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Flocculation and Deflocculation of Veegum Suspensions by Polyoxyethylene Hydrogenated Castor Oil[1]

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The mechanism of the flocculation and deflocculation of Veegum (Montmorillonite) in an aqueous medium by polyoxyethylene hydrogenated castor oil which has a various length of polyoxyethylene chains, has been examined by adsorption isotherm, viscosity, zeta potential and contact angle measurements. Adsorption isotherms for these surfactants on Veegum showed flectional points (S-shaped) at a certain concentration of the surfactants added. The maximum flocculation occurred around the flectional points accompanying high viscosity in the suspension, and the measurement of contact angles showed that the Veegum surface at these points was most hydrophobic.

These results suggest that the maximum flocculation occurs when all the Veegum surfaces are covered by surfactants orientating the hydrocarbon chains toward the solution, which renders the surface more hydrophobic. The deflocculation caused by the further addition of the surfactants is interpreted as being due to the bimolecular layer adsorption of the surfactants by van der Waals forces or by hydrophobic bonding between the Veegum particles adsorbed surfactants monomolecularly and the surfactants added.

Drug particles suspended in an aqueous medium have a tendency to form a sediment or caking at the bottom of a container with time and the resulting caking is usually very difficult to redisperse by shaking before use. Prevention of the sedimentation and caking of particles during storage is an important subject in formulating pharmaceutical suspensions.

There are a couple of methods to solve the problems described above. One of the methods being available in such systems is to use clay minerals as the suspending agent.[3] When drug particles are maintained in a loose network of clays which is formed by the addition of proper amount of flocculants, such as water soluble polymers or surfactants, they could be easily redispersed by gentle shaking before use.

Many detailed papers concerning the rheological properties of clay suspensions[4] and the interaction between clays and additives such as surfactants,[5] water soluble polymers,[6] dyes[7] and preservatives[8] have been presented, *i.e.*, the adsorption of polyvinyl alcohol on montmorillonite,[6a] the adsorption of crystal violet on kaolinite[7] and swelling of the interlayer of clay by the adsorption of nonionic surfactants[5a,b] *etc.* Mechanisms of the flocculation of

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[1] This work was presented at the 72nd Annual Meeting of Pharmaceutical Society of Japan, Osaka, April 1972.

[2] Location: *Juso, Yodogawa-ku, Osaka.*

[3] P.W. Gerding and G.J. Sperandio, *J. Am. Pharm. Assoc. Pract. Ed.*, **15**, 356 (1954); M. Barr, *J. Am. Pharm. Assoc.*, **NS4**, 180 (1964).

[4] G. Levy, *J. Pharm. Sci.*, **51**, 952 (1962); J.H. Wood, G. Catacalos and S.V. Lieberman, *J. Pharm. Sci.*, **52**, 354 (1963); J.C. Samyn and W.Y. Jung, *J. Pharm. Sci.*, **56**, 188 (1967); R.J. Hunter and S.K. Nicol, *J. Colloid Interface Sci.*, **28**, 250 (1968).

[5] *a*) H. Schott, *Kolloid-Z. Z. Polym.*, **199**, 158 (1964); *b*) H. Schott, *J. Amer. Oil Chem. Soc.*, **45**, 414 (1968); *c*) R.L. Parfitt and D.J. Greenland, *Clay Minerals*, **8**, 305 (1970).

[6] *a*) D.J. Greenland, *J. Colloid Interface Sci.*, **18**, 647 (1963); *b*) C.W. Francis, *Soil Sci.*, **115**, 40 (1973).

[7] N.A. Armstrong and C.D. Clake, *J. Pharm. Pharmacol.*, **23**, 95S (1971).

[8] J.T. Carstensen and K.S.E. Su, *J. Pharm. Sci.*, **60**, 733 (1971).

colloidal silica by ionic surfactants and polyamine sulfate,[9] have also been reported, but little is known about the mechanisms of the flocculation and deflocculation of clay suspensions by nonionic surfactants.

