[Chem. Pharm. Bull. 31(12)4476—4482(1983)]

Studies on Microcapsules. II.[1] Influence of Molecular Weight of Ethylcellulose in the Microencapsulation of Ascorbic Acid[2]

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(Received March 7, 1983)

Microcapsules of ascorbic acid were prepared by phase separation of ethylcellulose (EC) from cyclohexane solution by lowering the temperature. The effects of molecular weight of EC on the aggregation of microcapsules and on the sustained release of the microencapsulated ascorbic acid were investigated. Polyisobutylene (PIB) was used as a coacervation-inducing agent. The molecular weight of EC significantly affected the aggregation of microcapsules; the aggregation decreased with increasing molecular weight of EC. The release rate of ascorbic acid from microcapsules was influenced significantly by the molecular weight of EC and the minimum release rate was given by EC with a molecular weight of 13×10^4 if PIB with a molecular weight of 1.12×10^6 was used. The molecular weight of EC which gave minimum release rate was affected by the molecular weight of PIB used. The relationship between the release rate and molecular weight of EC depended mainly on the compactness of the wall rather than the thickness of the wall.

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

In the previous paper[1] we showed that polyisobutylene (PIB), a coacervation-inducing agent, was useful to prepare microcapsules containing ascorbic acid, giving reduced aggregation and a slow release rate. Ethylcellulose (EC) was used as a wall-forming material in this microencapsulation. It is known that the wall characteristics of microcapsules are influenced by the molecular weight of the wall-forming polymer. Deasy[3] reported that sodium salicylate was microencapsuled with EC (100 cP) to give a finer product, with slower drug dissolution, than that obtained with the 10 cP grade of EC. However, the effect of molecular weight has not been studied in detail. In this work, an attempt was made to observe the effect of molecular weight of EC on the release rate of ascorbic acid from microcapsules and on the aggregation of microcapsules.

Experimental

Materials—Ascorbic acid (J.P. grade) passing through a 65 mesh sieve and remaining on a 100 mesh sieve (particle size: 149—210 μm) was used. PIB (VISTANEX MML-100 and LMMH) and EC (standard type, 100 cP) were obtained from Esso Chemical Co., Ltd. and Dow Chemical Company, respectively.

Fractionation of EC—Under agitation, water was added to acetone solution containing 3% EC (standard type, 100 cP) at 25 °C. The addition of water was continued until the solution became cloudy. The solution was allowed to stand, and the precipitated coacervate droplets were recovered and dried. The same operation was repeated.

Determination of Molecular Weight of EC—Molecular weight and molecular weight distribution of EC were estimated by gel-permeation chromatography using three columns (μ-Styragel 10^3 and 10^4 and 10^5 Å, Waters Associates Inc.). The solvent was tetrahydrofuran (THF) at a flow rate of 1.5 ml/min. A differential refractometer was used as a detector. A calibration curve using polystyrene standards is shown in Fig. 1. The number-average molecular weight ($\bar{M}_n$) and weight-average molecular weight ($\bar{M}_w$) were calculated from the chromatogram.

Determination of Molecular Weight of PIB—Viscosity-average molecular weight ($\bar{M}_v$) of PIB was determined

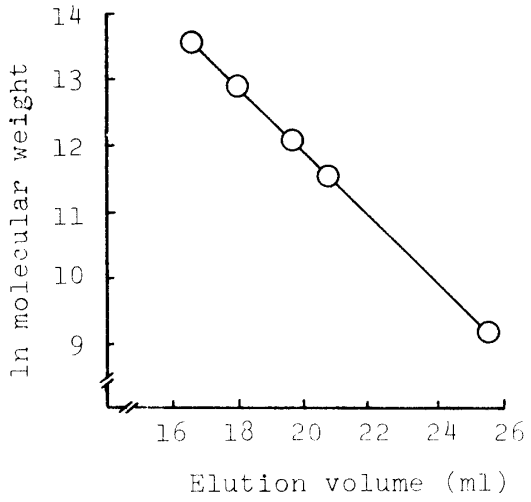

Fig. 1. A Calibration Curve Obtained by Gel Permeation Chromatography of Polystyrene Standards

from the intrinsic viscosity.[4]

