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Studies on Microcapsules. IV.[1] Influence of Properties of Drugs on Microencapsulation and Dissolution Behavior[2]

YOSHIYUKI KOIDA,* MASAO KOBAYASHI and MASAYOSHI SAMEJIMA

Products Formulation Research Laboratory, Tanabe Seiyaku Co., Ltd., 16–89 Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan

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The influence of drug properties such as solubility and core shape on microencapsulation with ethyl cellulose (EC) by the phase separation method was studied. Drugs having various solubilities from about 1% to 37% in the 1st fluid of the disintegration test in JP (vitamin C, vitamin B_6, isoniazid, trimebutine maleate and theophylline) were pulverized, granulated into spherical or cylindrical shapes, and used as core materials to eliminate the influence of crystal shape. To obtain spherical microcapsules (MC) having a uniform wall, various preparation conditions were tested; wall thickness could be adjusted by changing the cooling time. It was found by use of spherical core materials of vitamin C and isoniazid that the permeability constants, P_m, linearly decreased as the wall thickness increased up to 12 μm, and then remained constant. Comparison of microcapsules containing the above five drugs revealed that the content of EC in MC decreased with increasing drug hydrophilicity. The dissolution rates from MC having a wall thickness of 12—15 μm were slower for less water-soluble drugs, though the plots of dissolution percent against the so-called reduced time showed similar dissolution patterns. P_m values were almost the same for all drugs except theophylline. As regards core shape, crystalline material showed the fastest dissolution, followed by cylinder and sphere in that order.

Keywords——microcapsule; ethyl cellulose; polyisobutylene; core material shape; core material solubility; *in vitro* dissolution rate; permeability constant; dissolution kinetics

Microcapsules (MC) of ethyl cellulose (EC) prepared by the phase separation method have been widely studied, especially for use as sustained-release dosage forms or drug delivery systems. For this purpose, the control of drug release from MC is important. Many theoretical and empirical equations have been proposed to describe the dissolution of drugs from MC.[3] Among them, Eq. 1 is simple but is regarded as one of the most fundamental equations derived from Fick's law. For the case where the sink condition is satisfied, Eq. 1 can be written as Eq. 2 at the early stages of dissolution.

$$dq/dt = A\ P_m\ (C_i - C_o)/H \quad (1)$$

$$dq/dt = A\ P_m C_s/H \quad (2)$$

where q is the total amount of drug dissolved in the surrounding medium at time t, A is the surface area of the microcapsule, P_m is the permeability constant, H is the wall thickness, C_i and C_O are the concentrations of solute in the MC and in the medium, respectively, and C_s is the solubility. Many researchers have applied Eq. 2 to the analysis of their data. However, most of them treated only one or two kinds of drugs and no systematic study on the relationship between such properties as the solubility of individual drugs and the dissolution rate has been performed. One problem in such a study is the range of crystal shapes of drugs.

In this paper, to eliminate factors due to differences in the shape of crystals, drugs with different properties were pulverized, granulated into a definite shape and microencapsulated, and then dissolution measurement was performed and the applicability of Eq. 2 was examined. At the same time, the effect of the shape of the core was investigated.

Experimental

Materials——Vitamin C, vitamin B_6, isoniazid and theophylline were of JP grade. Trimebutine maleate was of the internal standard of Tanabe Seiyaku Co., Ltd. Microcrystalline cellulose (Avicel® PH-102), polyvinyl alcohol (Gohsenol® GL-05), polyisobutylene (PIB; Vistanex® MML-100 (M_r: 1.12×10^6), LMMH (M_r: 3×10^4)) and EC (Ethocel® standard type, 100 cP) were obtained from Asahi Chemical Industry Co., Ltd., The Nippon Synthetic Chemical Industry Company, Esso Chemical Co., Ltd. and Dow Chemical Company, respectively. Glass beads passing through a 28 mesh sieve and remaining on a 36 mesh sieve (particle size: 420—590 μm) were used after washing.

