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Studies on Pharmaceutical Suspension. IV.[1] Flocculation of Dispersed Phase and Structural Viscosity

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Sedimentation and flocculation of dispersed phase were studied using Newtonian and non-Newtonian suspensions of calcium carbonate. The constant K in the Robinson equation proved to be dependent upon the degree of flocculation rather than upon particle shape and roughness only as was previously reported by Robinson. It was also revealed that the K was closely related to the structural viscosity of suspension, showing a figure near to 4 for Newtonian suspension and larger than 4 as the suspension's structural viscosity increased.

Relations were also studied between the volume of the immobilized medium on particle surface and the structural viscosity of suspension. It was revealed that the volume of the immobilized medium on particle surface varied depending upon the kind of suspending medium and the larger the volume of the immobilized medium the greater the relative effect on structural viscosity.

Flocculated suspension, wherein particles form network, generally flows in non-Newtonian fashion. It is generally admitted that flocculation in suspension mainly results from particle–particle and/or particle–medium interaction.[3] Particle–medium interaction is governed by affinity of the particle surface for a suspension medium.

A study[4] on particle–medium interaction in oil suspension revealed that dispersing medium in Newtonian suspension showed high affinity for dispersed phase and non-Newtonian suspension showed low affinity. It was also revealed that changes in structural viscosity of suspensions were due largely to the degree of flocculation in dispersed phase.[5]

Einstein[6] derived a theoretically valid equation for the flow of suspension with low volume concentration of dispersed phase,

$$(\eta-\eta_0)/\eta_0=K\cdot V \qquad (1)$$

where η is suspension viscosity, η_0 is the viscosity of dispersing medium, V is the volume fraction per unit volume of suspension of dispersed phase and K is a constant with a value of 2.5 for spheres. However, the equation applies only to the flow under some required conditions. Robinson[7] expanded a range of application of Einstein's equation to higher concentration,

$$\eta_{sp}=K\cdot V/(1-S\cdot V) \qquad (2)$$

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[1] Part III: M. Aoki, *et al.*, *Yakuzaigaku*, **28**, 213 (1968).

[2] Location: *a*) *Fukushima-ku*, *Osaka*; *b*) *Toneyama*, *Toyonaka*, *Osaka*.

[3] A.S. Michaels and J.C. Bolger, *Ind. Eng. Chem. Fundamentals*, **1**, Feb., 24, No. 3, Aug., 153, (1962), **3**, No. 1, Feb., 14, (1964); A.I. Medalia and E. Hagopian, *Rheologica Acta*, **3**, 100, (1963).

[4] M. Aoki, A. Kamada, H. Fukuchi, and Y. Sumiyama, *Yakuzaigaku*, **28**, 213 (1968).

[5] M. Aoki, H. Fukuchi, and S. Nakaya, *Chem. Pharm. Bull.* (Tokyo), **16**, 171, (1968).

[6] A. Einstein, *Ann. Phys. Lpz.*, **34**, 591, (1911).

[7] J.V. Robinson, *J. Phys. Colloid Chem.*, **53**, 1042 (1949); **55**, 455, (1951); *Trans. Faraday Soc.*, **1**, 15, (1957).

where η_{sp} is specific viscosity, S is relative sediment volume, *i. e.*, sediment volume per unit volume of solids, and K is tentatively assigned as factor to be influenced by particle roughness, shape and the presence or absence of an adsorbed shell of medium around particles.

In case of thick suspension, however, Robinson's K seems to be more influenced by the degree of flocculation in dispersed phase than factors such as particle roughness and shape.

The present study was made in clarifying relations between Robinson's K and the degree of flocculation in terms of suspension's structural viscosity. A study was also made on relations between $S \cdot V$, the sediment volume fraction per unit volume of suspension, and suspension's structural viscosity.