Preparation of Microcapsules——Microcapsules were prepared in a way similar to that described in the previous paper.[1] PIB of $\bar{M}_v$ of 1.12×10^6 (VISTANEX MML-100) and PIB of $\bar{M}_v$ of 7.0×10^5 (mixture of equal weights of VISTANEX MML-100 and LMMH), were used as coacervation-inducing agents. Ascorbic acid (3 g), EC (0.6 g) and cyclohexane solution (60 ml) containing 3% PIB were placed in a flask of 100 ml capacity. The flask was heated to 80 °C and cooled linearly to 40 °C at a rate of 0.67 °C/min with stirring at 400 rpm. The cooling was continued at a rate of 2 °C/min until the temperature reached 20 °C. The microcapsules formed were recovered by decantation, washed with cyclohexane and dried.

Classification of Microcapsules——Classification of microcapsules was carried out using JIS standard sieves.[1]

Determination of Ascorbic Acid Content——Ascorbic acid content was determined spectrophotometrically.[1]

Determination of Wall Thickness——If the particles are assumed to be uniform, smooth and spherical, the average wall thickness is given by Lafont's equation[5]:

$$h = \frac{r}{3} \cdot \frac{(1-p)d_1}{pd_2 + (1-p)d_1}$$

where r is the radius of microcapsules, p is the ascorbic acid content in microcapsules, d_1 is the density of core material and d_2 is the density of the wall. Densities were measured using n-heptane as a displacement fluid at 25 °C.

Release Studies——Release rate of ascorbic acid from microcapsules in the 1st fluid for the disintegration test (JP X) was observed using the paddle method.[1]

Determination of Solubility of Ascorbic Acid——Solubility of ascorbic acid in the 1st fluid for the disintegration test (J.P. X) at 37 °C was determined spectrophotometrically at 244 nm.

Observation of Surface and Cross Section of Microcapsules——The surface and cross section of microcapsules were observed using a scanning electron microscope.[1]

Observation of Microencapsulation with an Optical Microscope——Microencapsulation at 55 °C was observed under an optical microscope.[1]

Results and Discussion

EC with various values of $\bar{M}_w$ was obtained by the fractionation of commercial EC. Microencapsulation of ascorbic acid was carried out by the phase separation method using fractionated EC ($\bar{M}_w/\bar{M}_n$: 1.4—2.3).

Concerning the aggregation of microcapsules, Nixon[6] reported that the most obvious factor influencing the size of microcapsules was stirring rate, and a second important variable was the rate of cooling. Donbrow[7] and Samejima[1] reported that a coacervation-inducing agent such as PIB, prevented the formation of aggregates of microcapsules. The relationship between $\bar{M}_w$ of EC and the yield of microcapsules in the 149—250 μm size fraction is shown in Fig. 2. The yield of the microcapsules of 149—250 μm increased with increasing $\bar{M}_w$ of EC in both systems. PIB of high $\bar{M}_v$ resulted in less aggregation of the microcapsules than PIB of low $\bar{M}_v$ at the same $\bar{M}_w$ of EC. Deasy[3] reported that 100 cP grade of EC gave finer

