling the sample in the annular space between two concentric cylinders.

Experimental Results and Discussions

(I) In order to investigate the effect of repeated mechanical work on the flow properties of vegetable oil—Al-St system, the following experiments were carried out.

Peanut oil—Al-St gel was prepared and divided into equal portions. One portion was placed in a glass cylinder of the same size as used for the outer cylinders in the apparatus and allowed to stand quietly at room temp. for 8 days (Sample I). Another portion was also placed in a similar cylinder and allowed to stand, but transformed into a sol state by thorough shaking at every 24 hrs. In these procedures air emulsion was formed but they were removed by keeping the sample for several hours. This treatment was repeated for 8 days to apply mechanical work on the gel structure (Sample II).

Rheological measurements were carried out on Samples I and II, (a) immediately, and (b) 5 mins., (c) 10 mins., and (d) 30 mins. after stirring the sample.

The results obtained were compared with those of the fresh gel immediately after preparation, which were obtained under the same conditions. In Fig. 1, the dotted lines

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2) T. Alfrey, C. W. Rodewald : J. Colloid Sci., **4**, 283(1949).

The working equations employed in the present investigation are as follows :

Apparent viscosity for Newtonian flow (immediately after stirring)

$$\eta = K\cdot(1/R_1^2 - 1/R_2^2)\cdot(\theta_0-\theta)/4\pi h\cdot d\theta/dt$$

Rigidity for non-Newtonian flow

$$G = K\cdot(1/R_1^2 - 1/R_2^2)\cdot(\theta_0-\theta_G)/4\pi h\cdot \theta_G$$

where η : apparent viscosity (poise)
G : rigidity (dyne/cm²)
K : torsion constant of the wire
R_1 : radius of the inner cylinder
R_2 : radius of the outer cylinder
h : depth of the inner cylinder immersed in the sample
θ_0 : rotational angle initially given to the top of the torsion wire
θ : rotational angle of the lower end of the wire at the time, **t**
θ_G : rotational angle of the lower end of the wire as elastic deformation
$d\theta/dt$: initial rate of deformation

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are those of the fresh gel. Under the condition (a), Samples I and II were both found to decrease in viscosity compared to the fresh gel, this tendency being particularly marked in Sample II. The effect of repeated mechanical work (destruction of gel structure) seems to be represented as the increase in fluidity of the system. Under conditions (b), (c), and (d), under which the flow of the systems was non-Newtonian, Samples I and II were both found to have greater rigidity, except in the case of (d), compared to the gel immediately after preparation, and under all conditions, Sample I had greater value than Sample II (Fig. 2). In the case of the gel immediately after preparation,

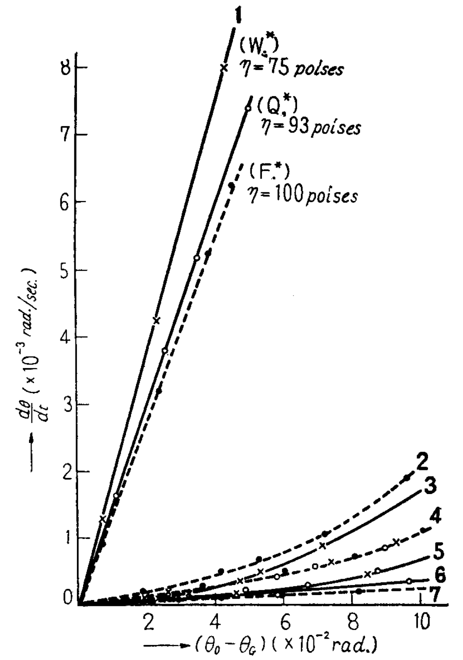

Fig. 1. Effect of Repeated Mechanical Work on the Gel

1 immediately after stiring
2 5 mins. after stirring F*
3 5 mins. after stirring W*
4 { 5 mins. after stirring Q*(○) / 10 mins. after stirring F*(●) / 10 mins. after stirring W*(×) }
5 { 10 mins. after stirring Q*(○) / 30 mins. after stirring W*(×) }
6 30 mins. after stirring Q*
7 30 mins. after stirring F*

