a daily dose of a chemical to be tested was injected intraperitoneally into each mouse of a corresponding groups for 7 successive days. In another experiments, only one administration of 1.0 ml of suspension of a chemical to be tested was done as in the case of Table II.

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Studies on Pharmaceutical Suspensions. (1). On the Structural Viscosity of Oil Suspensions

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It is generally accepted that the physical properties of aqueous suspensions, including pharmaceuticals, are extremely complex requiring a profound knowledge of rheological characteristics in suspension formulation.

Despite many excellent discussions on the theory of flow concerning Newtonian and non-Newtonian materials so far published,[2-4)] little seems to have been clarified about the influence of dispersed phase on the rheological properties of suspensions, particularly at high concentration of dispersed phase. Thick suspenison showing an isothermal reversible sol-gel transformation under any rate of shear offer many problems to a pharmaceutical rheologist regarding manufacturing processes, storage and practical application.

This paper deals with some of the rheological factors which are responsible for the changes in flow properties of oil suspensions. It also refers to the influence of dispersed phase upon the structural viscosity of suspensions which are prepared with oils commonly used for external application.

Experimental

Materials——Three calcium carbonate powders different in particle size distribution were kindly provided by the Nittoh Powder Chemical Industry (Hiroshima).

The oil suspension vehicles used throughout this experiment were as follows: mineral oil-heavy (MO-350)[5)]; mineral oil-light (MO-70)[6)]; isopropyl myristate (IPM)[7)]; lanolinalcohol acetylate (AC)[8)]; olive oil.[9)]

In order to remove free acids, the last three materials were washed thoroughly with 0.1 N Na_2CO_3 solution and with purified water. By this procedure the acid value was lowered from 0.079 to 0.015, 0.077 to 0.047

1) Location: *Dojima-hamadori, Fukushima-ku, Osaka.*
2) C.C. Mill, "Rheology of Disperse Systems," Pergamaon Press, London, 1959.
3) J.J. Hermans, "Flow Properties of Dispersed Systems," North-Holland Publishing Co., Amsterdam, 1953.
4) E.K. Fisher, "Colloidal Dispersions," 3rd ed., John Wiley & Sons, Inc., New York, 1959.
5) Silcol P-350, Matsumura-Sekiyu Co., Nishinomiya, Hyogo.
6) Silcol P-70, Matsumura-Sekiyu Co., Nishinomiya, Hyogo.
7) Containing 99.5% of isopropyl myristate. Abrac, England.
8) Acecol-L, Croda, England.
9) J.P. VII.

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and 0.253 to 0.058, respectively. The particle size distribution of calcium carbonate powders determined by sedimetation and transillumination method with Micronphotosizer Model MSKK[10] is shown in Fig. 1.