The purpose of the presented paper is to elucidate the mechanisms of the flocculation and deflocculation of Veegum (Montmorillonite) by the water soluble nonionic surfactants, polyoxyethylene hydrogenated castor oil.

Experimental

Materials——The Veegum (montmorillonite) used was supplied from R.T. Vanderbilt Company, Inc., N.Y., U.S.A. The nonionic surfactants, polyoxyethylene hydrogenated castor oil (Nikkol HCO-30, Nikkol HCO-50 and Nikkol HCO-80: The numbers indicate the nominal number of oxyethylene units per molecule) and polysorbate 80 (Tweem 80) were of commercial grade and supplied by Nikko Chemicals Co., Ltd., Tokyo, and Kao Atlas Co., Ltd., Tokyo, respectively. Polyethylene glycols (PEG-1540 and PEG-4000) used were prepared by Sanyo Kasei Kogyo Co., Ltd., Kyoto.

Preparation of Dispersions——Five percent (w/v) of Veegum slurries were processed once through a Manton-Gaulin homogenizer at a pressure of 350 kg/cm^2. The stock suspensions thus obtained were diluted with suitable amount of 10% (w/v) of HCO-50 aqueous solutions and water under stirring at the rate of 500 rpm for 60 min at 25°. Sample suspensions containing other surfactants or polymers were prepared in the same manner as HCO-50. In this study, the concentration of Veegum dispersions were 0.25, 0.5 and 1% (w/v).

Rheological Examination——The apparent viscosities were measured using a Rotation Viscometer BL type, Tokyo Keiki Seizosho Co., Ltd., Tokyo. A BL Adapter was used when Veegum concentrations were 0.25 and 0.5%, and a Rotor No. 1 was used in the case of 1%. Flow curves of each suspension were obtained using a rheometer, Rotovisko Model FJ/EE, Gebrüder Haake, West Germany, with NV type inner cup and bob, permitting shear rates from 116.3 to 1570 sec.$^{-1}$ The temperature was maintained at 25° while all flow curves were obtained.

Turbidity——The turbidity of the supernatant was determined by using a Turbidimeter Model SEP-T, Nippon Seimitsu Kogaku Co., Ltd., Tokyo, after Veegum suspensions had been kept at 25° for three weeks. Calculation of the turbidity was carried out according to the following equation (1).

$$\text{Turbidity (\%)} = \frac{Td - Tf \times Tt/100}{Tt} \times 100 \qquad \text{(I)}$$

Td: light scattered by the instrument and specimen
Tf: light scattered by the instrument
Tt: total light transmitted by the specimen

Water and the white plate of magnesium oxide were chosen as the references at 0% and 100% of the turbidity, respectively.

Zeta Potential——Zeta potentials were determined at 25° with a Zetameter, Model D, Zeter-Meter Inc., N.Y., U.S.A., by measuring the electrophoretic mobilities of the Veegum particles. Samples were prepared by dilution with clear supernatant solutions obtained by the centrifugation of Veegum suspensions. Values of the zeta potential were calculated from the Helmholz-Smoluchowski equation.

Adsorption Study——Adsorption isotherms were determined by measuring the concentrations of HCO-50 in a clear supernatant obtained by the centrifugation of a sample suspension at 14500 *g* for 30 min. The

(1) sample (2 ml)+water (1 ml)
(2) color producing reagents
cobaltous nitrate (hexahydrate) 15 g, ammonium thiocyanate 100 g $\left.\right\} \longrightarrow$ 500 ml (water)……(A)
(A): DMSO=1:2 (volume)
(3) ethylene dichloride
(4) (1) 3 ml+(2) 5 ml+(3) 10 ml
(5) shaking, 5 min
(6) centrifugation, remove upper aqueous phase
(7) determination, absorbance st 620 mμ in ethylene dichloride

Chart 1

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[9] H.E. Ries, Jr. and B.L. Meyers, *Science*, **160**, 1449 (1968).

