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Studies on Microcapsules. III.¹⁾ Influence of Molecular Weight of Polyisobutylene in the Microencapsulation of Ascorbic Acid

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The effect of molecular weight (\bar{M}) of polyisobutylene (PIB), used as a coacervation-inducing agent in the preparation of ethylcellulose (EC) microcapsules (MC) in cyclohexane, was studied with ascorbic acid as the core material. PIBs of various \bar{M} were obtained by the fractionation of commercially available PIB and microencapsulation was performed. It was found that aggregation of MC decreased with increasing \bar{M} and was almost wholly prevented at \bar{M} of above 6×10^5 and that the release rate of ascorbic acid became minimum at \bar{M} of around 2×10^5 . The effect of mixing of commercially available high \bar{M} PIB (9.5×10^5) and low \bar{M} PIB (3×10^4) on microencapsulation was also investigated. In this case the release rate became minimum at a mixing ratio of around 1 : 4 (high \bar{M} : low \bar{M}). With increase of low \bar{M} PIB, average wall thickness and compactness increased and the wall became less uniform. Thus, it was presumed that the most prolonged MC was produced when the compactness, thickness and uniformity of the wall were well balanced. The influence of \bar{M} of PIB on the coacervation process was also investigated by measuring the volume fraction, EC contents and viscosity of the coacervate phase. From these data, it was presumed that \bar{M} of PIB affects the properties of the coacervation droplet, and consequently influences the properties of the wall formed from the droplet.

Keywords—microcapsule; ascorbic acid; ethylcellulose; coacervation-inducing agent; coacervation; polyisobutylene; molecular weight; *in vitro* release

Ethylcellulose (EC) microcapsules (MC) of pharmaceutical active ingredients are known to be useful for the improvement of chemical stability, masking of bitter taste, providing sustained-release characteristics and so on. Coacervation is a well known technique for the EC microencapsulation and the film prepared by this method is known to be very compact. In this method, a drug, EC and a coacervation-inducing agent such as polyisobutylene (PIB)²⁾ are added to cyclohexane. The mixture is heated to about 80 °C, then cooled gradually under agitation; EC droplets are deposited on the surface of the solid drug. Liquid-liquid phase separation (coacervation) is a very complicated physical phenomenon, and many factors probably affect the properties of the produced MC. The molecular weight of the polymers, EC and coacervate-inducing agent, probably have a significant effect, but it has not been studied in detail. Thus, we investigated the influence of molecular weight of EC in the previous paper.¹⁾ In this work, the influence of molecular weight of PIB on the microencapsulation was examined with ascorbic acid as a model core material. The release rate, degree of aggregation of particles, wall thickness and so on of the produced MC were determined. Further, the viscosity, volume of coacervate phase, shape of droplets of the coacervate and so on were measured during the phase separation process. On the basis of the properties of the produced MC and the observed phase separation phenomena, we discuss the function of the coacervation-inducing agent.

Experimental

Materials—Ascorbic acid (JP grade, particle size: 149–210 μm) was used. PIB (VISTANEX MML-80, MML-100, MML-120 and LMMH) and EC (standard type, 100 cP) were obtained from Esso Chemical Co., Ltd. and Dow Chemical Company, respectively.

Fractionation of PIB—Under agitation, acetone was added to *n*-hexane solution containing 5% PIB (VISTANEX LMMH, MML-80 or MML-100). The addition of acetone was continued until the solution became cloudy. The solution was allowed to stand and the precipitated PIB was recovered and dried. The same procedure was repeated.

Determination of Molecular Weight of PIB—Viscosity-average molecular weight (\bar{M}) of PIB was determined by viscosity measurement.³⁾

Preparation of Microcapsules—Ascorbic acid (15 g), EC (3 g) and cyclohexane solution (300 ml) containing 3% PIB were used for microencapsulation. Microcapsules were prepared in a way similar to that described in the previous paper.¹⁾

Studies of Properties of Microcapsules—Classification of MC was carried out by using JIS standard sieves. The yield of MC in the 149–250 μm sieve was measured and denoted as $Y_{149-250}$.

Release studies were carried out with microcapsules of 149–250 μm diameter. The release rate of ascorbic acid from microcapsules in the 1st fluid for the disintegration test (JP X) was observed spectrophotometrically by using the paddle method.²⁾ The apparent zero-order release rate constant (k_{app}) was calculated from the slope of the release curve.