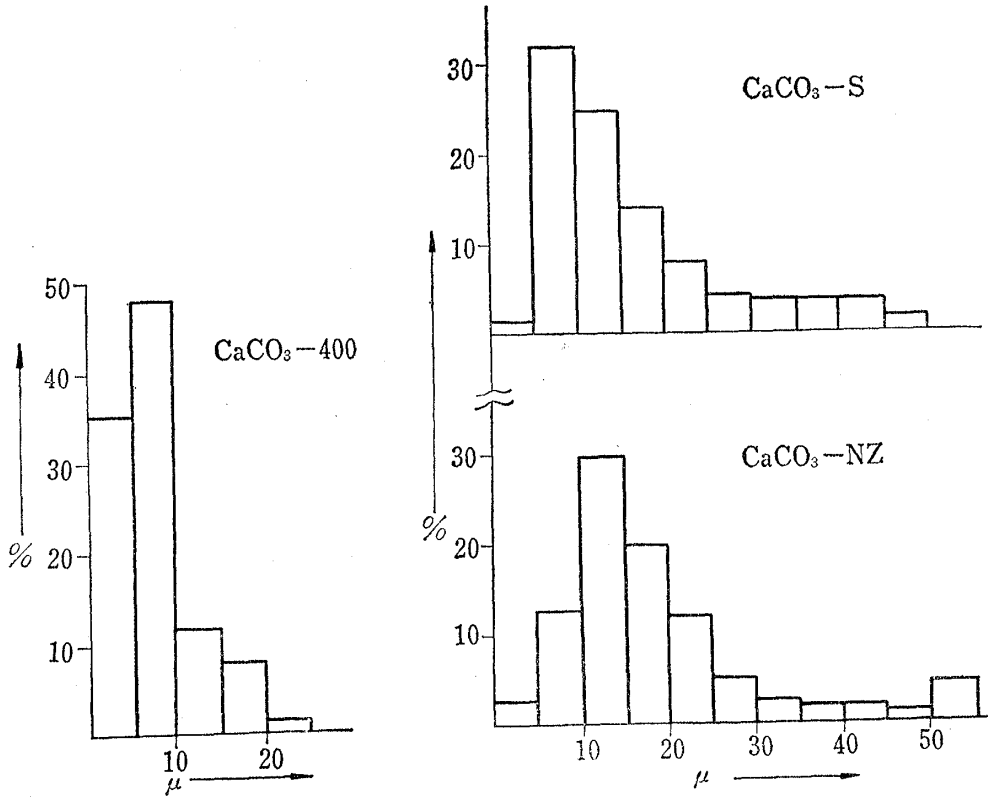

Fig. 1. Paticle Size Distribution of $CaCO_3$-powders

Preparation of Suspensions——Suspensions of calcium carbonate powder were prepared on weight-weight basis at the concentrations of 20, 30, 40 and 50%. The required amount of powder was weighed in a glass beaker. A sufficient amount of oil was added and mixed well with calcium carbonate powder by TK-Homomixer[11] at 5000 rpm for 2 minutes. The suspensions were then placed in a vacuum desiccator for about 24 hours before the initial rheogram was obatined.

Rheological Study——The rheology of oil suspension was studied with a Shimaz Universal Rheometer UR-1 M (rotational viscometer)[12] in which a cup containing the sample rotated, and a bob or inner cylinder hung into the cup by torsion wire. Care was taken to assure that no air was entrapped within the sample when the bob was mounted on the viscometer. To maintain the sample at a constant temperature, a water jakect was placed around the sample cup. Constant-temperature water was circulated througn the jakect and the sample was kept at $31°\pm0.2$ during measurement. The sample stood undisturbed for 15 minutes before it began to run,.

The cup could be manipulated to rotate from 6.0 rpm to 400 rpm. Rpm-torque relationships were measured at 6.9, 12.5, 25.0, 50.0 and 62.5 rpm with an increase and decrease of speed. A thirty-second observation was made for each rpm in terms of rotation and torque. With appropriate constants, rpm-torque values were converted to rate of shear (sec^{-1})-shearing stress ($dyne/cm^2$) values.

An empirical equation has been proposed by Porter[13] and other investigators[14,15] to express the flow curves produced by non-Newtonian mateials. Their expression is

$$D=A\cdot S^n \qquad \text{(Eq. 1)}$$

Where D=rate of shear, S=shearing stress, and A is constant. Written in a logarithmic form the equation is

$$\log D=n\cdot\log S+\log A \qquad \text{(Eq. 2)}$$

10) Seiko-Boeki Co., Ltd., Minato-ku, Tokyo.
11) TK-Homomixer type M. Tokushukika-Kogyo Co., Fukushima-ku, Osaka.
12) Shimaz Seisakusho, Ltd., Kyoto.
13) A.W. Porter and P.A.M. Rao, *Trans. Faraday Soc.*, **23**, 311 (1927).
14) F. Farrow, G. Lowe, and S. Neals, *J. Textile Inst.*, **19**, T18 (1928).
15) I.M. Krieger and S.H. Maron, *J. Colloid Sci.*, **6**, 528 (1951).

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The above equation gives a straight line where n is a slope. The value n is considered to be an index which describes the characteristic of flow curve and the structural change of non-Newtonian material, *i.e.*, when $n=1$ the flow is Newtonian, when greater than 1 it is pseudoplastic, and when less than 1 it is dilatant.