Experimental

Materials——Commercially available three calcium carbonate powders[8] different in their particle size distribution (PSD) and oil vehicles, *i.e.*, mineral oil–light (MO–70),[9] -heavy (MO–350)[9] and olive oil[10] were used. Determination was made on acid value in olive oil after being washed thoroughly with 0.01 N Na_2CO_3 solution and purified water. Acid value was lowered from 0.253 to 0.058. Physical properties of oil vehicles, *i.e.*, surface tension, viscosity and density were determined at 31°, using DuNouy tensiometer, Ubbellohde viscometer and Gay–Lussac type pychnometer, respectively (Table I).

Previously, flow curve of the oil vehicles employed here was found to be Newtonian.[5]

Table I. Physical Properties of Oil Vehicles (at 31°)

Oil	Surface tension (dyne/cm)	Viscosity (cps)	Density
Olive oil	37.9	50.8	0.908
MO–70	34.3	14.1	0.837
MO–350	36.3	97.9	0.878

Characteristics of $CaCO_3$–powders employed were as follows: $CaCO_3$–NZ, consisting of the largest particles in size and the broadest PSD. (29.6% of consisting particles are 10—15 μ in size, the largest being less than 55 μ); $CaCO_3$–S, less in size with narrower PSD than –NZ. (32.0% are 5—10 μ, the largest being less than 50 μ); $CaCO_3$–400, the smallest in size and with the narrowest PSD. (32.5% are less than 5 μ, 48.2% are between 5—10 μ and the largest is less than 30 μ). The specific surface area of powder was determined from nitrogen adsorption measurements by using the BET method, revealing 4.85×10^3 cm^2/g for –NZ, 8.98×10^3 cm^2/g for –S and 11.60×10^3 cm^2/g for –400. Density of the powder, 2.71 g/cm^3, was determined with Beckman pychnometer. With a gravimetric method, determination was made on moisture content of the powder after being kept in a 0.1 mmHg vacuum desiccator containing P_2O_5 as a desiccant for 24 hours at 60°, revealing 0.395% for –400, 0.195% for –S and 0.350% for –NZ.

Preparation of Suspensions——Suspensions of $CaCO_3$–powders were prepared on volume–volume basis at the volume fraction of 0.03, 0.05, 0.07 and 0.09. The required amount of powder, calculated from density, was weighed in a glass beaker. A sufficient amount of oil was added and mixed well with calcium carbonate powder by a TK–Homomixer[11] at 5000 rpm for 2 minutes. The suspensions were then placed in a vacuum desiccator for about 24 hours at 31° before the initial rheogram was obtained.

Analysis for Powder Content——An analysis for powder content was made on each suspension by vaporizing the vehicle over low gas flames and burning the powder in an electric muffle furnace at 1000°. The weight of calcium carbonate was calculated from the residual CaO. From those data and powder density, the volume per cent of powder was determined. The precision of this analysis was about 99.90%.

Rheology——Flow curve of suspensions was obtained with a Shimadzu Universal Pheometer UR-1M (rotationl viscometer)[12] from a shearing rate of 27.5 sec^{-1} to 265 sec^{-1} at 31°±0.2°. Further details for the rheological procedure were decribed in a previous paper.[5]

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8) Nittoh Chemical Industry (Hiroshima). A histogram for the PSD of $CaCO_3$–powders was shown in previous paper.[5]
9) Silcol P–70 and P–350, Matsumura–Sekiyu Co., Nishinomiya.
10) Japanese Pharmacopeia VII.
11) TK–Homomixer type M. Tokushukika–Kogyo Co., Fukushima-ku, Osaka.
12) Shimadzu Seisakusho Ltd., Kyoto.

Following Porter's method,[5,13] the structural viscosity of suspension was calculated from the flow curve plotted on log–log paper. With a comparison method using a standard oil,[14] determination was made for suspension viscosity at 31°. In non-Newtonian suspensions, a definite curvature set in at low shearing rate, but curves were linear at higher shearing rate. Thus, the plastic viscosity was calculated from the slope of the linear portion of the flow curve.