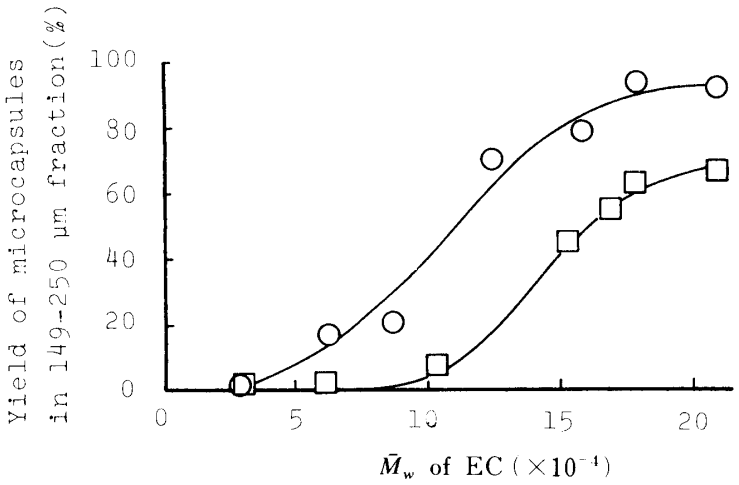

Fig. 2. Effect of $\bar{M}_w$ of EC on Aggregation of Microcapsules
$\bar{M}_v$ values of PIB were 1.12×10^6 (—○—) and 7.0×10^5 (—□—).

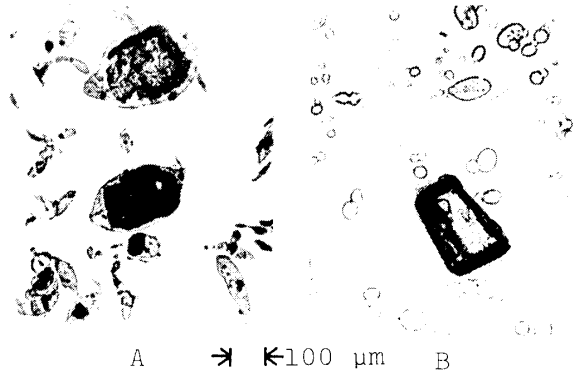

Fig. 3. Micrographs Taken During the Formation of Microcapsules at 55 °C
$\bar{M}_v$ values of PIB was 1.12×10^6. $\bar{M}_w$ values of EC were 2.1×10^5 (A) and 3.1×10^4 (B).

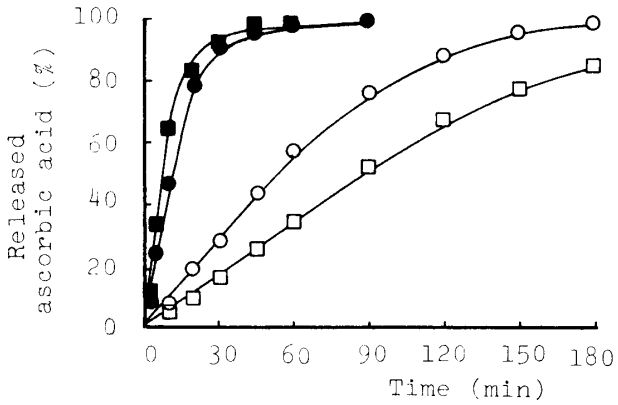

Fig. 4. Release Curves of Ascorbic Acid
$\bar{M}_v$ values of PIB were 1.12×10^6 (—○—, —●—) and 7.0×10^5 (—□—, —■—). $\bar{M}_w$ values of EC were 2.1×10^5 (—●—), 1.5×10^5 (—□—), 1.3×10^5 (—○—) and 6×10^4 (—■—).

microcapsules than 10 cP grade of EC without a coacervation-inducing agent. Micrographs of the formation of microcapsules at 55 °C are shown in Fig. 3. EC of low $\bar{M}_w$ produced spherical or ellipsoidal coacervate droplets (Fig. 3B) and EC of high $\bar{M}_w$ produced greatly deformed coacervate droplets (Fig. 3A). The deformation may relate to the rigidity of coacervate droplets. It seems possible that the difference of the deformation of coacervate droplets is closely related to the compactness of the wall and the formation of aggregates of microcapsules.