The average wall thickness (H) were calculated by Lafont's equation⁴⁾ as described previously.

The permeability constant (P) was calculated by means of the following equation:¹⁾

$$P = k_{\text{app}} V H / A C_s \quad (1)$$

where A is the surface area of the microcapsules, V is the volume of medium (900 cm^3) and C_s is the solubility of ascorbic acid in the 1st fluid (0.355 g cm^{-3}).

The surface and cross section of microcapsules were observed by using a scanning electron microscope (JSM-T100, JEOL).

The uniformity of the wall was observed in cyclohexane by means of an optical microscope.

Determination of Coacervate Volume—EC (5.0 g) and cyclohexane solution (500 ml) containing 3% PIB (VISTANEX MML-80 or LMMH) were placed in a flask, agitated for 2.5 h at 400 rpm at 80 °C (Fig. 1A) and allowed to stand for 1–5 d at 80 °C until the equilibrium liquid phase (upper phase) became clear (Fig. 1B). The coacervate volume was determined from the height of the lower phase.

Determination of the Amount of EC and PIB in the Coacervate Phase—The upper phase described above was removed by suction at 80 °C. Then the lower phase (coacervate phase) was dried under a vacuum. EC was extracted twice with 250 ml of acetone and PIB was extracted twice with 250 ml of *n*-hexane. After evaporation of the acetone or *n*-hexane, the residue was dried under a vacuum and weighed. The percent of separated EC was calculated based on the charged EC (5 g). EC and PIB concentration in coacervate phase were calculated from the coacervate volume and the amount of EC or PIB in the coacervate phase, respectively.

Determination of Viscosity of Coacervate—The upper phase described above was removed by suction at 80 °C. Then the rotor of a Brookfield viscometer (Tokyo Keiki Seizoshō) was immersed in the coacervate phase (Fig. 1C) and the viscosity of the coacervate was measured at 80 °C. The temperature was lowered and the measurement was repeated.

Determination of EC Utilized for Microencapsulation—Ascorbic acid (15 g), EC (3 g) and cyclohexane solution (300 ml) containing 3% PIB were placed in a flask equipped with a thermometer, a stirrer and a reflux condenser at 80 °C. This mixture was cooled to 75, 70, 65, 60, 50, 40 or 20 °C and maintained at that temperature for 1 h under

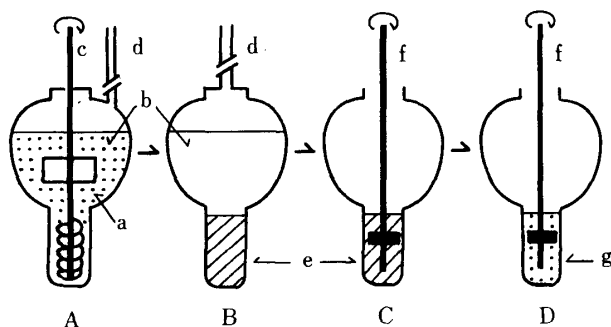


Fig. 1. Schematic Illustration of Phase Separation of EC

A, dispersion of coacervate droplets; B, collection of coacervate droplets; C, determination of viscosity; D, occurrence of gel-like phase; a, coacervate droplet; b, equilibrium phase; c, stirrer; d, cooler; e, coacervate phase; f, viscometer; g, gel-like particle.

stirring at 400 rpm. Then the mixture was poured into 500 ml of cold cyclohexane. Thus the EC used for microencapsulation and that not used were separated by decantation because the EC used was sedimentated as microcapsules, whereas that not used was still dispersed in the cyclohexane phase. The microcapsules obtained were washed with cyclohexane and dried. The ascorbic acid content in microcapsules was determined spectrophotometrically and the percent of EC utilized was calculated as follows:

$$\text{Percent of EC utilized} = \{(100/C) - 1\} 500 \quad (2)$$

where C is the ascorbic acid content (%) in the microcapsules.

Observation of the Shape of EC Droplets—EC (3.0 g) and cyclohexane (300 ml) containing 3% PIB were placed in a flask equipped with a thermometer, a stirrer and a reflux condenser. The flask was heated to 80 °C and maintained at that temperature for 30 min. Then it was cooled to 75 °C, and 3 ml was pipetted out and poured into 150 ml of cold cyclohexane. The resulting EC droplets were separated from the supernatant solution by decantation, washed with cold cyclohexane and freeze-dried. Thus, EC particles which retained the shape of the droplets in hot cyclohexane could be obtained. The particles were observed by means of a scanning electron microscope (JSM-T100, JEOL). The residual solution was further cooled to 65 and 55 °C and samples were similarly obtained at each temperature.