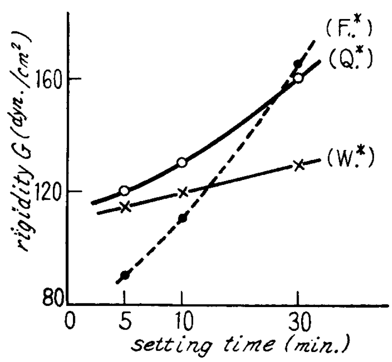

Fig. 2. Relations between Rigidity and Setting Time

* F : Fresh sample immediately after preparation.
Q : Sample which had been allowed to stand quietly (sample I).
W : Sample applied with mechanical work (sample II).

In these papers, all samples contained 2% (w/v) of aluminum stearate to peanut oil, measurements were taken at 25°, and apparatus conditions were all the same throughout the experiments as follows : $K=2.37\times10^2$ dyn./cm. $R_1=0.54$ cm. $R_2=0.91$ cm. $h=3.0$ cm.

construction of the gel structure after stirring seemed to proceed slowly, indicating an increase of gradient of rigidity (G) vs. setting time (shown by dotted lines), whereas the gel which had been allowed to stand quietly forms the gel structure more rapidly after stirring to exhibit larger values of G at (b) and (c), but the gradient of G vs. setting time is no greater. Sample II has the smallest G gradient of the three. Therefore, the rigidity in (d) was found to give a greater value with the gel immediately after preparation than with both Samples I and II.

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As for apparent fluidity, tangential gradient of curve at each shearing stress is to be compared because the system is non-Newtonian. It was observed that Sample II had a greater apparent fluiditiy at every setting time than Sample I. The effect of repeated mechanical works on the gel, therefore, was considered to be the tendency to increase the apparent fluidity.

(II) From the fact that the gel allowed to stand for several days had greater rigidity and smaller fluidity under conditions (b) and (c), it can naturally be considered that the formation of a gel structure in peanut oil—Al-St system tends to proceed with passage of time (days). Accordingly, in order to observe the effect of temperature on the formation of gel structure, freshly prepared gel was allowed to stand quietly, one at a comparatively higher temperature and the other at lower temperature, and changes brought about in flow properties were examined with passage of days.

i) In the case of higher temperature, the gel in sealed cylinders was kept at 37° in an incubator and the measurements were carried out after 1, 8, 19, 28, and 73 days of storage, and compared with the fresh gel immediately after preparation. All the samples were measured 10 mins. after stirring (condition (c)). As seen in Fig. 3, on comparing

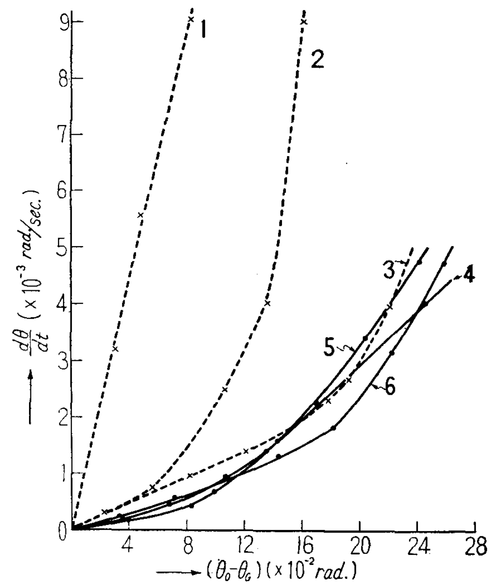

Fig. 3.
Flow Curves obtained after Different Period of Storage at 37°

1 73 days' storage
2 28 days' storage
3 19 days' storage
4 1 days' storage
5 8 days' storage
6 Control (immediately after preparation)

the flow properties of each sample with storage time (days), it may be considered that the rate of flow (deformation) towards stress tends to increase, i.e. to become progressively more fluid with aging for more than 19 days, and the longer the days of storage, the greater its values, and at last after 73 days, it shows a pure viscous flow.