In order to examine the effect of $\bar{M}_w$ of EC on the release rate, a kinetic study was attempted. The release of ascorbic acid through the EC membrane of microcapsules is presumed to be dependent on the concentration gradient between the inside and outside of the microcapsules. In the steady state, the following equation (1) holds:[8]

$$\frac{dQ}{dt} = \frac{AP}{H}(C_i - C_o) \tag{1}$$

where Q is the total amount of ascorbic acid released in the surrounding medium at time t, A is the surface area of the microcapsule, P is the permeability constant, H is the wall thickness,

and C_i and C_o are the concentrations of ascorbic acid in the microcapsules and in the medium. Under the sink condition ($C_i \gg C_o$), Eq. (1) can be reduced to the following equation:

$$\frac{dQ}{dt} = V\frac{dC_o}{dt} = \frac{AP}{H}C_i \tag{2}$$

where V is the volume of the medium (900 cm^3). At the beginning of the dissolution, a linear relation between time and the amount of ascorbic acid released was obtained (Fig. 4). The zero order release continued up to about 50% release because sufficient ascorbic acid would be present to maintain saturation in the internal phase of the microcapsules occupied by the 1st fluid. Therefore, the apparent release rate constant, k_{app} is given by Eq. (3):

$$k_{app} = \frac{AP}{VH}C_s \tag{3}$$

where C_s is the solubility of ascorbic acid in the 1st fluid within microcapsules (0.355 g cm^{-3}).

The effect of $\bar{M}_w$ of EC on the release rate is shown in Fig. 5. When PIB of $\bar{M}_v$ 1.12×10^6 was used, k_{app} took a minimum value (3.8×10^{-8} g cm^{-3} s^{-1}) with EC of $\bar{M}_w$ 13×10^4. In the case of PIB of $\bar{M}_v$ 7.0×10^5, k_{app} took a minimum value (2.3×10^{-8} g cm^{-3} s^{-1}) with EC of $\bar{M}_w$ 15×10^4. It was found that the dissolution rate of ascorbic acid from microcapsules was influenced significantly by the $\bar{M}_w$ of EC and a minimum k_{app} was given at a certain $\bar{M}_w$ of EC. The $\bar{M}_w$ of EC which gave minimum k_{app} was affected by the $\bar{M}_v$ of PIB.

In order to elucidate the finding that k_{app} took a minumum value, a plot of wall thickness versus $\bar{M}_w$ of EC was drawn (Fig. 6). When PIB of $\bar{M}_v$ 1.12×10^6 was used, the wall thickness took a maximum value with EC of $\bar{M}_w$ 9×10^4. In the case of PIB of $\bar{M}_v$ 7.0×10^5, the wall thickness took an indistinct maximum value with EC of $\bar{M}_w$ 17×10^4. The $\bar{M}_w$ of EC which gave maximum wall thickness did not always give minimum k_{app} values. From these results, it is clear that the difference of release rate could not be explained solely by the wall thickness. The effect of $\bar{M}_w$ of EC on the permeability constant (P) is shown in Fig. 7. P took a minimum value with EC of $\bar{M}_w$ 13×10^4 if PIB of $\bar{M}_v$ 1.12×10^6 was present during the microencapsulation process. When PIB of $\bar{M}_v$ 7.0×10^5 was used, the value of $\bar{M}_w$ of EC that gave a minimum P value was 15×10^4. The relationship between k_{app} and P is shown in Fig. 8.

