aqueous solution with 16.6 g. of KCN afforded a fraction of b.p_{16} 125~130°, which crystallized to 5.52 g. (32.6%) of colorless needles, m.p. 51~52°. *Anal.* Calcd. for $C_8H_8N_2$: C, 72.7; H, 6.1; N, 21.2. Found: C, 72.36; H, 5.95; N, 20.86.

2-Cyano-3-ethyl-6-methylpyridine—A mixture of 7.2 g. of 2-chloro-3-ethyl-6-methylpyridine 6.0 g. of Na_2SO_3, and 80 cc. of water was heated in an autoclave at 210~220° for 10 hrs. Treatment as in the foregoing cases afforded 4.5 g. of the recovered material and fusion of the residue with 2.3 g. of KCN afforded 1.26 g.(49.7%) of a colorless liquid, b.p_{32} 145~151°. *Anal.* Calcd. for $C_9H_{10}N_2$: C, 73.9; H, 6.9; N, 19.2. Found: C, 73.53, H, 7.21; N, 18.97.

4-Cyano-3-ethyl-6-methylpyridine—A mixture of 4.7 g. of 4-chloro-3-ethyl-6-methylpyridine, 3.9 g. of Na_2SO_3, and 40 cc. of water was heated in an autoclave at 180~200° for 3 hrs. Treated as in the foregoing cases, 1.75 g. of the starting material was recovered and fusion with 3.3 g. of KCN afforded 1.68 g.(60.6%) of colorless liquid, b.p_{17} 107~110°.

Picrate: Yellow needles (from EtOH), m.p. 123~124°. *Anal.* Calcd. for $C_9H_{10}N_2 \cdot C_6H_3O_7N_3$: C, 48.0; H, 3.5; N, 18.7. Found: C, 48.00; H, 3.41; N, 18.78.

Summary

Methylpyridines possessing chlorine in 2(or 4)-position were derived to the corresponding 2(or 4)-cyano-methylpyridines by heating with sodium sulfite in water in an autoclave at 150~220° for 10 hours and heating the sodium sulfonate thereby obtained with potassium or sodium cyanide to fusion.

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U. D. C. 615.412.5

5. **Jun Hasegawa**: Studies on Tablets. III.[1] Weight Variation of Compressed Tablets.

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Weight variation is the most important point in the evaluation of compressed tablets and many investigators have reported the deviation in weight of compressed tablets, but most of them discussed the matter from the standpoint of consumers[2] or the survey[3~5] on a marketed tablets. A tablet consists of many ingredients and is compressed through many manufacturing processes, so that deviation of tablet weight is affected by many factors. Some of them may be as follows: (1) Diameter of punch (diameter of tablet), (2) depth of die cavity,[6] (3) particle size of granules to be compressed (granulated sieve mesh), (4) fluidity of granules[7] (kind and amount of lubricant added), (5) properties of ingredients (physical and micromeritical charactors of powder), (6) speed of compression, and (7) tabletting machine used (single punch or rotary type).

When manufacturing tablets in a hospital pharmacy, it is very important to solve such practical problems and only a few reports[8,9] on these points have been seen.

The object of this study is to learn in a relatively short period the effect of (1) tablet

* Hongo, Tokyo (長谷川 淳).

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2) J. F. Liverseege: Pharm. J., **116**, 232.
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5) M. Aoki, T. Fukuda: Japan. J. Pharm. & Chem., **26**, 184(1954).
6) K. Asahina: J. Pharm. Soc. Japan, **76**, 47(1956).
7) A. M. Raff, *et al.*: J. Am. Pharm. Assoc., **44**, 290(1955).
8) A. S. Arambulo, *et al.*: *Ibid.*, **42**, 690, 692(1953).
9) Dansk Tidskr. Farm., **2**, 151(1928) (C. A., **22**, 4203(1928)).

base to be compressed, (2) diameter of punch, (3) granulated sieve mesh, and (4) speed of compression on the deviation in weight of compressed tablets.

