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Studies on Pharmaceutical Drug Design for Suppositories. I. Effect of Physicochemical Properties of Surfactants and Polymers on Emulsion-Type Bases

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In general, it is recognized that emulsion-type bases have outstanding characteristics for suppository products as compared with simple hydrophilic or hydrophobic bases. The purpose of this work was to investigate the effect of some surfactants or polymers on the physicochemical properties of emulsion-type suppository bases.

Witepsol S-55, which is a trilauryl acid glycerin ester derivative, was used as the oil phase. The emulsifiers used were commercial grade Amisoft; CS-11, GS-11, and HS-21, and the polymers used were sodium alginate, sodium carboxymethylcellulose and sodium polyacrylate. In addition, the emulsion stability was evaluated in terms of (1) the rheological properties, (2) the particle size and its distribution, (3) the mean and distribution of electrophoretic mobility.

It was found that (1) Amisoft surfactants are excellent emulsifiers when compared with sodium dodecyl sulfate or Tweens based on the particle size and viscosity measurements, and (2) the addition of aqueous polymers is effective in stabilizing emulsion bases.

Accordingly, emulsion-type bases should be suitable for pharmaceutical use in suppository products.

Keywords——agitation; aqueous polymer; electrophoretic mobility; emulsion; particle size distribution; rheology; suppository; surfactant; viscoelasticity

In recent years a great deal of consideration has been given to the suppository from the standpoint of base formulation.[1-4] However, the bases used so far are not necessarily suited to local conditions, including those of the anorectal area, in spite of their wide use. As compared with hydrophilic or hydrophobic bases, emulsion type bases are expected to have some outstanding characteristics as suppository bases.[5] Thus, the volume ratio of water phase to oil phase can be aribitrarily changed depending on the condition of the rectum, and highly viscous bases or less viscous bases can be prepared as desired by controlling the concentration or size of particles in the emulsion.

With these considerations in mind, the o/w-type emulsion, which is a dispersion of microscopic oil droplets in a water phase, seems to be most interest as a suppository base. The purpose of this work was to investigate the effect of some surfactants or polymers on the physicochemical properties of suppository base. We chose Amisofts as surfactants since they cause only minor stimulation of the rectal mucous membrane.[6] Further, some hydrophilic polymers were added to the suppository base in order to stabilize the emulsion and prolong drug release.[7] In addition, the emulsion stability of the suppository base was evaluated in terms of (1) the rheology of the emulsion product,[8] (2) the particle size and distribution of oil droplets,[9] (3) the mean value and distribution of electrophoretic mobilities of the droplets.[10]

Experimental

1. **Preparation of Emulsion-Type Suppository**——As a dispersed phase, Witepsol S-55 (WS-55) was selected. Witepsol S-55 is a mixture of mono-, di-, and triglycerides of naturally occurring saturated fatty acids (C_{12}—C_{18}), with a melting range of 32—35°C. The specific gravity of Witepsol S-55 at 20°C ranges from 0.950 to 0.980; it has an iodine number of less than 3, a saponification value of 230 to 240 and a hydroxyl value of less than 15. Its melting behavior both *in vitro* and *in vivo* means that a suppository of Witepsol

S-55 without any additional drug substance melts almost completely in the human rectum within 10 min.[11] Furthermore, Witepsol has excellent properties in both emulsification and dispersion as an emulsion-type base, as compared with other glycerin ester derivatives.[7]

The emulsifiers used were commercial grade Amisofts; CS-11, GS-11, and HS-21 (Ajinomoto Co., Tokyo). Amisofts are synthesized from L-glutamate and natural fatty acids, and their chemical structure is represented as follows $^{-}OOC\text{–}CH_2CH_2CH(NH\text{–}OCR)COO^{-}$. CS-11 is N-palm oil fatty acyl-*l*-mono sodium glutamate, and its molecular weight is 359. GS-11 is *N*-fatty acyl-*l*-mono sodium glutamate, and its molecular weight is 420. HS-11 is *N*-stearoyl-*l*-disodium glutamate, and its molecular weight is 452.

The polymers used were sodium alginate (M.W. $= 1.4 \times 10^5$), sodium carboxymethylcellulose (M.W. $= 8.0 \times 10^4$) and sodium polyacrylate (M.W. $= 8.0 \times 10^4$).