Preparation of Core Materials——Powdered drugs (400 g) were mixed with microcrystalline cellulose (90 g) and kneaded with 100 ml of 10% polyvinyl alcohol (PVA) solution. If necessary, an adequate amount of water was added. The kneaded materials were extruded through a 0.5 mm screen by the use of a blade-type extruder (basket-type granulator) and the wet strings extruded were cut into pieces of an appropriate length, which were then spheronized by treatment with a marumerizer. After drying the granules at 45 °C for 14 h, the particles which passed through a 28 mesh (590 μm) screen and remained on the 36 mesh (420 μm) screen were used as spherical core materials. To prepare cylindrical core materials, the wet strings were cut into pieces of an appropriate length by extremely brief treatment with the marumerizer. After drying, the granules were sieved with the same screen as used for the spheronized core materials. In the above granulation, addition of more than 18% microcrystalline cellulose was necessary to obtain spherical core material. It was ascertained that almost 100% of drugs dissolved rapidly from the core materials in all cases.

Preparation of MC——Core materials (6 g) and EC (4.5 g) were dispersed into 60 ml of cyclohexane solution containing PIB (1.8 g) at 80 °C. PIB was used as a mixture of 19 parts of MML-100 and 11 parts of LMMH. Microencapsulation was carried out in a way similar to that described previously.[4] However, in this experiment, the cooling time was varied from 10 to 80 min so that the wall thickness could be adjusted. The particles of MC passing through a 24 mesh sieve and remaining on a 36 mesh sieve were used in the following experiments.

Evaluation of MC Properties——The drug contents in MC were determined spectrophotometrically as in the previous paper.[4a] The wavelengths used for the assay of vitamin C, vitamin B_6, isoniazid, trimebutine maleate and theophylline were 244, 291, 267, 269 and 271 nm, respectively. The EC content in MC was calculated from the difference in drug content between core materials and MC. In the case of glass beads, the EC content was determined from the weight difference before and after removal of EC by chloroform, extraction.

Dissolution studies were carried out in the 1st fluid for the disintegration test (JP X) by means of the paddle method at the agitation speed of 200 rpm, using the dissolution apparatus with the auto-sampler (Toyama Sangyo Co., Ltd.). An amount of MC containing 200 mg of drugs was accurately weighed and placed in 900 ml of the 1st fluid maintained at 37 °C. The concentrations of drugs were determined spectrophotometrically. The apparent zero-order dissolution rate constants (K_{app}) were calculated from the slope of the early linear portion of the dissolution curve. The permeability constant, P_m, was calculated from Eq. 3 as previously:[4b]

$$P_m = \frac{K_{app} VH}{AC_s} \tag{3}$$

where V is the volume of medium, and H is the wall thickness calculated from the euqation of Lafont *et al.*[5]

Observation of MC with an Optical Microscope——The obtained MC were dispersed in cyclohexane and observed under an optical microscope.

Results and Discussion

Preparation of MC with Uniform Film Coating

Spherical MC with a uniform wall of various thicknesses were required for the purpose of this study. At first, we tried to obtain spherical MC by the same method as adopted for crystalline vitamin C in the previous paper.[4] However, the wall thickness was not uniform around the spherical core materials. Thus the preparation conditions were re-examined using glass beads as a model core material. The influence of the molecular weight of PIB on sphericity and EC content in MC were examined by changing the $f_{PIB\text{-}H}$ value defined by Eq. 4; the results are shown in Table I.

$$f_{PIB\text{-}H}(\%) = \frac{100\ W_{PIB\text{-}112}}{W_{PIB\text{-}3} + W_{PIB\text{-}112}} \tag{4}$$

TABLE I. Influence of f_{PIB-H} Values and the Amount of EC Used for the Microencapsulation on the Shape and Wall Thickness of Glass Beads MC

No.	f_{PIB-H} (%)	Amount of EC (g)	S_i	EC content in MC (%)
1	0	4.5	1.55	34.7
2	50	4.5	1.88	11.3
3	63	4.5	1.10	10.1
4	75	4.5	1.05	5.5
5	88	4.5	1.04	3.3
6	100	4.5	1.00	2.5
7	63	1.5	1.46	3.8
8	63	3.0	1.15	4.1

Cooling time in microencapsulation: 60 min.

