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## Studies on Microcapsules. I. Role and Effect of Coacervation-inducing Agents in the Microencapsulation of Ascorbic Acid by a Phase Separation Method<sup>1)</sup>

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The role and effect of coacervation-inducing agents such as butyl rubber, polyethylene and polyisobutylene in microencapsulation were investigated by using phase separation from cyclohexane solution with change of temperature. Ascorbic acid was used as a core material and ethylcellulose was used as a wall-forming material. Among the three different coacervation-inducing agents, polyisobutylene was suitable for microencapsulation, resulting in low aggregation of microcapsules and a slow dissolution rate. The role of coacervation-inducing agents in microencapsulation was investigated with polyisobutylene. Polyisobutylene changed the gel into a coacervate and resulted in the formation of smooth and thick-walled microcapsules. It also largely prevented the aggregation of microcapsules.

**Keywords**—microcapsule; coacervation-inducing agent; coacervation; ascorbic acid; ethylcellulose; polyisobutylene; butyl rubber; polyethylene; *in vitro* release rate; microencapsulation

Microencapsulation is a useful technique to alter the apparent physical and chemical properties of a drug without changing its essential properties. In the pharmaceutical field, microencapsulation techniques have been widely investigated.<sup>2)</sup> Drugs can be microencapsulated by diverse methods, among which coacervation from aqueous solution, probably the most typical method of microencapsulation, is the most suitable for microencapsulating water-insoluble drugs. However, this method is unsuitable for microencapsulating water-soluble drugs and moisture-sensitive drugs such as ascorbic acid and aspirin. However, coacervation from an organic solvent vehicle (ethylcellulose-cyclohexane solution) by change of temperature is a useful method for microencapsulating the above-mentioned drugs. Many patents on this method indicate that polymers such as polybutadiene,<sup>3)</sup> butyl rubber,<sup>3)</sup> polyisobutylene (PIB)<sup>4)</sup> and polyethylene<sup>5)</sup> must be added to the system in order to induce coacervation from ethylcellulose-cyclohexane solution. However, the role and effect of the above-mentioned coacervation-inducing agents have scarcely been studied in detail. In this paper, an attempt was made to observe the effect and role of coacervation-inducing agents in microencapsulation. Ethylcellulose was used as a wall-forming material on account of its safety, stability, hydrophobicity and compact film-forming nature among water-insoluble polymers. Ascorbic acid was selected as a model core material.

### Experimental

**Materials**—Ascorbic acid (J.P. grade) passing through a 65 mesh sieve and remaining on a 100 mesh sieve (particles size: 149–210  $\mu\text{m}$ ) was used. PIB (Vistanex MML-100), polyethylene (Flo-Thene UF 1.5) and butyl rubber (Polysar Butyl 101) were obtained from Esso Chemical Co. Ltd., Seitetsu Kagaku Kogyo Co. Ltd. and Polysar Ltd., respectively. Ethylcellulose (Ethocel, viscosity: 90–110 cP ethoxy content: 48.0–49.5%) was obtained from Dow Chemical Company. Cyclohexane was of reagent grade. All the materials were used without further purification.

**Preparation of Microcapsules**—The method of preparation was modified from those described by Miller and others.<sup>3)</sup> Three hundred ml of cyclohexane solution containing from 0 to 6 w/w% of coacervation-inducing agent, *i.e.* PIB, butyl rubber or polyethylene, was placed in a 500 ml three-necked round-bottomed flask equipped with an air-tight stirrer, a thermometer and a reflux condenser. With stirring at 400 rpm,

3 g of ethylcellulose was added at room temperature. The system was heated to 78°C to form a homogeneous solution, then ascorbic acid particles were suspended in the solution. With continued stirring, the system was cooled to 40°C in 60 min and then cooled quickly to 25°C. The microcapsules formed were recovered by decantation, washed with cyclohexane and dried.

**Classification of Microcapsules**—The different sizes of microcapsules present in a batch were separated into suitable fractions by sieving on a mechanical shaker using a JIS standard sieve for five minutes.