On the other hand, under short aging, such as 8 days in this case, some differences are seen in the gel behavior and the aged gels have smaller rate of flow compared to fresh gel when the stress angles are under 10×10^{-2} radian, whereas the rate of flow tends to increase with passage of days at above 14×10^{-2} radian. Similarly, larger values are found in the rigidity ascribed to gel structure by this abnormality than the fresh gel, the value increasing to the maximum by 8 days of comparatively short aging and then falling gradually with further passage of days (Fig. 4). It is considered that the gel structure loosely formed earlier is converted to a more closely bound structure with passage of time. With respect to the flow immediately after stirring, the system showed Newtonian flow, and at the first interval (3 days of storage), the viscosity increased, subsequently falling to the constant level, and indicated no marked difference in fluidity until 73 days of storage. The results are shown in Fig. 5.

ii) The same experiments were carried out in the case of storing the samples at a

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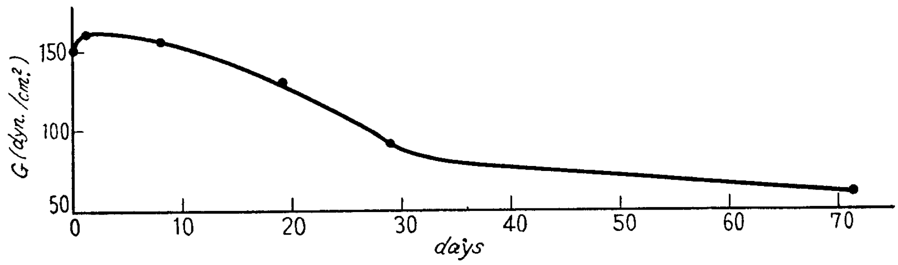

Fig. 4. Change in Rigidity with Storage at 37° (10 mins. after stirring)

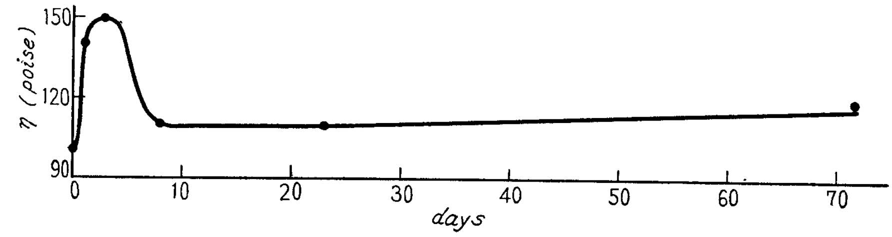

Fig. 5. Change in Apparent Viscosity with Storage at 37° (immediately after stirring)

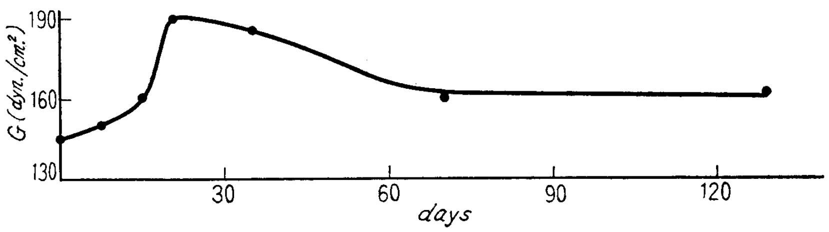

Fig. 7. Change in Rigidity with Storage at −3° to +2° (10 mins. after stirring)

