Summary

Infrared spectra of substituted pyridine 1-oxides with various kinds of substituent mainly at 3- or 4-position were determined. Their N-O stretching frequencies (strong absorption in the region of 1200 and 1300 cm^{-1}) were found to be correlated with the nature of a substituent, and a linear relation between these frequencies and σ-values of the substituents was pointed out. The ring C-H out-of-plane bending frequencies of these compounds showed a regular shift from those of the parent pyridines, shifting always to a higher frequency in 2- and 4-substituted derivatives, and always to a lower frequency in 3-substituted derivatives. Absorptions in the regions of 900~1200 cm^{-1} and 1450~1630 cm^{-1} were also correlated with the structure. From a comparison of the frequency shift in a characteristic vibration of the ring substituent, the σ-values of 0.25 and 1.18 were respectively obtained for 4- and 3-positions of pyridine 1-oxides.

All these points were discussed in terms of an electronic effect of the N-oxide function.

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21. **Jun Hasegawa and Tsuneji Nagai**: The Change of Particle Size in an Aqueous Suspension.

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According to the colloid chemical investigations, there is a tendency for small particles to dissolve into solution more than larger ones from their physical properties. The concentration of the solute around small particles is higher than that of larger ones, so the replacement of the solute occurs from small particles to larger one, and the larger crystal grows further with decrease of small particle. The explanation of this relation has been given by Ostwald-Freundlich's equation.[1] They expanded the theory, which was thermodynamically driven by Thomson for the behavior of liquid particles in the air, to the relation of solubility and particle size in a suspension. This equation is as follows:

$$\frac{RT}{M}\ln\frac{S_2}{S_1}=\frac{2\sigma}{\rho}\left(\frac{1}{r_2}-\frac{1}{r_1}\right).$$

where R is the gas constant, T the absolute temperature, M the molecular weight of the solid in solution, ρ the density of the solid, σ the surface tension between the solid and its solution, and S_1 and S_2 are the solubilities of the particles of radii r_1 and r_2, respectively. In some cases, this equation is useful for the determination of the surface tension of a solid.[2] Jones and Partington attempted to examine the validity of this equation at several temperatures and observed that the influence of particle size practically disappeared in the region over 50 μ radius in the case of gypsum.[3]

It is well known empirically that the particles grow in size during the period of preservation in preparations, such as injections and ointments. The medical effects

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[1] W. Ostwald: Z. physik. Chem., **34**, 503(1900); H. M. F. Freundlich: Kapillarchemie, Bd. I, Leipzig (1930).

[2] M. L. Dundon, *et al.*: J. Am. Chem. Soc., **45**, 2479(1923).

[3] M. Jones, J. R. Partington: J. Chem. Soc., **107**, 1019(1915).

of these preparations are affected by their particle size distribution of the principal medicine, so the absorption and duration may be different when they are applied to the patients.

According to J. P. VI, the medicinal powders passing 100-mesh (150 μ) sieve or finer are used for the suspensional preparations. Since the colloidal properties of particles may not appear in these conditions, it is not necessary to adapt Ostwald-Freundlich's equation in its original form. The phenomenon of particle growth occurring in these preparations may be different from the one in a supersaturated solution. Since a suspension contains particles which have some size distribution, treatment of the preparation becomes more difficult.

The object of the present study is to discuss the change of particle size in the aqueous suspension of sulfadiazine from a macroscopical viewpoint, and not to treat the behavior of an individual particle, because such work as described above has not been presented and may be suitable to the study of pharmaceutics.

Since the solubility of sulfadiazine is very small and the behavior of its suspension is not affected easily during the determination procedures, this preparation may be considered as suitable for the present purpose. Throughout this study the sedimentation process was used for the determination, which is very reliable, accurate, and convenient in the condition adopted. Among the factors which may affect the behavior of suspensional preparations, the added substance, the pH value of the vehicle, the temperature, and the period of preservation were examined and factorial experiment of 3×3×4×4 was carried out.