Results and Discussion

I. Effect of Molecular Weight of PIB on the Properties of MC

a) Microencapsulation Using Fractionated PIB—In order to determine the influence of \bar{M} of PIB, commercially available PIB was divided into fractions of various molecular weights, and microencapsulation was performed using these fractionated PIB. Then $Y_{149-250}$ of the MC produced was determined and the apparent zero-order release rate constant, k_{app} , was calculated from the linear part of the release curve up to 50% release (Fig. 2). As shown in Fig. 2, \bar{M} of PIB greatly affected both $Y_{149-250}$ and k_{app} . In the case where \bar{M} was higher than about 6×10^5 , $Y_{149-250}$ was more than 90% and was almost constant irrespective of \bar{M} , whereas in the case where \bar{M} was smaller than 6×10^5 , it decreased with decreasing \bar{M} . Without PIB, $Y_{149-250}$ was about 40%. These results suggested that PIB with \bar{M} of above 6×10^5 acted as a good protective colloid and prevented the aggregation of microcapsules, whereas PIB of lower \bar{M} than 5×10^5 did not have these effects. The values of k_{app} were also almost constant when the \bar{M} of PIB was above 6×10^5 , but decreased when \bar{M} was less than 6×10^5 and showed minimum values at \bar{M} of about 2×10^5 .

The existence of a minimum k_{app} , which corresponds to the most prolonged-release MC, suggested that MC having the desired properties can be obtained by the selection of a proper \bar{M} of PIB. These phenomena were very interesting from both the fundamental and the practical viewpoint, and more detailed studies were performed as follows.

b) Effect of Mixing of Commercially Available PIBs Having Different \bar{M} Values—As described above, an optimal \bar{M} of PIB for the microencapsulation seems to exist. However, the fractionation of PIB is a complicated procedure and would be expensive on a commercial

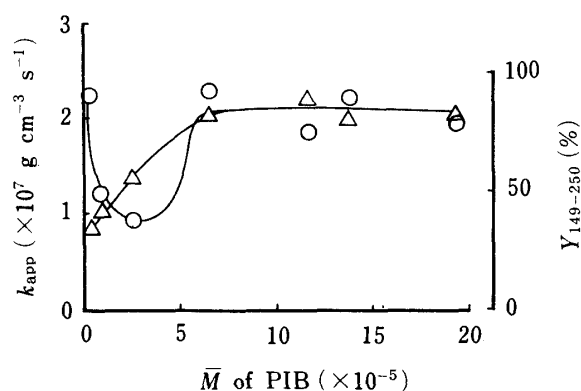


Fig. 2. The Properties of MC Prepared Using Fractionated PIB

—○—, k_{app} ; —△—, $Y_{149-250}$.

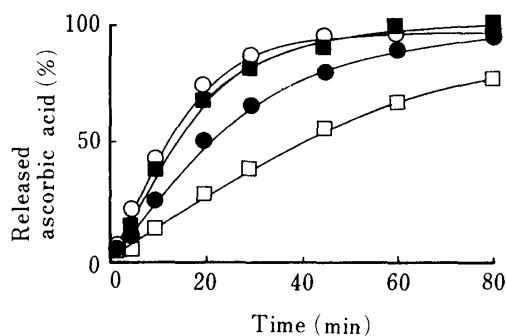


Fig. 3. Release Curves of Ascorbic Acid from Microcapsules Prepared by Mixing PIB-95 and PIB-3

f_H : 0% (—■—), 20% (—□—), 60% (—●—) and 100% (—○—).