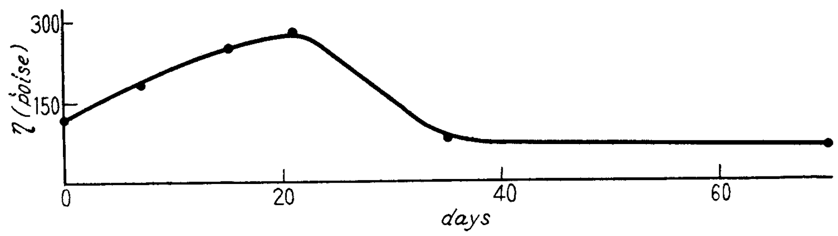

Fig. 8. Change in Apparent Viscosity with Storage at −3° to +2° (immediately after stirring)

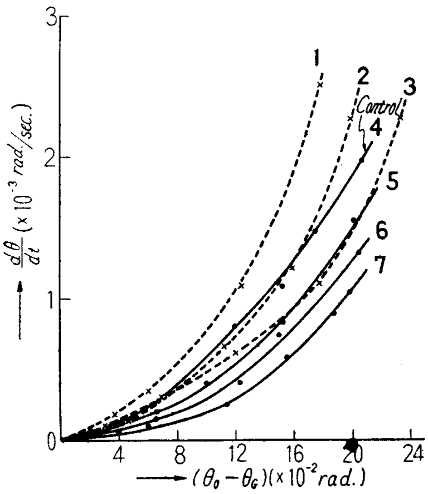

Fig. 6.

Flow Curves obtained after Different Periods of Storage at −3° to +2° (10 mins. after stirring)

1 129 days' storage
2 70 days' storage
3 35 days' storage
4 immediately after preparation
5 7 days' storage
6 15 days' storage
7 21 days' storage

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comparatively lower temperature (−3° to +2°). The results obtained are shown in Fig. 6. The rate of flow at every shearing stress was found to be always smaller with passage of days, ascribable to the decrease of fluidity. It is considered that the formation of gel structure proceeded for a longer period at a low temperature than at a higher temperature.

When the storage time (days) extends over 20 days, the increase of apparent fluidity appeared simiarly to (i), as shown by the dotted lines in Fig. 6, but steady in this case.

In the variation of rigidity, its values also increase gradually up to the maximum after some intervals and then, without decreasing so much, holds the constant level of 160 dynes/cm^2 or more for a considerably long interval in these experiments. As seen in Fig. 8, the viscosity immediately after stirring also showed similar tendency as shown in Fig. 5, the first interval while the values increase up to the maximum being delayed to about 20 days or more and subsequent decrease was also observed.

Similar phenomenon at the initial stage was indicated by Gray and Alexander[3] on Al–St–benzene system and by Mysels[4] on Al laurate–cyclohexane system, indicating that the gel structure was building up.

These facts seem to suggest that the formation of gel structure is slower but fairly stronger-bound at a lower than at a higher temperature.

At the same time, the destruction of gel structure begins to proceed gradually to the state of equilibrium between formation and destruction, the latter affecting the system. The structure formed at a lower temperature is maintained for a fairly long interval. On the contrary, at a higher temperature (37°), the formation and destruction of gel structure likewise progress, and the destruction is very much accelerated to affect the system in such short intervals.

As to the external appearance of gel state under each condition, there first appeared a flocculant cloudiness on standing the gel at a lower temperature for 20 days, whereas the corresponding gel immediately after preparation was transparent. On the other hand, at higher temperatures, the gel became rapidly cloudy and clear syneresis appeared on standing for 8 days. It seemed necessary to carry out all the measurement under the same conditions with peanut oil itself not containing Al–St. The oils under all conditions showed Newtonian flow and there was no marked difference in viscosities during the intervals experimented as illustrated in Table I.

