December 1989 Chem. Pharm. Bull. 37(12) 3367—3371 (1989) 3367

Characterization of Powder-Coated Microsponge Prepared by Dry Impact Blending Method[1]

Kenji Ukita,*,[a] Minoru Kuroda,[a] Hirotaka Honda,[b] and Masumi Koishi[b]

OTC Research Group, Research Institute, Daiichi Pharmaceutical Co., Ltd.,[a] 16-13, Kitakasai 1-chome, Edogawa-ku, Tokyo 134, Japan and Faculty of Industrial Science and Technology, Science University of Tokyo,[b] Tomino, Oshamanbe-cho, Yamakoshi-gun, Hokkaido 049-35, Japan.

Received April 3, 1989

A novel powder particle, nominated as powder-coated microsponge (PMS) containing sunset yellow (SY), was prepared by dry impact blending, and the subsequent dissolution behavior of SY from PMS was studied. Two kinds of spherical and porous cellulose particles known as microsponge (10.3 or 53.9 μm in volume-surface mean diameter) containing SY were coated with spherical polymethylmethacrylate particles (PMMA, 0.15 or 0.40 μm in diameter) and titanium dioxide particles (anatase-type, 0.25 μm in diameter). This coating was carried out without solvents. The angle of repose and the bulkiness of PMS were largely dependent on the amount of PMMA. The dissolution rate of SY from PMS decreased greatly as the amount of PMMA was increased, and was also influenced by the particle size of the microsponges and PMMA, but its correlation with the coating amount of titanium dioxide was very poor. On the basis of these results, a novel preparation of a micron-order powder offering a controllable release of ingredients is proposed.

Keywords sustained release; controlled release; microcapsule; microencapsulation; microsponge; polymethylmethacrylate; titanium dioxide; dry impact blending; powder-coated microsponge

Microencapsulation techniques related to sustained release of drugs have been studied widely, and many methods have been established.[2,3] However, most of these, such as coacervation,[4,5] solvent evaporation,[6,7] *etc.* require careful selections of solvents for dissolving the encapsulating materials or drugs, and involve complicated preparation processes. To overcome these disadvantages, a less time-consuming method for microencapsulation without the use of solvents was studied.

Recently, the so-called "dry mixing"[8] or "dry blending"[9,10] method has been used in the investigation of surface modification techniques of particles in the powder technology field.[11-16] Mixing the fine and the coarse particles with an auto ceramic mortar or with a centrifugal rotating mixer[8] gives a specific state of powder mixture called an "ordered mixture."[17-21] This mixture can be modified to a novel type of particles whose physical characteristics are derived both from the fine particles (coating material) and the coarse particles (core material) by further mixing at high stress (shear rate $1.1 \times 10^5\,s^{-1}$). In the cosmetics field, a skin foundation manufactured by this method is now commercially available.[22] Improvement of the dissolution rates of poorly soluble drugs by coating potato starch with them using this method has been also reported.[10]

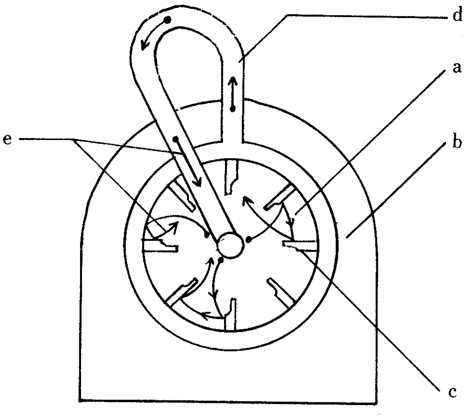

Fig. 1. Schematic Illustration of Impact-Type High-Speed Mixer

a) rotor; b) treatment vessel; c) striking pin; d) circulation route; e) trace of powder. The rotor is 140 mm in diameter and turns at 15000 rpm. The clearance between the rotor and the treatment vessel is 1 mm. The calculated shear rate is $1.1 \times 10^5\,s^{-1}$.