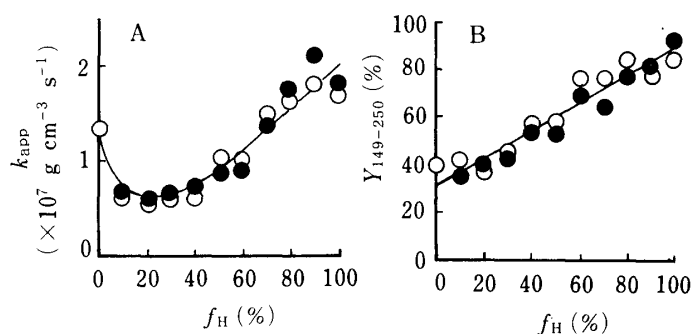


Fig. 4. Effect of Mixed PIB on k_{app} (A) and $Y_{149-250}$ (B)

PIB-3 was mixed with either PIB-95 (—○—) or PIB-176 (—●—).

scale. Moreover, to obtain PIB of the desired \bar{M} by fractionation with good reproducibility might be difficult. Thus, the method of controlling \bar{M} by mixing PIBs having different \bar{M} values was investigated as an alternative. PIBs, having low \bar{M} of 3×10^4 (denoted as PIB-3) and high \bar{M} of 9.5×10^5 (denoted as PIB-95) and 1.76×10^6 (denoted as PIB-176) were mixed to obtain appropriate PIBs (combinations of PIB-3–PIB-95 and PIB-3–PIB-176). Typical release curves of ascorbic acid from the MC prepared with such combinations of low \bar{M} PIB and high \bar{M} PIB are shown in Fig. 3. Zero-order release continued up to about 50% release. In Fig. 4, $Y_{149-250}$ and k_{app} calculated from the linear parts at the beginning of release are plotted against f_H , the fraction of high \bar{M} in the mixed PIB (f_H) defined by equation 3:

$$f_H(\%) = W_{PIB-H} 100 / (W_{PIB-3} + W_{PIB-H}) \quad (3)$$

where W_{PIB-3} and W_{PIB-H} mean the amounts of PIB-3 and the high \bar{M} PIB (either PIB-95 or PIB-176). It was found that prolonged-release MC could be obtained by mixing of commercial low and high \bar{M} PIBs. As shown in Fig. 4, k_{app} and $Y_{149-250}$ showed almost the same relationship to f_H irrespective of \bar{M} of the PIB-H, i.e., k_{app} took the minimum value when f_H was around 20% and $Y_{149-250}$ increased with increase of f_H . As \bar{M} of the PIB-3–PIB-176 mixture was about twice that of the PIB-3–PIB-95 mixture, the results in Fig. 4 indicate that the properties of MC are not determined only by the \bar{M} of PIB. Previously we²⁾ showed that microcapsules prepared using only high \bar{M} PIB took a minimum t_{50} value (this corresponds to maximum k_{app} value) at the PIB concentration of 1% and took maximum t_{50} values at 3%. Even though the viscosity of the 0.6% solution of high \bar{M} PIB (without low \bar{M} PIB) was nearly equal to that of the mixed solution whose f_H value was 20%, k_{app} of the produced MC took a nearly maximum value in the former case whereas it took a nearly minimum value in the latter case (Fig. 4). Thus it was suggested that PIB of low \bar{M} has an important role in determining the MC properties as well as PIB of high \bar{M} . In connection with this, Fig. 5 shows that the average wall thickness decreased with increase of f_H and P took a minimum value at the f_H value of 20%.

To obtain information on the compactness of the wall, the surfaces and cross sections of films of MC were observed by means of an electron microscope. Typical electron micrographs are shown in Fig. 6. The microcapsules prepared with high \bar{M} PIB ($f_H = 100$) had some small holes on the surface. Some small vacant spaces were also observed in the cross section of the wall. When f_H was 0 and 20%, both the surface and cross section of produced MC were smooth. However, in the former case ($f_H = 0\%$), the permeability constant P was large (Fig. 5), showing that the core contents were released rapidly despite the apparent compactness of the wall (Fig. 6). However, this could be explained by observation of the overall shape of

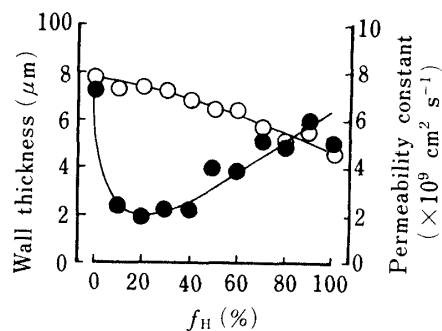


Fig. 5. Effect of Mixed PIB on Wall Thickness and Permeability Constant

—○—, wall thickness; —●—, permeability constant.