Before starting emulsification, the surfactant and polymer were dissolved in the water phase. The volume concentration of the continuous phase in each emulsion was varied widely within the range of 10 to 90%. The agitator used was a Chemistirrer B-100 (Tokyo Rika Kikai Co., Ltd., Tokyo), with four baffles and six blades of standard Rushton type. The temperature of the mixture was maintained at 38.0°C after starting agitation in the tank. The impeller speed was kept constant within the range of 200 to 1500 rpm. After agitation, the resulting oil-in-water emulsion was poured into brass molds and stored in the refrigerator for at least one night until required. After one night, each suppository was carefully examined for any evidence of physicochemical change. Furthermore, it was confirmed that the physicochemical properties such as melting range, viscosity and particle size distribution were almost unchanged after 30 d at 4°C. The preparation procedure for emulsion-type suppository is summarized in Fig. 1.

2. Measurement of Physicochemical Properties of Suppository Bases——The stability of an emulsion as a suppository base was evaluated by measuring physicochemical properties such as viscosity, particle size, electrophoretic mobility and so on.

First, the rheological properties (viscosity and elasticity) were measured with a Vismetron (Shibaura System Co., Tokyo) or a rheometer type RM-1 (Shimadzu Seisakusho Co., Kyoto). These measurements were carried out at 37 ± 0.1°C.

Second, the particle size distribution and the mean diameter of oil droplets were measured with a Coulter counter (Model ZB, Coulter Electronics, Florida, U.S.A.). The tube having a 50 μm aperture was chosen and 1% NaCl in water (electric resistance, 550Ω/cm) was used as an electrolyte medium.

Third, the mean electrophoretic mobility and mobility histogram were obtained with the Laser Zee™ System 3000 (Penkem Ink. U.S.A.). The system 3000 is a fully automatic microelectrophoresis instrument consisting of a laboratory sampler tray, a sensor unit, and a computer terminal. It measures the particle mobility of an emulsion, from which the zeta potential can be calculated. All measurements were performed at a thermostatically controlled temperature of 37 ± 0.1°C.

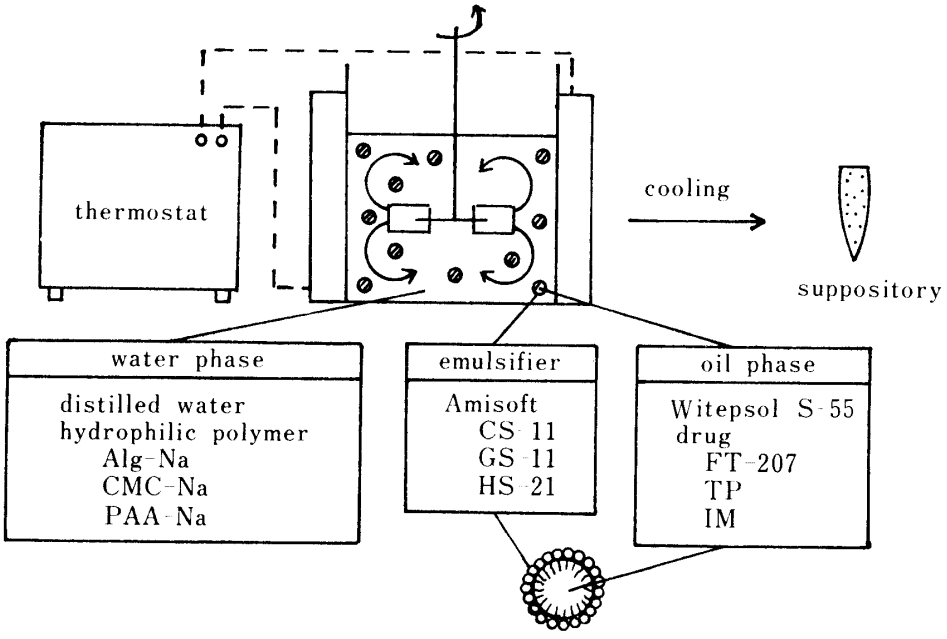

Fig. 1. Preparation Procedure for Emulsion-Type Suppository Bases

Results and Discussion

1. Effects of Surfactant and Polymer on the Preparation of Emulsion-Type Suppository

The effects of the kind and concentration of surfactant and polymer on the viscosity and elasticity of the resultant emulsion were studied.