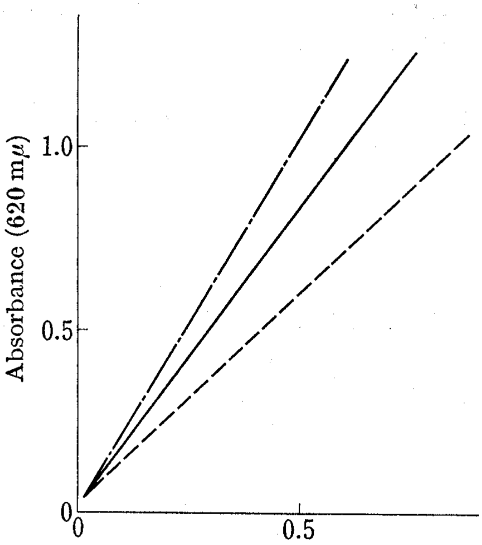

Fig. 1. Calibration Curves of HCO-30, HCO-50 and HCO-80

key: ———: HCO-50
-------: HCO-30
—·—·—: HCO-80

whole operations of adsorption studies were carried out at 25°. A preliminary experiment showed that no further adsorption of HCO-50 on Veegum took place after 60 min of stirring. Concentrations of HCO-50 were determined by the modified cobalt-thiocyanate colorimetry[10] as shown in Chart I, and calibration curves obtained are illustrated in Fig. 1.

The specific area of Veegum was determined by the Brunauer–Emmett–Teller method with nitrogen adsorption and by the continuous flow method. The equipments used were a Model P–300, Shibata Kagakukikai Co., Ltd., Tokyo and a Sorptograph Model ADS-1B, Shimazu Seisakusho Co., Ltd.,Kyoto.

Contact Angle——Contact angles for water on Veegum disks adsorbing HCO-50 were measured by the drop-on-plate method using an Erma Goniometer Model G-1, Erma Kogaku Kikai Co., Ltd., Tokyo, in a similar manner as Nakagaki, *et al.*[11] studied with sulfamine disks. The residue obtained by centrifugation of the Veegum suspension was vacuum-dried in a desiccator over phosphorous pentoxide for 72 hours at 25° and then the dried Veegum was compressed at 2 ton/cm^2 in the form of a disk of 60 mg. The water content in each disk was confirmed to be less than 3% by the Karl Fischer method.

Results and Discussion

1. Flocculation and Deflocculation of Veegum by HCO-50

The dispersion behavior of an aqueous Veegum suspension was changed by the addition of HCO-50 from the dispersed system the flocculated system and again to the deflocculated system by the further addition of HCO-50. The maximum degree of flocculation was recognized by adding 0.1—0.2% of HCO-50 into 0.5% of the aqueous Veegum suspension. Further addition made the flocculated system to the deflocculated again. This change was assured by the fact that the supernatants of the suspensions were changed from turbid to clear and then to turbid again with increasing the amount of HCO-50 added (Fig. 2). Although the Veegum suspension containing 0.4% of HCO-50 exhibited a loose network of Veegum flocs enough to retain suspended drug particles unsettled, separation of the network was hardly observed. Deflocculated suspensions obtained by the further addition of HCO-50, above the concentration of 0.5%, were more stable suspensions than that obtained without HCO-50. As shown in Fig. 3, the turbidity showed the minimum at the range of 0.05—0.1%, 0.1—0.25% and 0.2—0.5% of HCO-50 added in the suspensions containing 0.25%, 0.5% and 1% of Veegum, respectively. The concentration of HCO-50 required for the minimum turbidity, possibly corresponded to the maximum flocculation of Veegum particles, was approximately proportional to the concentration of Veegum. The experimental results obtained in turbidity measurements were compatible with the phenomena of the flocculation and deflocculation that occurred with the addition of HCO-50 as shown in Fig. 2.

While, suspensions containing various concentrations of Veegum (0.25, 0.5 and 1%) showed the maximum apparent viscosity at a certain concentration of HCO-50 (Fig. 4). The concentration of HCO-50 required for the maximum flocculation was, as recognized in the case of turbidimetry, approximately proportional to the concentration of Veegum in the aqueous solution. However, the apparent viscosity at 1% of Veegum showed the maximum at a less

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[10] N.T. Crabb and H.E. Persinger, *J. Amer. Oil Chem. Soc.*, 41, 752 (1964); R.A. Creff, E.A. Setzkern and W.D. Leslie, *J. Amer. Oil Chem. Soc.*, **42**, 180 (1965).