In our preliminary investigation,[23] coating the surface of spherical and porous cellulose particle, what is called a microsponge,[24,25] with spherical polymethylmethacrylate (PMMA) and anatase-type titanium dioxide by means of an impact-type high-speed mixer[9] (IH-mixer; Fig. 1) gave an interesting particle, which we designated as a powder-coated microsponge (PMS). These PMSs gave different release rates of ingredients compared with uncoated microsponge. In this study, therefore, the dissolution behavior of sunset yellow (SY) from PMS coated with PMMA and titanium dioxide was examined in order to clarify the effects of the amount and the particle size of these coating materials on the dissolution rate.

Experimental

Materials Two types of microsponges were used as core materials. The coarse microsponge (Cellulofine GH-25 m, 53.9 μm in volume-surface mean diameter in the dry state) was purchased from Chisso Corporation, Tokyo, Japan. Each particle was washed with a sufficient amount of water to remove sodium azide added as an antiseptic agent in the package. Then, the wet microsponge was collected on a paper filter (Toyo Roshi No. 2, Toyo Roshi Co., Ltd., Tokyo, Japan), and dried at 80 °C for 8 h. The fine microsponge (Cellulofine GH-25uf, 10.8 μm in volume-surface mean diameter in the dry state) was kindly donated by Chisso Corporation. Two sizes of PMMA and one type of titanium dioxide were used as coating materials. Both the large PMMA (MP-1000, 0.40 μm in diameter) and the small PMMA (MP-1451, 0.15 μm in diameter) were kindly presented by Soken Chemical & Engineering Co., Ltd., Tokyo, Japan. Anatase-type titanium dioxide (A-100, 0.25 μm in diameter) was a gift from Ishihara Sangyo Kaisha Ltd., Osaka, Japan. As a model water-soluble drug, sunset yellow FCF (SY; San-Ei Chemical Industries, Ltd., Osaka, Japan) was used.

Preparation of SY-Containing Microsponge In 200 g portions, the dried microsponge was thrown into 500 ml of a 1% aqueous solution of SY contained in an airtight cylindrical vessel. The vessel was revolved around its shaft at 30 rpm for 3 h. The slurry was collected on a paper filter (Toyo Roshi No. 2) under reduced pressure followed by drying at 80 °C for 8 h. Finally, the dried and SY-containing microsponge was sieved through a stainless steel screen of 200 mesh. The contents of SY in fine and coarse microsponges were 2.41% and 1.41%, respectively, and the water contents of both microsponges were below 5%.

Preparation of PMS Either coarse or fine microsponge containing SY was mixed with PMMA (small or large) and titanium dioxide using an auto ceramic mortar (Labo-mill UT-21, Yamato Scientific Co., Ltd.,

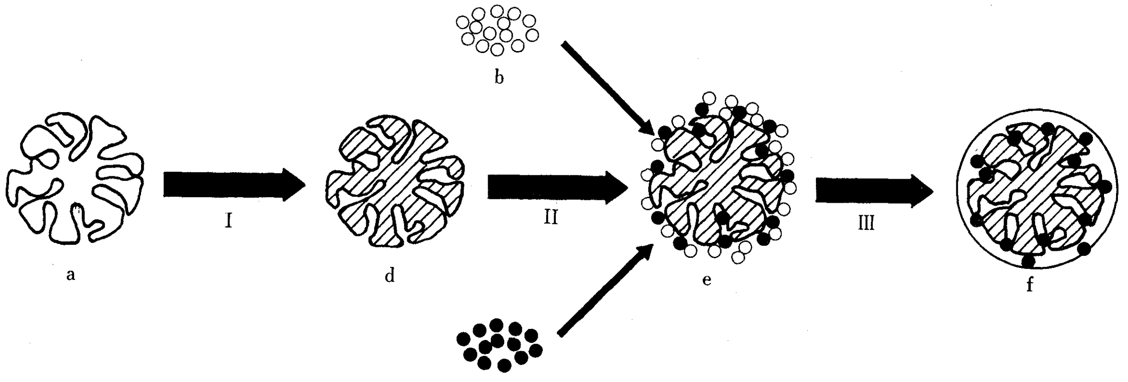

Fig. 2. Schematic Diagram of the Process for Preparing Powder-Coated Microsponge

a) microsponge (MS); b) polymethylmethacrylate (PMMA); c) anatase type titanium dioxide; d) SY-containing microsponge; e) ordered mixture; f) powder-coated microsponge (PMS); I) incorporation step; II) pre-blending step; III) coating step.