Many investigators consider that the distribution of tablet weight in a batch may satisfactorily be represented by a normal distribution. The most effective measure of deviation in a normal distribution is a standard deviation. On comparing statistical populations, whose mean value is different, however, a coefficient of variance would be more suitable. This value was used for the purpose in this study and the effect of above factors on coefficient of variance of each batch was studied.

Experimental

Tablet base—Three kinds of tablet base used for this study were as follows :

A)	Precipitated calcium carbonate J. P. VI	50
	Lactose J. P. VI	40
	Potato starch J. P. VI	10
B)	Lactose	100
C)	Lactomin J. N. F. I	90
	Potato starch J. P. VI	10

Whole amount of each was mixed completely in a mechanical mixer, sifted through a 100-mesh sieve, and stored in containers.

Granulation—Five kinds of sieves described below were used : 12 mesh (SWG 25), 14 mesh (SWG 25), 16 mesh (SWG 25), 18 mesh (SWG 27), and 20 mesh (SWG 29). A given amount of 5% starch paste (22% for base A, 15% for base B, and 40% for base C) was added to a specified amount of the base (1000 g. of the base for a 13-mm. punch, 600 g. of the base for a 10-mm. punch, and 400 g. of the base for a 7-mm. punch), mixed throughly, and granulated through an appropriate sieve by hands. After drying in hot air stream at 40~50°, coarser granules were removed by a sieve, such as a 10-mesh sieve, when granulated through a 12-mesh sieve, fine particles below 33-mesh were removed, and the resultant granules were compressed.

5% Starch paste : 400 cc. of water was boiled in a 500-cc. beaker, 25 g. of potato starch suspended in 75 cc. of water was added under stirring, washed in with little water, and made to 500 cc. Starch paste was used for granulation after cool. Whole amount of potato starch used for the study was mixed homogenously and stored in a container.

Tabletting—Three kinds of punch used were 7, 10, and 13 mm. in diameter. They were bevel-edge type and depth of die cavity was fixed at 5/12 inch throughout the present study. 2% of talc was added to a given granulation, mixed thoroughly, and compressed using a single-punch tabletting machine (Kimura Model KT-2) in two speeds, 76 and 42 tabs./min. Tabletting speed was changed by the change of the pulley fixed on a driving motor.

Sampling—During operation of the tablet machine, a group of consecutive 5 tablets at every 50 tablets was collected and 10 groups of tablets were taken at each tabletting rate. Then 20 groups of sample from 1000 tablets were collected for each granule batch and weighed to a nearest mg. An $\bar{X}$-R chart was drawn for each compression rate and the sample was accepted when it was recongnized to be within a control limit. Mean weight, standard deviation, and coefficient of variance of the sample were calculated, and deviation of tablet weight was represented by a percentage of variance coefficient for each batch.

Experimental design—This study includs 4 factorials, i.e. tablet base, diameter of punch, granulated sieve mesh, and speed of compression. Among these factorials, speed of compression was selected as a secondary factorial, since it was not so important, and the others as primary factorial in a randomized blocks design. On operating a tablet machine, the height of granules in a hopper is lowered and pressure given to the granules in a feeder will be changed. It may be that this relationship may affect the weight variation of tablets in the initial and later portions. However, this effect was not taken up in detail, since it was found that the effect was almost negligible. Therefore, only the main effect of second factorial was separated as described previously.

Result and Analysis

The results obtained from the present study are shown in Table I, in which a figure represents a coefficient of deviation in per cent. It is seen from these results, that the deviation of each group increases with its mean value, so that original data were transformed as follows : For the assumpsion of the same variance, $Y=\log(y\times 10)$, where y is the original data and Y the transformed value. Analysis of variance was carried out and the result obtained is shown in Table II.

