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Studies on Microcapsules. I. Preparation of Polyurethane and Polyphenolester Microcapsules

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In recent years, much attention has been paid to the microencapsulation of chemicals and drugs within semipermeable polymer membranes because of its importacne in the chemical and pharmaceutical industries. There exist many patents and reports on the preparation of microcapsules,[2–4] and some encapsulated chemicals and drugs are already commercially available. The method of encapsulation in these cases is based on the coacervation phenomenon in solutions of certain polymers such as gelatine.

On the other hand, a few years ago, Chang, MacIntosh, and Mason developed a new method of microencapsulation by making use of interfacial polycondensation.[5,6] The nylonmicrocapsules were easily prepared by this method, and some of their physicochemical properties[7] and applications in physiology[8–10] were reported.

The aim of this paper was to extend the interfacial polycondensation method to prepare microcapsules with membranes other than nylon and to study some of their properties.

Experimental

Preparation of Microcapsules——The preparation of polyurethane microcapsules was done by utilizing the interfacial polycondensation reaction between a diamine and a bischloroformate studied in detail by Wittbecker and Katz.[11] As in the case of nylon microcapsules,[5,6] the procedure consisted of the following three steps: 1) To 1.5 ml of aqueous 1% solution of polyethylene glycol in a 100 ml beaker was added an equal volume of 0.4 M 1,6-hexamethylenediamine solution in aqueous 0.45 M Na_2CO_3 solution.[12] The mixed solution was then mechanically emulsified with a magnetic stirrer for 1–3 minutes in 15 ml of an organic solvent (either benzene or chloroform—cyclohexane (1:4), both containing 15% Span 85 as an emulsifying agent) to yield a water-in-oil emulsion. The alkali served to neutralize hydrogen chloride formed during the polymerization reaction. 2) Without stopping the stirring, 15 ml of 2,2′-dichlorodiethyl ether solution was quickly added to the emulsion, and the stirring was continued for another 3 minutes. The dichlorodiethyl ether solution was prepared immediately before use by adding 0.1 ml of pure 2,2′-dichlorodiethyl ether to 25 ml of the organic solvent. 3) To this dispersion was added 30 ml of the organic solvent, and the dispersion was centrifuged at 350 *g* to separate the newly formed microcapsules. The microcapsules thus obtained

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[2] B.K. Green, U.S. Patent 2800458 (July 23, 1957).

[3] R.E. Phares, Jr., and G.J. Sperandio, *J. Pharm. Sci.*, **53**, 515 (1964).

[4] J.E. Flinn and H. Nack, *American Ink Maker*, pp. 27—70, April (1967).

[5] T.M.S. Chang, *Science*, **146**, 524 (1964).

[6] T.M.S. Chang, F.C. MacIntosh, and S.G. Mason, *Can. J. Physiol. Pharmacol.*, **44**, 115 (1966).

[7] T. Kondo and S.G. Mason, forthcoming publication.

[8] T.M.S. Chang and F.C. MacIntosh, *Pharmacologist*, **6**, 198 (1964).

[9] T.M.S. Chang, Ph. D. Thesis, McGill University, Montreal, 1965.

[10] T.M.S. Chang, *Trans. Amer. Soc. Artif. Int. Organ*, **12**, 13 (1966).

[11] E.L. Wittbecker and M. Katz, *J. Polymer Sci.*, **40**, 367 (1959).

[12] The use of $NaHCO_3$ instead of Na_2CO_3 did not give the microcapsules.

were washed with the same organic solvent containing Span 85. Finally, the washed microcapsules were completely dispersed in 10 ml of aqueous 50% v/v Tween 20 solution and diluted with distilled water to give a dispersion of a desired concentration.

The polyphenol ester microcapsules were prepared in much the same way by using the interfacial polycondensation reaction between a bisphenol and an acid dichloride.[13] In this study, bisphenol A and sebacoyl chloride were chosen as the reagents for the polycondensation reaction. The solvent used was benzene.

Determination of Shape and Size of Microcapsules——The shape and size of microcapsules were observed under a microscope, and the microcapsules were photographed where necessary. In each photograph, a number of microcapsule diameters were measured and the average was calculated.

Permeability of Microcapsule Membranes toward Small Ions——The permeability of the polyurethane and polyphenolester membranes toward sodium hydroxide was estimated from the rate of change in pH of the dispersions. Thus, sodium hydroxide had been added to the solution to be emulsified in the step 1 of the preparation, and the pH readings were started immediately after dispersing the microcapsules in Tween 20 solution in the step 3.

Results and Discussion

Shape and Size of Microcapsules

The shape of both polyurethane and polyphenol ester microcapsules was invariably spherical probably due to the osmotic pressure exerted by the polyethylene glycol solution inside the capsules. Fig. 1 and 2, and 3 and 4 show the microphotographs of polyurethane and polyphenol ester microcapsules, respectively.

A concentration of 15% v/v of the emulsifying agent in the step 1 was chosen to ensure the complete emulsification. Under this condition, the size of the microcapsules decreased to a certain extent with increasing time of emulsification but was independent of the speed setting of the magnetic stirrer.