**Determination of Ascorbic Acid Content**—Microcapsules of 149–250  $\mu\text{m}$  diameter were used for the following assay. Microcapsules (100 mg) were dissolved in methanol (5 ml) and the solution was made up to 100 ml with the 1st disintegration test fluid specified in J.P. IX. The resultant precipitate was removed on filter paper. The 1st fluid was added to the filtrate (1 ml) to make 100 ml. Ascorbic acid content was analyzed spectrophotometrically at 244 nm.

**Dissolution Studies**—Microcapsules of 149–250  $\mu\text{m}$  diameter were used to obtain the dissolution profile of ascorbic acid from microcapsules in the 1st fluid of the disintegration test specified in J.P. IX. Method II for dissolution specified in USP XIX (4th supplement) was used to determine the dissolution profile. The dissolution fluid was maintained at 37°C and stirred constantly at 100 rpm. Microcapsules containing a given amount (200 mg) of ascorbic acid were accurately weighted and placed in the fluid. At suitable intervals, a 1 ml aliquot was removed using a pipet fitted with a filter paper. Then 1 ml of fresh dissolution fluid was added to maintain the original volume. The concentrations of ascorbic acid were determined spectrophotometrically at 244 nm.

**Observation of Microencapsulation with an Optical Microscope**—As described in “preparation of microcapsules,” ascorbic acid was suspended in warm microencapsulation medium, and the system was cooled slowly. At the temperatures of 65, 55 and 40°C, a certain amount of suspension was removed from the vessel and placed in a glass cell (diameter: 14.5 mm, depth: 2.5 mm). The cell was covered with a glass plate, and the state of microencapsulation at each temperature was observed under an optical microscope at a magnification of 100X.

**Observation of the Surface of Microcapsules with a Scanning Electron Microscope**—Microcapsules were coated with gold vapor under a high vacuum. Their surface characteristics were observed under a scanning electron microscope (model LSM-U3, Japan Electron Optics Laboratory) at a magnification of 3000X.

**Determination of Wall Thickness**—If the particles are assumed to be uniform, smooth and spherical, the average wall thickness is given by Madan's equation:<sup>6)</sup>

$$\text{wall thickness} = \frac{W_w}{W - W_w} \cdot \frac{\rho}{\rho_w} \cdot \frac{d}{6}$$

where  $W$  is the weight of microcapsules,  $W_w$  is the weight of wall material,  $\rho_w$  is the density of wall material,  $\rho$  is the density of ascorbic acid and  $d$  is the mean diameter of ascorbic acid particles. The densities of wall material (ethylcellulose) and core material (ascorbic acid) were calculated from the displacement volume of a known weight of ethylcellulose and ascorbic acid using *n*-heptane as a displacement fluid. The calculated values are 1.11 g/cm<sup>3</sup> for ethylcellulose and 1.70 g/cm<sup>3</sup> for ascorbic acid at 25°C.

## Results and Discussion

### I. Effect of Coacervation-inducing Agents in Microencapsulation

The effects of coacervation-inducing agents such as PIB, butyl rubber and polyethylene were compared. As shown in Fig. 1, 50% of the original ascorbic acid particles (without microencapsulation) dissolved in the 1st fluid within one minute. The time required to dissolve 50% of ascorbic acid from microcapsules ( $t_{50}$ ) was 7 min if the microcapsules were

TABLE I. Effects of Coacervation-inducing Agents in Microencapsulation

Coacervation-inducing agent	Ascorbic acid content (%)	Wall thickness ( $\mu\text{m}$ )	Sieve fraction (%)			
			149—250	250—420	420—1000	1000<
			( $\mu\text{m}$ )			
Butyl rubber	98.4	0.75	96.8	1.2	1.8	0.2
Polyethylene	94.1	2.87	54.2	32.2	9.4	4.2
PIB	92.5	3.72	91.7	6.2	1.6	0.5
None	94.8	2.51	41.3	21.0	14.6	23.1

The concentration of coacervation-inducing agents was 3 w/w%.