In this study, the n-values of each suspension were calculated from the flow curves which were plotted on log-log paper and the flow characteristics of suspensions were classified on the basis of suspensions' n-values.

Results and Discussion

All the flow curves obtained were linear apparently starting from origin of coordinates, and it was assumed that all the suspension vehicles studied were Newtonian materials (Fig. 2).

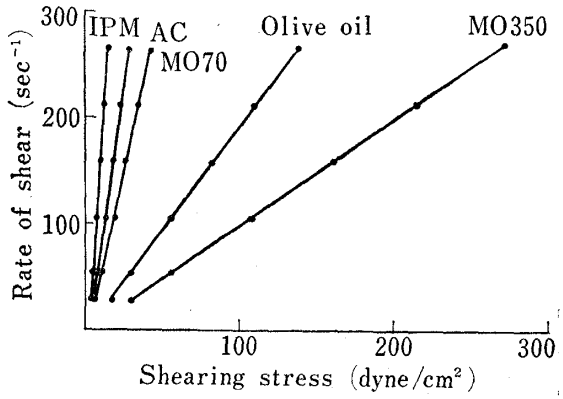

Fig. 2. Flow Curves of Suspension Vehicles

The flow curves for $CaCO_3$–NZ suspensions containing various concentrations of dispersed phase are shown in Fig. 3. Through a concentration range of dispersed phase, $CaCO_3$–NZ suspensions in AC and in olive oil exhibited Newtonian behavior. Newtonian behavior was also exhibited by suspensions with concentration of less than 40 weight per cent $CaCO_3$–NZ in IPM. However, a suspension with the highest concentration of dispersed phase in IPM and all suspensions of MO–70 and MO–350 showed a pseudoplastic flow. Attention should be paid to the flow behavior of suspension of MO–70. A mineral oil–light vehicle showed less shearing stress than an olive oil vehicle. But the addition of 50 weight per cent of dispersed phase to MO–70 vehicle gave a higher shearing stress than olive oil suspension having the same concentration (Fig. 3).

Fig. 4 illustrates the rheograms for $CaCO_3$–S preparations. Suspensions with concentrations of less than 40 weight per cent in AC showed Newtonian flow but 50 wieght per cent suspension was pseudoplastic. The flow curves for IPM also proved to be Newtonian up to concentration of 30 weight per cent. However, above this concentration, the shear stress axis was found intercepted when the flow curves were extraporated. At a concentration of 50 weight per cent in IPM, a shear thickening behavior was observed in the flow curve when the descending curve was shifted to the right of the ascending curve. A similar phenomenon was observed in the flow curves for 40 and 50 weight per cent suspensions in MO–70.

Fig. 5 illustrates the rheograms for $CaCO_3$–400 preparations. Suspensions with $CaCO_3$–400 in AC exhibited Newtonian behavior similar to those with $CaCO_3$–S in AC. However, a shear thickening behavior was found at 40 and 50 weight per cent concentrations of $CaCO_3$–400 suspensions in IPM, MO–70 and MO–350.

The descending curve obtained from the above runs was made into a logarithmic scale for the purpose of calculating the n values of each suspension. Assuming that a suspension product is subjected to a rate of shear in practical application, the physical property of the product would depend on the rate and degree of disorientation of the dispersed particles or floccules in suspension media. The descending curve of a rheogram represents a disorientation state of the suspension system, so that in this experiment descending curves were used for the calculation of n values.

Fig. 6 illustrates the logarithmic rheograms for suspensions of $CaCO_3$–NZ and $CaCO_3$–S. A linear relationship was found between the rate of shear and shearing stress throughout a shear rate range. The slopes of straight lines, being expressed by n, were calculated for each concentration of the dispersed phase.