TABLE I. Change in Apparent Viscosity of Peanut Oil under Various Conditions (at 25°)

	at −3° to +2°			at 37°		
Storage time (in days)	0	16	75	0	16	ca. 7 months.
10 mins. after stirring	0.96 poises	0.99	0.99	0.96	0.92	0.84
Immediately after stirring	0.92	0.96	0.99	0.92	0.90	0.84

iii) The storage conditions of the gel, which had become greatly fluid owing to storage at a higher temperature, was altered to a lower temperature, and effect on the flow was examined. The apparent fluidity of gel was sufficiently varied by standing for 2 weeks at 37° after preparation. The resultant gel was placed at a lower temperature (−3° to +2°), and the flow at 10 mins. after stirring was investigated for about 50 days. The results obtained are shown in Fig. 9. Even in this case, starting with the gel state aged at 37° for 2 weeks, the first effect which appears when stored at a lower temperature (as seen in Fig. 6) was also found. In this case, however, the rate of flow was never less than that of the fresh gel. Rigidity, which had decreased once by a higher temperature, was gradually restored as shown in Fig. 10. A little difference was observed in the rate of

3) V. R. Gray, A. E. Alexander: J. Phys. & Colloid Chem., **53**. 9(1949).
4) K. J. Mysels: J. Colloid Sci., **2**, 375(1947).

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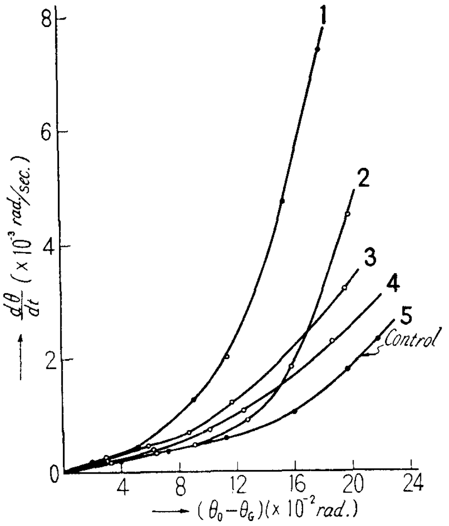

Fig. 9.

Flow Curves obtained after altering Temperature Condition from Higher (37°C) to Lower (−3° to +2°) (10 mins. after stirring.)

1 2 weeks' storage at 37°
2 48 days' storage at −3° to +2°
3 4 days' storage at −3° to +2°
4 12 days' storage at −3° to +2°
5 Immediately after preparation

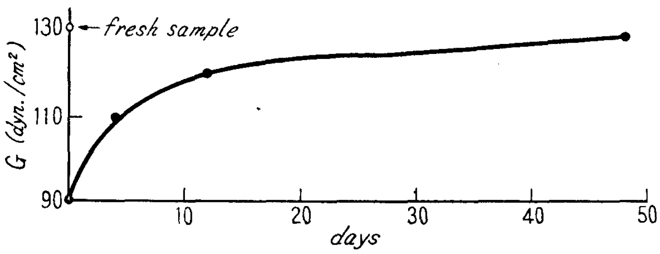

Fig. 10.

Restoration of Rigidity after altering its Storage Condition from 37° to −3° to +2° (10 mins. after stirring)

increase, in contrast to that of Fig. 7, which was obtained by standing the sample at a lower temperature immediately after preparation. It was restored near to but never over the level of fresh gel during the intervals examined.

In spite of altering the condition of storage to a lower temperature, the effect of first storage at a higher temperature influences the gel behavior thereafter, distinguishing from the gel stored at a lower temperature without altering the storage conditions.

Summary

Effect of repeated mechanical work on peanut oil–aluminum stearate gel system was indicated rheologically to be more fluid and to give gentler curve of rigidity vs. setting time.

By obtaining flow curve of the gel, effect of storage at various temperatures on gel was also investigated. When stored at a higher temperature (37°), the gel became gradually fluid and finally behaved like a linear flow. In the course of storage, there appeared an initial stage, where the values of both viscosity immediately after stirring and rigidity 10 minutes after stirring the sample increased up to the maximum. On the other hand, when stored at a lower temperature (−3° to +2°), similar increase of fluidity did not occur so rapidly and its initial stage was also delayed much longer.

The cooling effect on the gel, which had been fluid, were also observed in restoration of its gelation properties, but the initial effect was always predominant thereafter.

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