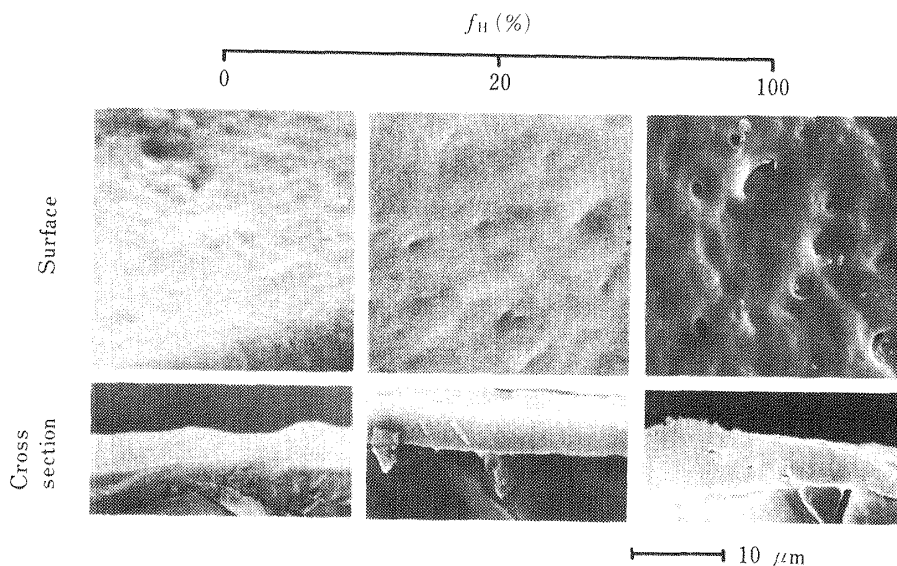


Fig. 6. Electron Micrographs of Surface and Cross Section of Microcapsules Prepared by Using PIB Having Various f_H Values

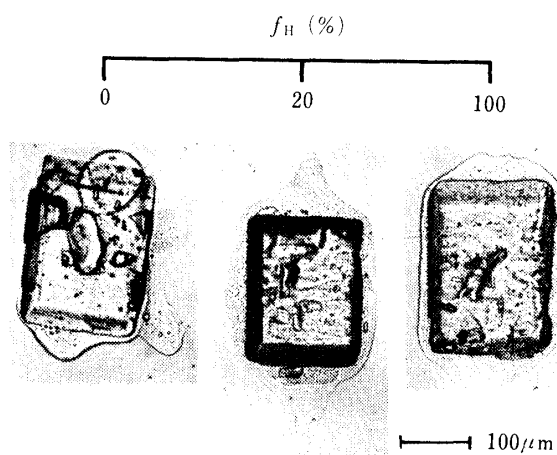


Fig. 7. Photomicrographs of Microcapsules Prepared by Using PIB Having Various f_H Values

microcapsules. Typical micrographs were shown in Fig. 7. As shown in Fig. 7, high \bar{M} PIB ($f_H = 100\%$) resulted in a uniform wall, while the use of mixed PIB ($f_H = 20\%$) gave walls with thick protuberances on the shorter sides, and the use of low \bar{M} PIB ($f_H = 0\%$) gave walls of irregular thickness. In the case of low \bar{M} PIB, it was presumed that the effective wall is not as thick as the average wall calculated from the EC content in the microcapsules, and P may take a smaller value if the effective wall thickness is taken into consideration. Microcapsules were also prepared by changing the agitation speed to 300 or 500 rpm, but they showed similar

characteristics to those in Fig. 7 (Fig. 7 shows the result at 400 rpm). Therefore the changes in Fig. 7 are probably attributable principally to the differences of molecular weight of PIB.

From these results, the reason why the most prolonged-release microcapsules were obtained by mixing of low and high \bar{M} PIB may be as follows. The compactness of the wall and wall thickness increases with increasing amount of low \bar{M} PIB, but the uniformity of the wall becomes worse. Thus the release rate is determined by the balance between compactness, thickness and uniformity of the wall. As high \bar{M} PIB tends to produce a thin and porous wall, the release rate was fast. With mixing of high and low \bar{M} PIB, a thick and compact wall was produced and the most prolonged-release microcapsules (e.g. 20% f_H) were obtained.