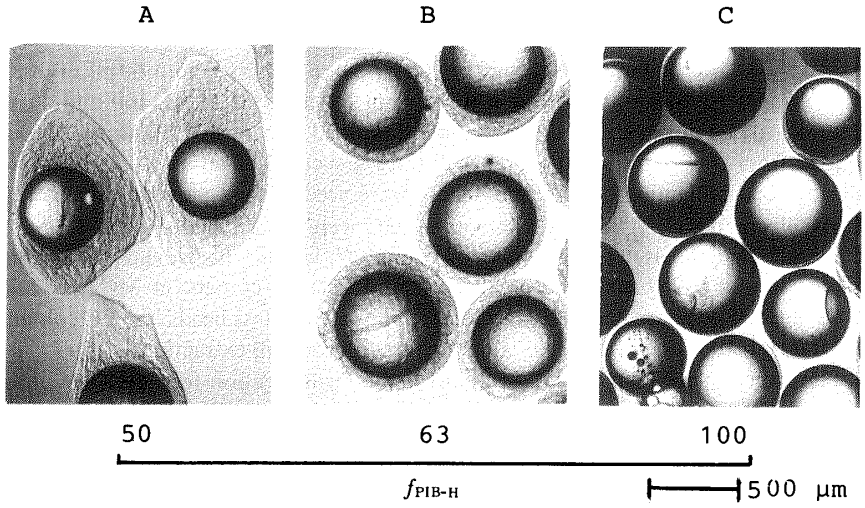

Fig. 1. Microphotographs of Glass Beads MC Prepared with Various Mixing Ratios of High- and Low-Molecular-Weight PIB

$W_{PIB-112}$ and W_{PIB-3} are the amounts of PIB-112 (MML-100) and PIB-3 (LMMH) used as coacervation inducing agents, respectively.[1] The index of sphericity, (S_i), was determined as the ratio of the mean length of the longest diameter (D_l) and that of the perpendicular diameter to the longest one (D_p) passing through the middle point from the micrographs of MC dispersed in cyclohexane (Eq. 5). The mean values were obtained by measurements on more than 50 granules.

$$S_i = D_l/D_p \tag{5}$$

As shown in Table I (Nos. 1—6), EC contents in MC increased with decrease of f_{PIB-H} value, while the S_i values approached unity with increase of f_{PIB-H}. Examples of micrographs of glass beads MC prepared with various mixing ratios of PIB are shown in Fig. 1. Sphericity was good when f_{PIB-H} was above 63%, and the EC content in MC was more than 10% when f_{PIB-H} was below 63%. Thus MC having a thick and unifrom wall were obtained when the f_{PIB-H} value was 63%.

The effect of the amount of EC used for the microencapsulation is also shown in Table I (Nos. 3, 7, 8). The use of more than 4.5 g of EC was not appropriate because the viscosity of the medium became too high. The shape of MC was influenced significantly by EC

TABLE II. Relationship between the Properties of Drugs in the Core Materials and Microencapsulation Efficacy

Core material	EC content in MC (%)	Solubility (g/ml)	
		Cyclohexane (at 25 °C)	1st fluid (at 37 °C)
Vitamin C	7.0	$<3\times10^{-7}$	3.68×10^{-1}
Vitamin B_6	6.0	$<3\times10^{-7}$	2.28×10^{-1}
Isoniazid	5.9	$<3\times10^{-7}$	2.05×10^{-1}
Trimebutine maleate	11.9	3.3×10^{-6}	2.80×10^{-2}
Theophylline	13.8	$<3\times10^{-7}$	1.02×10^{-2}

Cooling time in microencapsulation: 20 min.

concentration. A small amount of EC (1.5 g) resulted in MC similar to those in Fig. 1A, while a higher amount (4.5 g) of EC resulted in a nearly spherical shape as in Fig. 1B. The EC content in MC increased with increase of EC supplied for microencapsulation. When 4.5 g of EC was used for microencapsulation, a thick and uniform wall was obtained. These phenomena seem to be related to the viscosity of the preparing medium as Jizomoto[6] presumed in preparing gelatin MC of spherical shape. In highly viscous microencapsulation medium in which the $f_{\text{PIB-H}}$ value or EC concentration is high, the movement of MC is slow so that the adsorbed droplets of EC coacervate do not migrate on the surface of MC and consequently form uniform walls. Further, the nature of the coacervate itself adhering to the surface of core materials might affect the results. The prepartion conditions described in the experimental section ($f_{\text{PIB-H}}$: 63%, EC: 4.5 g) were adopted for the preparation of MC.

