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Studies on Microcapsules. II.[1] Preparation of Polyphthalamide Microcapsules

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Polyphthalamide microcapsules were prepared by the interfacial polycondensation reactions between each of 1,6-hexamethylenediamine and diethylenediamine and each of *o*-, *m*-, and *p*-phthaloyl dichlorides under various conditions. The size and size distribution of the microcapsules formed were determined and the factors affecting them were of studied. Favorable conditions were suggested to obtain the microcapsules of uniform size in a high yield.

Some of interfacial polycondensation reactions[1,3,4] have been applied to the microencapsulation of chemicals within semipermeable polymer membranes. Thus, nylon microcapsules were prepared by Chang and his coworkers,[3,4] and polyurethane and polyphenolester microcapsules were made in our laboratory.[1]

In view of applying microcapsules to diverse fields of science and industry, however, it is necessary to study the preparation and properties of many kinds of microcapsules as much as possible. This series of papers has been planned, therefore, to present detailed studies on various microcapsules.

This paper deals with the preparation of polyphthalamide microcapsules.

Experimental

Preparation of Microcapsules——A) Preparation of Polyphthalamide Microcapsules: The preparation of polyphthalamide microcapsules was made by utilizing the interfacial polycondensation reaction between diamine and phthaloyl dichloride studied in detail by Katz,[5] and Shashoua and Eareckson.[6] Thus, the procedure consisted of the following three steps: 1. To 7.5 ml of distilled water in a 1 liter round bottom flask surrounded by ice was added an equal volume of 0.4M 1,6-hexamethylenediamine or piperazine (diethylenediamine) solution in aqueous 0.45M sodium carbonate solution. To this solution was added 75 ml of mixed solvent (chloroform–cyclohexane, 1:4 or 1:3, v/v, containing 0—20% (v/v) Span 85 as an emulsifying agent). The mixed solution was then mechanically emulsified with a Chemistirrer (Tokyo Rika Kikai Co., Model B-100) at each of four speed settings of 237, 382, 620, and 1100 rpm for 5 min to yield a water-in-oil emulsion. The alkali served to neutralize hydrogen chloride formed during the polymerization reaction. 2. Without stopping the stirring, 75 ml of phthaloyl dichloride (each of *o*-, *m*-, and *p*-phthaloyl dichlorides) solution was quickly added to the emulsion, and the stirring was continued for another 3 min. The phthaloyl dichloride solution was prepared immediately before use by adding 0.6 g of pure phthaloyl dichloride to 75 ml of the mixed solvent. 3. To this dispersion was added 75 ml of the mixed solvent, and the dispersion was centrifuged at 350—2000 g to separate the newly formed microcapsules. Finally, the microcapsules were completely dispersed in 40 ml of aqueous 50% (v/v) Tween 20 solution. After stirring for 30 min, 40 ml of distilled water was added to the dispersion, and it was centrifuged again at 350—2000 g. The separated polyphthalamide microcapsules were dispersed in 80 ml of aqueous 20% (v/v) Tween 20 solution and diluted with distilled water to give a dispersion of a desired concentration.

1) Part I: S. Suzuki, T. Kondo, and S.G. Mason, *Chem. Pharm. Bull.* (Tokyo), **16**, 1629 (1968).
2) Location: *12 Funakawara-machi, Ichigaya, Shinjuku-ku, Tokyo.*
3) T.M.S. Chang, *Science*, **146**, 524 (1964).
4) T.M.S. Chang, F.C. MacIntosh, and S.G. Mason, *Can. J. Physiol. Pharmacol.*, **44**, 115 (1966).
5) M. Katz, *J. Polymer Sci.*, **40**, 337 (1959).
6) V.E. Shashoua and W.M. Eareckson, III, *J. Polymer Sci.*, **40**, 343 (1959).

B) Partition of Diamines between Aqueous and Organic Phases: There should be an optimum value of diamine concentration in the organic phase for the interfacial polycondensation between phthaloyl dichloride and diamine, and consequently, for the formation of microcapsules in a given solvent system. If the concentration is too low, the polymer will not be produced enough to form the microcapsules at the interface of the mixed solvent and water droplets. On the other hand, if the concentration is too high, the polymerization reaction will take place not only at the interface but also in the organic phase, thereby making it difficult to separate the microcapsules from the polymer particles formed in the organic phase. Moreover, the presence of Span 85 may alter the partition of diamine. An attempt was made, therefore, to determine the diamine partition between the aqueous and the organic phase under the same conditions as those in the preparation of microcapsules. Thus, the partition coefficients were determined by the following method: To 30 ml of 0.4M 1,6-hexamethylenediamine or diethylenediamine solution in aqueous 0.45M sodium carbonate solution in a 100 ml Erlenmyer flask surrounded by ice was added an equal volume of the mixed solvent. The mixed liquid was then mechanically stirred with a Chemistirrer at each of four speed settings of 237, 382, 620, and 1100 rpm for 5 min. In case an emulsion was formed, it was centrifuged to completely separate into two liquid layers.