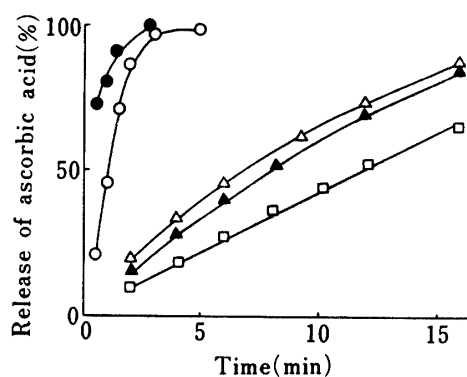


Fig. 1. Release of Ascorbic Acid from Microcapsules prepared with 3% Coacervation-inducing Agents

□ : PIB, ▲ : polyethylene, ○ : butyl rubber,  
 △ : without coacervation-inducing agent, ● : unmicrocapsulated ascorbic acid.

prepared without coacervation-inducing agent. When butyl rubber, polyethylene and PIB were used as coacervation-inducing agents, the  $t_{50}$  values were 1, 8 and 12 min, respectively. Namely, the dissolution rate of ascorbic acid from microcapsules followed the order butyl rubber > none > polyethylene > PIB. Takamura,<sup>7)</sup> Nixon<sup>8)</sup> and their co-workers reported that the dissolution rate of core material from microcapsules was related to variables such as wall thickness, porosity, density and other wall characteristics. As shown in Table I, the wall thickness of the microcapsules produced with or without coacervation-inducing agent increased in the order butyl rubber < none < polyethylene < PIB. Thus, one of the factors controlling the dissolution rate is probably the difference of wall thickness of those microcapsules.

Scanning electron micrographs of microcapsules are presented in Fig. 2. The surface of the microcapsules prepared without coacervation-inducing agent was rough and irregular (Fig. 2a). In the case of butyl rubber, the surface was poorly covered with ethylcellulose and resembled that of uncoated ascorbic acid (Fig. 2b). Although polyethylene made the surface smooth, many small holes were apparent (Fig. 2c). When PIB was used, the surface was smooth with a few small holes (Fig. 2d). It is reasonable to assume that another factor in the above-mentioned difference of the dissolution rates is the difference of the surface characteristics of microcapsules.

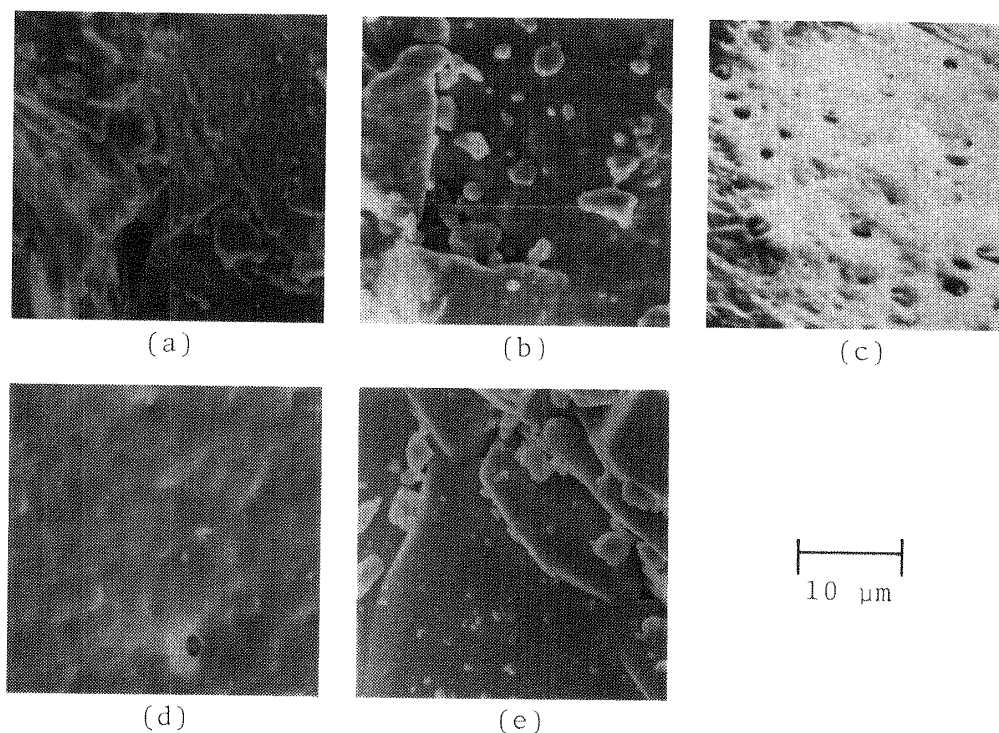


Fig. 2. Scanning Electron Micrographs of Microcapsule Surfaces and Uncoated Ascorbic Acid

