# NOTES

## *Drug Release from and Properties of Polystyrene Microcapsules*

Microencapsulations have been extensively studied on miscellaneous materials, and various methods have been proposed by different investigators.[1] The method of evaporating an organic solvent from an aqueous system is often used to encapsulate various materials under mild experimental conditions. Therefore, the method has frequently been employed for microencapsulation of labile agents such as drugs or enzymes.

In a series of recent studies on microcapsulated enzymes, Chang et al.[2] have found semipermeability of the microcapsule (capsule) membranes and tried to adapt the microencapsulated catalase to acatalasemic mice.[3] Kitajima et al.[4] also investigated the properties of polystyrene (PS) and ethyl cellulose capsules containing urease or catalase. Kondo et al. studied the semipermeability of polyurethane[5] and polyphthalamide[6] capsules prepared by the method of interfacial polycondensation reactions. The properties of the membranes of PS capsules are closely discussed hereinafter.

To study in detail the properties and permeabilities of capsule membranes, PS capsules containing $\alpha$-amylase or sodium salicylate (Sal) were prepared. Preparations of the capsules were carried out with the following procedures:[4]

(i) A mixture of 10 parts of 10% methylene chloride solution of PS and one part of aqueous solution containing 2.5% $\alpha$-amylase or 30% Sal was throughly emulsified after adding one part of 8% aqueous solution of gelatin used as a protective colloid agent.

(ii) The water in oil-type emulsion (W/O) obtained above was carefully added into a large amount of 1% aqueous gelatin solution regulated at 37°C. The methylene chloride was then slowly evaporated from the aqueous system by stirring continuously for 5 hr. Finally, the dispersed water-containing PS capsules were produced in the water system.

(iii) The drying of the capsules was performed in a fluidized bed.

The shape of the capsules was spherical and their diameter was in the range of 100–400 $\mu$ for both the dried and the water-containing capsules. An optical micrograph of the capsules is shown in Figure 1. The presence of some fine bubbles was observed on the surface of the capsules.

A scanning electron micrograph is given in Figure 2. A thin film of gold was evaporated on the specimens. Some pockmark-like holes (1–10 $\mu$ in diameter) are clearly observed on the surface. This fact is the new and interesting finding in our studies. The exact mechanism of the hole formation is still not completely elucidated at present.

In order to clarify the existence of holes in the capsule membranes, microencapsulations of $\alpha$-amylase were performed in a similar manner as described above. The enzyme activity of the encapsulated $\alpha$-amylase was spectrophotometrically observed by reacting soluble starch with KI–$I_2$ solution.[7] The change in transmittance at 700 m$\mu$ is shown in Figure 3. The capsules were removed from the reaction vessel after 1 hr, indicated by the circular symbol in the figure. The transmittance increased continuously even after the removal of the capsules and reached 90% after 3 hr. This means that some of the $\alpha$-amylase molecules were released from the capsules through the holes of the capsule membranes; indeed, the presence of holes was obviously confirmed by these facts.

For drug release studies, PS capsules containing Sal and enteric coating materials, such as MPM-06 (Tanabe Seiyaku Co. LTD., methacrylate–methacrylic acid–methyl methacrylate copolymer) or dialdehyde starch (DAS, oxydized by periodic acid), were prepared. The release curves of Sal from both the dried and the water-containing capsules are given in Figure 4. The quantities of released Sal were spectrophotometrically determined[8] by the use of ferrous chloride solution at 520 m$\mu$. It was noted that the release was affected by the pH of the medium and was higher from the dried capsules than from the water-containing capsules.

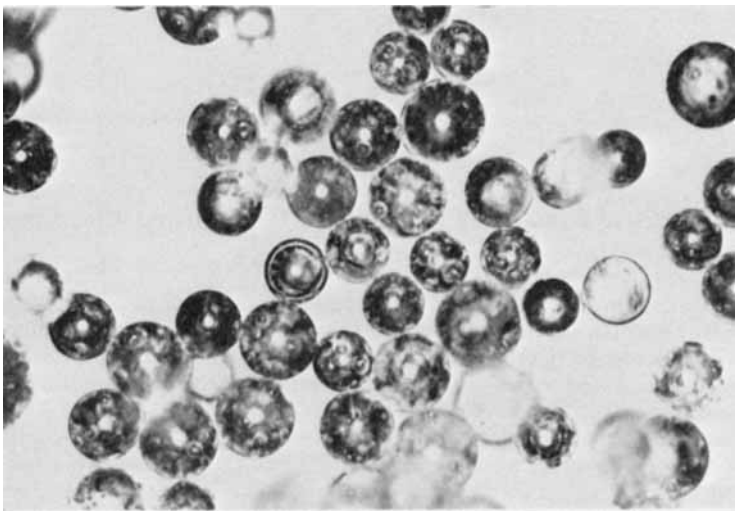

Fig. 1. Optical micrograph of dried microcapsules.