Microencapsulation of Various Drugs

To examine the influence of active ingredients on the microencapsulation, drugs having various levels of solubility (vitamin C, vitamin B_6, isoniazid, trimebutine maleate and theophylline) were encapsulated. The efficiency of microencapsulation (in terms of the EC content in MC) is shown in Table II.

In spite of the use of the same core size and the same microencapsulation procedure, the EC content in MC differed considerably from drug to drug. In the case of gelatin microencapsulation by the simple coacervation method, Okada[7] reported that the coating efficiency was better for less water-soluble materials. However, as shown in Table II, these five drugs were all scarcely soluble in cyclohexane, and the relationship between microencapsulation efficiency and the solubility of the core material in the microencapsulation medium could not be clarified.

However, comparison of the solubilities in the 1st fluid (also shown in Table II) with the EC contents in MC indicates that the lower the solubility, the better the microencapsulation efficiency, as in the case of gelatin.[7] Thus, it is presumed that EC coacervate droplets, having poorly hydrophilic characteristics, may deposit preferentially on the drug surface with lowest affinity to water. The result in Table II also indicates that the microencapsulation adopted here is applicable to both highly and poorly water-soluble drugs.

Dependency of Release Rate on Wall Thickness

Usually the thickness of EC wall can be altered by changing the amount of EC with respect to the crystalline materials, but in the case of spherical granules, this resulted in MC of irregular shape. However, spherical MC having a uniform wall of controllable thickness could be obtained by changing the cooling time. As an example, spherical MC of 5.0, 8.6, 11.9, 14.0 and 20.4 μm wall thickness were obtained at cooling times of 10, 20, 40, 60 and 80 min,

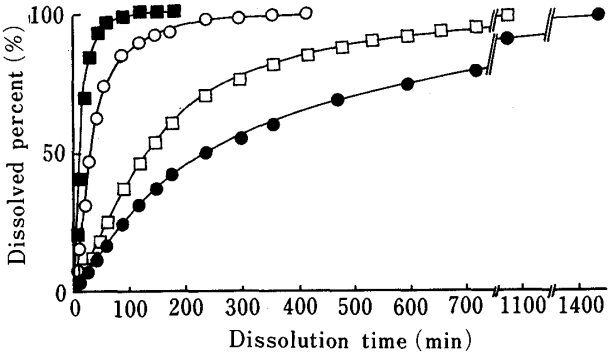

Fig. 2. Dissolution Curves of Isoniazid from MC of Various Wall Thicknesses

Wall thickness: 5 μm (■), 8.6 μm (○), 11.9 μm (□) and 20.4 μm (●).

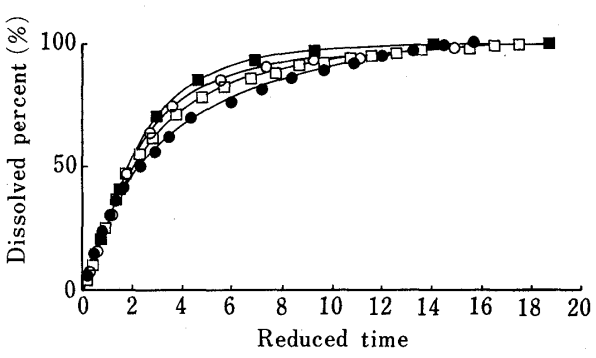

Fig. 3. Re-plotting of Dissolution Percent in Fig. 2 against Reduced Time

Wall thickness: 5 μm (■), 8.6 μm (○), 11.9 μm (□) and 20.4 μm (●).