Experimental

a) **Level of Factors**—The selected level of factors was as follows:

i) Added substance (S) to the vehicle: S_1: 0.5% of Tween 65 (HLB=10.5); S_2: 0.25% of Tween 65 and 0.25% of Tween 20 (HLB=13.6); S_3: 0.5% of Tween 20 (HLB=16.7). Only Tweens were used to avoid complication, such as the effect of aggregation, viscosity, etc. This effect was not significant as will be described later.

ii) pH-value (P) of the vehicle: P_1: pH 6.8; P_2: pH 7.2; P_3: pH 7.6. Sörensen's phosphate buffer was used.

iii) Temperature (T) of preservation: T_1: 0°(in ice and water); T_2: 20°; T_3: 40°; T_4: 60°(thermostatically controlled bath adjusted at each temperature).

iv) Period (M) of preservation: M_1: 1 month (30 days); M_2: 2 months (60 days); M_3: 3 months (90 days); M_4: 4 months (120 days).

b) **Preparation and Preservation of the Sample**—A suitable amount of sulfadiazine (J. P. VI) passing through a 200-mesh sieve was collected, mixed thoroughly, and used as the sample. The mean diameter and standard deviation of the particle-size distribution were determined as will be described below. 1.00 g. of the sample and 10.0 cc. of the specified vehicle were sealed in a vial, and kept in desired conditions. In total, 144 vials were prepared and determinations were carried out with the randomized sample.

c) **Determination of Particle Size**—A vial was taken out according to the experimental schedule, the content was transfered to a glass-stoppered centrifugal tube, and centrifuged for 7 mins. at 3000 r.p.m. The upper layer was used for the determination of solubility. The precipitate was suspended again in 0.05% solution of Tween 80, in which the sedimentation volume of sulfadiazine was minimal, and sedimentation of particles was observed. Andreasen pipette[4] used for the study is shown in Fig. 1, at the top of which a separation funnel with a 3-way cock K_1 is attached. This apparatus was placed in a thermostatically controlled bath at 20°±0.1°. 5 cc. of the suspension was pipetted by suction through G (L indicates the 5-cc. line), taken out from E operating the cock K_2, and the remaining particles were washed out with water kept in the funnel W. The washing procedure was repeated and a total of about 8 cc. of water was enough to remove the particles in the pipette completely. The sampling procedure was as follows: After agitation with a stainless stirrer A, which moved vertically about 60 times during 1 min. and 10 times gently during the next 30 secs., samples were collected at the following points: 0 sec., 1′ 28″(Stokes radius=50 μ), 2′ 16″(40 μ), 3′ 59″(30 μ), 8′ 52″(20 μ), 15′ 35″(15 μ), and 34′ 37″(10 μ). These samples and the upper layer in the vial were used for

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[4] A. H. M. Andreasen: Angew. Chem., 48, 283(1935).

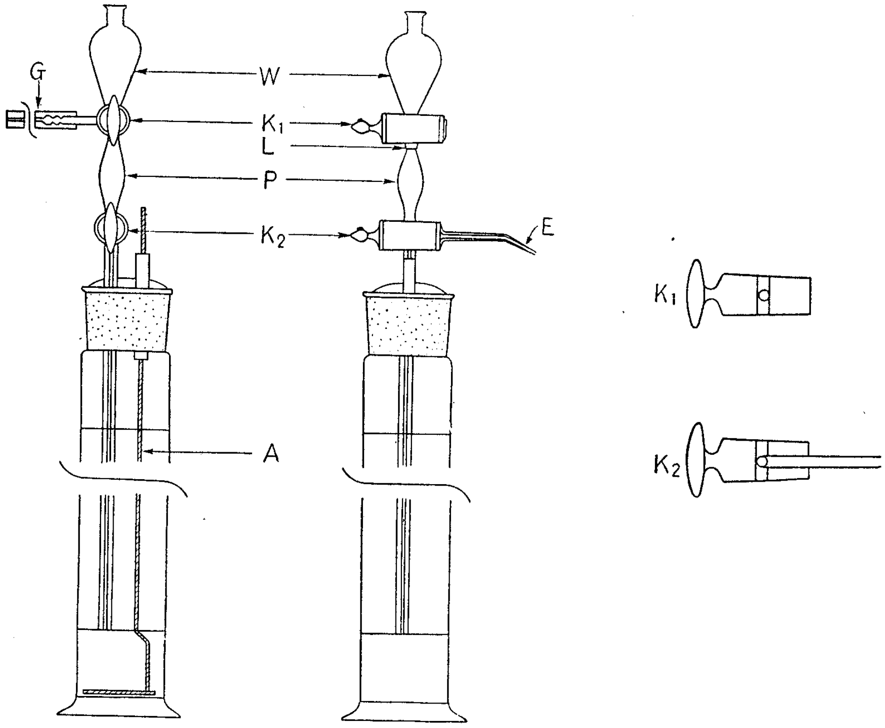

Fig. 1. Sedimentation Apparatus

colorimetory.