Table I. Coefficient of Variance (original data, in %)

Diam. of punch (mm.)	Base	Speed*	Granulated sieve mesh (mesh) 12	14	16	18	20
7	A	S_0	7.58	8.02	6.32	2.49	1.71
		S_1	7.74	4.03	3.55	2.59	2.01
	B	S_0	9.09	5.04	5.25	1.95	1.66
		S_1	8.65	4.92	2.41	2.06	1.83
	C	S_0	1.85	6.58	4.48	2.87	2.30
		S_1	1.76	4.39	2.59	1.82	1.61
10	A	S_0	2.98	2.18	1.19	1.17	0.98
		S_1	3.66	1.80	1.80	1.13	0.90
	B	S_0	2.86	1.82	1.79	1.47	0.95
		S_1	3.48	2.14	1.26	1.52	1.20
	C	S_0	2.94	1.92	2.09	1.16	0.83
		S_1	1.86	1.79	1.55	1.48	1.59
13	A	S_0	2.95	1.33	0.98	1.09	0.85
		S_1	2.56	1.77	1.66	1.04	1.03
	B	S_0	1.62	1.65	1.24	0.92	1.10
		S_1	2.22	2.01	1.66	1.08	1.05
	C	S_0	2.51	1.51	1.08	0.93	1.73
		S_1	1.36	1.77	1.16	1.27	0.69

* S_0=76 tabs./min., S_1=42 tabs./min.

Table II. Analysis of Variance on Transformed Value

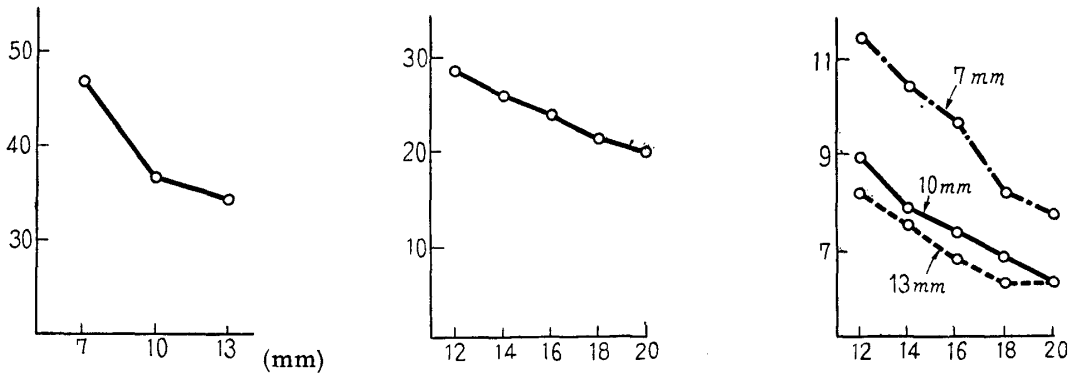
Factorial	S.S.	ϕ	M.S.	F_0
(Primary Fact.)				
Base (B)	0.00939	2	0.00470	
Diameter (D)	2.95089	2	1.47540	219**
D_l	2.60417	1	2.60417	386**
D_q	0.34672	1	0.34672	51.4**
Mesh (M)	2.49632	4	0.62408	92.5**
M_l	2.45701	1	2.45701	364**
M_q	0.03089	1	0.03089	4.58*
residual	0.00843	2	0.00422	
Interaction (M×D)	0.21059	8	0.02633	3.90
$M_l \times D_l$	0.16875	1	0.16875	25.0**
$M_q \times D_q$	0.01191	1	0.01191	1.76
residual	0.02994	6	0.00499	
Error (Prim.)	0.18900	28	0.00675	
Total	5.84180	44		
(Secondary Fact.)				
Speed of Comp.(S)	0.01521	1	0.01521	3.26
Int.(S×T)	0.50187	16	0.03137	7.38*
Error (Sec.)	0.11908	28	0.00425	
Gross total	6.49315	89		

From the result in Table II, following conclusions were drawn.