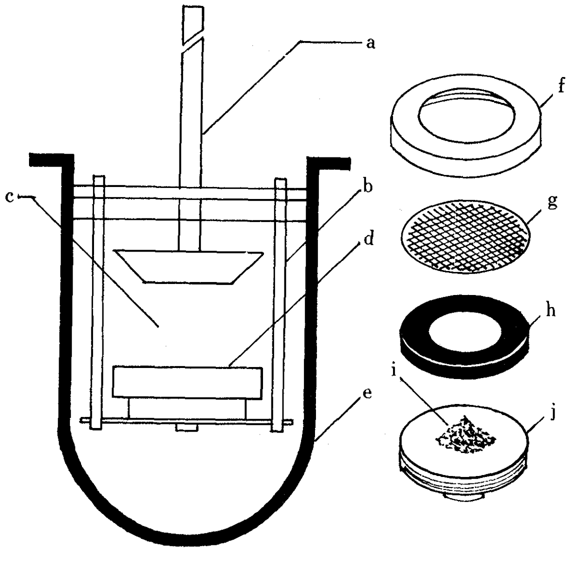

Fig. 3. Schematic Illustration of Apparatus for Dissolution Test of Powder-Coated Microsponge

a) paddle; b) sample cell holder; c) purified water; d) sample cell; e) test vessel; f) upper cover; g) #300 stainless steel screen; h) rubber O-ring; i) sample; j) lower cover.

Tokyo, Japan) at 60 rpm for 30 min. The weight of each batch was 50 g. The total amount of coating materials was varied between 0 and 30%. The mixture was then treated in an impact-type high-speed mixer[26]; IH-mixer (Hybridizer NHS-0; Nara Machinery Co., Ltd., Tokyo, Japan) for 10 min. The weight of each batch in the IH-mixer was 30 g. These processes are schematically illustrated in Fig. 2.

Measurement of Physicochemical Properties of Microsponge and PMS The volume-surface mean diameter of each microsponge was determined with an image analyzer (Luzex IID; Nireco Co., Ltd., Tokyo, Japan). The numbers of particles counted were 507 for coarse microsponge and 724 for fine microsponge, respectively. The angle of repose and the bulkiness of the prepared PMS were measured with a powder tester (Type PT-E; Hosokawa Micron Co., Ltd., Osaka, Japan). The ring for measuring the angle of repose was 20 mm in diameter and the vessel for measuring the bulkiness was 22 mm in inner diameter and 52 mm in inner height. Each observation was carried out three times.

Morphological Study of Microsponge and PMS The intact microsponge and the prepared PMS were coated with gold vapor using an ion spattering machine (JFC-1100; JEOL, Tokyo, Japan) and observed under a scanning electron microscope (SEM; JSM-T20, JEOL, Tokyo, Japan).

Dissolution Test The dissolution test was carried out with the apparatus shown in Fig. 3. Three hundred milligrams of PMS was packed into the sample cell, which was placed in a test vessel containing 900 ml of purified water maintained at 37 °C. The water was agitated at 50 rpm with a paddle. The stainless steel screen of 300 mesh, having been previously cured as follows, was used to keep the PMS in the cell. The circular screen was dipped in a 0.1% aqueous solution of polyethyleneglycol monostearate (MYS-40; NIKKO Chemicals Co., Ltd., Tokyo, Japan) for 8 h and then it was dryed at 100 °C for 3 h. At appropriate time intervals, 2 ml of the test medium was withdrawn through a membrane filter (MILLEX-FG; Millipore, pore size; 0.2 μm) with a syringe, and immediately replaced with an equal volume of fresh water kept at 37 °C. The concentration of SY in the sample solution was determined photometrically with a photometric analyzer (U-3200; Hitachi Co., Ltd., Tokyo, Japan) at 482 nm. The total amount of SY released was determined by measuring the concentration of SY in the test medium agitated for 1 h with a paddle at 150 rpm after the dissolution test. During this agitation, PMS was released from the cell.