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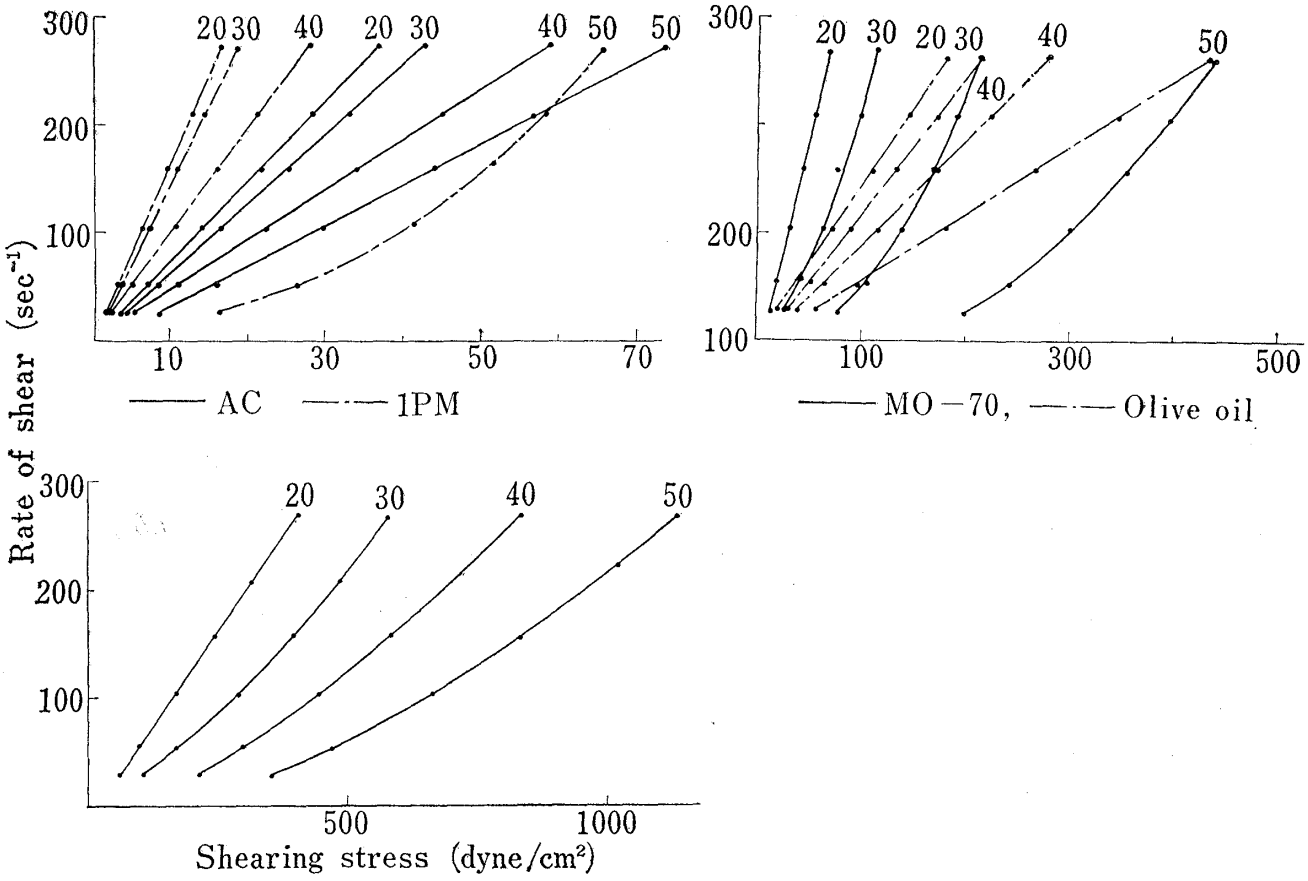

Fig. 3. Flow Curves for $CaCO_3$–NZ Suspensions

Relations between n and the concentration of dispersed phase are presented in Fig. 7. The n values of IPM and MO–70 suspensions showed a marked increase as the concentration of dispersed phase increased. A shear thickening behavior was observed when n became more than 3, as denoted by the line AB. On the other hand, n of AC and olive oil suspensions always showed a figure near to 1. Thus it appears that further addition of calcium carbonate powder to IPM and MO–70 suspensions greatly influenced the suspensions' structural viscosity but that of AC and olive oil suspensions.