(a) without coacervation-inducing agent, (b) butyl rubber, (c) polyethylene, (d) PIB, (e) uncoated ascorbic acid.

From a commercial point of view, it is very important to obtain free-flowing discrete microcapsules. The results of sieving analysis of the microcapsules prepared using various coacervation-inducing agents are shown in Table I. The yield of microcapsules having a diameter of 149–250  $\mu\text{m}$  could be used as an indicator of the degree of aggregation, because ascorbic acid particles having a diameter of 149–210  $\mu\text{m}$  were used as core material. The yields of 149–250  $\mu\text{m}$  microcapsules obtained using butyl rubber, PIB, polyethylene and no coacervation-inducing agent were 96.8, 91.7, 54.2 and 41.3%, respectively. A remarkable preventive effect on the formation of aggregates of microcapsules was seen with PIB and butyl rubber. When coacervation-inducing agent was not used, the diameter of 23.1% of the microcapsules was at least 1000  $\mu\text{m}$ . In the view of its preventive effect on aggregation of microcapsules and sustained dissolution effect, PIB at the concentration of 3% seemed most suitable for the preparation of ethylcellulose microcapsules among the tested coacervation-inducing agents.

## II. Role of PIB in Microencapsulation

To determine the optimum concentration for microencapsulation, the influence of PIB concentration on microencapsulation was observed. The relationship between PIB concentration and yield of microcapsules in the 149–250  $\mu\text{m}$  fraction is shown in Fig. 3. The preven-

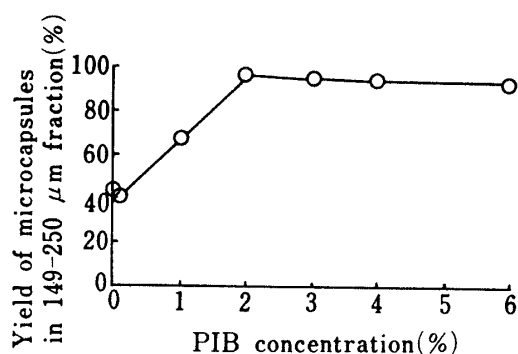


Fig. 3. Influence of PIB Concentration on the Aggregation of Microcapsules

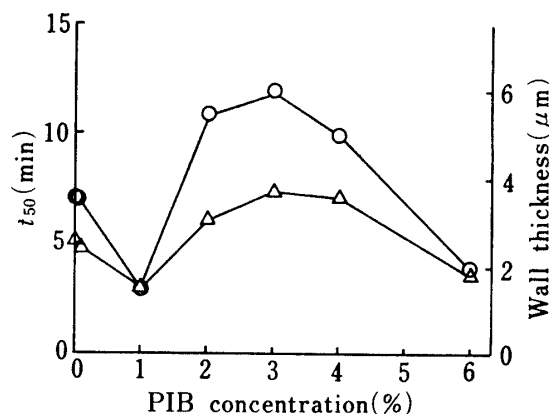


Fig. 4. Influence of PIB Concentration on  $t_{50}$  and Wall Thickness

—○— :  $t_{50}$ , —△— : wall thickness.

tive effect on aggregation of microcapsules was recognized from 1 to 6% PIB concentration. PIB acted effectively as a protective colloid in the microencapsulation process at concentrations above 2%. Figure 4 shows the influence of PIB concentration on  $t_{50}$  and wall thickness. The  $t_{50}$  versus PIB concentration curve exhibited a distinct minimum and maximum at PIB concentrations of 1% and 3%, respectively. This tendency is the same as that of wall thickness. The change of  $t_{50}$  is parallel to the change of wall thickness. From this result it was concluded that one of the reasons for the changes of release rate was variations in wall thickness. Thus, 3% PIB is suitable for microencapsulation from the viewpoints of low aggregation of microcapsules and slow dissolution rate of the core material. Levels of 0, 1 and 3% PIB were therefore selected to study the role of PIB in microencapsulation. The microencapsulation course was observed under an optical microscope. Micrographs of various stages in the formation of microcapsules are shown in Fig. 5.