Results and Discussion

Surface Appearance of Microsponge and PMS Scanning electron microscopy (SEM) photographs of the fine and the coarse microsponges used in this study are shown in Figs. 4a and 4b or 4b′, respectively. An obvious difference between the two samples was observed in the surface roughness. The surface of fine microsponge was rougher than that of coarse microsponge. In addition, SEM photographs of PMS prepared with fine and coarse microsponges are shown in Figs. 4c and 4d or 4d′, respectivey. Owing to the treatment with the IH-mixer, the surface of these PMSs became smoother than that of the intact microsponges. It is clear that the PMMA particles and titanium dioxide particles which were mixed with microsponges were deformed[27-29] or embedded to form a seamless capsule wall on the surface of the microsponge. This surface modification was observed even when PMS lacked titanium dioxide. On the other hand, the modification was insufficient when PMS lacked PMMA. So it would be suitable to consider that the capsule wall was formed mainly by the conjugation or fusion of PMMA particles.

Physicochemical Properties of Microsponge and PMS The particle size distributions of fine and coarse microsponges used in this study are shown in Fig. 5. The angle of repose and the bulkiness of PMSs are shown in Fig. 6. The respective values for these properties were 59° and 0.21 g/ml for fine microsponge and 51° and 0.11 g/ml for coarse microsponge. The angle of repose increased and the bulkiness decreased with increase in the PMMA content, and both rapidly approached the values of PMMA

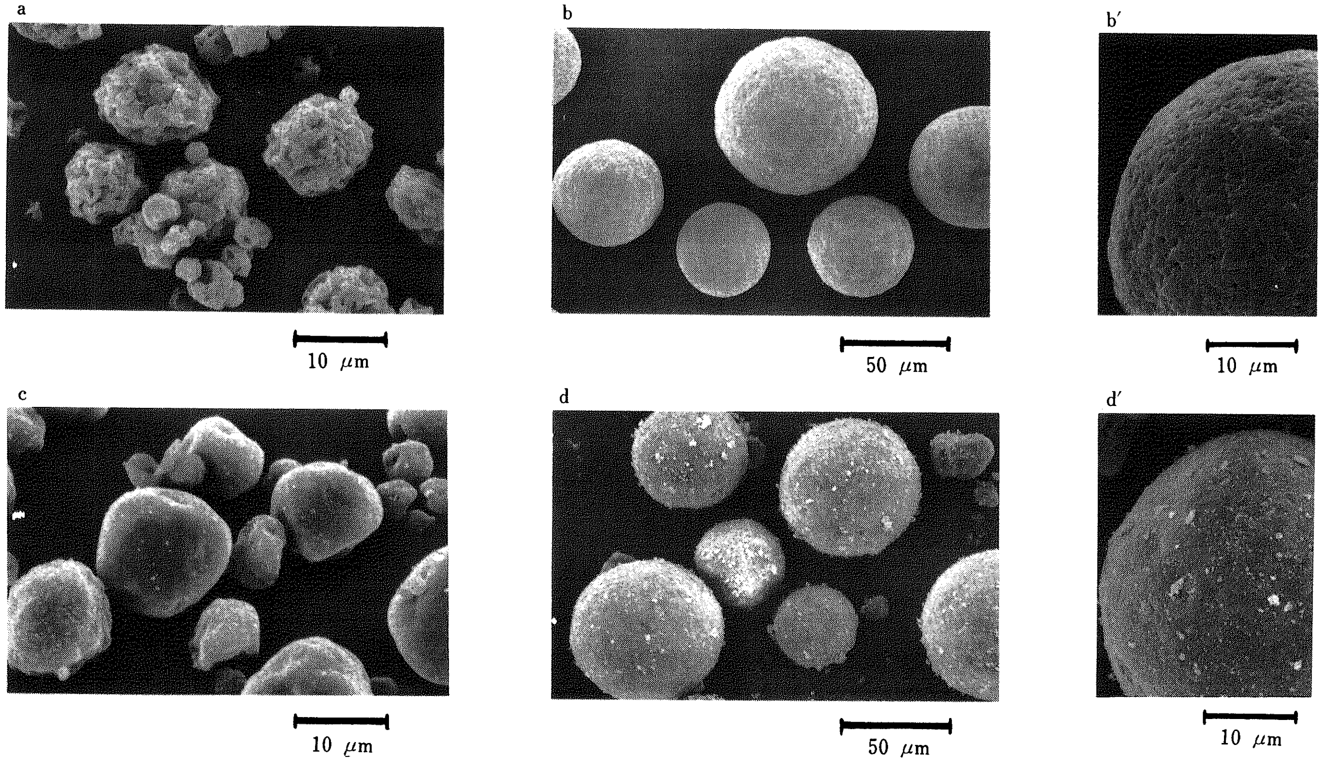

Fig. 4. Scanning Electron Micrographs of Microsponges and Powder-Coated Microsponges