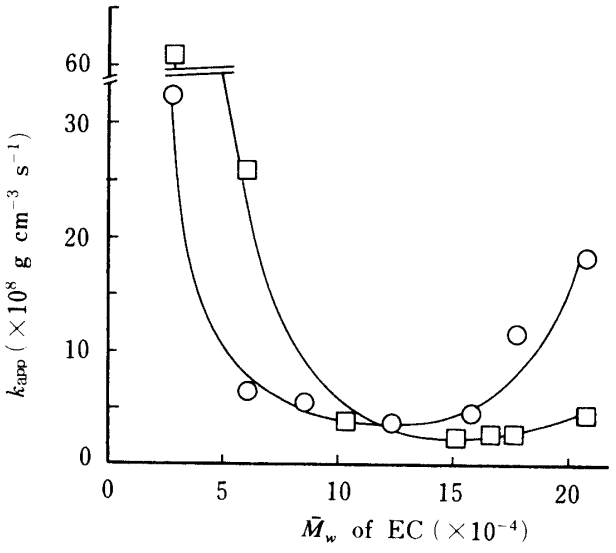

Fig. 5. Effect of $\bar{M}_w$ of EC on the Release Rate of Microcapsules

$\bar{M}_v$ values of PIB were 1.12×10^6 (—○—) and 7.0×10^5 (—□—).

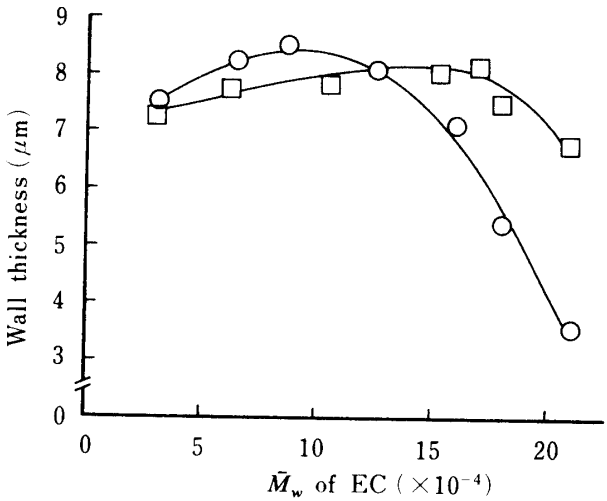

Fig. 6. Effect of $\bar{M}_w$ of EC on the Wall Thickness of Microcapsules

$\bar{M}_v$ values of PIB were 1.12×10^6 (—○—) and 7.0×10^5 (—□—).

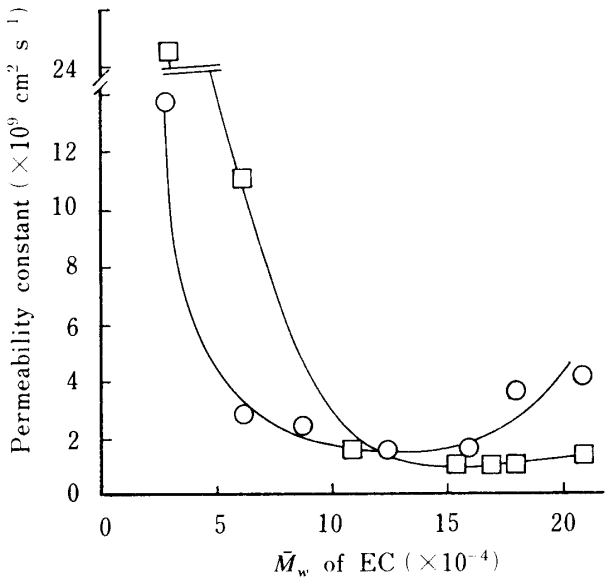

Fig. 7. Effect of $\bar{M}_w$ of EC on the Permeability Constant

$\bar{M}_v$ values of PIB were 1.12×10^6 (—○—) and 7.0×10^5 (---□---).