respectively, for isoniazid core materials. Using these spherical MC, release experiments were performed for MC of various wall thicknesses (Fig. 2). As shown in Fig. 2 the thicker the membrane, the slower the dissolution rate. If H, A and P_m in Eq. 2 are unchanged in all the dissolution tests and the rate of dissolution of core drugs inside MC is faster than the rate of permeation through the membrane, then zero-order dissolution should continue as long as crystals of the drugs remain inside the MC, because the aqueous phase in MC is saturated with the core drugs and the concentration is always C_s. The zero-order region of released percent should be the same irrespective of the wall thickness if the above assumption is valid. However, as seen in Fig. 2, the zero order region differs from case to case. Other release kinetic equations such as 1st order and Higuchi equations were applied, but none could describe the whole dissolution process satisfactorily. For such a case where the kinetic mechanism is not clear, the use of reduced time, T_r, defined by Eq. 6 is useful to compare the whole release patterns.

$$T_r = t/T_s \tag{6}$$

where T_s is the time necessary for a definite amount of drug to dissolve from MC. Here, the quarter release time t_{25} was chosen for T_s because all MC showed linear dissolution at the early stages. Figure 3 shows the result of re-plotting the data in Fig. 2. If the dissolution proceeds with similar patterns and only the rates differ from each other, then the curves in Fig. 3 should be superposed perfectly.[8] As shown in Fig. 3, up to about 40% release, all of the plots coincide and are linear, but at more than 40% dissolution, the curves deviate from each other and the deviation from linearity is larger for MC with thicker walls. This suggests that either H, A or P_m changed during the dissolution experiments. Swelling of the polymer or closing of the pores in the membrane might produce these changes, and the effect might be larger for a thicker wall. As these changes seem to be rather small at the beginning of dissolution, values of P_m were obtained from K_{app} by the use of Eq. 3 for MC of vitamin C and isoniazid of various wall thicknesses. As shown in Fig. 4, P_m of both isoniazid and vitamin C decreased with increasing wall thickness when the film thickness was below 12 μm (region A). This phenomenon is consistent with the rusults described by Benita and Donbrow[3b] for MC of crystalline theophylline: they observed that P_m values decreased with increasing wall thickness. However, in our experiment, the P_m values were almost constant irrespective of the core material at wall thicknesses of more than 12 μm (region B). The reason for the decrease below 12 μm may be the rough surface of the core material; a part of the EC might not be used as membrane but to "smooth out" the roughness. On the other hand, at more than 12 μm, the polymer was mainly used for membrane formation, so the P_m values were constant. In the

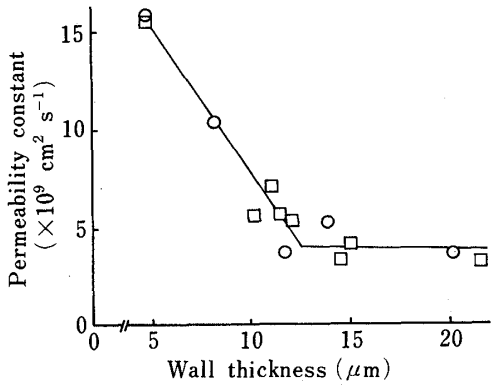

Fig. 4. Dependency of P_m on Wall Thickness of MC Prepared from Spherical Core Materials

Isoniazid (○) and vitamin C (□).

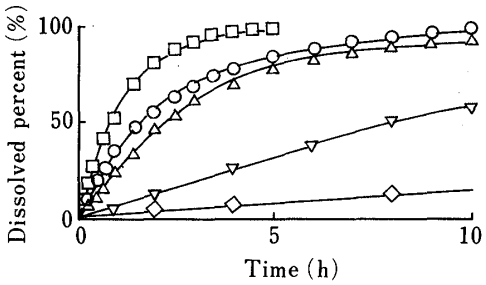

Fig. 5. Dissolution Percent of Drugs from Spherical MC Containing Various Drugs

Vitamin C (□), vitamin B_6 (○), isoniazid (△), trimebutine maleate (▽) and theophylline (◇).