Figure 2 shows the effect of surfactant concentration on the rheological properties of the base. Both viscosity and elasticity increased initially and then levelled off as the concentration of CS-11 (Amisoft) was increased. However, the resultant emulsion became unstable and a separated phase appeared when the concentration of CS-11 was below 0.5%. Therefore, the surfactant concentration was kept constant at 1.0% in the subsequent experiments.

Figure 3 shows the effect of polymer concentration on the viscosity and elasticity of the emulsion base. They increased markedly with increasing polymer concentration. When the concentration of polymer was lower than 0.5%, the emulsion was unstable, while at polymer concentrations over 2.0%, mechanical agitation was not adequate since the viscosity of the continuous phase was too high. Accordingly, the subsequent experiments were carried out at a polymer concentration of 1.0%. Comparison of Fig. 2 with Fig. 3 reveals that change in the polymer concentration influences the viscosity of the base more than change in the surfactant concentration.

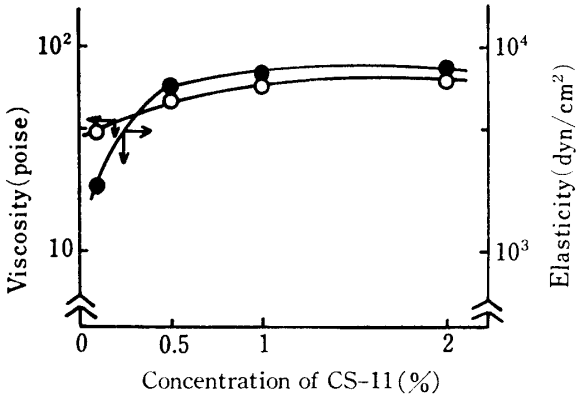

Fig. 2. Effect of Concentration of CS-11 (Amisoft) on the Viscosity and Elasticity of the Base

○: viscosity, ●: visco-elasticity.
Polymer, Alg-Na 1.0%.
Ratio of water phase to oil phase, 1: 1.

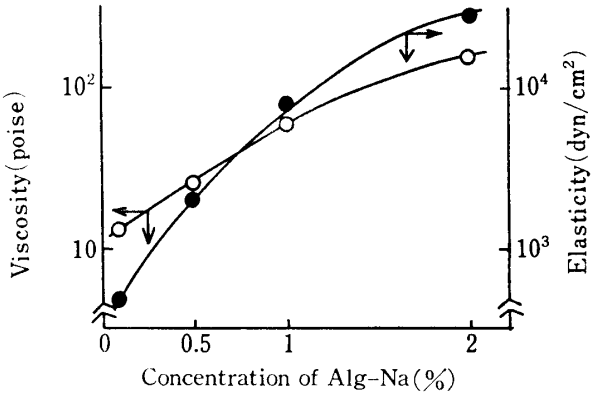

Fig. 3. Effect of Sodium Alginate Concentration on Viscosity and Elasticity of the Base

○: viscosity, ●: visco-elasticity.
Emulsifier, Amisoft CS-11 1.0%.
Ratio of water phase to oil phase, 1: 1.

2. Effect of Dynamical Factors on the Viscosity and Particle Size of Emulsion-Type Suppositories

Agitation time[12] and impeller speed[13] are important dynamical factors in the preparation of the base.

The influence of the agitation period of emulsification is shown in Fig. 4. The viscosity of the base increased markedly at the early stage of agitation, and it then levelled off as the agitation time increased further. The levelling off was observed after about 30 to 40 min of agitation. This phenomenon probably occurs because, at the early stage of agitation, shear stress is not homogeneously supplied to the whole emulsion base. During a long agitation time, the destruction and aggregation rates of emulsion droplets would be balanced, and then the mean diameter of droplets would become constant.

Figure 5 indicates the effect of impeller speed of agitation on the viscosity and the particle size of suppository base. Increase in the revolution rate in the process of emulsification increased the viscosity but decreased the mean diameter. Both of them levelled off at about

854 rpm.

Agitation time and revolution rate are clearly very important dynamical factors in the preparation of a stable emulsion. Thus, agitation time and revolution rate were kept constant at 30 min and 854 rpm, respectively, for all subsequent experiments.