a) fine microsponge containing 2.41% SY; b), b′) coarse microsponge containing 1.41% SY; c) PMS consists of 80% fine microsponge, 10% small PMMA and 10% titanium dioxide; d), d′) PMS consists of 80% coarse microsponge, 10% small PMMA and 10% titanium dioxide.

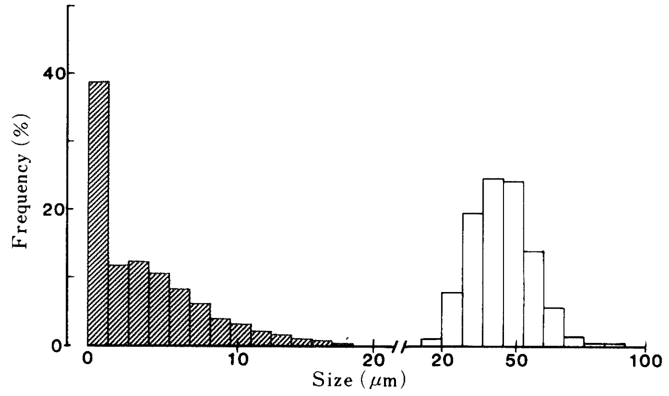

Fig. 5. Particle Size Distribution of Microsponges

▨, fine microsponge; □, coarse microsponge.

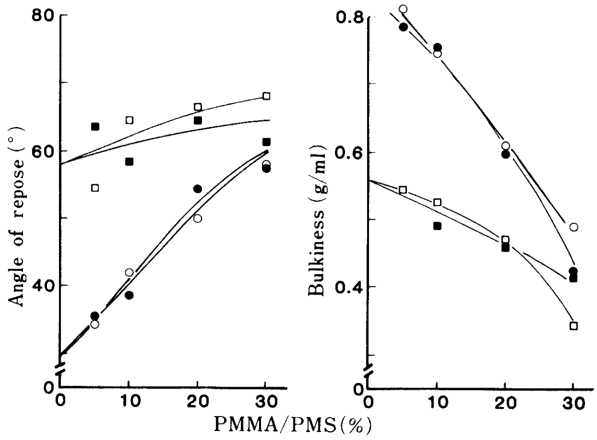

Fig. 6. Angle of Repose and Bulkiness of Powder-Coated Microsponges

PMS consists of 10% titanium dioxide and: ■, fine microsponge and small PMMA; □, fine microsponge and large PMMA; ●, coarse microsponge and small PMMA; ○, coarse microsponge and large PMMA.

particle itself. This seems to suggest that there were many intact PMMA particles in PMS when the PMMA content was more than 20%.

These properties give us useful information concerning feasible mixing ratios between microsponge and coating materials for practical applications.

Dissolution Study The dissolution profiles of SY from PMS are shown in Fig. 7. A comparison between Figs. 7a and 7b was made to ascertain the effect of the particle size of the core material on the dissolution rate. When fine microsponge was used as a core material, the dissolution rate was reduced, in general, as the amount of PMMA was increased. On the other hand, the correlation between the dissolution rate and the PMMA content was relatively poor when coarse microsponge was used as a core material. It may be simply assumed that the smaller the microsponge is, the larger its relative surface area would be, so that coating materials were used effeciently. This is supported by the existence of excess or non-treated coating particles observed on the PMS with 20 to 30% PMMA. Moreover, the difference of surface roughness of microsponge shown in Figs. 4a and 4b′ would affect the coating amount of PMMA and titanium dioxide. That is, PMMA and titanium dioxide particles might have been embedded in the crevasse-like micropores, but not in the case of coarse microsponge. These embedded particles were presumably bound firmly on the capsule wall, leading to the slow