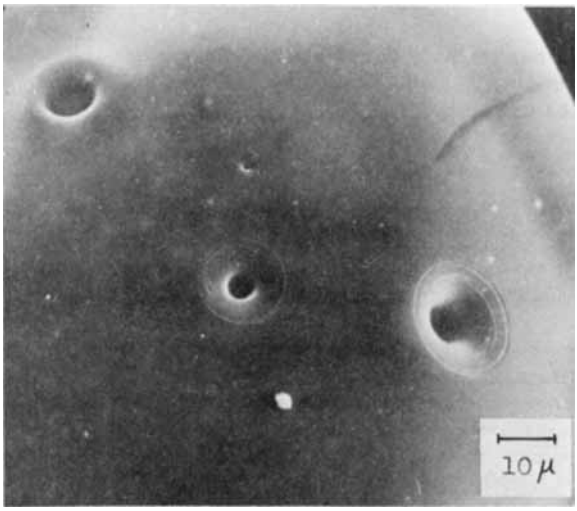


Fig. 2. Scanning electron micrograph of microcapsules.

The release curves of the Sal from the dried capsules containing the enteric coating materials are shown in Figure 5. The pH of the medium was changed from acidic to alkaline regions after 2 hr, when the release increased discontinuously. The characteristic behavior of the release curves is considered to be associated with the properties of the enteric coating materials themselves. The properties of the DAS used will be discussed below.

It was found with poly(vinyl alcohol) membranes containing DAS that the permeabilities of the membranes apparently increased under alkaline conditions rather than in acidic regions and also that they exhibited[9] a reversible change in permeations at pH 2 and pH 11. The increase of the permeabilities in alkaline regions could be explained by the swelling of the membranes due to the electrostatic interactions between the ionic species produced by the dissociation of aldehyde groups in the DAS molecules.

From these results and discussions, it was concluded that (1) the presence of some holes 1–10 $\mu$ in diameter on the surface of the capsules is confirmed by the drug release studies and by scanning electron microscopic observations, (2) the release of Sal from the capsules takes place through the holes and is controlled by the pH of the medium because the holes were filled with the enteric coating materials. The capsules prepared in the described manner may be used in further applications such as for sustained drug release, agricultural medicines, and fertilizers.

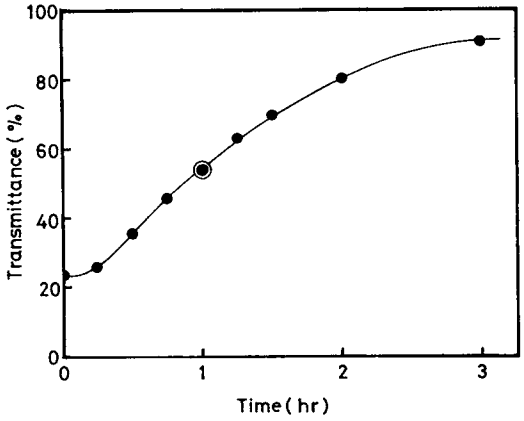


Fig. 3. Optical transmittance at 700 mμ of starch and KI–$I_2$ solution containing microencapsulated α-amylase. The microcapsules had been removed from the reaction vessel after 1 hr, indicated by circle.

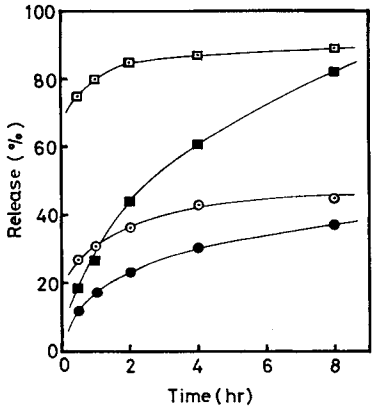


Fig. 4. Release curves for sodium salicylate from dried microcapsules and water-containing microcapsules containing enteric coating materials: (□) dried microcapsules, pH of medium 7.6; (■) water-containing microcapsules, pH 7.3; (○) dried microcapsules, pH 2.0; (●) water-containing microcapsules, pH 2.1.

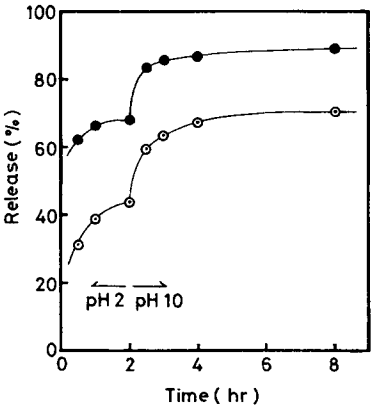


Fig. 5. Release curves of sodium salicylate from dried microcapsules containing dialdehyde starch (●) or MPM-06 (○). The pH of the medium was changed from 2 to 10 after 2 hr.

The results obtained in this study are considered to be essentially different from the current view that the membranes of PS capsules are semipermeable. A detailed discussion of the properties of the capsules will be reported elsewhere.

## References

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