[11] M. Nakagaki and N. Kawamura, *Yakugaku Zasshi*, **88**, 151 (1968).

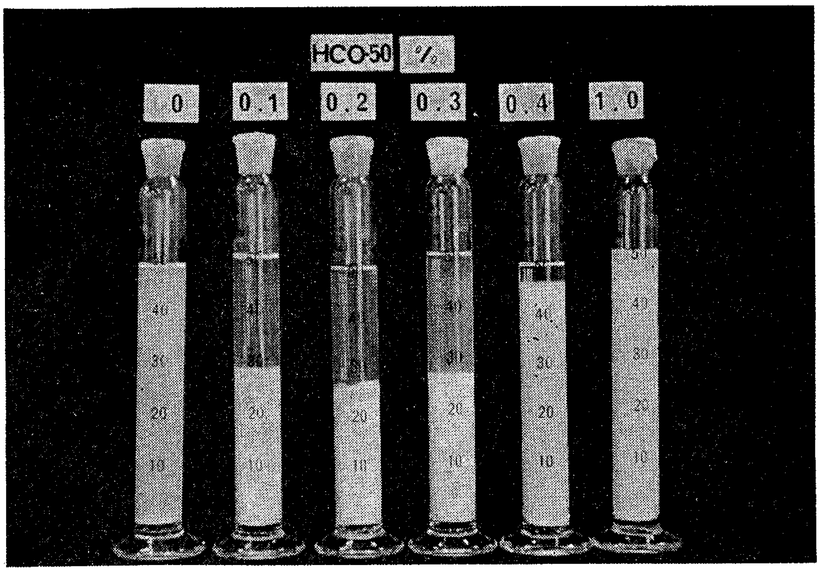

Fig. 2. Influence of HCO-50 Concentrations on Flocculation and Deflocculation of Veegum Suspensions

(Veegum 0.50 w/v %, 25°, after 3 weeks)

concentration of HCO-50 than expected. This was probably due to the stronger interaction between Veegum particles owing to the relatively high concentration of Veegum in the system. Fig. 4 shows the rheological evaluation of the suspensions containing 1% of Veegum with various concentrations of HCO-50. The rheograms of the suspensions corresponding to A and C in Fig. 4, which exhibit low values of apparent viscosities show the Newtonian flow which pass through the origin. While the rheogram corresponding to B which gives a maximum apparent viscosity, shows the thixotropy with a hysteresis loop between the up-curve and the down-curve (represented by the curve B in Fig. 4). The result means that the system is flocculated with the network at point B.

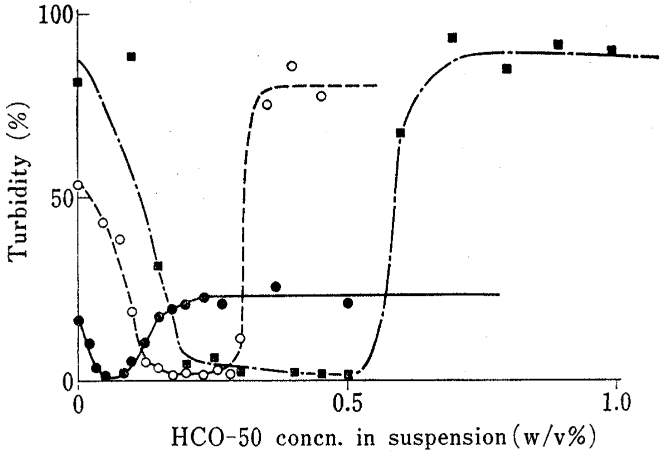

Fig. 3. Influence of HCO-50 Concentrations on Turbidities of Veegum Suspensions

key: ■: Veegum 1.00%; ○: Veegum 0.50%; ●: Veegum 0.25%.