Primary Factorial—a) Effect of tablet base : Main effect of the base was 39.51 (transformed value) for the base A, 39.16 for the base B, and 38.76 for the base C, and significant difference was not recongnized, since $F_0<1$. It was considered that the same effect of granule size and diameter of punch on variation in weight would be expected for each base. If these bases are random set-up instead of systematic set-up, it will be considered that the relationship described below would be adapted to the population represented by three bases, but the surface-chemical and micromeritical considerations must be necessary as to what population it belongs.

b) Effect of diameter of punch : Main effect of diameter of punch was 46.76 for 7-mm., 36.51 for 10-mm., and 34.21 for 13-mm. punch. The result is shown in Fig. 1a and highly significant, since F_0=219. The main effect is separated into two components, D_l(linear) and D_q(quadurate), and both of them were highly significant. From these results it may be said that decrease of the diameter of punch increases the variation of tablet weight, and the degree of increase is quadratic.

c) Effect of granulated sieve mesh : Main effect of granulated sieve mesh was highly significant, as shown in Fig. 1b, being 28.07 for 12-mesh, 25.35 for 14-mesh, 23.33 for 16-mesh, and 19.78 for 20-mesh. As seen in Fig. 1b, increase of the granulated sieve mesh decreases the deviation in



Diameter of punch
a) Effect of D

Granulated sieve mesh
b) Effect of M

Granulated sieve mesh
c) Effect of M×D

Fig. 1. Effect of Diameter, Mesh Granulated, and Interaction

weight and the degree of decrease was considered linear, since the main effect was separated into 3 components; F_0 of M_l being 364 and highly significant, F_0 of M_q slightly over the 5% level from statistical table, and other component not significant. From these results, it is considered that there is a highly linear relationship between the variation in weight of tablets and mesh granulated (granular size), but deviation from the regression was not negligible. However, judging from general circumstances, this deviation was doubtful and it might be better to consider that the deviation was accidental.

d) Effect of interaction M×D : Average effect of interaction was not significant, but separating the components, $M_l \times D_l$ was highly significant, since $F_0=25.0$, but other components were not significant. Since $M_l \times D_l$ is highly significant, it may be concluded that the degree of decrease in weight variation of tablets is separate from diameter of punch. The effect is as shown in Fig. 1c.

Secondary factorial—e) Effect of compression speed : The effect was 59.30 for 76 tabs./min. and 58.13 for 42 tabs./min., but not significant, since $F_0=3.26$. From this result it is not considered that compression rate will affect the variation in weight of tablets.

f) Interaction T×S : The interaction effect was significant at the 5% level, but these interactions were not intented to be investigated in such detail at the beginning of experiment, and practical mean of the interaction was not clear and complicated, so that further investigation was not carried out. It was considered that significance of the interaction would be due to the very high D- and M-effects.

Discussion

From the result and analysis, great difference of the effect of granular size on variance in weight of tablets was evident. Therefore, mean value, standard deviation from regression (error of estimation), regression coefficient b, variance of b, and confidence limit of b were calculated for each punch. These values are tabulated in Table III.

TABLE III. Result of Calculation of Regression for each Punch

Diam. of Punch (mm.)	General mean $\bar{y}$	Stand. dev. from regr.	Regr. coeff. (b)	Variance of (b)	Confid. limit of (b) 95%	Confid. limit of (b) 99%
7	3.114	0.1221	−0.1597	0.01115	−0.1838 −0.1356	−0.1933 −0.1261
10	2.434	0.1500	−0.1053	0.00310	−0.1120 −0.0986	−0.1147 −0.0960
13	2.281	0.1143	−0.0855	0.01043	−0.1080 −0.0630	−0.1169 −0.0541

From the values in Table III, each regression line is as follows :

$\hat{Y}=3.114-0.1597\,(X-16)$ for 7-mm. punch,

$\hat{Y}=2.434-0.1053\,(X-16)$ for 10-mm. punch,

$\hat{Y}=2.281-0.0855\,(X-16)$ for 13-mm. punch,

where X is granulated sieve mesh and $\hat{Y}$ is estimated value of y (transformed value, coefficient of variance in %) and obtained as two-fold value, since y is the sum of each compression rate.

These are shown in Fig. 2, in which solid line represents each regression line and two dotted lines are upper and lower confidence limits in 95%, which was calculated from the value in Table III and t-value from statistical table.