Sedimentation——Sedimentation was studied with a graduated glass cylinder 150 mm in height and 13 mm in inner diameter. The inner diameter was made constant throughout the whole length of the cylinder. The glass cylinder with the suspension was vertically kept in an oven at 31° for 2 weeks, and ultimate sedimentation height, Hu, was measured. The present experiments showed that suspensions containing up to 0.09 volume fraction of dispersed phase settled completely in about 24 hours. Determination was made on redispersibility of the completely settled suspension with a vertical rotator at 25 rpm for 5 minutes. The reduced sedimentation height, *H*r, by rotation was measured and the redispersibility was calculated,

$$\text{Redispersibility} = (H_u - H_r)/H_u \times 100$$

Results and Discussion

Through a concentration range of dispersed phase, olive oil suspension exhibited Newtonian behavior. Newtonian behavior was also shown by MO–70 and –350 suspensions having the lowest volume concentration. However, other suspensions were pseudoplastic. Typical flow curves were shown in Fig. 1.

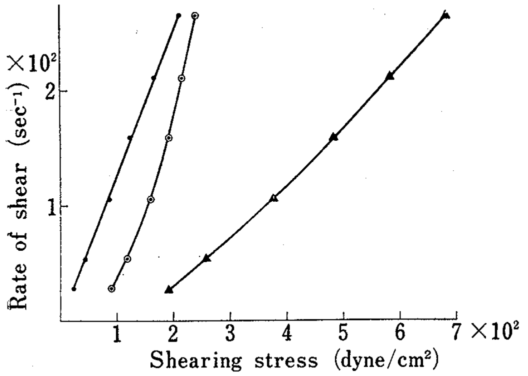

Fig. 1. Typical Flow Curves for $CaCO_3$–400 Suspensions of 0.09 Volume Fraction

—●—: olive oil —⊙—: MO-70 —▲—: MO-350

The quantity H_u/H_0 (ratio of ultimate sediment height to initial height of suspension), redispersibility and structural viscosity *N* were shown in Table II.

In comparison with MO–suspensions, olive oil suspension showed extremely low H_u/H_0 and high redispersibility. Olive oil suspension redispersed 100% but MO–suspensions were 25—70%. Structural viscosity *N* of olive oil

Table II. Structural Viscosity, Redispersibility and H_u/H_o Ratio of Suspensions

Vehicle		Olive oil			MO–70			MO–350		
Powder	V.F.[a]	H_u/H_o (%)	R.D.[b] (%)	N[c]	H_u/H_o (%)	R.D.[b] (%)	N[c]	H_u/H_o (%)	R.D[b] (%)	N[c]
$CaCO_3$-NZ	0.03	6.1	100.0	1.0	14.0	100.0	1.0	15.3	32.5	1.0
	0.05	10.5	100.0	1.0	22.5	55.6	1.1_3	23.5	30.7	1.0_7
	0.07	14.3	100.0	1.0	30.5	56.2	1.2_4	32.1	33.1	1.1
	0.09	18.2	100.0	1.0_5	38.7	54.3	1.3_4	41.7	32.8	1.1_9
$CaCO_3$-S	0.03	7.8	100.0	1.0	22.6	100.0	1.0	27.0	47.5	1.0
	0.05	12.3	100.0	1.0	37.3	64.3	1.2_7	41.9	26.0	1.1_8
	0.07	16.0	100.0	1.0	65.1	47.8	1.4_6	53.0	26.1	1.4_2
	0.09	21.0	100.0	1.0_5	51.9	70.5	1.7_4	69.7	22.5	1.4_3
$CaCO_3$-400	0.03	8.8	100.0	1.0	37.3	100.0	1.0_1	38.9	54.6	1.1
	0.05	14.0	100.0	1.0	53.9	74.7	1.6_8	58.5	43.6	1.4_1
	0.07	20.0	100.0	1.0	71.7	49.8	1.8_3	82.3	23.9	1.5_7
	0.09	25.3	100.0	1.0_5	92.0	25.5	2.1_4	94.3	6.0	1.7_7

a) volume raction of dispersed phase *b*) redispersibility of suspension *c*) structural viscosity of suspension

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13) A.W. Porter and P.A.M. Rao, *Trans. Faraday Soc.*, 23, 311 (1927).