2. Zeta Potential

It is important to know the surface charge on Veegum particles covered with the flocculant, HCO-50, for a good understanding of the flocculation and dispersion of the system. Ries, *et al.*[9] have presented that the zeta potential (—27 mV) on colloidal silica in an aqueous medium initially showed negative sign of the charge, while the zeta potential changed remarkably by the addition of polyaminesulfate accompanying the change in the behavior of the suspensions. The initial zeta potential of Veegum particles in an aqueous solution was about —25 mV. Similarly, as with colloidal silica, the absolute values of zeta potential on the Veegum particles decreased gradually with the addition of HCO-50 (Fig. 5). Obtained data suggest that Veegum particles which might be initially dispersed by the electrical repulsive force between particles or by the hydration showed the weaker electrical repulsive force due to the shielding effect of the HCO-50 adsorbed.

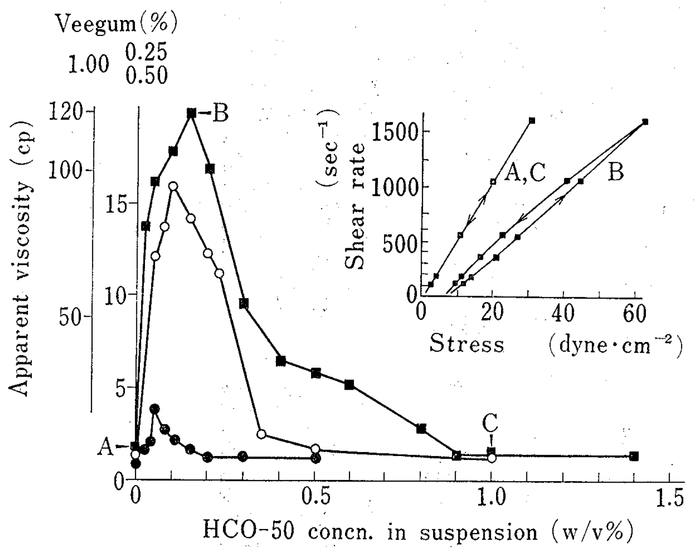

Fig. 4. Apparent Viscosities and Flow Curves of Veegum Suspensions

Key: ●: Veegum 0.25%; ○: Veegum 0.50%; ■: Veegum 1.00%; A, Veegum suspension without HCO-50; B, Veegum suspension containing 0.15% HCO-50; C, Veegum suspension containing 1.00% HCO-50.

3. Adsorption Isotherm and Contact Angle

As shown in Fig. 6, flectional points in adsorption isotherms were observed with both the suspensions containing 0.25 and 0.5% of Veegum. From the adsorption isotherms, it can be assumed that the mechanism of the adsorption of HCO-50 on Veegum possibly changes near the flectional points. Measurements of contact angles for water on Veegum disks were made for studying the orientation of HCO-50 molecules on Veegum adsorbed. Contact angle obtained with the samples, point A (flectional point) and B (at equilibrium), were found to be about 48° and 33°, respectively. The value of contact angle for water on Veegum free from HCO-50 was below 10°. Therefore, it is reasonable to assume that the Veegum surface was more hydrophobic at the flectional point A. The hydrophilic moiety of the HCO-50 molecule might be directed towards the Veegum surface orientating the hydrophobic groups outside. At point B, the molecules of HCO-50 are adsorbed bimolecularly on the Veegum surfaces and the resulting Veegum particles were subjected to lipophilization again.