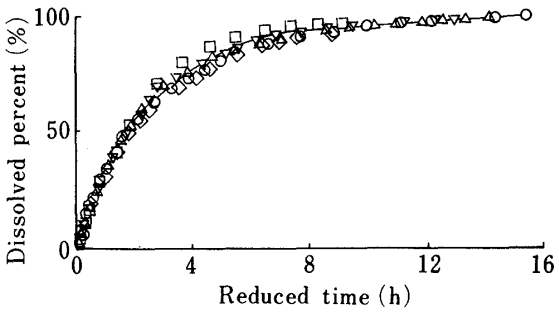

Fig. 6. Re-plotting of Dissolution Percent of Drugs from Spherical MC against Reduced Time

Vitamin C (□), vitamin B_6 (○), isoniazid (△), trimebutine maleate (▽) and theophylline (◇).

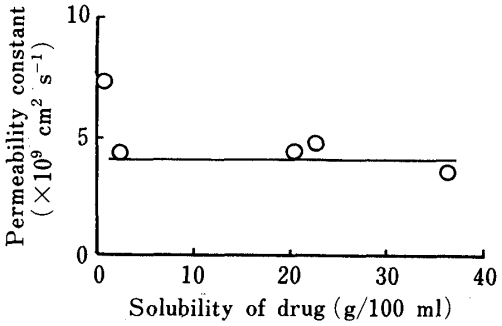

Fig. 7. The Relationship between Solubilities of Core Material and P_m Values

case of Benita and Donbrow,[3b] it is presumed that the wall thickness was not enough to enter region B because of the complex and irregular shape of the crystal materials.

Influence of the Core Materials on Release Rate

As shown in Fig. 4, P_m values were constant when the wall thickness was over 12 μm. Thus, spherical MC of various drugs were prepared with wall thicknesses of 12 to 15 μm, and the drug dissolution patterns were evaluated. Figure 5 shows the dissolution data for individual drugs from MC. From the time of 25% dissolution, T_r was calculated by means of Eq. 6 and the dissolved amount (percent) was plotted (Fig. 6). The deviation seems to be smaller than when the wall thickness was changed (Fig. 3), and all the patterns were similar, being mostly superposed up to 70% dissolution. This suggests that the dissolution mechanism does not depend much on the properties of the core materials if the wall thickness is constant.

From the early dissolution curve, P_m values were calculated and plotted against the solubility in the 1st fluid (Fig. 7). As shown, the P_m values of vitamin C, isoniazid, vitamin B_6, and trimebutine maleate were almost the same irrespective of the ten-fold difference in their solubility. Thus the applicability of Eq. 2 was confirmed for these cases. However, theophylline showed a higher value than the other materials. Here, it should be noted that spheronization of the theophylline core was the most difficult among the drugs. This might be because of the low hydrophilicity of theophylline. The sphericity indices of the cores of the other four drugs were between 1.10 to 1.20, whereas that of theophylline was 1.40. As

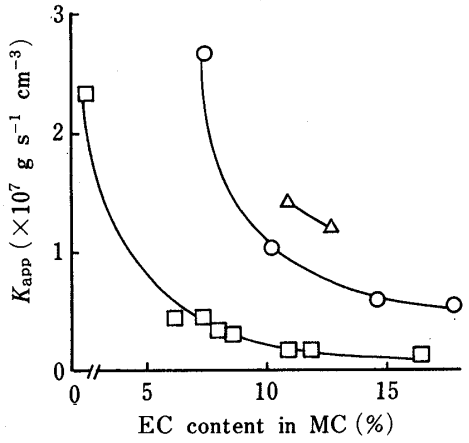

Fig. 8. Influence of Shapes of Vitamin C Core Materials on Dissolution Rate

Spherical MC (□), cylindrical MC (○) and crystalline vitamin C (△).