14) Japan Industrial Standard, JS–20, –50, –100, –200, Showa–Sekiyu, Rigo-sha, Tokyo.

suspension was always similar to 1.0, revealing the flow to be Newtonian. On the other hand, N of MO–suspensions showed a marked increase as the volume fraction of dispersed phase increased, especially in MO–70 suspension. The effect of PSD of $CaCO_3$–powder on N was very significant. Calcium carbonate–400 powder having the most narrow PSD and the largest surface area showed the maximum N and the minimum was shown by calcium carbonate–NZ having the broadest PSD and the smallest surface area.

In view of the above findings, it seemed reasonable to assume that MO–suspensions had higher degree of flocculation of dispersed phase than olive oil suspension. It was reported that the higher the H_u/H_0 ratio the greater was the degree of flocculation of dispersed phase.[15] In MO–suspenions, primary particles were not responsible for the basic flow unit but floccules with enclosed dispersing medium were responsible.[4] These floccules had certain amount of mechanical strength with which to retain their forms under low shear rates. It has been shown that floccules tend to approach a uniform size in any shear field.[16] This size increased as suspension concentration increased or as shear rate decreased.[5] At low shear rates, the floccules tend to group into clusters of floccules. These floccules would join together to form expanded networks and give the suspension its structural viscosity. On the other hand, olive oil suspension showed small H_u/H_0 ratio, easy redispersibility and Newtonian flow. The flow unit in olive oil suspension consisted of primary particles or floccules in low degree (primary floccules).[4] If subjected to shear, those primary particles or floccules freely settled or freely flowed towards a shearing direction with no interactions, resulting in low H_u/H_0 ratio and the Newtonian flow. Thus, it can be said that the viscosity of suspension was more influenced by the degree of flocculation in dispersed phase than the original property of suspended particles. Accordingly, the constant K in Eq. 2 seems to show a varying degree of flocculation in dispersed phase.

Equation 2 can be rearranged into Eq. 3

$$1/\eta_{sp}=1/K\cdot V-S/K \qquad (3)$$

By plotting $1/V$ against $1/\eta_{sp}$, constant K is obtained by the reciprocal of the slope of straight line. Constant S is also obtained by the determined K and the Y intercept (Fig. 2).

The larger the tangent of the straight line the smaller is the constant K. The constant K of MO–suspensions having a high degree of flocculation showed marked changes with variations of dispersed phase. MO–70 suspension showed larger K than –350 suspension. Despite variations with dispersed phase, olive oil suspension showed almost constant K. Table III presents data in a form suitable for comparing K with the structural viscosity of suspensions of the 0.09 volume fraction.

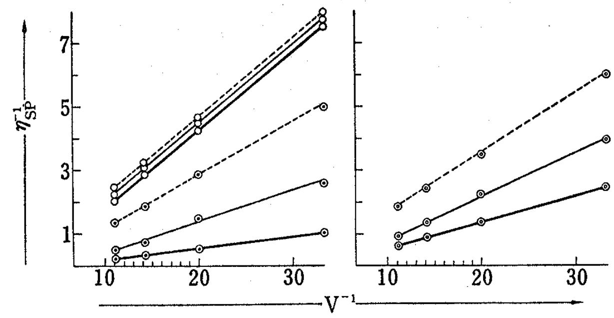

Fig. 2. Relation between η_{sp}^{-1} and V^{-1} in Robinson's Equation

$CaCO_3$-NZ	$CaCO_3$-S	$CaCO_3$-400
---○---: olive oil	—○—: olive oil	—○—: olive oil
---⊙---: MO-70	—⊙—: MO-70	—⊙—: MO-70
---◎---: MO-350	—◎—: MO-350	—◎—: MO-350

Despite variations with dispersed phase, K of olive oil suspension was always near to 4. In the MO–suspensions showing flocculation in high degree, K was always larger than 4 with an increase as the suspension's structural viscosity increased. Again, K of MO–70 suspension was always larger than that of MO–350; so was the structural viscosity.