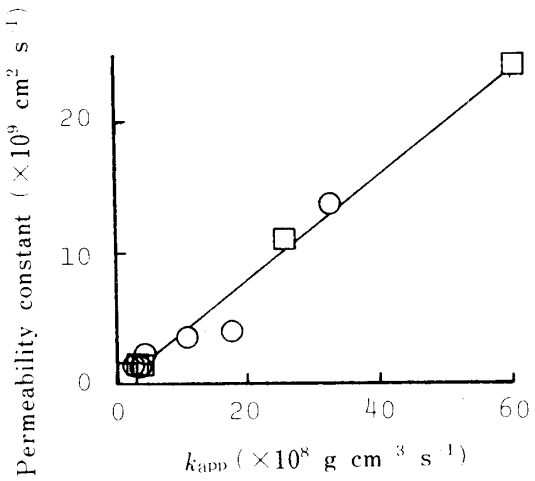

Fig. 8. Relationship between the Permeability Constant and k_{app}

$\bar{M}_v$ values of PIB were 1.12×10^6 (—○—) and 7.0×10^5 (---□---).

Although it was not expected from Eq. (3), a linear relation between k_{app} and P was obtained. The linear dependence of k_{app} on P may be mainly attributable to differences of compactness of the EC membrane. In order to confirm the above-mentioned relationship, the surface of microcapsules was observed by means of an electron microscope (Fig. 9). Figure 9A—C show micrographs of microcapsules prepared with PIB of $\bar{M}_w$ 1.12×10^6. A number of large holes was observed on the surface of microcapsules obtained with high $\bar{M}_w$ EC (Fig. 9A). Moderate and low $\bar{M}_w$ EC resulted in a smooth surface with less holes (Fig. 9B, C). In the case of PIB of $\bar{M}_v$ 7.0×10^5, the surface of the microcapsules was smooth (Fig. 9D—F). $\bar{M}_v$ of PIB as well as $\bar{M}_w$ of EC influenced the surface of microcapsules, and PIB of low $\bar{M}_w$ made the surface smooth. The value of P in each type of microcapsule was supported by this microscopic observation except in the case of Fig. 9F. The microcapsule shown in Fig. 9F had a smooth surface, but the permeability constant value was very high. The surface of the microcapsule was therefore observed at lower magnification. As shown in Fig. 9G, cracks were observed on the edge of the microcapsule. The microencapsulated ascorbic acid should dissolve quickly through the resulting fissure. Rowe[9] reported that the molecular weight of hydroxypropyl methylcellulose affected the incidence of edge splitting on tablets and that it markedly increased as the $\bar{M}_w$ was decreased. As a wall made with EC of low $\bar{M}_w$ has only a small tensile strength, the wall may crack during drying. Another reason for fast release may be lack of uniformity of the wall. A certain part of EC of low $\bar{M}_w$ was aggregated and the effective wall might not be as thick as was estimated from the amount of EC. To validate the above mentioned considerations, the cross sections of microcapsules were observed. As shown in Fig. 10A, cracks were observed in every direction on the cross section of EC wall of microcapsules which had many holes on the surface (Fig. 9A). On the other hand microcapsules having a smooth surface (Fig. 9B—F) did not show big cracks in the cross sections of EC wall (Fig. 10B—F). A good relationship was recognized between the surface characteristics of microcapsules and the cross sections of EC wall. The above mentioned considerations were supported by these observations.

From these results it was concluded that $\bar{M}_w$ of EC significantly influences the