The effect of particle size distribution (PSD) of calcium carbonate powder on n value was very significant. Calcium carbonate–400 powder having the most narrow PSD (Fig. 1) showed the highest n value and the lowest was shown by calcium carbonate–NZ having the broadest PSD.

IPM and MO–70 suspensions having a dispersed phase of narrow PSD showned a unique and seldom–encountered flow property, *i.e.*, shear thickening at high concentration of dispersed phase. This phenomenon is the reverse of thixotropy which is the so called antithixotropy or negative thixotropy.[16] However, magnesia magma U.S.P. is the only example which has been reported as shear thickening pharmceutical.[17]

A shear thickening behavior of suspension can be attributed to the existence of two states of floccules, one having a large number of small floccules, and the other, a small number of large floccules. Numerous small floccules seem to exist when no or very low rate of shear is applied. With an increase in shear rate, floccules collide increasingly making floccule size larger and floccules less in number. Since large floccules give higher resistance to shear

16) J. Eliassaf, A. Silberberg, and A. Katchalsky, *Nature*, **176**, 1119 (1955).
17) C. W. Chong, S. P. Eriksen, and J. V. Swintosky, *J. Am. Pharm. Assoc. Sci. Ed.*, **49**, 547 (1960).

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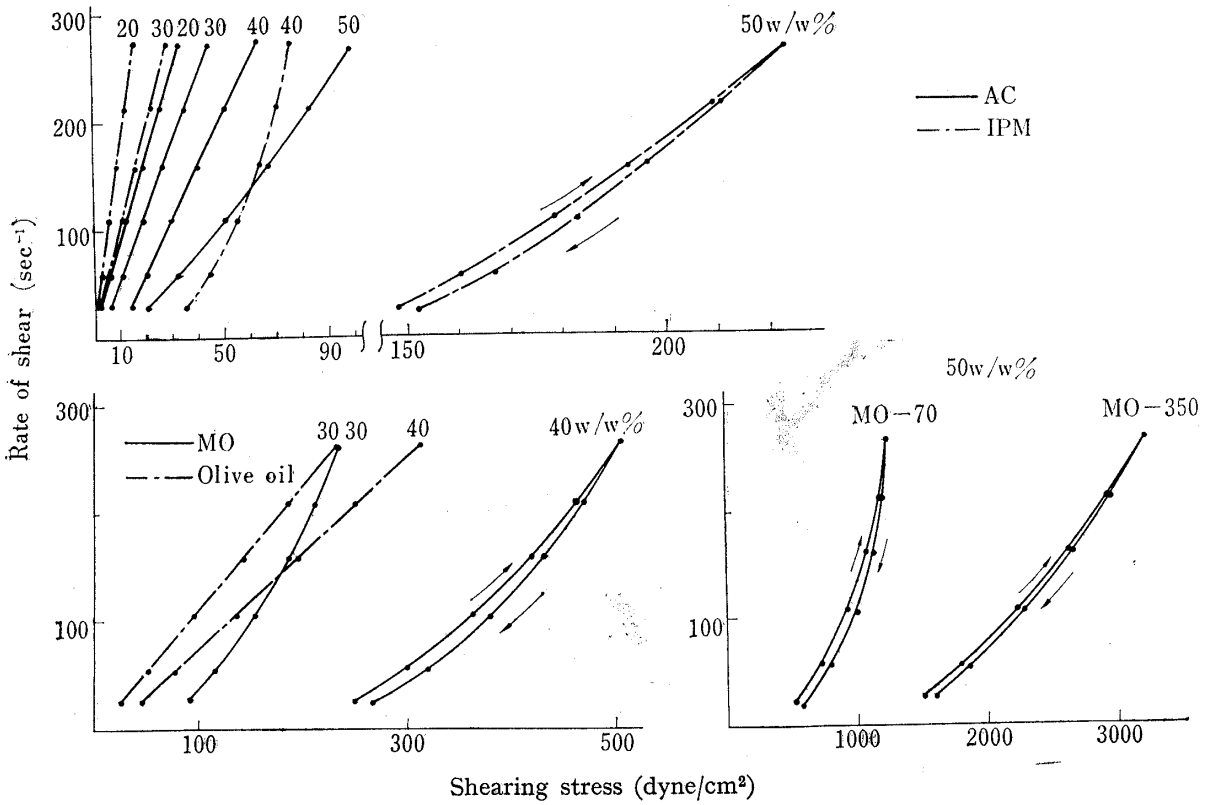