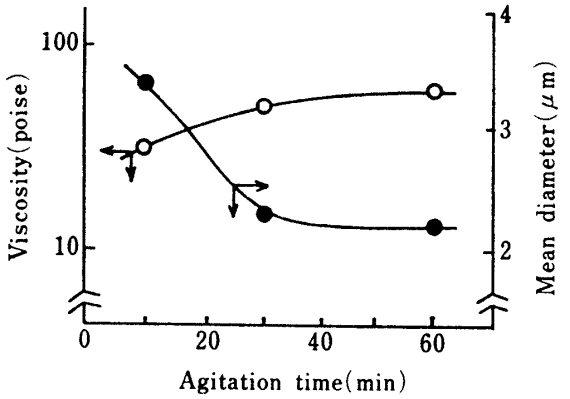

Fig. 4. Effect of the Agitation Time of Emulsification on Viscosity and Particle Diameter of the Base

○: viscosity, ●: diameter.
Emulsifier, Amisoft CS-11 1.0%.
Polymer, Alg-Na 1.0%.
Ratio of water phase to oil phase, 1: 1.

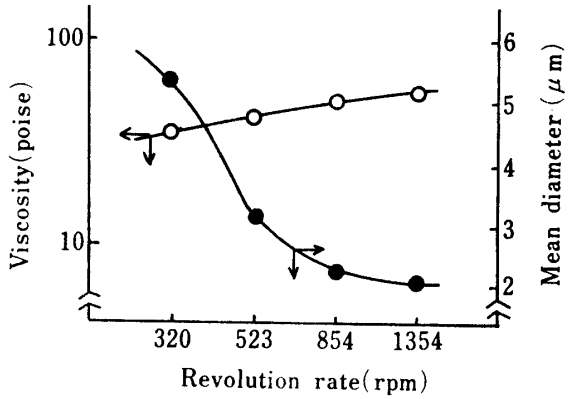

Fig. 5. Effect of Revolution Rate on Viscosity and Particle Diameter of the Base

○: viscosity, ●: diameter.
Emulsifier, Amisoft CS-11 1.0%.
Polymer, Alg-Na 1.0%.
Ratio of water phase to oil phase, 1: 1.

3. Effects of Surfactant and Polymer on the Particle Size Distribution of Emulsion-Type Suppository

To study the effects of surfactant and polymer on the particle size distribution of emulsion base, a large particle size range from 0.5 to 2.0 μm was employed.

The particle size distribution curves of emulsions stabilized with the three Amisoft surfactants or SDS are shown in Fig. 6. No significant effect of the differences in chemical structure of the Amisofts was found on the size distribution curve. The mean diameters were about 2—2.5 μm in the emulsions prepared with the three Amisoft surfactants. On the other hand, a broader size distribution and a larger standard deviation were observed when the emulsion base was prepared with SDS. Accordingly, these Amisofts seem to be superior to SDS for the preparation of systemic emulsion type suppositories having a samll and uniform droplet size.

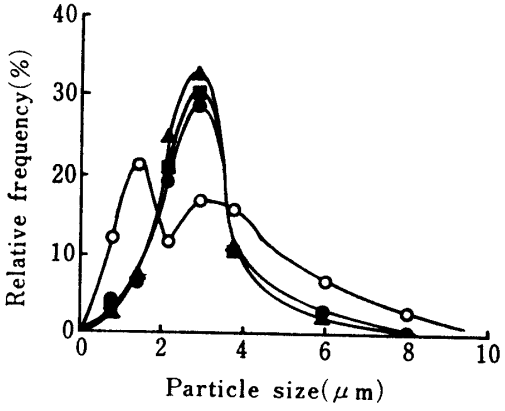

Fig. 6. Effect of Surfactants on the Particle Size Distribution of the Bases

▲: HS, ■: GS, ●: CS, ○: SDS.
Polymer, Alg-Na 1.0%.
Ratio of water phase to oil phase, 1: 1.