The concentration of the diamine plus sodium carbonate remaining in aqueous phase was determined by titration with hydrochloric acid using a piston burette and BCG–BTB mixed indicator. The initial concentrations of the diamine plus sodium carbonate and sodium carbonate alone were also determined by the same procedure.

Finally, the transferred amount of diamine was calculated from the initial and final concentrations of the diamine in the aqueous phase, and the diamine partition coefficients between the aqueous and organic phases were estimated.

Determination of the Size and Size Distribution of Microcapsules——Each sample of microcapsules prepared by the above described method was placed on a hemocytometer and was observed under a photomicroscope, and the microcapsules were photographed. In each photographed strip film, 800 microcapsule diameters were measured in the following way. The film was projected on a large section paper by a Color cabin slide projector (Cabin Industry Co.), and the enlarged images of microcapsules were measured to the nearest 0.8 μ. The scales in the hemocytometer were used for calibration. If the contour of projected images was of a complex or indistinct shape, these images were eliminated from the measurement. Then, the calculations were made on the length mean diameter, size distribution, standard deviation, mean surface diameter, and mean volume diameter by using an IBM 1620 computer.

Results and Discussion

Formation of Microcapsules

The formation of polyphthalamide microcapsules was affected by the composition of solvent mixture, the concentration of Span 85, and the chemical structure of diamine and phthaloyl dichloride used.

The reaction of 1,6-hexamethylenediamine with phthaloyl dichlorides gave microcapsules equally easily in 1:4 and 1:3 mixtures of chloroform and cyclohexane, while the use of diethylenediamine instead of 1,6-hexamethylenediamine could yield microcapsules slightly more easily in the 1:3 mixture than in the 1:4 mixture. This is presumably due to the fact that diethylenediamine is slightly more soluble in the 1:3 mixture than the 1:4 mixture as will be shown in Table II.

Span 85 was found to enhance the formation of microcapsules in both of the solvent mixtures. Thus, the amount formed of microcapsules increased as the concentration of Span 85 became higher. The increased yield of microcapsules may be caused by an abrupt rise in the solubility of diamines in the organic phase owing to the presence of Span 85. The formation of polymer particles was not observed in the organic phases containing Span 85 of the concentration range studied in this work.

The microcapsules prepared by using 1,6-hexamethylenediamine were usually less resistant to centrifugation than those prepared by using diethylenediamine. This may be ascribable to the difference in the membrane structure of microcapsules.

The shape of microcapsules was invariably spherical in all cases studied. Typical examples are shown in Fig. 1 to 4.

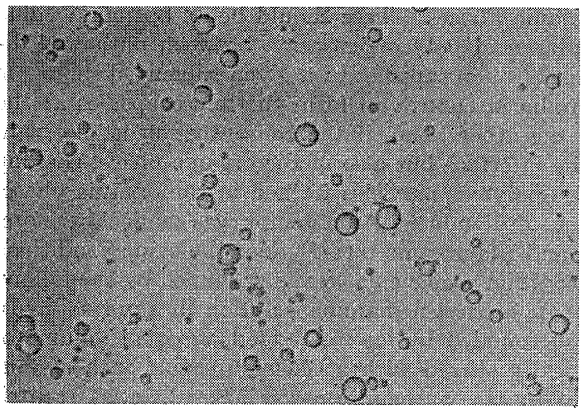

Fig. 1. Microcapsules prepared from 1,6-Hexamethylenediamine and *o*-Phthaloyl Dichloride in Chloroform–Cyclohexane (1:4) containing 5% (v/v) Span 85 at a Speed Setting of 382 rpm

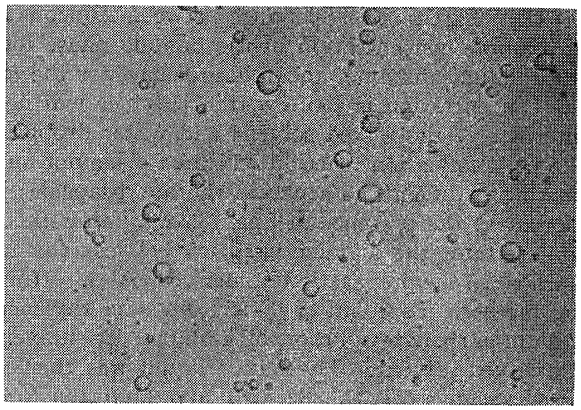

Fig. 2. Microcapsules prepared from 1,6-Hexamethylenediamine and *m*-Phthaloyl Dichloride in Chloroform–Cyclohexane (1:4) containing 5% (v/v) Span 85 at a Speed Setting of 620 rpm