d) Colorimetry of Sulfadiazine—8 cc. of $5N$ HCl was added to the sample and diluted with distilled water to 200 cc. 1.0 cc. of the diluted solution was taken out in a test tube, 6 cc. of $0.05N$ HCl and 1 cc. of water were added, when pH value became about 1.4. 3 drops of 0.2% $NaNO_2$ solution was added, shaken for 3 mins., 1 drop of 10% $NH_4SO_3NH_2$ solution added, and shaken again for 1.5 mins. 4 drops of 0.2% 1-dimethylaminoethylaminonaphthalene (Tsuda's reagent[5]) was then added and the total volume was adjusted to 10.0 cc. After 15 mins., the determination was carried out using Shimadzu DF-II electric photometer, with 550-mμ filter and cell of 0.50 cm. The calculation was made from formula $Y=1.185X$, where Y is the concentration of sulfadiazine in mg% and X is the optical density ($X < 0.7$).

e) Determination of Mean Diameter and Standard Deviation of Particle Size Distribution—It is well known that in many cases the distribution of particle size of a powder is logarithmic normal and at this state the mean diameter and the standard deviation can be estimated plotting the distribution on log-probability paper.[6] In this study the weight-undersize percentage was plotted on the log-probability paper (Japan Stand. Assoc.), and a straight line was obtained, from which 50% diameter in log (μ) and the difference between 84% (or 16%) diameter and 50% diameter in log (μ) was considered as log of geometric weight mean diameter and that of geometric weight standard deviation, respectively. The reproducibility of this procedure was very satisfactory and gave the following values for the starting material.

Run	Log of mean diam.	Log of standard deviation
1	1.561	0.275
2	1.563	0.276
3	1.562	0.273

Result

The result obatained from the present series of experiments is given in Table I, in which the values are given in the logarithm of geometric-weight mean diameter and geometric-weight standard deviation, and these values are used throughout in further discussions.

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5) K. Tsuda, *et al.*: Yakugaku Zasshi, **62**, 362(1942); *ibid.*, **67**, 239(1947).

6) J. B. Austin: Ind. Eng. Chem., **11**, 334(1939); R. C. Cadle: "Particle Size Determination," Interscience Publ. Inc., New York (1955); G. Herdan: "Small Particle Statistics," Elsevier, New York (1953).

The distribution obtained experimentally were recognized as the logarithmic normal in all cases, the same as in the starting material. The solubility is also given in Table I.