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15) B.A. Haines, Jr. and A.N. Martin, *J. Pharm. Sci.*, **50**, 228, (1961).

16) I. Reich and R.D. Vold, *J. Phys. Chem.*, **63**, 1497, (1957).

Table III. Comparison between Robinson's K and the Structural Viscosity (N) of Suspensions at the Volume Fraction of 0.09

Vehicle / Powder	Olive oil		MO–70		MO–350	
	K	N	K	N	K	N
$CaCO_3$–NZ	4.0_0	1.0_5	6.0_8	1.3_4	5.2_9	1.1_9
$CaCO_3$–S	4.0_5	1.0_5	10.5_0	1.7_4	7.4_1	1.4_3
$CaCO_3$–400	4.0_7	1.0_5	27.8_7	2.1_4	12.1_7	1.7_7

In olive oil preparation showing flocculation in low degree with a free flowing towards a shearing direction, K remained unaffected, despite changes in the property of dispersed particles.

It seems reasonable to assume that K, which is considered by Robinson to refer to roughness and shape factors, depends on the degree of flocculation.

The denominator in Eq. 2, $(1-S\cdot V)$, is considered as the volume fraction of free suspension medium, S defined (Robinson) as a relative sediment volume. Thus, $S\cdot V$ corresponds to the sediment volume fraction per unit volume of suspension. $S\cdot V$ multiplied by a total volume of suspension gives a total sediment volume. The total sediment volume consists of the volume of settled particles plus the volume (designated as the volume of immobilized shell) of an absorbed or adsorbed medium around the particles. The dispersed particles are considered to contain a large number of small interstices so that more immobilized shell might be formed on their surface area. It is likely that larger the volume of immobilized shell the greater the relative effect on structural viscosity.

The quantity S in Eq. 3 was considered to be related to the volume of immobilized shell. S was calculated from the determined value of K and the Y intercept in Eq. 3 (Table IV). The volume of immobilized shell, *i. e.*, the volume of interparticle medium, can be obtained as follows:

$$V_{ip}=V_t\cdot S\cdot V-V_p \qquad (4)$$

where V_{ip} is the volume of interparticle medium (cm^3), V_t is a total volume of suspension (cm^3) and V_p is a particle volume (cm^3) obtained by particle density and weight.

The total sediment volume of suspension, $V_t\cdot S\cdot V$, and the volume of interparticle medium, V_{ip}, are shown in Table IV.

Table IV. Sedimentation Data obtained from Equation 3 and 4

Vehicle Powder	$V.F.$	Olive oil			MO–70			MO–350		
		$V_t\cdot S\cdot V$ a) (cm^3)	V_{ip} b) (cm^3)	S	$V_t\cdot S\cdot V$ a) (cm^3)	V_{ip} b) (cm^3)	S	$V_t\cdot S\cdot V$ a) (cm^3)	V_{ip} b) (cm^3)	S
$CaCO_3$–NZ	0.03	0.96	0.36	1.59	1.57	0.98	2.64	0.96	0.40	1.66
	0.05	1.57	0.58		2.63	1.63		1.65	0.66	
	0.07	2.21	0.82		3.68	2.29		2.31	0.92	
	0.09	2.85	1.06		4.72	2.93		2.99	1.19	
$CaCO_3$–S	0.03	1.23	0.63	2.06	2.53	1.93	4.24	1.86	1.26	3.11
	0.05	2.05	1.06		4.22	3.22		3.09	2.10	
	0.07	2.87	1.48		5.91	4.51		4.33	2.94	
	0.09	3.69	1.90		7.59	5.80		5.57	3.78	
$CaCO_3$–400	0.03	1.57	0.98	2.66	3.38	2.66	5.67	2.33	1.73	3.92
	0.05	2.65	1.65		5.65	4.66		3.90	2.91	
	0.07	3.70	2.31		7.90	6.51		5.45	4.06	
	0.09	4.76	2.97		10.23	8.44		7.01	5.21	