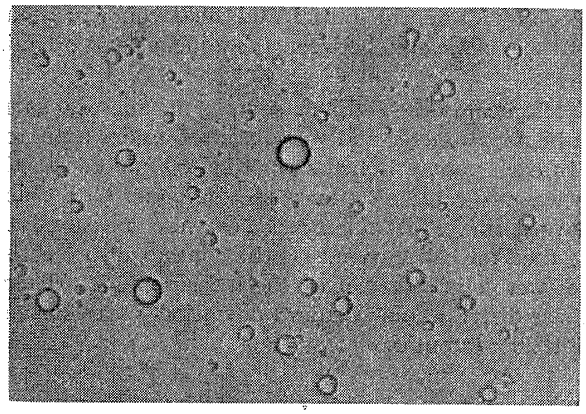

Fig. 3. Microcapsules prepared from 1,6–Hexamethylenediamine and *p*-Phthaloyl Dichloride in Chloroform–Cyclohexane (1:4) containing 5% (v/v) Span 85 at a Speed Setting of 620 rpm

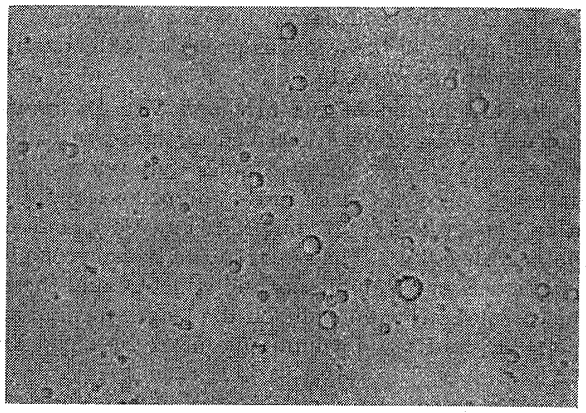

Fig. 4. Microcapsules prepared from Diethylenediamine and *p*-Phthaloyl Dichloride in Chloroform–Cyclohexane (1:3) containing 5% (v/v) Span 85 at a Speed Setting of 620 rpm

Partition of Diamines between Aqueous and Organic Phases

The partition coefficients of diamines varied with the concentration of Span 85 and mechanical agitation. Thus, the partition coefficients determined at a constant stirring speed increased with increasing concentration of Span 85 as shown in Table I and II.

Table I. Effect of the Concentration of Span 85 on the Partition Coefficient of 1,6-Hexamethylenediamine at a Speed Setting of 620 rpm

Span 85 conc. % (v/v)	Chloroform/Cyclohexane (v/v)	Partition coefficient K (C_{aq}/C_{org})
0	1/3	20.71
5.0	1/3	7.93
0	1/4	20.71
2.0	1/4	11.35
5.0	1/4	8.04
7.5	1/4	5.93
10.0	1/4	5.22
12.5	1/4	4.78
15.0	1/4	3.99

Table II. Effect of the Concentration of Span 85 on the Partition Coefficient of Diethylenediamine at a Speed Setting of 620 rpm

Span 85 conc. % (v/v)	Chloroform/Cyclohexane (v/v)	Partition coefficient K (C_{aq}/C_{org})
0	1/3	55.01
2.0	1/3	42.24
5.0	1/3	26.00
7.5	1/3	22.14
10.0	1/3	18.83
12.5	1/3	15.47
15.0	1/3	13.85
20.0	1/3	12.26
0	1/4	55.57
5.0	1/4	36.04

In the absence of Span 85, the transfer of diamines from aqueous to organic phase showed an upward tendency when the stirring speed increased. This seems to be resulted from the increased transfer rate of diamines caused by stirring. The presence of Span 85, however, diminished the effect of stirring speed and gave rise to a drastic increase in the solubility of diamines. In Table III are given the values of partition coefficient obtained in these cases.