**At 65°C**—When PIB was not used in the microencapsulation process (system I), ethylcellulose aggregates caused by demixing were clearly seen around the crystals. When 1% PIB was used (system II), gel-like spheroids were observed. When 3% PIB was used (system

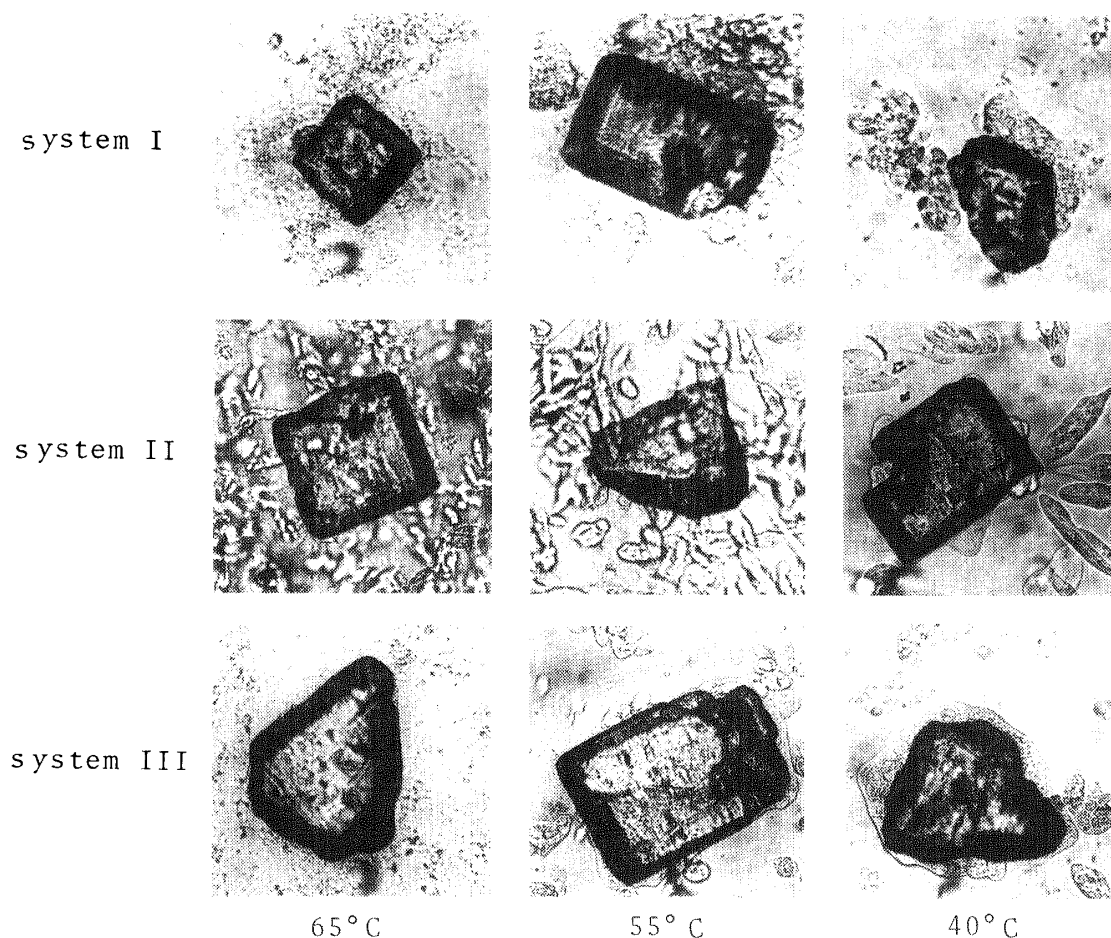


Fig. 5. Micrographs of Stages in the Formation of Ethylcellulose Microcapsules

System I: without PIB, system II: 1% PIB, system III: 3% PIB.