TABLE I. Original Data

comb. S P T M	solb.	diam.	stdv.	comb. S P T M	solb.	diam.	stdv.	comb. S P T M	solb.	diam.	stdv.
1 1 1 1	21	1.517	0.279	2 1 1 1	16	1.553	0.267	3 1 1 1	10	1.548	0.296
1 1 1 2	31	1.555	0.279	2 1 1 2	20	1.532	0.306	3 1 1 2	12	1.530	0.296
1 1 1 3	11	1.563	0.291	2 1 1 3	10	1.531	0.303	3 1 1 3	9	1.539	0.299
1 1 1 4	16	1.559	0.271	2 1 1 4	22	1.577	0.293	3 1 1 4	10	1.549	0.289
1 1 2 1	20	1.548	0.290	2 1 2 1	18	1.543	0.287	3 1 2 1	19	1.549	0.295
1 1 2 2	30	1.565	0.291	2 1 2 2	26	1.572	0.300	3 1 2 2	22	1.564	0.288
1 1 2 3	24	1.561	0.275	2 1 2 3	23	1.589	0.285	3 1 2 3	22	1.548	0.280
1 1 2 4	24	1.592	0.278	2 1 2 4	25	1.588	0.264	3 1 2 4	24	1.592	0.282
1 1 3 1	47	1.549	0.287	2 1 3 1	61	1.572	0.262	3 1 3 1	46	1.587	0.279
1 1 3 2	49	1.605	0.287	2 1 3 2	45	1.581	0.265	3 1 3 2	48	1.601	0.271
1 1 3 3	49	1.617	0.247	2 1 3 3	50	1.602	0.264	3 1 3 3	56	1.597	0.275
1 1 3 4	57	1.609	0.237	2 1 3 4	51	1.592	0.244	3 1 3 4	57	1.601	0.251
1 1 4 1	134	1.618	0.274	2 1 4 1	128	1.605	0.261	3 1 4 1	113	1.622	0.272
1 1 4 2	123	1.624	0.254	2 1 4 2	125	1.620	0.274	3 1 4 2	125	1.630	0.252
1 1 4 3	133	1.635	0.237	2 1 4 3	142	1.642	0.252	3 1 4 3	144	1.632	0.252
1 1 4 4	145	1.632	0.232	2 1 4 4	165	1.642	0.250	3 1 4 4	165	1.623	0.225
1 2 1 1	23	1.549	0.301	2 2 1 1	20	1.531	0.289	3 2 1 1	19	1.550	0.268
1 2 1 2	27	1.568	0.296	2 2 1 2	25	1.547	0.269	3 2 1 2	20	1.529	0.299
1 2 1 3	20	1.571	0.273	2 2 1 3	17	1.553	0.287	3 2 1 3	17	1.580	0.272
1 2 1 4	20	1.574	0.266	2 2 1 4	22	1.550	0.276	3 2 1 4	18	1.570	0.270
1 2 2 1	77	1.558	0.296	2 2 2 1	60	1.558	0.286	3 2 2 1	28	1.574	0.288
1 2 2 2	43	1.548	0.288	2 2 2 2	39	1.579	0.279	3 2 2 2	39	1.580	0.282
1 2 2 3	45	1.583	0.285	2 2 2 3	38	1.591	0.269	3 2 2 3	43	1.579	0.279
1 2 2 4	45	1.567	0.259	2 2 2 4	41	1.592	0.272	3 2 2 4	40	1.591	0.267
1 2 3 1	103	1.605	0.265	2 2 3 1	81	1.599	0.235	3 2 3 1	83	1.590	0.288
1 2 3 2	87	1.605	0.265	2 2 3 2	84	1.600	0.250	3 2 3 2	86	1.598	0.254
1 2 3 3	86	1.600	0.262	2 2 3 3	86	1.640	0.244	3 2 3 3	86	1.600	0.250
1 2 3 4	83	1.619	0.261	2 2 3 4	88	1.616	0.236	3 2 3 4	97	1.610	0.250
1 2 4 1	203	1.619	0.249	2 2 4 1	178	1.605	0.249	3 2 4 1	192	1.600	0.240
1 2 4 2	212	1.634	0.242	2 2 4 2	195	1.614	0.236	3 2 4 2	193	1.619	0.231
1 2 4 3	201	1.639	0.235	2 2 4 3	205	1.621	0.229	3 2 4 3	215	1.641	0.221
1 2 4 4	219	1.642	0.234	2 2 4 4	222	1.640	0.228	3 2 4 4	230	1.646	0.226
1 3 1 1	51	1.560	0.304	2 3 1 1	46	1.548	0.280	3 3 1 1	50	1.575	0.277
1 3 1 2	53	1.580	0.276	2 3 1 2	41	1.568	0.278	3 3 1 2	40	1.576	0.284
1 3 1 3	38	1.581	0.283	2 3 1 3	37	1.580	0.258	3 3 1 3	32	1.585	0.275
1 3 1 4	38	1.583	0.273	2 3 1 4	35	1.585	0.273	3 3 1 4	36	1.601	0.271
1 3 2 1	81	1.573	0.287	2 3 2 1	97	1.582	0.286	3 3 2 1	64	1.586	0.280
1 3 2 2	74	1.585	0.297	2 3 2 2	76	1.584	0.280	3 3 2 2	66	1.594	0.280
1 3 2 3	77	1.603	0.275	2 3 2 3	74	1.568	0.254	3 3 2 3	66	1.597	0.273
1 3 2 4	85	1.605	0.267	2 3 2 4	83	1.613	0.257	3 3 2 4	67	1.590	0.260
1 3 3 1	150	1.606	0.278	2 3 3 1	156	1.607	0.277	3 3 3 1	146	1.590	0.270
1 3 3 2	175	1.609	0.275	2 3 3 2	166	1.601	0.249	3 3 3 2	154	1.600	0.260
1 3 3 3	144	1.614	0.248	2 3 3 3	168	1.606	0.266	3 3 3 3	155	1.612	0.256
1 3 3 4	158	1.615	0.239	2 3 3 4	167	1.619	0.239	3 3 3 4	169	1.629	0.251
1 3 4 1	308	1.612	0.242	2 3 4 1	302	1.612	0.248	3 3 4 1	290	1.639	0.233
1 3 4 2	298	1.613	0.243	2 3 4 2	320	1.608	0.230	3 3 4 2	285	1.640	0.224
1 3 4 3	300	1.643	0.231	2 3 4 3	304	1.661	0.225	3 3 4 3	304	1.665	0.217
1 3 4 4	302	1.663	0.211	2 3 4 4	320	1.665	0.225	3 3 4 4	320	1.640	0.224