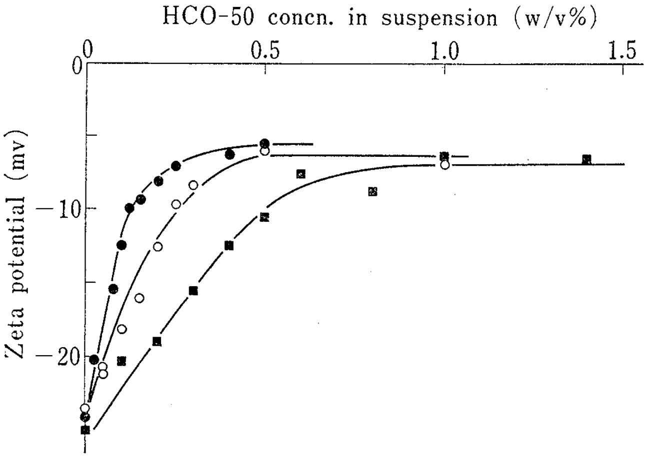

Fig. 5. Influence of HCO-50 Concentrations on Zeta Potentials of Veegum Particles

key: ●: Veegum 0.25%, ○: Veegurn 0.50%; ■: Veegum 1.00%.

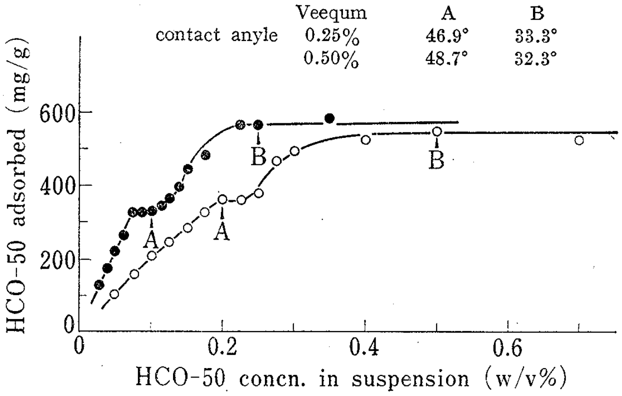

Fig. 6. Adsorption Isotherms of HCO-50 on Veegum and Contact Angles of Veegum Tablets

key: ●: Veegum 0.25%; ○: Veegum 0.50%.

On the other hand, the specific area of Veegum determined by the Brunauer-Emmett-Teller method and by the continuous flow method was found to be about 72 m^2 per gram of Veegum by both methods. If all the Veegum surfaces are covered by HCO-50 molecules, assuming that the projected area of each segment of HCO-50 is 100 Å^2 per molecule,[12] the theoretical amount of HCO-50 adsorbed would be 377 mg per gram of Veegum. The amount

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[12] Martin J. Schick, "Nonionic Surfactants," Marcell Dekker, Inc., New York Press, 1967, pp. 634—635.

of HCO-50 adsorbed monomolecularly on Veegum, which was determined from the adsorption data at the flectional point in Fig. 6, was approximately 340 mg per gram of Veegum. This value is in reasonable agreement with the theoretical value calculated.

A couple of methods, such as a flushing method which is related to the partition of the powder toward an oil or water phase and a penetration velocity method of a solvent into powder, are well known for the determination of the orientation of surfactants on powder surfaces. In this case, however, neither method was suitable for this purpose, because the former showed the desorption of HCO-50 from Veegum surfaces or the emulsification by HCO-50 desorbed, and the latter showed the desorption of HCO-50 and a swelling of Veegum particles.

4. Flocculation and Deflocculation of Veegum by other Nonionic Surfactants

It is also an interesting subject to know whether Veegum particles show a change from the dispersed system to the flocculated system and again to the deflocculated system by the addition of nonionic surfactants besides HCO-50. Viscosity changes of Veegum suspensions containing a homologous series of HCO-50 (HCO-30, HCO-80), Tween 80, PEG-1540 and PEG-4000 are shown in Fig. 7 and 8. Except for PEG, the experimental results are similar in the behavior of the apparent viscosity to those obtained by Samyn[13] on the Veegum HV suspension containing Tween 40. The maximum viscosity was also observed in the suspensions containing HCO-30 and HCO-80 and the region of the flocculation was extended with a decrease in the number of ethylene oxide in the surfactants (Fig. 7).