a) total sediment volume of suspension *b)* volume of interparticle medium

The V_{ip} of MO–70 suspension was always larger than that of –350 suspension, the largest being $CaCO_3$–400 in –70 suspension. In addition, the V_{ip} increased proportionally as the volume fraction of dispersed phase increased (Fig. 3). Again, MO–70 suspension showed larger tangent of the straight line than –350 suspension.

The above data can be interpreted by an assumption that the thickness of immobilized shell on the particle surface differes depending upon the kind of suspending medium. Then, calculation was made of the thickness of the immobilized shell around particles.

Assuming that the immobilized shell has a constant thickness around each particle, the thickness can be expressed by the following equation,

$$T=1/2\cdot V_{ip}/V_p\cdot d_p\cdot W_{sp} \qquad (5)$$

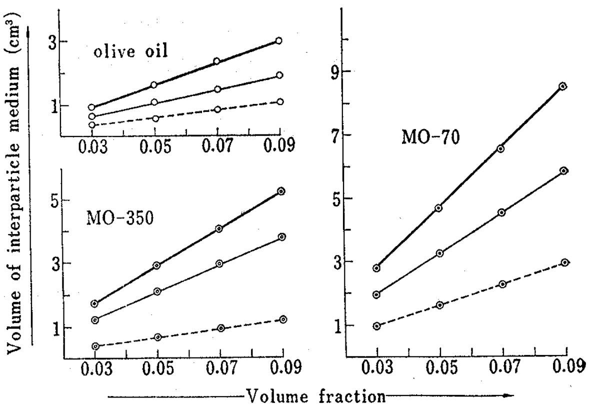

Fig. 3. Relation between Volume Fraction of Dispersed Phase and the Volume of Interparticle Medium

$CaCO_3$-NZ: ----- $CaCO_3$-S: —— $CaCO_3$-400: ——

where T is shell thickness around the particle in cm, d_p is particle density in g/cm^3 and W_{sp} is specific surface area of the particle in cm^2/g.

The results are tabulated in Table V.

Table V. Thickness of the Immobilized Shell around Particles (cm)

Powder	V.F.	Olive oil	MO–70	MO–350
$CaCO_3$–NZ	0.03	0.22×10^{-4}	0.62×10^{-4}	0.25×10^{-4}
	0.05	0.22	0.62	0.25
	0.07	0.22	0.62	0.25
	0.09	0.22	0.62	0.25
$CaCO_3$–S	0.03	0.22×10^{-4}	0.67×10^{-4}	0.43×10^{-4}
	0.05	0.22	0.67	0.43
	0.07	0.22	0.67	0.43
	0.09	0.22	0.67	0.43
$CaCO_3$–400	0.03	0.26×10^{-4}	0.74×10^{-4}	0.46×10^{-4}
	0.05	0.26	0.74	0.46
	0.07	0.26	0.74	0.46
	0.09	0.26	0.75	0.46

The shell thickness was affected in various degrees by suspending media and specific surface area of the particle but far less affected by volume fraction. The olive oil suspension whose structural viscosity was near to 1 showed the thinest shell thickness and the thickest was shown by MO–70 suspension, which was non-Newtonian.

These findings indicate that the thickness of the immobilized shell around particles was closely related to the structural viscosity of suspension. An increase in the shell thickness tends to increase the effective volume fraction of the dispersed particle, which makes a considerable contribution to the flow property of suspension.