Figure 7 shows the effect of the kind of polymer on the particle size distribution curve. In the case of emulsion bases prepared with Alg-Na and CMC-Na, the distribution curves were very similar in shape, and the peak heights were also similar. Namely, a sharp size distribution and peak at about 3.0 μm were observed. On the other hand, a rather broad size distribution with a peak at about 2.0 μm particle size was obtained when the emulsion base was prepared with PAA-Na. The results in Fig. 7 may suggest that polymers are probably adsorbed on the surface of droplets and stabilize the emulsion without droplet flocculation and coalescence.[14]

The effect of the volume concentration of the continuous phase on the particle size distribution of emulsion-type suppository is shown in Fig. 8. The size distribution curve became broader and lower with increase of the volume concentration of the continuous phase. This result can be interpreted as follows. The energy efficiency in mechanical emulsification decreases with increase of the continuous phase concentration because the viscosity of the continuous phase containing polymer is significantly higher than that of the dispersed phase of Witepsol S-55.

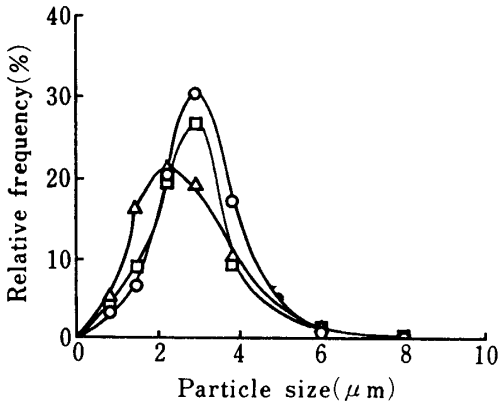

Fig. 7. Effect of Polymer on the Particle Size Distribution of the Bases

○: Alg-Na, □: CMC-Na, △: PAA-Na.
Emulsifier, Amisoft CS-11 1.0%.
Ratio of water phase to oil phase, 1: 1.

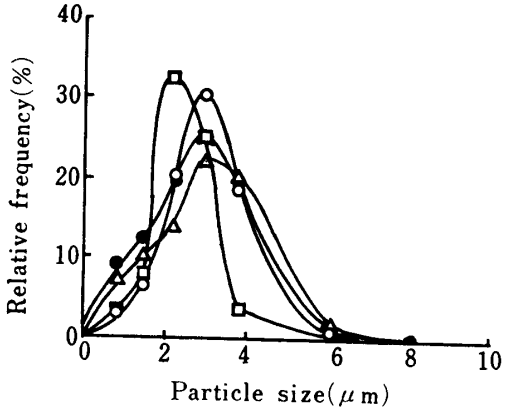

Fig. 8. Effect of Volume Concentration of Continuous Phase on Particle Size Distribution of the Bases

Ratio of water phase to oil phase: □; 4:6, ○; 5: 5, △; 6: 4, ●; 7: 3.
Emulsifier, Amisoft CS-11 1.0%.
Polymer, Alg-Na 1.0%.

4. Effect of Surfactants and Polymers on the Electrophoretic Mobility Histogram of Particles in Emulsion-Type Suppository

Particle mobility (zeta potential) is a controlling parameter in determining the stability of emulsion. It can be used to establish the optimum conditions for obtaining a stable emulsion system when this is desirable. Although the mean electrophoretic mobility is extremely important, in many applications it is also important to understand how the mobility is distributed about the mean value.

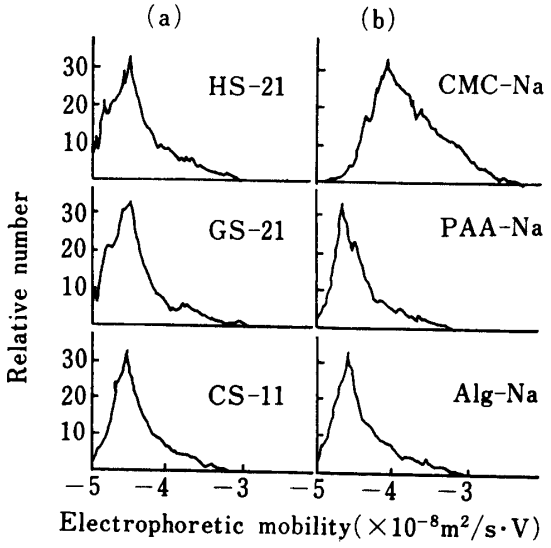

Fig. 9. Effect of Surfactant and Polymer on the Histogram of Electrophoretic Mobility of Particles in the Bases

(a): polymer, Alg-Na 1.0%, (b) surfactant, CS-11 1.0%.
Ratio of water phase to oil phase, 1: 1.