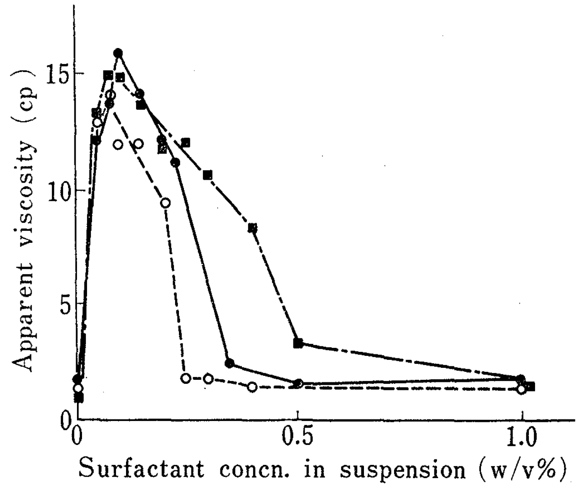

Fig. 7. Apparent Viscosities of 0.5% Veegum Suspensions

key: ■: HCO-30; ●: HCO-50; ○: HCO-80

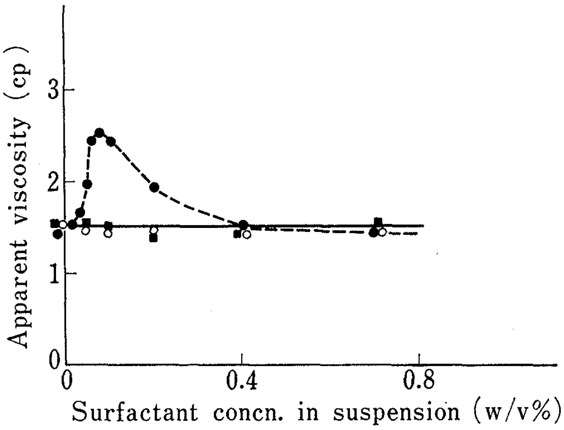

Fig. 8. Apparent Viscosities of 0.5% Veegum Suspensions

key: ●: Tween-80; ○: PEG-1540; ■: PEG-4000.

In the case of Tween 80 the maximum apparent viscosity was also observed, however the value was very small and the turbidity of the supernatant was slightly greater than that of the suspension containing HCO-50 (Fig. 9). This difference suggests that the chemical structure of the surfactants plays an important role in the flocculation of Veegum particles adsorbing surfactants. From these facts, the formation of a network structure of Veegum particles by the addition of Tween 80 might be difficult.

Further, each of PEG-1540 and PEG-4000 was adsorbed by Veegum (Fig. 10), although neither flocculation nor changes in the apparent viscosity were observed (Fig. 8), that is, no PEG molecules were bridged between adjacent Veegum particles of a dispersion to build up

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13) J.C. Samyn, *J. Pharm. Sci.*, **50**, 517 (1961).

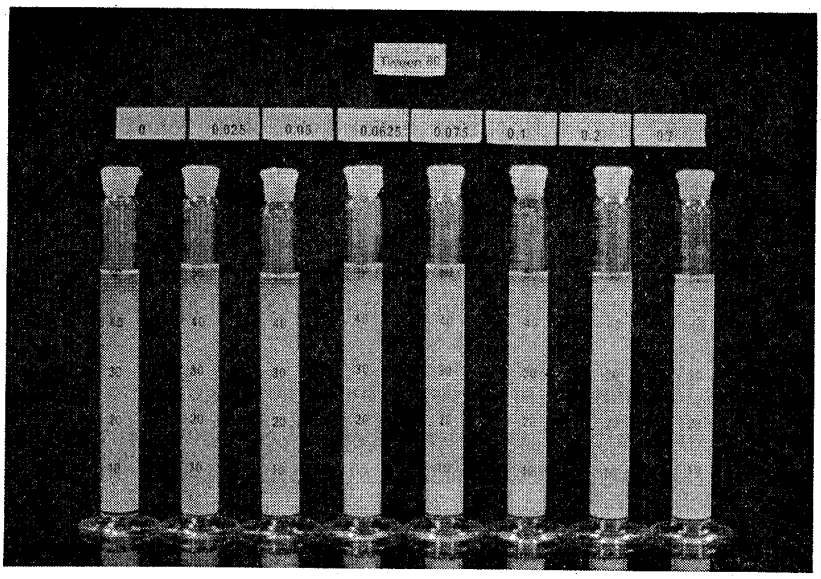

Fig. 9. Influence of Tween-80 Concentrations (%) on Flocculation and Deflocculation of Veegum Suspensions