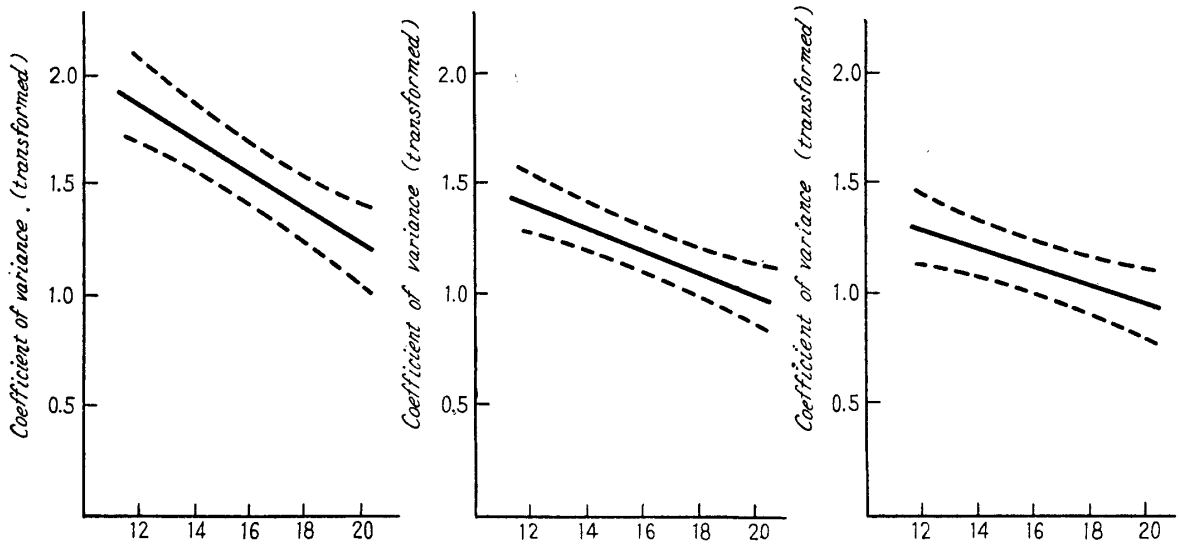


Fig. 2. Regression Line and Confidence Limits of each Punch

Fig. 2. is shown in transformed value, the regression lines are shown by original value in Fig. 3, and 95% and 99% upper confidence limits are shown in Figs. 4 and 5.

In the review of various pharmacopoeias, Smith[10] reported that several countries now include tests for controlling variation in weight of compressed tablets. The details of these tests are different but follow a common principle. The weight of not more than 10 % of the tablets examined may differ from the average examined by more than a specified amount, but no tablet differs by more than a double of that amount. Japanese Pharmacopeia does not include an article on weight variation of compressed tablets, but specifies the content of chief ingredient in the following manner. "Unless otherwise indicated, there is no more deviation from the labeled amount than 5 per cent of it in the content of active ingredient and the materials used."

Such an article is not consistent with the actual circumstances of manufacturing

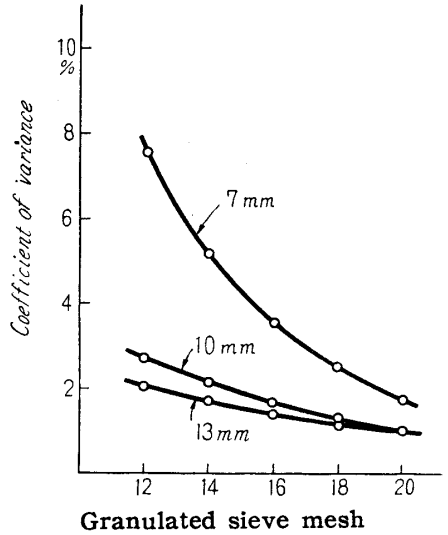
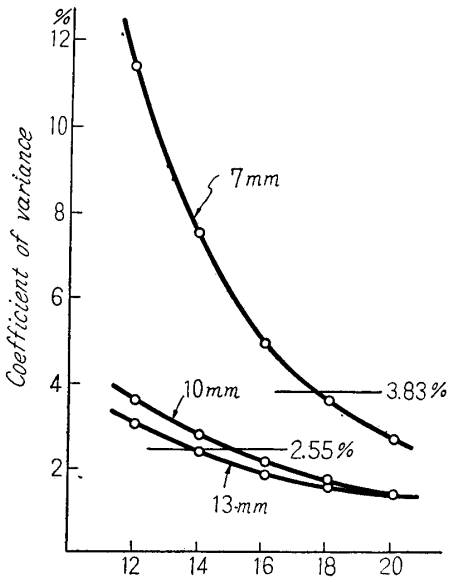