Fig. 4. Flow Curves for $CaCO_3$–S Suspensions

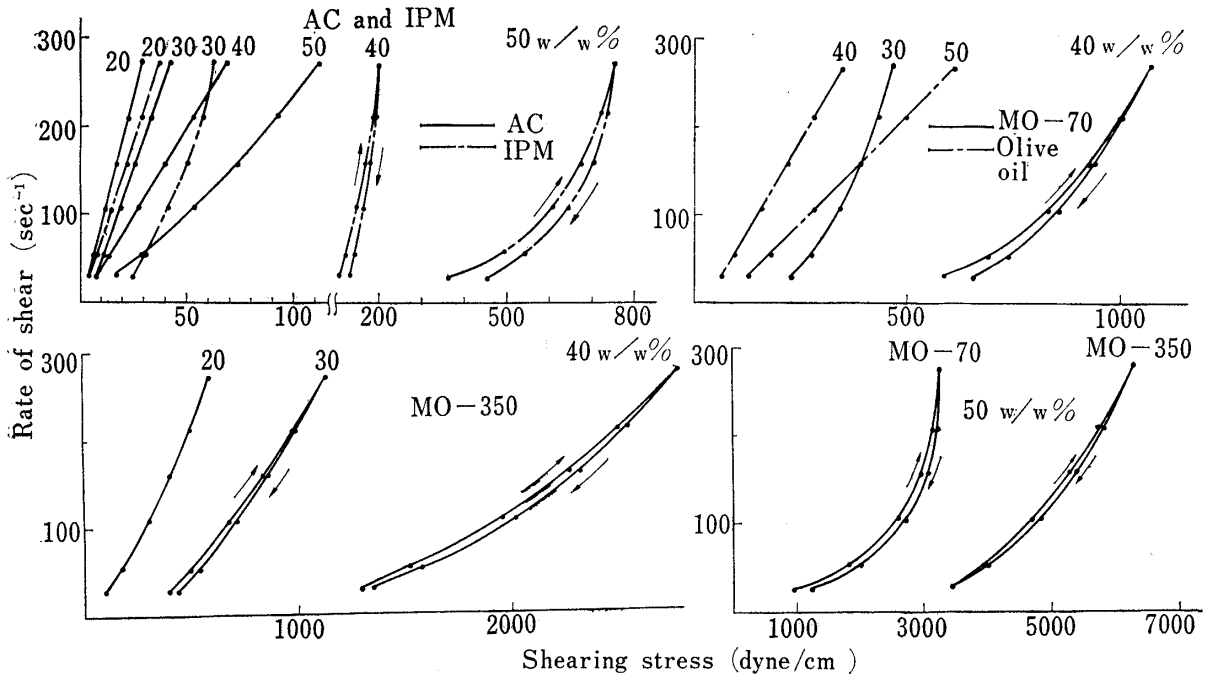

Fig. 5. Flow Curves for $CaCO_3$–400 Suspensions

than small floccules, more torque is given to a bob by large floccules than small floccules, shear thickening was increased with an increased shear rate.

Effects of PSD studied in terms of dispersed phase are to be taken into consideration. Small particles with narrow PSD increase a homodispersity in the suspension system. An increased homodispersity with relatively similar sized particles, offers more resistance to flow.