comb. : Combination
diam. : Log of geometric weight mean diameter (μ)
stdv. : Log of geometric standard deviation (μ) of weight distribution
solb. : Solubility in mg%

The minimum and the maximum were as follows :

	Min.	Max.
Mean Diam.	1.517 (32.9 μ)	1.665 (46.2 μ)
Standard Deviation	0.211	0.304
Solubility	9.0 mg%	320 mg%

The mean diameters of some preparations, such as in T_1 and T_2M_1 groups, were smaller than that of the starting material. It may be considered that such a state comes from the difference in wettability. Since the contact between a crystal and a vehicle becomes complete during preservation and a free sedimentation may occur, a determination after preservation would be closer to the true behavior of particles.

0.1 to 3.0% of the material dissolved to saturation, and the influence of such a circumstance is not known easily, but, it may not disturb to analyse the result.

Analysis of the Result

1. Analysis of Variance of Mean Diameter—The original datum was transformed as follows:

$$Y=(y-1.562)\times 1000$$

where Y is the transformed value and y is the original datum. The analysis of variance of the mean diameter obtained is given in Table II and the main effects P, T, and M are highly significant, and the interaction P×T is significant. The effect P is shown in Table III, in which the values are the mean of 48 determinations in log (μ).

TABLE II. Analysis of Variance Table of Mean Diameter

Factor	S.S.	D.F.	M.S.	F_0
Additive (S)	119	2	60	
pH value (P)	9989	2	4995	33.8**
Temperature (T)	103703	3	34568	233.6**
Period (M)	14505	3	4835	32.7**
S×P	403	4	101	
S×T	814	6	136	
S×M	896	6	149	1.0
P×T	2044	6	341	2.3*
P×M	486	6	81	
T×M	746	9	83	
Error	14229	96	148	
Total	147934	143		

* Significant at 5% level ** Significant at 1% level

TABLE III. Main Effect, P

P	Mean Diameter	P	Mean Diameter	P	Mean Diameter
P_1(pH 6.8)	1.583	P_2(pH 7.2)	1.591	P_3(pH 7.6)	1.604

Figs. 5 and 6 show the main effect T and M. The interaction P×T is shown in Fig. 2, in which each point is the mean of 12 determinations and the dotted curves are approximate regression curves assumed, and it may be caused by the different increases of solubility. The solubility curve of sulfadiazine is given in Fig. 3, in which each point represents the mean of 12 determinations.