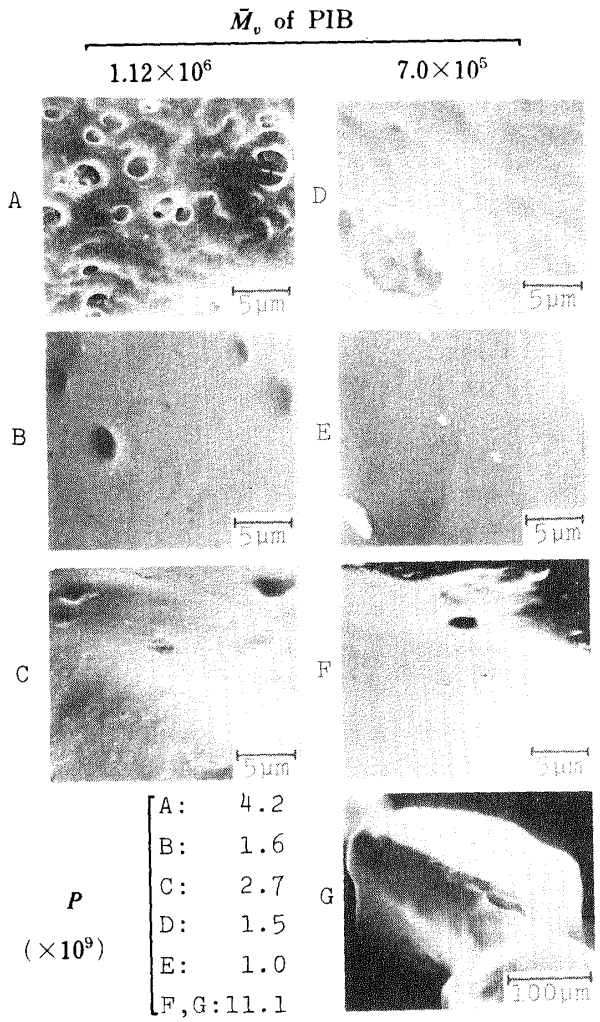

Fig. 9. Scanning Electron Micrographs of Microcapsule Surfaces

$\bar{M}_w$ values of EC were 2.1×10^5 (A, D), 1.6×10^5 (B), 1.5×10^5 (E) and 6×10^4 (C, F, G).

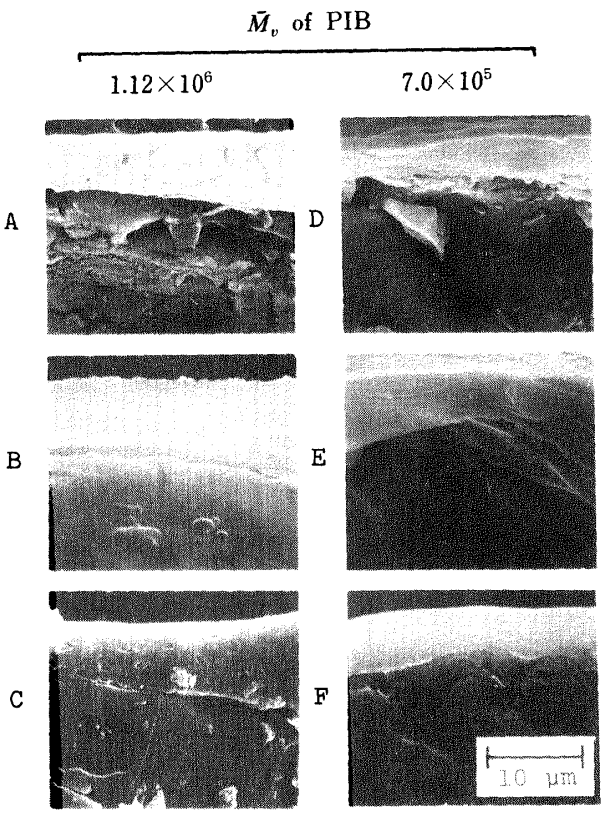

Fig. 10. Scanning Electron Micrographs of the Cross Section of Microcapsules

A—F correspond to Fig. 9A—F, respectively.

aggregation of microcapsules in the microencapsulation process. The aggregation of the microcapsules decreased with increasing $\bar{M}_w$ of EC. As regards the release rate, k_{app} depended significantly on the $\bar{M}_w$ of EC and a minimum k_{app} was given by EC of a certain $\bar{M}_w$. The variation of release rate with $\bar{M}_w$ of EC depended mainly on the compactness of the wall rather than the thickness of the wall.

Acknowledgement The authors are greatly indebted to Dr. Tadao Ida, the general manager of this laboratory, for his kind encouragement.

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