(Veegum 0.50 w/v %, 25°, after 2 weeks)

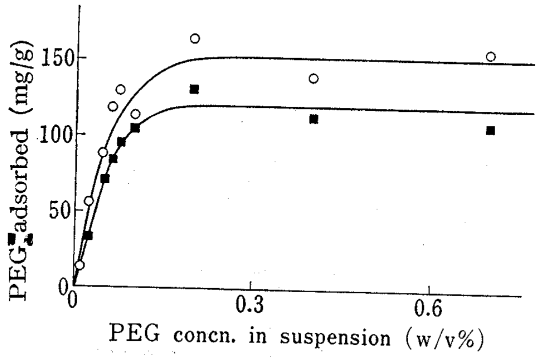

Fig. 10. Adsorption Isotherms of PEG-4000 and PEG-1540 on Veegum

key: ○: PEG-4000; ■: PEG-1540

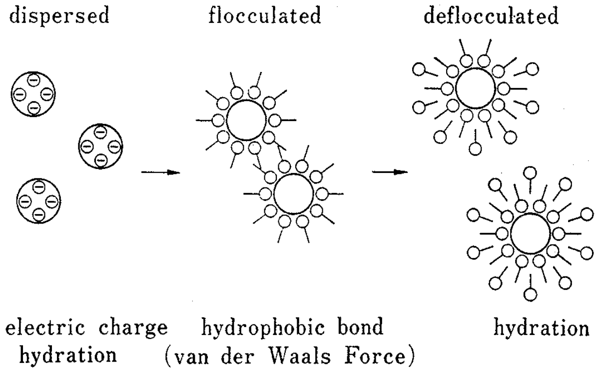

Chart 2. Proposed Model for Dispersion and Flocculation of Veegum Particles by Addition of HCO-50

key: ○: Veegum particle; ○— hydrophilic group, →hydrophobic group

a floc. This finding suggests that the hydrophilic and lipophilic balance in a surfactant adsorbed is an important factor for the flocculation of Veegum particles. The reason why no flocculation occurred by the addition of PEG was supposedly caused by the absence of the hydrophobic group in PEG molecules which was concerned in the control for the flocculation. Further studies with regards to the conformation of the surfactants adsorbed on Veegum will be needed.

5. The Mechanisms of Flocculation and Deflocculation

From experimental results mentioned above, the postulated mechanism of the flocculation and deflocculation of Veegum particles by HCO-50 is presented in Chart 2. Veegum particles negatively charged in an aqueous solution in the absence of HCO-50 are initially well dispersed due to an electrical repulsive force between the particles and to the hydration of Veegum. This suspension showed a low viscosity with the Newtonian flow. On the other hand, in the presence of HCO-50, the contribution of an electrical repulsive force was diminished by a shielding of the charged particle caused to the adsorption of HCO-50 by

Veegum. Veegum particles, due to the selective adsorption of the hydrophilic moiety of HCO-50 easily build up a floc, *i.e.*, a loose three-dimensional network of Veegum particles which is held together by van der Waals forces or hydrophobic bonding. In the flocculation region, the systems were accompanied by high apparent viscosities with thixotropic characteristics which have yield values.

The bimolecular layer adsorption of HCO-50, possibly due to van der Waals attractive forces or hydrophobic bonding could occur by the further addition of HCO-50 to the flocculated system and the bimolecular layer adsorption made Veegum particles redispersible owing to the hydration of the surface layer. The apparent viscosity of the deflocculated system is low with the Newtonian flow. These proposed mechanisms of flocculation and deflocculation of Veegum particles are supported by the adsorption isotherms and the measurements of the contact angles (Fig. 6).

Therefore, physically stable pharmaceutical suspensions with a desired network can be obtained by controlling the flocculation with the optimum concentration of HCO-50 in the Veegum suspension system.

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