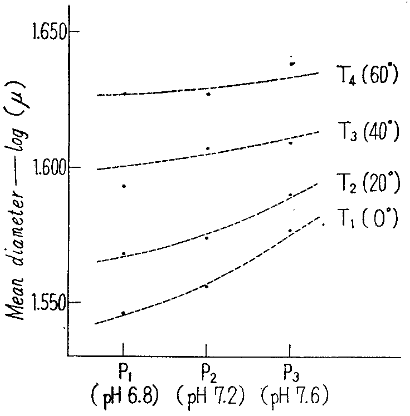

Fig. 2. Interaction P×T

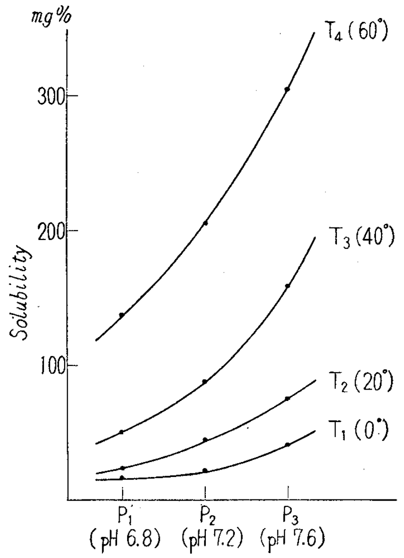

Fig. 3. Solubility Curve of Sulfadiazine

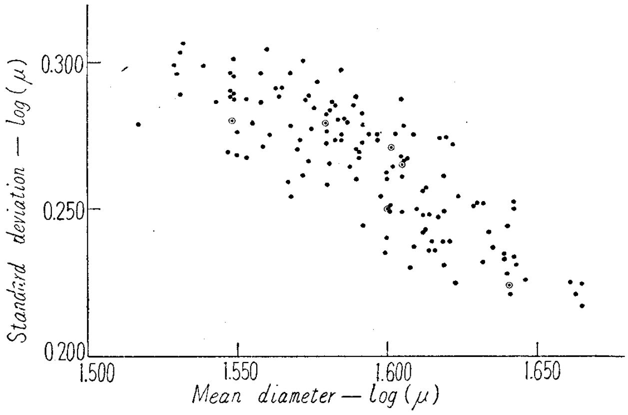

Fig. 4. Scatter Diagram

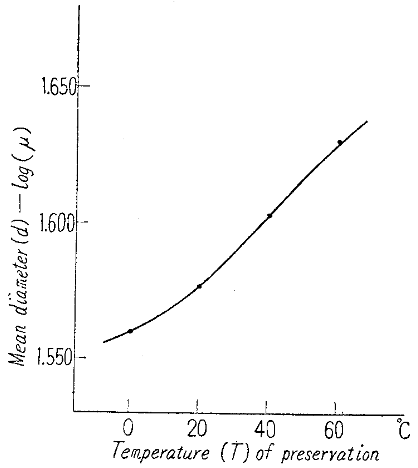

Fig. 5. Relation between Mean Diameter and Temperature of Preservation

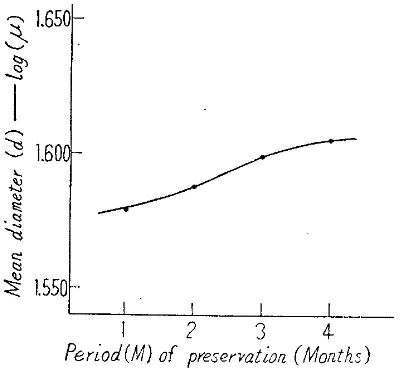

Fig. 6. Relation between Mean Diameter and Period of Preservation

— Calculated curve • Value obtained

2. Analysis of Variance of Standard Deviation—The original datum was transformed as follows:

$$Y' = (y' - 0.250) \times 1000$$

where Y' is the transformed value and y' is the original datum. The analysis of variance of mean diameters obtained is given in Table IV and the result is the same as that of mean diameter, main effects P, T, and M being highly significant and interaction P×T significant. The unexpected interaction S×P, however, is also significant. Tween 65 and 20 are nonionic surfactants and their interaction with pH can not be considered. The reason is not known why this interaction is significant. Perhaps the very high significance of main effect P has caused such a result.