II. Effect of \bar{M} of PIB on Phase Separation

The percent of EC utilized for the wall formation is plotted against temperature in Fig. 8 for PIB-3 or PIB-95 as the coacervation-inducing agent. As shown in Fig. 8, only a small amount of EC was utilized to form the wall in both cases at 80 °C. With decreasing temperature, the amount of EC utilized increased. In the case of low \bar{M} PIB, a large amount of EC was used for the formation of the wall at 60–70 °C and almost all of the EC added was utilized below 50 °C. In the case of higher \bar{M} PIB, EC was scarcely used at above 65 °C, and only 50% of EC was utilized even at 20 °C. From the data in Fig. 8, it is clear that the wall-forming temperature was lower with higher \bar{M} PIB.

Nixon⁵⁾ and Rosenberg⁶⁾ reported that coacervation-inducing agents such as PIB and polyethylene reduced the solubility of EC in cyclohexane. Therefore the phase separation behavior of EC from hot cyclohexane was observed at 80 °C, slightly below the boiling point of cyclohexane (Table I). Without PIB, EC of 1% concentration dissolved in cyclohexane readily at 80 °C, but about 60% of the added EC was already phase-separated if 3% PIB was present. A larger coacervate volume was produced by using high \bar{M} PIB. The concentration of EC in the coacervate phase of PIB-3 was about 1.3 times larger than that of PIB-95. PIB was scarcely contained in the coacervation phase irrespective of the \bar{M} of PIB.

The viscosity of the coacervate phase of each PIB is shown in Fig. 9. The measurement of viscosity was started at 80 °C and repeated as the temperature was reduced. Low \bar{M} PIB

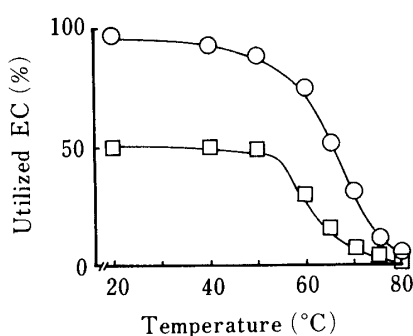


Fig. 8. Effect of Molecular Weight of PIB on Wall-Forming Temperature
PIB: PIB-3 (—○—), PIB-95 (—□—).

TABLE I. Influence of \bar{M} of PIB on Phase Separation at 80 °C

	PIB-3	PIB-95	Without PIB
Coacervate volume (ml)	38	58	0
Phase-separated EC (%)	57	64	0
EC concentration in coacervate phase (g/100 ml)	7.4	5.5	—
PIB concentration in coacervate phase (g/100 ml)	0.32	0.15	—

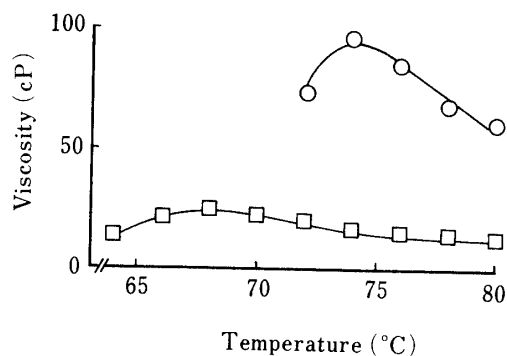


Fig. 9. Influence of Molecular Weight of PIB on the Viscosity of the Coacervate Phase

PIB: PIB-3 (—○—), PIB-95 (—□—).