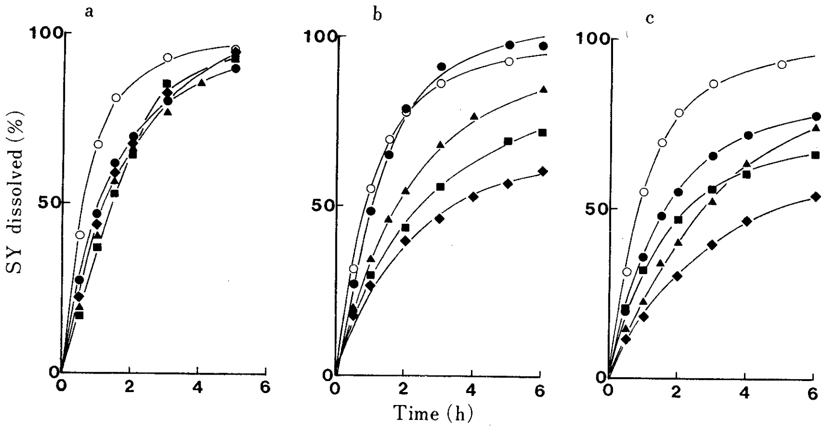

Fig. 7. Dissolution Profiles of SY from Powder-Coated Microsponges

PMS consists of 10% titanium dioxide and: a), coarse microsponge and small PMMA; b), fine microsponge and small PMMA; c), fine microsponge and large PMMA. ○, intact microsponge. PMMA content; ●, 5%; ▲, 10%; ■, 20%; ◆, 30%.

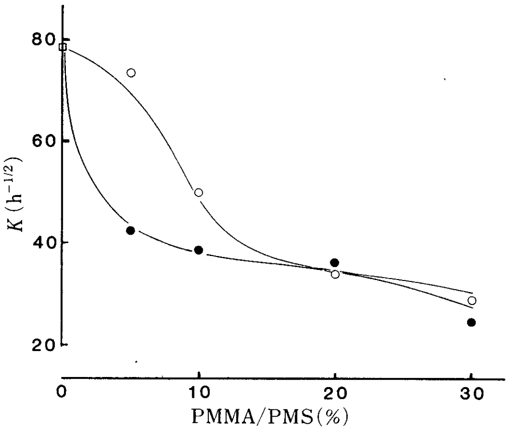

Fig. 8. Relationship between PMMA Content and Observed Dissolution Rate

□, intact microsponge. PMS consists of 10% titanium dioxide and: ○, fine microsponge and small PMMA; ●, fine microsponge and large PMMA.

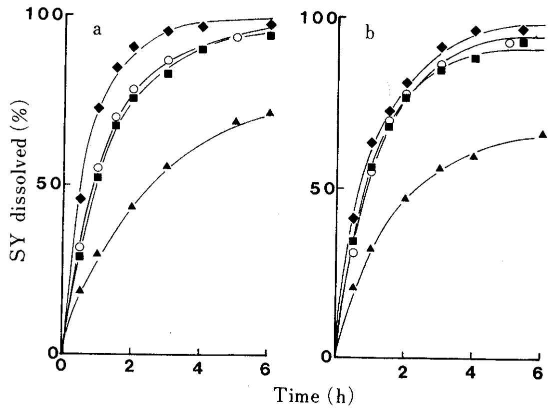

Fig. 9. Effect of Titanium Dioxide on SY Dissolution

PMS consists of titanium dioxide and: a), fine microsponge and 20% small PMMA; b), fine microsponge and large PMMA. ○, intact microsponge. Titanium dioxide content: ▲, 10%; ■, 20%; ◆, 30%.

dissolution of SY. Therefore, fine microsponge was considered to be superior to coarse one in yielding a slow dissolution.