TABLE IV. Analysis of Variance Table of Standard Deviation

Factor	S.S.	D.F.	M.S.	F_0
Additive (S)	334	2	167	1.9
pH value (P)	4252	2	2126	24.7**
Temperature (T)	43732	3	14577	169.5**
Period (M)	8494	3	2831	32.9**
S×P	1024	4	256	3.0*
S×T	1070	6	178	2.1
S×M	700	6	116	1.3
P×T	1303	6	217	2.5*
P×M	490	6	81	
T×M	1154	9	128	1.5
Error	8237	96	86	
Total	70790	143		

* Significant at 5% level ** Significant at 1% level

3. Relation between Mean Diameter and Standard Deviation—As expected from Tables II and IV, a negative correlation is found between mean diameter and standard deviation, and the scatter diagram is shown in Fig. 4. The correlation coefficient is −0.799 and highly significant by t-test:

$t_0=15.86>t(142, 0.01)$. This indicates that the standard deviation decreases with the increase of mean diameter.

In the same way, the regression coefficient of 1st and 3rd quatile diameter to the mean diameter was calculated. These diameters are represented as follows :

1st quatile diameter $d_{q1}=d-0.7s$
3rd quatile diameter $d_{q3}=d+0.7s$

where d is the mean diameter and s is the standard deviation. The regression coefficients were $b_{q1d}=1.387$ and $b_{q3d}=0.613$. Therefore the increasing rate of the 1st quatile diameter is about twice that of 3rd quatile diameter, and from this fact it may be said that the rate of change on the part of smaller particles is greater than that on the part of larger particles.

Discussion on the Change of Mean Diameter

Several considerations may be possible from the experimental result as obtained in this study. A discussion will be made on the change of mean diameter.

At first, the two large and small particles will be taken into consideration. It seems more reasonable to expect that there is a difference of solute concentration around these particles, judging from Ostwald-Freundlich's equation. If there is such a tendency, then the small particle will become smaller and the large one larger by diffusion, and the change of diameter occurs. Then such a tendency is accelerated further even if it is small. This relationship will be expressed by

$$k_1(A+d)^m \tag{1}$$

where k_1, m, and A are constants and d is the mean diameter.

Next, all the fine particles suspended will be taken into consideration. There are an enormous number of combinations of large and small particles and the change of mean diameter may be recognized as the integrated function of such combinations. From the analysis of the result obtained, a negative correlation was found between the mean diameter and standard deviation. Therefore it may be considered that the increase of a mean diameter produces the depressing effect to itself because of the decrease of standard deviation. The relationship will be expressed by

$$k_2(B-d)^n \tag{2}$$

where k_2, n, and B are constants.

In the whole suspension system composed of each combination of two particles, the changing rate of mean diameter is considered to be in proportion to the product of expressions (1) and (2), and it will finally be represented as Equation (3)

$$\frac{\partial(d)}{\partial(e)}=k_1(A+d)^m\times k_2(B-d)^n \tag{3}$$

where e is the factor promoting the change of mean diameter d.

In this study, though the levels are few, there was observed such a tendency as given by Equation (4), where m and n in (3) are taken as 1 and $k_1\times k_2$ is replaced with k.

$$\frac{\partial(d)}{\partial(e)}=k(A+d)(B-d) \tag{4}$$

Since the change of mean diameter was not so distinct and the preparations were placed directly in the studied conditions, the exact differential is considered to be possible and the integrated equation of Equation (4) is obtained as follows :

$$e=\frac{1}{k}\frac{1}{A+B}\ln\frac{A+d}{B-d}+I \tag{5}$$

where I is the constant of integration.

The values of constants k, A, B, and I are considered to be influenced by physical and chemical properties of the material used, for example, solubility, diffusion coefficient, shape factor, particle size distribution, etc., and further by properties of added substances and the condition of preservation. A suspensional preparation has so many kinds of complicated elements and consequently it is very difficult to estimate these constants by merely determining the foregoing properties.

It is often experienced that the crystal of sulfanilamide becomes larger in the hydrophilic ointment J. P. judging from the tactual sense. This is considered to be influenced by the greater solubility of sulfanilamide (1 g./125 cc. of water) and physical and chemical properties of the several substances added to the base ointment, such as the solubilizing effect of surfactant, etc. In this study the particle of sulfadiazine did not grow so large as to become visible to the naked eye. The difference is considered to be attributable to the smaller solubility of sulfadiazine (1 g./13000 cc. of water) and less influence of other physical and chemical properties.