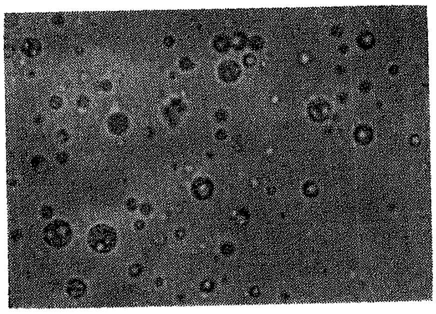

Fig. 1. Microphotograph of Polyurethane Microcapsules

mean diameter 3.5 μ, emulsification time 1 min

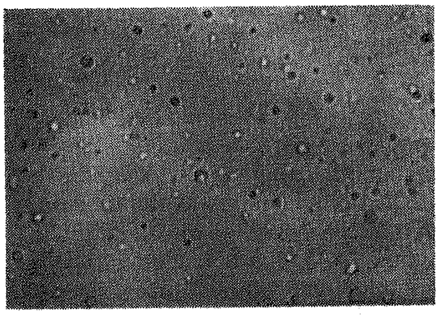

Fig. 2. Microphotograph of Polyurethane Microcapsules

mean diameter 1.5 μ, emulsification time 3 min

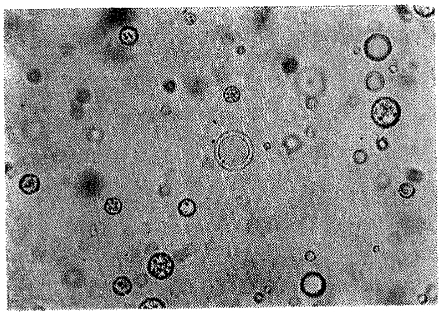

Fig. 3. Microphotograph of Polyphenolester Microcapsules

mean diameter 5.8 μ, emulsification time 1 min

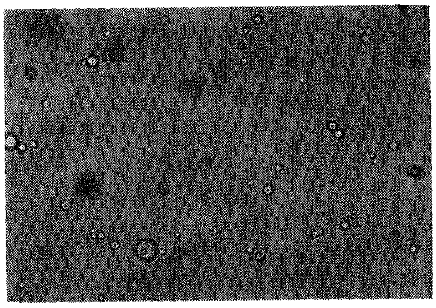

Fig. 4. Microphotograph of Polyphenolester Microcapsules

mean diameter 2.6 μ, emulsification time 3 min

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[13] W.M. Eareckson, *J. Polymer Sci.*, **40**, 399 (1959).

Permeability of Microcapsule Membranes

In all cases studied, the distribution equilibrium of sodium hydroxide between in and outside the microcapsule membranes was almost established within a few minutes, though the time necessary for equilibration was somewhat dependent on the initial alkali concentration inside the membranes and on the microcapsule concentration. Fig. 5 and 6 give some typical results on the permeability of the poylurethane and polyphenol ester membranes toward sodium hydroxide, respectively.

This rapid equilibration will be due to the small size of sodium and hydroxyl ions and to the considerably thin membranes.

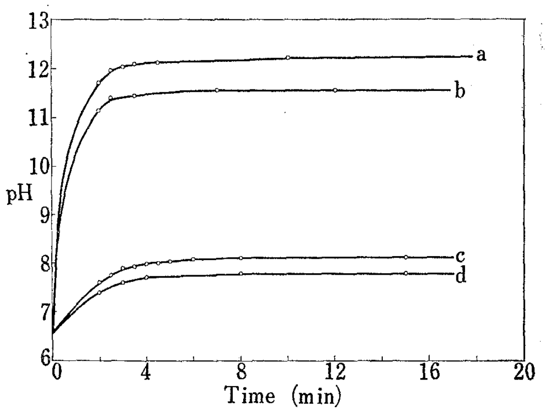

Fig. 5. Rate of Change in pH of Polyurethane Microcapsule Dispersion

a : initial alkali concentration 4 N, microcapsule concentration 3% v/v
b : initial alkali concentration 4 N, microcapsule concentration 1.5% v/v
c : initial alkali concentration 2 N, microcapsule concentration 3% v/v
d : initial alkali concentration 2 N, microcapsule concentration 1.5% v/v

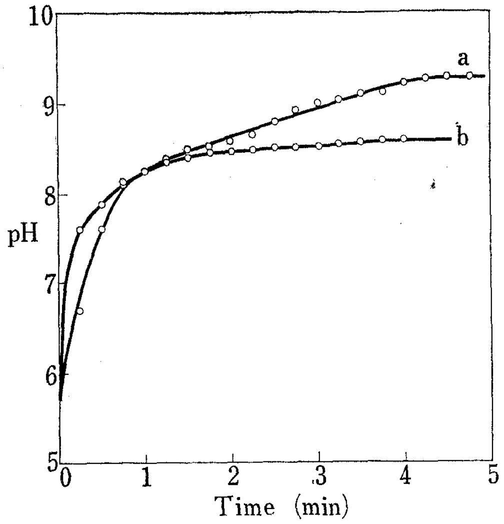

Fig. 6. Rate of Change in pH of Polyphenolester Microcapsule Dispersion

a : initial alkali concentration 2 N, microcapsule concentration 1.5% v/v
b : initial alkali concentration 1 N, microcapsule concentration 1.5% v/v

The membrane thickness was estimated to be of the order of several hundred angstroms from the amount used of the reagents in polymerization, the size of the microcapsules, and the density of the membranes formed.

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