Table III. Effect of Mechanical Agitation on the Partition Coefficient of Diamines at Two Concentration of Span 85

Span 85 conc. % (v/v)	Speed setting rpm	Chloroform/Cyclohexane (v/v)	Partition coefficient $K(C_{aq}/C_{org})$
1,6-Hexamethylenediamine			
0	237	1/4	28.16
0	620	1/4	20.71
0	1100	1/4	14.82
5.0	237	1/4	8.21
5.0	382	1/4	8.10
5.0	620	1/4	8.04
Diethylenediamine			
2.0	237	1/3	42.24
2.0	382	1/3	42.25
2.0	620	1/3	42.24
5.0	237	1/3	26.49
5.0	382	1/3	26.00
5.0	620	1/3	26.00

These findings will provide the key for choosing the optimum conditions under which the preparation of polyphthalamide microcapsules may be performed most favorably.

Size Distribution and Mean Size

The size distribution of microcapsules was strongly affected by the concentration of Span 85 and mechanical agitation in the first step of the preparation.

Fig. 5 and 6 show the effect of the concentration of Span 85 on the size distribution of microcapsules prepared from 1,6-hexamethylenediamine and diethylenediamine, and *p*-phthaloyl dichloride at a speed setting of 620 rpm, respectively. The size distribution curves clearly become narrower and sharper with increase in the Span 85 concentration up to 5%, above which no appreciable change in their shape is observed. No significant effect of solvent

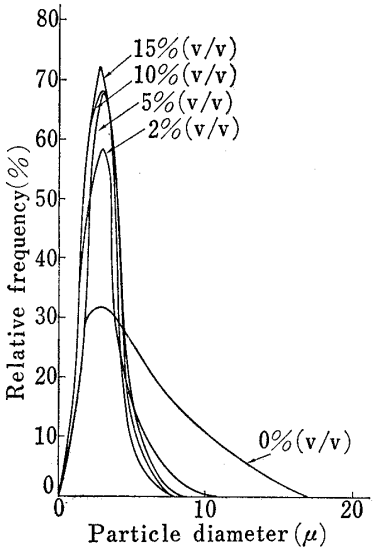

Fig. 5. Effect of the Concentration of Span 85 on the Size Distribution of Microcapsules prepared from 1,6-Hexamethylenediamine and *p*-Phthaloyl Dichloride in Chloroform–Cyclohexane (1:4) at a Speed Setting of 620rpm

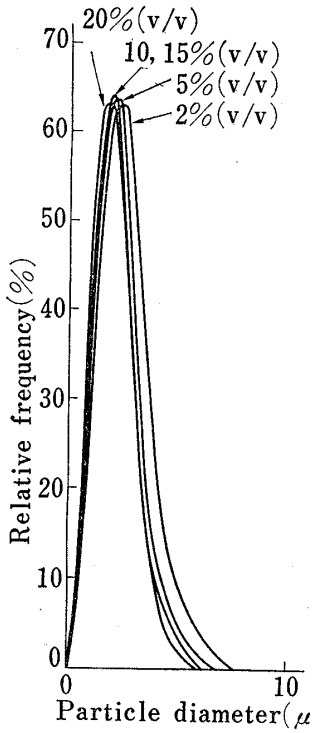

Fig. 6. Effect of the Concentration of Span 85 on the Size Distribution of Microcapsules prepared from Diethylenediamine and *p*-Phthaloyl Dichloride in Chloroform–Cyclohexane (1:3) at a Speed Setting of 620 rpm

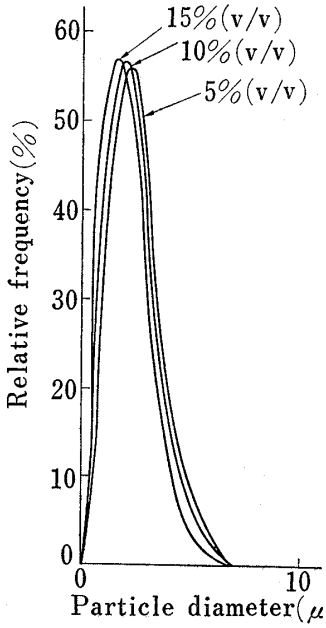

Fig. 7. Effect of the Concentration of Span 85 on the Size Distribution of Microcapsules prepared from 1,6-Hexamethylenediamine and *p*-Phthaloyl Dichloride in Chloroform–Cyclohexane (1:3) at a Speed Setting of 620 rpm

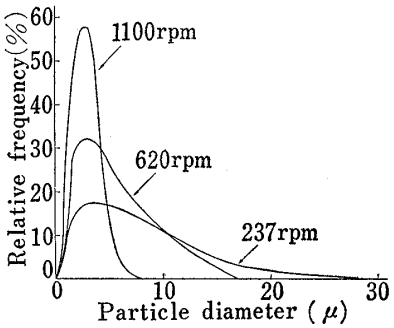

Fig. 8. Effect of the Stirring Speed on the Size Distribution of Microcapsules prepared from 1,6-Hexamethylenediamine and *p*-Phthaloyl Dichloride in Chloroform–Cyclohexane (1:4) without Span 85