Equation (5) represents a sigmoid function and the value of d cannot be larger than B. If it is desirable for suspensions that the mean diameter does not become so large, then the value of $(A+B)$ must be small. Concerning the examples described above, it may be possible that the value of $(A+B)$ in the sulfadiazine suspension is smaller than that of the sulfanilamide ointment.

A small standard deviation of the particles is also desirable for the stability of suspension. This condition means that the mean diameter is close to the value of B, in other words, to the final stage of change. The flocculation and aggregation of particles must be avoided for the same purpose.

By fitting the Equation (5) for the result obtained, the relation between the mean diameter (d) and temperature (T in °C) of preservation is obtained as Equation (6), shown in Fig. 5, in which each point represents the mean of 36 determinations.

$$T=50.18\times\log\frac{d-1.544}{1.668-d}+41.9 \tag{6}$$

Equation (6) was obtained by the following procedure. At first the mean diameter at each subdivided point of T was estimated by Newton's interpolation formula and then the slope at each point was calculated using again the interpolation formula. Such a slope as calculated in this procedure is nearly equal to the differential coefficient. The constants k, A, and B were estimated by fitting these values to Equation (4) by the method of least squares. Finally constant l was estimated by fitting the values obtained to Equation (5). These estimated constants are therefore statistical values.

Using the same procedure, Equation (7) was obtained on the relationship between mean diameter (d) and period (M) of preservation in month, shown in Fig. 6, in which each point represents the mean of 36 determinations.

$$M=1.594\times\log\frac{d-1.575}{1.607-d}+2.23 \tag{7}$$

From Figs. 2 and 3, the same tendency was expected between the mean diameter and pH value or solubility, that is, the changing rate of mean diameter is not parallel with solubility, but related to the increase of mean diameter itself.

Combining Equations (6) and (7), Equation (8) was obtained on the relationship of mean diameter vs. temperature and period, shown in Fig. 7, in which each point represents the mean of 9 determinations.

$$\begin{aligned} d=&\left\{1.544+1.668\exp\left(\frac{T-41.9}{21.79}\right)\right\}\Big/\left\{1+\exp\left(\frac{T-41.9}{21.79}\right)\right\}\\ &+\left\{1.575+1.607\exp\left(\frac{M-2.23}{0.6921}\right)\right\}\Big/\left\{1+\exp\left(\frac{M-2.23}{0.6921}\right)\right\}-1.593 \end{aligned} \tag{8}$$

where constant 1.593 is the mean of all the determinations.

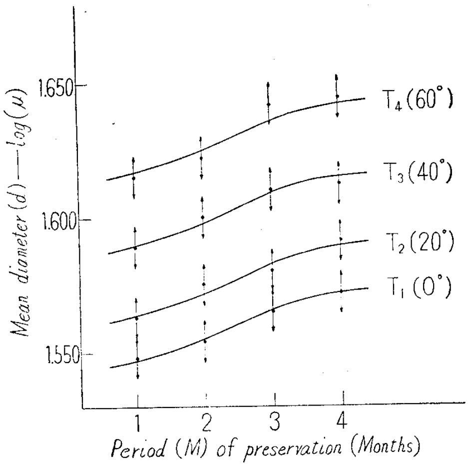

Fig. 7. Relation of Mean Diameter vs. Temperature and Period of Preservation

— Calculated curve

• Value obtained

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Summary

The effect of added substance (S) and pH (P) of the vehicle, and temperature (T) and period (M) of preservation on the change of mean diameter of suspended particles was investigated with a sulfadiazine suspension, and the following conclusions were drawn:

1) The distribution of particle size was logarithmic normal throughout the determinations, the same as in the starting material.

2) As a result of factorial analysis of the mean diameter, main effects P, T, and M were highly significant and interaction $P \times T$ was significant.

3) The same result was obtained on the analysis of standard deviation.

4) A highly significant negative correlation was found between the mean diameter and standard deviation.

5) As observed in this study, it may be considered that there is a maximum to the increase of particle size and the tendency is represented as follows :

$$e=\frac{1}{k}\frac{1}{A+B}\ln\frac{A+d}{B-d}+I$$

where e is the factor promoting the change of mean diameter d, and k, A, B, and I are constants which are expected to be influenced by physical and chemical properties of the material used, the vehicle, and other conditions.

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