III), a large number of small spherical coacervate droplets produced by coacervation gathered almost uniformly around the crystals.

**At 55°C**—In system I, some large aggregates of ethylcellulose were deposited on the crystals irregularly. In system II, a large number of gel-like spheroids caused by demixing and coacervation gathered around the crystals. In system III, aggregated coacervate droplets deposited on the crystals and seamless film began to form.

**At 40°C**—In system I, the crystals were covered with a thin wall and aggregates of ethylcellulose deposited on the crystals locally. Both coacervate droplets and aggregates of ethylcellulose were produced in system II. The coacervate droplets would be consumed to coat both ascorbic acid particles and aggregates of ethylcellulose, so the wall of the microcapsules would be relatively thin. In system III, coacervate droplets formed thick and seamless walls. As shown in Fig. 4, nearly uniform and thick-walled microcapsules were obtained with 3% PIB. Scanning electron micrographs of samples of the products are shown in Fig. 6.

Rough and irregular surfaces were observed on the microcapsules prepared without coacervation-inducing agent (Fig. 6a). The microcapsules prepared with 1% PIB were covered with ethylcellulose all over the crystal surface, but the surface had some large holes (Fig. 6b). Three percent PIB resulted in smooth-walled encapsulated crystals (Fig. 6c). From these results, it was clear that the dissolution rate was dependent on the phase type produced upon phase separation. In the absence of PIB, ethylcellulose aggregates were formed, whereas a low concentration (1%) of PIB yielded a gel-like mixture of aggregates and coacervates. At higher concentrations (>2%) of PIB, coacervates were formed. Namely, these results

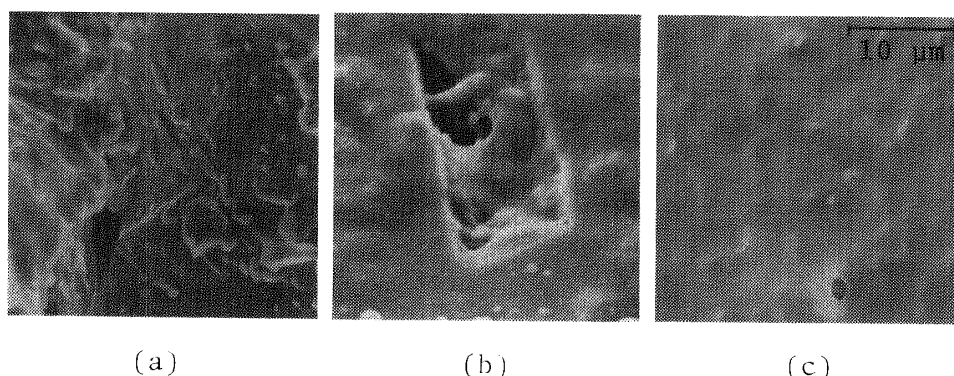


Fig. 6. Scanning Electron Micrographs of Microcapsule Surfaces  
(a) without PIB, (b) 1% PIB, (c) 3% PIB.

suggest that PIB acts as a good solvent in cyclohexane and changes the gel (or aggregate) into a coacervate. The coacervate phase makes the wall film of microcapsules smooth and thick as compared with the gel phase or aggregate phase. Another role of PIB is to prevent the aggregation of microcapsules. Benita<sup>9)</sup> reported that PIB was not coprecipitated but adsorbed on the surface of ethylcellulose droplets produced by phase separation in the presence of PIB, and that it functions as a stabilizer for the coacervate droplets. Thus, the function of PIB as a protective colloid in the microencapsulation process may be qualitatively interpreted as follows. PIB is adsorbed on the coacervate wall produced on the crystal surface of ascorbic acid particles and forms an adsorbed layer of PIB on it; consequently, it acts as a stabilizer preventing the agglomeration of single microcapsules into aggregates. At higher concentrations of PIB (from 2% upwards), PIB would completely cover the surface of microcapsules and more effectively prevent the aggregation of microcapsules.

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