Another comparison may be made between Figs. 7b and 7c in order to grasp the effect of the particle size of PMMA on the dissolution behavior. When the PMMA content was below 20%, the PMS with large PMMA showed slower release than that with small PMMA, but the dissolution profiles for both types of PMS seemed alike when PMMA was added at a level as high as 30%. To clarify these results, the correlation between the square root of time and dissolved ratio of SY from PMS was determined. Between 10 to 70% dissolved ratio, good linearity (correlation coefficients varied between 0.98 and 0.99) was observed for both kinds of PMS, which presumably indicates that SY was released by diffusion based on Higuchi's equations in this area. On the basis of these considerations, the relationship between the observed dissolution rate constant, K derived from Higuchi's formula (Eqs. 1 and 2)[30] and the PMMA content was studied (Fig. 8).

$$Q=(Dt(2A-C_s)C_s)^{1/2} \quad (1)$$

$$=Kt^{1/2} \quad (2)$$

here $K=(D(2A-C_s)C_s)^{1/2}=\text{constant}$

where Q = the amount of SY dissolved after time t per unit exposed area, D = the diffusivity of SY in test medium (water), A = the total amount of SY presents in the microsponge per unit volume, and C_s = the solubility of SY in test medium (water). The K value for PMS with large PMMA showed a significant lowering compared with that in the case of small PMMA up to 20% content, but afterwards, both curves slightly declined up to 30% in a similar manner. The minimum values of K for both PMSs were obtained at 30% PMMA and the difference between the two values was very small compared with those for 0 to 20% PMMA. So it is clearly noticed that the size difference of PMMA did not affect the dissolution rate significantly when it was added over 20%.

The effect of titanium dioxide content on the dissolution rate is shown in Fig. 9. The PMS with 10% of titanium dioxide showed a significantly slower release than intact microsponge, but the release profiles of PMSs containing 20% or 30% titanium dioxide were similar to or slightly faster than that of intact microsponge. The PMMA itself acts as a dissolution-delaying agent with an dose dependency, as shown in Fig. 7. Thus, the slow release observed for PMS with 10% titanium dioxide is supported by the presence of 20% PMMA. As for PMSs containing more titanium dioxide, however, it was considered that the

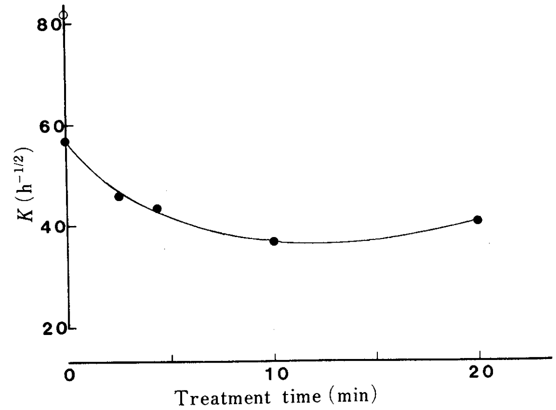

Fig. 10. Relationship between Treatment Time for Coating and Observed Dissolution Rate

○, intact microsponge; ●, consists of 90% coarse microsponge, 5% small PMMA and 5% titanium dioxide.

dissolution-delaying action of PMMA was not revealed or was actually inhibited by titanium dioxide, with its high wettability to water. The SEM photographs of these PMSs shows that their surfaces are rough with identifiable titanium dioxide particles, and the seamless capsule wall mentioned above is not built up. On the other hand, titanium dioxide has been reported to have the so-called "anchor effect,"[31] which is considered to enhance the impacts applied to the ordered mixture by the IH-mixer. Owing to this effect, the wall materials would be tightly fastened to the core material (microsponge), and slower dissolution would be expected. Further study is needed to establish the contribution of titanium dioxide to this kind of preparation.

Effect of Treatment Time on Dissolution Rate The relationship between the treatment time for coating in the IH-mixer and the dissolution rate is shown in Fig. 10. The K value for intact coarse microsponge, which was $82\,\mathrm{h}^{-1/2}$, decreased to $56\,\mathrm{h}^{-1/2}$ after pre-blending. So it is clear that the pre-blending affected the dissolution rate significantly. Then the rate declined as the treatment time was prolonged and approached the minimum at 10 min. The PMS treated for 20 min, however, showed a slightly faster dissolution than that treated for 10 min. So it is probable that a prolonged coating treatment has an adverse effect on the dissolution rate.

Conclusion

Micron-order powder particles which offer a slow dissolution of SY were prepared by blending microsponge with PMMA and titanium dioxide for only 10 min using the IH-mixer. The dissolution rate of SY from PMS could be varied significantly by adjusting the amount of PMMA. Moreover, the rate was altered by changing the particle sizes of microsponge and PMMA.