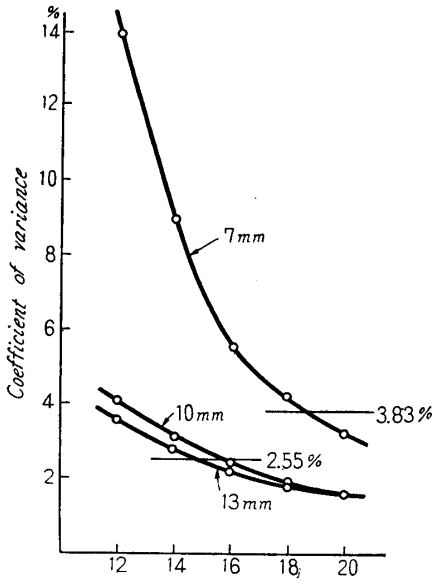
Fig. 3. Regression Line of each Punch

10) Smith : Pharm. J., **167**, 143, 270, 323(1951).



Granulated sieve mesh

Fig. 4. Upper Confidence Limit in 95%



Granulated sieve mesh

Fig. 5. Upper Confidence Limit in 99%

the tablets or from the statistical viewpoint. Weight variation of compressed tablets is the most important factor in evaluation as described previously. Therefore, it is considered that this point should be incorporated in the Japanese Pharmacopoeia from modern statistical standpoint.

In their report on the operating characteristics of weight variation test of tablets, Dunnett and Crisafio[11] obtained experimentally OC-curve of the sample size of 10, 20, 50, and 100 tablets. Following their result, it is evident that percentage of acceptance of a batch containing 5% of defective tablets is 95% and one of a batch containing 20% of defective is 23%. Producer's risk and consumer's risk are of opposite characters like this. We assume that the lowest quality guarantee* of tablets produced in hospital pharmacy is as follows : A batch acceptable in 95% by U. S. P. weight variation test is manufactured in 95 or 99% probability.

Mean weight of tablets compressed in the present series of experiment was in the range of 0.15 to 0.18, 0.3 to 0.36, and 0.5 to 0.6 g. for 7-, 10-, and 13-mm. punch, respectively. The maximum allowance of weight variation in U. S. P. XV is 7.5% for 7-mm. punch and 5.0% for 10- and 13-mm. punch. A batch containing 5% of defective tablets is one, whose deviation coefficient is $5/1.960=2.551\%$ or $7.5/1.960=3.826\%$ for 10- (13-) and 7-mm. punch, since t-value $(0.05)=1.960$.

From the assumption described above, it may be concluded that, if tablets are compressed accoding to conditions listed in Table IV, a batch can be obtained in probability of 95 or 99%, which is acceptable by U. S. P. test in 95%. However, these considerations are based on weight variation of tablets in a short period and it must be considered that the variation of mean weight is added to industrial lots, since the mean weight of tablets changes with operating time by several factors.

Table IV. Tabletting Condition Recommended

Diam. of punch (mm.)	U. S. P. max. allow. %	95%	99%
7	7.5	below 18 mesh	below 19 mesh
10	5.0	〃 15	〃 16
13	5.0	〃 14	〃 15

* The guarantee of a batch, which is compressed in a manufacturing company, is different from a hospital pharmacy one, since the circumstances to be considered are different.

11) C. W. Dunnett, R. Crisafio : J. Pharm. Pharmacol., **7**, 314(1955).

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 $0.95\times0.95=0.90$ and $0.99\times0.95=0.94$.

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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).