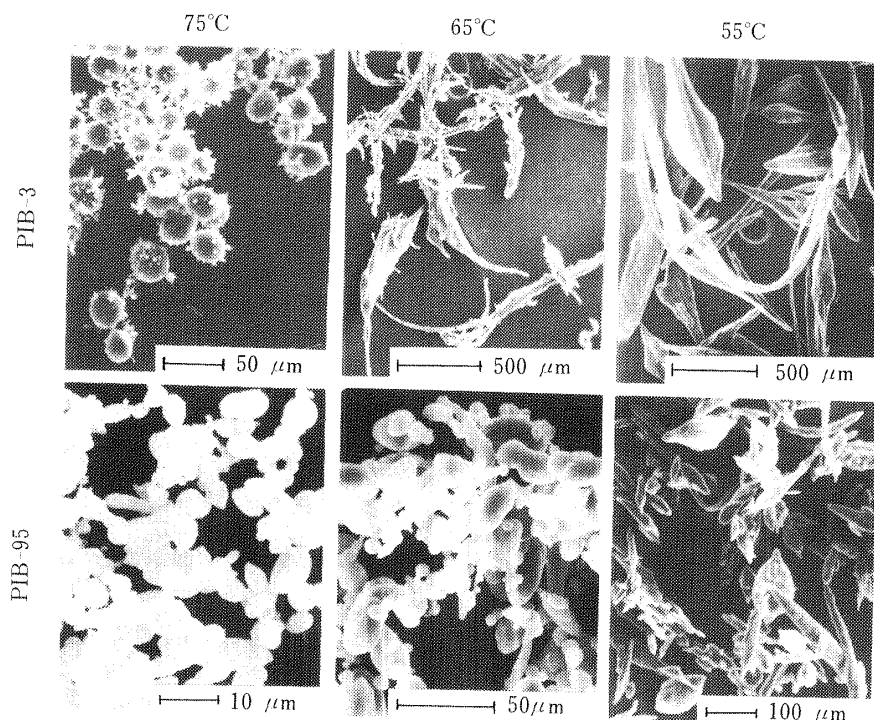


Fig. 10. Micrographs of Coacervate Droplets

produced more highly viscous coacervate than the high \bar{M} PIB at 80 °C. As little PIB was present in this phase, the difference of viscosity was regarded as being mainly due to difference of EC concentration. In both cases, the viscosity increased with reduction of temperature and reached a maximum (η -max). The temperatures at which viscosity was maximum were 68 and 74 °C for PIB-95 and PIB-3, respectively. The coacervate phase was at first clear but gradually became cloudy at the η -max temperature and small particles appeared in the coacervate phase as shown schematically in Fig. 1D. These small particles were presumed to be EC-rich phase (something like a gel phase), so for convenience we designated this phase as gel-like phase. It is known that the molecular weight of a polymer affects the phase separation of another polymer in a mixed solution and the effect increases with increasing molecular weight. Therefore it is presumed that a higher-molecular part of EC separates at the higher temperature and then a lower-molecular part separates as the temperature is reduced. The temperature of η -max seems to be the temperature at which the gelation of EC of higher molecular weight begins in the coacervate phase. Thereafter the viscosity of the coacervate phase decreased with reduction of the temperature. This may reflect gel formation of the lower molecular EC.

It is known that the viscosity of polystyrene cyclohexane solution is maximum at the

phase separation temperature.⁷⁾ Comparing the phenomena shown in Figs. 8 and 9, the temperature of η -max coincides with the wall-forming temperature. This temperature seemed to be the most important temperature for microencapsulation. To confirm this, the shape of the coacervate droplets at each temperature was observed in the absence of ascorbic acid. Micrographs of coacervate produced with either PIB-3 or PIB-95 are shown in Fig. 10. In both cases, coacervate droplets took quite uniform shapes (spherical or ellipsoidal) at 75 °C, but the size of coacervate droplets of the lower \bar{M} PIB was about 5 times larger than that of the higher \bar{M} PIB. In the case of the lower \bar{M} PIB the coacervate changed from spherical shape to a very large stringy and slender shape at 65 °C. High \bar{M} PIB gave EC droplets of spindle shape at 55 °C. The size of EC droplets became larger at the deformation temperature in both cases. The higher \bar{M} PIB produced smaller EC droplets at every temperature. The temperature at which deformation occurred also coincided with the wall-forming temperature. Donbrow⁸⁾ *et al.* studied the influence of the molecular weight of PIB on the particle size of EC, and showed that the particle size decreased with increasing molecular weight of PIB. He considered that the higher the \bar{M} of PIB, the more effective was the function of the protective colloid produced from the mutual repulsion of PIB adsorbed on the surface of the coacervate droplets. Part of the difference of wall thickness with differing \bar{M} of PIB may be attributable to the droplet size, because the size of coacervate droplets produced by the low \bar{M} PIB was much larger than that produced by the high \bar{M} PIB. Another reason may be the difference of the viscosity of the continuous phase, which consists mainly of cyclohexane solution containing PIB. The deposition of coacervate was presumed to be inhibited more in the high-viscosity solution containing the high \bar{M} PIB than in the low-viscosity solution containing the low \bar{M} PIB, so that thin-walled microcapsules would be obtained with high \bar{M} PIB. From these results, the mechanism of microencapsulation is presumed to be as follows. In the microencapsulation process, the EC exists as liquid coacervate droplets at 80 °C, and formation of the wall is minor at this temperature. As the temperature decreases and reaches the η -max temperature, the size of EC droplets increases and gel-like EC droplets deposit on the surface of drug. Then the deposited droplets fuse with each other and form the wall of microcapsules.

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