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In case $CaCO_3$–S or $CaCO_3$–400 is used as suspension, there are observed yield values (Fig. 3 through 5). In addition, a narrow PSD with small particle size corresponds to a large total particle–particle or particle–medium interfacial area. This large interfacial area facilitates more extended flocculated networks or other unknown particle–particle or particle–medium interactions.

On the basis of the arguments presented above, the changes in structural viscosity of oil suspensions having different vehicles and varying dispersed phases are due largely to particle–medium interactions. In this connexion, it would be interesting to study the interactions responsible for the changes in floccule size, and responsible for the differences in wetting process of dispersed particles with oil media. Further work is under way as to this problem.

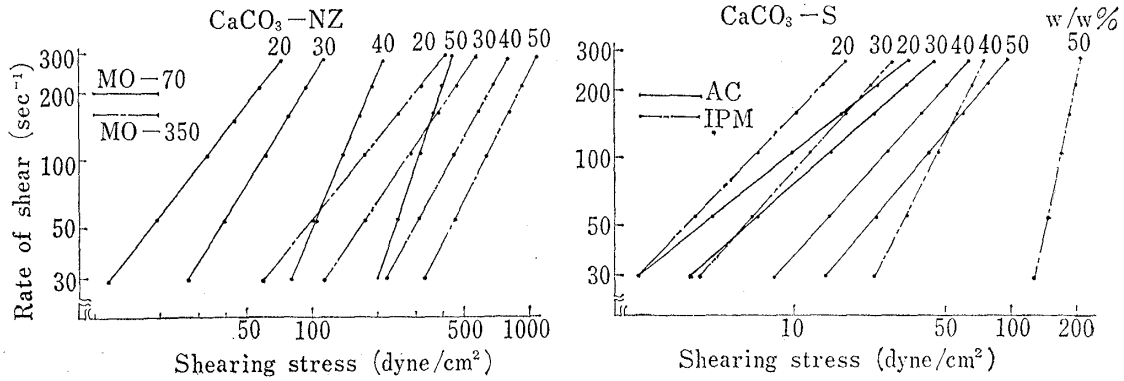

Fig. 6. Logarithmic Flow Curves of $CaCO_3$–NZ and $CaCO_3$–S Suspensions

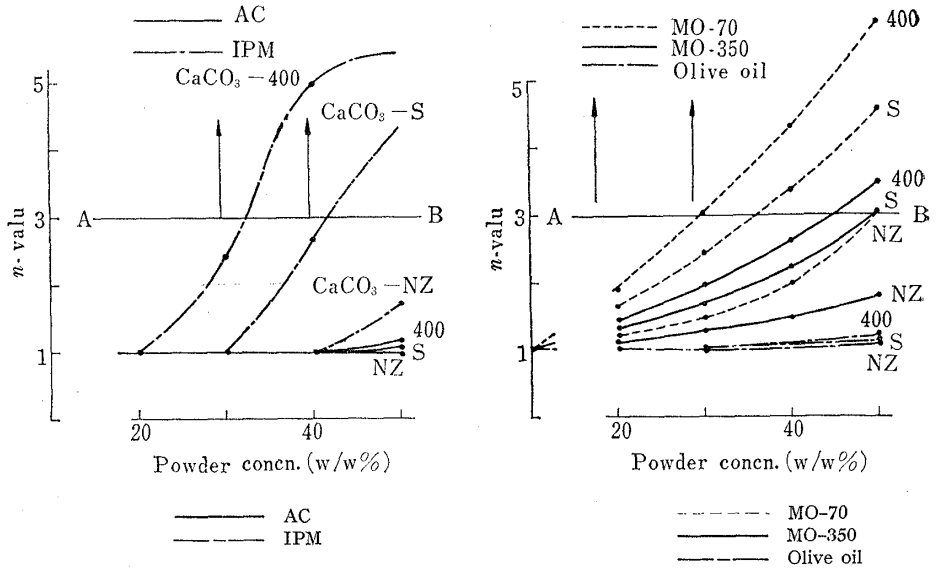

Fig. 7. Relations between n–Value and the Concetration of Dispersed Phase

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