These results suggest the feasibility of preparing a sustained release powder particle by dry impact blending, which is expected to be useful for many types of pharmaceutical formulation. Moreover, the use of a microsponge as a drug carrier in drug delivery systems (DDS) can be recommended owing to the large capacity for drug loading, although there is still room for improvement in the method of incorporating drugs into this kind of microsponge.

References

1) A part of this work was presented at the 108th Annual Meeting of the Pharmaceutical Society of Japan, Hiroshima, April 1988.
2) M. Koishi, "Biryushi Sekkei," Kogyo Chosakai Publishing Co., Ltd., Tokyo, 1987.
3) T. Kondo and M. Koishi, "Microcapsule," Sankyo-Shuppan Co., Ltd., Tokyo, 1977.
4) J. R. Nixon, *Endeavour*, **9**, 123 (1985).
5) W. K. Pathirana, *East. Pharm.*, **21**, 97 (1978).
6) R. Bodmeier and C. Deligiannis, *Acta Pharm. Technol.*, **34**, 9 (1988).
7) T. Sato, M. Kanke, H. G. Schroeder and P. P. DeLuca, *Pharm. Res.*, **5**, 21 (1988).
8) T. Ishizaka, H. Honda, K. Ikawa, N. Kizu, K. Yano and M. Koishi, *Chem. Pharm. Bull.*, **36**, 2562 (1988).
9) M. Koishi, H. Honda, T. Ishizaka, T. Matsuno, T. Katano and K. Ono, *Chimicaoggi*, **1987**, Luglio-Agosto, 43.
10) T. Ishizaka, M. Yamada, K. Yano and M. Koishi, *Yakuzaigaku*, **45**, 193 (1985).
11) H. Honda, K. Ono, T. Ishizaka, T. Matsuno, T. Katano and M. Koishi, *Funtai Kogakukaishi*, **24**, 25 (1987).
12) H. Honda, T. Ishizaka, K. Ohtaguro, T. Matsuno and M. Koishi, *Zairyo Gijutsu*, **5**, 216 (1987).
13) T. Ishizaka, T. Matsuno and M. Koishi, *J. Pharmacobio-Dyn.*, **9**, s-4 (1986).
14) M. Koishi, *Fragrance J.*, **80**, 15 (1986).
15) M. Koishi, *Fragrance J.*, **80**, 11 (1986).
16) A. Nakagawa, T. Ishizaka, K. Yano and M. Koishi, *Yakuzaigaku*, **45**, 254 (1985).
17) M. Westberg, B. Jonsson and C. Nyström, *Int. J. Pharm.*, **28**, 23 (1986).
18) W. J. Thiel, *Powder Technol.*, **39**, 147 (1984).
19) J. N. Staniforth, *J. Pharm. Pharmacol.*, **36**, 258 (1984).
20) H. Egermann and N. A. Orr, *Powder Technol.*, **36**, 117 (1983).
21) J. A. Hersey, *Powder Technol.*, **11**, 41 (1975).
22) R. Saito, S. Kumagaya and K. Ohno, *Shiseido Information Letter*, **62001**, 6 (1987).
23) K. Inoue, I. Kakubari, M. Kuroda and M. Koishi, Abstracts of Papers, the 107th Annual Meeting of the Pharmaceutical Society of Japan, Kyoto, April 1987, p. 847.
24) K. Saito, F. Hosoi, K. Makuuchi and M. Koishi, *Yakuzaigaku*, **47**, 154 (1987).
25) Y. Taniguchi, K. Saito, T. Ishizaka and M. Koishi, *Zairyo Gijutsu*, **3**, 233 (1987).
26) K. Ono, *Kagaku Souchi*, **9**, 19 (1986).
27) Y. Motohashi, *Risou*, **280**, 5 (1988).
28) O. Frank and J. Lehmann, *Colloid & Polym. Sci.*, **264**, 473 (1986).
29) A. Nakagawa, T. Ishizaka, K. Yano and M. Koishi, *Yakuzaigaku*, **45**, 254 (1985).
30) T. Higuchi, *J. Pharm. Sci.*, **52**, 1145 (1963).
31) Y. Motozato and C. Hirayama, *J. Chromatogr.*, **298**, 499 (1984).