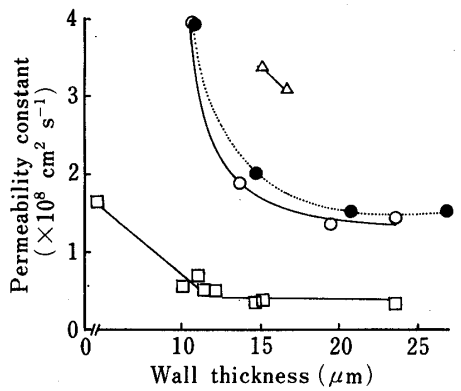

Fig. 9. Plotting of P_m Values of MC against Wall Thickness

Spherical MC (□), cylindrical MC for which the surface area was calculated based on a sphere (○) or a cylinder (●), vitamin C crystal (△).

discussed later, P_m values increased with increase of S_i, so the high P_m value of theophylline may be related to its core shape.

Influence of the Core Material Shape

To establish the influence of the shape of core materials, spherical granules, cylindrical granules and crystalline vitamin C of the same particle size were microencapsulated by the same method. The K_{app} values obtained were plotted against the EC content in MC (Fig. 8). As shown, crystalline vitamin C, which has nearly a square pillar shape, showed the fastest dissolution, followed by the cylindrical shape and the spherical shape in that order at any EC content. The P_m values for MC of spherical, cylindrical and crystalline vitamin C were calculated by using the wall thickness obtained from Eq. 3 and plotted against the wall thickness (solid line in Fig. 9).

Here, the film thickness was calculated according to Lafont *et al.*[5] on the assumption that the core materials are spherical. This assumption was usually adopted for convenience of calculation because the shape of crystals is always very complicated. However for a cylindrical pillar, it can be obtained without this assumption by solving Eq. 7.

$$\frac{Q_m}{Q_c}=\frac{(L_b/2)^2 D_c L_a}{(L_b/2)^2 D_c L_a + D_w((L_b+2H)^2(L_a+2H)/4-(L_b/2)^2 L_a)} \quad (7)$$

where Q_m and Q_c are the drug contents in MC and the core materials respectively, L_a is the length of the core cylinder, L_b is the core diameter, and D_c and D_w are the densities of the core materials and wall, respectively. The equations was solved by the trial-and-error method using a computer. In this calculation, values of 946 and 437 μm, the averages of about 50 core materials, were used for L_a and L_b, respectively. Thus, the P_m values were recalculated after correction of the film thickness and surface area and the results are shown in Fig. 9 by a dotted line. The result does not show a large discrepancy from that calculated using Lafont's equation. This suggests that the difference of P_m values is not due to the method used to calculate the wall thickness.

The calculated P_m value of cylindrical MC was about 4 times larger than that of spherical MC at the wall thickness of 20 μm, and the results suggest that the wall thickness at the edge of cylindrical MC is thinner than the calculated average wall thickness.

References and Notes

1) Part III: Y. Koida, M. Kobayashi, G. Hirata and M. Samejima, *Chem. Pharm. Bull.*, **32**, 4971 (1984).
2) A part of this work was presented at the 105th Annual Meeting of the Pharmaceutical Society of Japan, Kanazawa, April 1985.
3) *a*) P. B. Deasy "Microencapsulation and Related Drug Processes," Marcel Dekker Inc., New York, 1984, p. 289; *b*) S. Benita and M. Donbrow, *J. Pharm. Pharmacol.*, **34**, 77 (1982); *c*) J. R. Nixon and S. E. Walker, *ibid.*, **23** suppl., 147 (1971).
4) *a*) M. Samejima, G. Hirata and Y. Koida, *Chem. Pharm. Bull.*, **30**, 2894 (1982); *b*) Y. Koida, G. Hirata and M. Samejima, *ibid.*, **31**, 4476 (1983).
5) L. Si-nang, P. F. Carlier, P. Delort, J. Gazzola and D. Lafont, *J. Pharm. Sci.*, **62**, 452 (1973).
6) H. Jizomoto, *J. Pharm. Sci.*, **73**, 879 (1984).
7) J. Okada, The 1st Symposium of Seizai to Ryusi Sekkei, Sanda, Hyogo Prefecture, November 1984, p. 65.
8) H. Yoshino, M. Kobayashi and M. Samejima, *Chem. Pharm. Bull.*, **29**, 2661 (1981).