Histograms of electrophoretic mobility are shown in Fig. 9 for the emulsion-type suppositories prepared with three different surfactants or polymers. The horizontal axis corresponds to the electrophoretic mobility of the particle and the vertical axis to the relative number of particles having a particular mobility value.

With all three emulsifiers, the histogram showed a maximum at a mobility value equal to -4.5×10^{-8} m·^{2}s^{-1}·V^{-1}. The relative number of particles fell rather sharply on either side of the peak mobility. No significant effect of the difference in chemical

structure of the emulsifier was observed on the distribution curve. These results suggest that the use of Amisoft as an emulsifier not only facilitates subdivision of droplets, but also produces an electric double layer on the droplet surface.[15]

On the other hand, the mean electrophoretic mobility of particles in the emulsion was, though not greatly, affected by the kind of polymer, and it decreased in the order PAA–Na, Alg–Na, and CMC–Na. These polymers are probably adsorbed to form an electric double layer on the surface of droplets.[16] However, the influence of the interaction between surfactant and polymer on the electrophoretic mobility is not discussed in this paper. A detailed analysis of the electrophoretic data will be presented elsewhere.

A significantly high mean mobility and sharp mobility distribution were observed for the emulsions prepared with the three Amisoft surfactants and three polymers. Therefore, the emulsion-type suppository is considered to be sufficiently stable in terms of electric interaction.

Conclusions

1. From the results of particle size and viscosity measurements, the Amisoft surfactants were found to have excellent properties as compared with SDS and Tweens, and they appear to be very suitable for use as ingredients in emulsion-type suppository bases.

2. The addition of a polymer to the water phase greatly affects the viscosity and the particle size distribution of suppository bases. Aqueous polymers are effective in stabilizing the emulsion.

3. On the basis of physicochemical tests, it seems that emulsion bases containing 40—60 per cent of the dispersed phase show excellent stability.

4. Finally, the above-mentioned properties suggest that these o/w type emulsions prepared with Witeosol S-55, surfactant, polymer, and distilled water are suitable for the pharmaceutical preparation of suppositories for clinical use.

References and Notes

1) J.C. Larry and G.L. Nicholas, *J. Pharm. Sci.*, **69**, 955 (1980).
2) G. Mezey, G. Regdon, and K. Sztankovanszky, *Pharmazie*, **28**, 465 (1973).
7) I.W. Keelaway and C. Marriott, *J. Pharm. Sci.*, **64**, 1162 (1975).
4) W.J. Roy, E.W. Angela, J.W. Trevor, N.W. Richard, and G. Alan, *J. Rheumatol. Suppl.*, **6**, 20 (1980).
5) T. Takubo, S. Tsuchiya, and M. Hiura, *Yakuzaigaku*, **31**, 292 (1971).
6) M. Takehara, I. Yoshimura, K. Takizawa, and R. Yoshida, *J. Am. Oil Chem. Soc.*, **49**, 143 (1972).
7) S.A. Ibrahim, A. Abdelbary, H. Elsorady, and H. Abdelmonem, *Pharmazie*, **35**, 170 (1980).
8) A. Takamura, T. Minowa, S. Noro, and T. Kubo, *Chem. Pharm. Bull.*, **27**, 2921 (1979).
9) S. Tsukiyama, A. Takamura, and I. Takashima, *Yakugaku Zasshi*, **91**, 518 (1973).
10) J.P. Dickinson, E. A. Caspary, and E.J. Field, *Brit. J. Cancer*, **27**, 99 (1973).
11) W.A. Ritchel, "Angewandte Biopharmazie," Wissenschaftliche Verlagsgesellshaft, Stuttgart, 1973, pp. 465—487.
12) S. Noro, A. Takamura, and N. Nakura, *Chem. Pharm. Bull.*, **22**, 1902 (1974).
13) S. Noro, A. Takamura, and N. Nakura, *Yakugaku Zasshi*, **94**, 490 (1974).
14) R.H. Ottewill and T. Walker, *Kolloid-z. u. Z. Polym.*, **227**, 108 (1968).
15) A. Kitahara, M. Amano, K. Kawasaki, and K. Kon-no, *Colloid Polymer Sci.*, **225**, 1118 (1977).
16) T. Fujii and S. Katano, *Bull. Chem. Soc. Jpn.*, **44**, 3242 (1971).