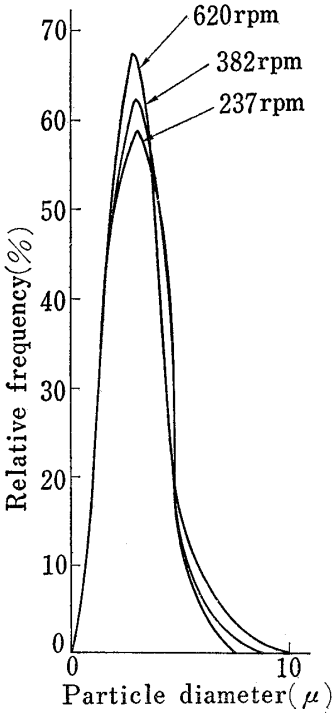

Fig. 9. Effect of the Stirring Speed on the Size Distribution of Microcapsules prepared from 1,6-Hexamethylenediamine and *p*-Phthaloyl Dichloride in Chloroform–Cyclohexane (1:4) containing 5% (v/v) Span 85

composition was found on the size distribution curve. This will be evident when a comparison is made between Fig. 5 and 7.

A pronounced change in the shape of the curve was noted in the absence of Span 85 when the stirring speed was raised. However, the effect of stirring almost disappeared in the presence of Span 85. These are shown in Fig. 8 and 9.

Table IV. Effect of Mechanical Agitation and the Concentration of Span 85 on the Length Mean Diameter (d_1), Standard Deviation (δ), Mean Surface Diameter (d_2), and Mean Volume Diameter (d_3) of Microcapsules prepared from 1,6-Hexamethylenediamine and Phthaloyl Dichlorides in Chloroform–Cyclohexane (1:4)

Speed setting rpm	Span 85 conc. % (v/v)	*o*-Phthaloyl dichloride $d_1(\mu)$	$d_2(\mu)$	$d_3(\mu)$	δ	*m*-Phthaloyl dichloride $d_1(\mu)$	$d_2(\mu)$	$d_3(\mu)$	δ	*p*-Phthaloyl dichloride $d_1(\mu)$	$d_2(\mu)$	$d_3(\mu)$	δ
237	0									8.55	17.89	45.18	15.71
620	0									5.12	5.89	6.58	2.91
1100	0									2.45	2.72	3.01	1.17
620	2.0									2.98	3.33	3.72	1.50
237	5.0					2.95	3.29	3.67	1.46	2.99	3.35	3.73	1.51
382	5.0	2.94	3.27	3.66	1.42					2.93	3.25	3.64	1.40
620	5.0					2.72	2.93	3.15	1.08	2.85	3.09	3.34	1.18
620	10.0									2.68	3.01	3.35	1.37
620	15.0									2.67	2.90	3.16	1.12

Table V. Effect of the Concentration of Span 85 on the Length Mean Diameter (d_1), Standard Deviation (δ), Mean Surface Diameter (d_2), and Mean Volume Diameter (d_3) of Microcapsules prepared from Diamines and *p*-Phthaloyl Dichloride in Chloroform–Cyclohexane (1:3) at a Speed Setting of 620 rpm

	Span 85 conc. % (v/v)	*p*-Phthaloyl dichloride $d_1(\mu)$	$d_2(\mu)$	$d_3(\mu)$	δ
1,6-Hexamethylenediamine	5.0	2.08	2.23	2.38	0.80
	10.0	2.00	2.12	2.25	0.70
	15.0	1.90	2.01	2.14	0.64
Diethylenediamine	2.0	2.44	2.71	3.04	1.19
	5.0	2.26	2.39	2.53	0.79
	10.0	2.00	2.12	2.25	0.70
	15.0	2.01	2.15	2.27	0.75
	20.0	1.94	2.08	2.21	0.76

In Table IV and V are summarized the results on the calculations of the length mean diameter, standard deviation, mean surface diameter, and mean volume diameter of the both polyphthalamide microcapsules.

A decrease in the mean diameters is apparent with an increase in the concentration of Span 85. Besides, the smaller mean diameters are indicated in the 1:3 mixture than in the 1:4 mixture.

From what have been described so far, it may be concluded that the presence of Span 85 (5% (v/v) or above) and the mechanical agitation (237 rpm or above) are needed to prepare the microcapsules of uniform size in a high yield.