Microencapsulation of Benzoic Acid Derivatives Using an Enteric Polymer by Surface Neutralization Method and Derivation of an Empirical Equation for Predicting Film Formation[1)]

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The effect of drug and polymer properties on microencapsulation of acidic drugs with enteric polymers by the surface neutralization method was studied using eight benzoic acid derivatives and three enteric polymers (carboxymethylethylcellulose (CMEC), hydroxypropylmethylcellulose acetate succinate-H (AS-H) and hydroxypropylmethylcellulose acetate succinate-L (AS-L)). Each core material containing a drug was granulated to beads from 500 to 710 μm in diameter to remove the effect of drug crystal morphology. Microcapsules (MCs) were prepared by suspending the beads in an enteric polymer solution, followed by filtration and drying. Then, the properties of the MCs produced were evaluated. The polymer content in MCs (*PC*) and recovery percent of the drugs in MCs were in the order AS-H > AS-L > CMEC, but the percent of recovered single-nuclear MCs was in the order CMEC > AS-L > AS-H. The *PC*s did not correlate with the solubilities of drugs, but showed an obvious dependency on the pH of the saturated solution of the drug. That is, as the pH decreased, the *PC*s increased. To estimate the *PC*s on the basis of drug and polymer properties, a mathematical model was established on the basis of an acid-base equilibrium equation, and the ratio of polymer acidic groups associated with hydrogen ion (*FS*) was calculated. A linear relationship was obtained between $\sqrt{(FS-\alpha_p)}$ values (α_p: equivalency ratio of hydrogen ion to acidic groups of polymer at which the polymer begins to precipitate) and the experimental *PC*s. Thus, microencapsulation efficiency seemed to be predictable by using this relationship.

Keywords microcapsule; enteric polymer; aqueous coating; benzoic acid derivative; hydroxypropylmethylcellulose acetate succinate; mathematical model

Introduction

Water insoluble polymers such as ethylcellulose form a very effective wall and constrain drug release from microcapsules (MCs). However, the use of too much insoluble polymer often causes a part of the encapsulated drug to remain unreleased and so lowers the bioavailability of the drug.

MCs prepared by the use of enteric polymers can overcome this disadvantage because these polymers dissolved and release all of the drug when they reach the small intestine, even if drug release is completely prevented in the stomach. Furthermore, as in the case of MCs of a water-insoluble polymer, masking of bitter taste, reduction of side effects and stabilization of drugs can also be expected in enteric-coated MCs.

Many methods have been developed for the preparation of such enteric polymer coated MCs. The fluid-bed method,[2)] centrifugal fluidized method and so on are frequently used in manufacturing processes and formulation research. However, these methods need special equipment, require much energy and sometimes use organic solvents. Thus, a simple microencapsulation preparation method using an aqueous solvent without any special equipment is desirable to reduce air pollution, increase safety in the work place and lower the manufacturing cost.

We have developed a new microencapsulation method with enteric polymer by means of surface neutralization, based on the following principle. When crystals of a poorly soluble acidic drug[3)] or particles consisting of a neutral drug and an acidic material[4)] are poured into a solution containing an enteric polymer previously dissolved with the aid of an appropriate amount of alkali, the dissolved enteric polymer becomes insoluble locally on the surface of crystals or particles and forms a seamless film enveloping the particles uniformly. This method is very simple and MCs can be prepared even on such a small scale that use of the fluid-bed method would be difficult.

In the previous study, crystalline aspirin was encapsulated using various polymers[5)] and the effects of the polymer species on the microencapsulation procedure and the properties of produced MCs were clarified. Carboxymethylethylcellulose (CMEC) formed a good enteric film without much particle coagulation, and hydroxypropylmethylcellulose acetate succinate-H (AS-H) enveloped aspirin with the least loss of the drug but had a fairly large coagulating tendency. Hydroxypropylmethylcellulose acetate succinate-L (AS-L) dissolved at almost the same pH as CMEC even though its chemical structure was almost the same as that of AS-H except for fewer acetate succinate moieties bound to the polymer framework. Thus, a comparison of the microencapsulation using these three enteric polymers seemed interesting and useful.

Drug properties also influence microencapsulation. We have studied this subject using a series of benzoic acid derivatives, since the physicochemical properties of their aqueous solution differ greatly from each other. Thus, the eight derivatives were encapsulated by this method using the three enteric polymers CMEC, AS-H and AS-L.

In these studies, morphological properties such as particle size, size distribution, and crystal shape could greatly affect the microencapsulation, in addition to the drug properties in aqueous solution. Thus, in this study, the drugs were all pulverized and granulated to beads to standardize the morphological factors and then the method was applied to the beads. Our aim was to clarify the influence of drug and polymer properties, so as to establish the applicability and limitations of this method.

Experimental

Materials Benzoic acid (BA), salicylic acid (SA) and *p*-hydroxybenzoic acid (*p*-HB) were obtained from Katayama Chemical Ind. Co., Ltd. *o*-Chlorobenzoic acid (*o*-CB), *m*-toluic acid (*m*-TA), *o*-nitrobenzoic acid (*o*-NB) and *m*-nitrobenzoic acid (*m*-NB) were obtained from Tokyo Kasei Kogyo Co., Ltd. Aspirin (AS) was of JP grade. AS-H and AS-L (succinoyl content, 5.5% and 14.6%, respectively) and CMEC (carboxylmethyl content 11.7%) were obtained from Shin-etsu Chemicals Ltd. and Freund Ind. Co., Ltd., respectively. Polyvinyl acetate was obtained from The Nippon Synthetic Chemical Industry Company. Table I shows the drugs used in this study and the physicochemical properties of their solutions.

Preparation of Core Materials Onto 300 g of the seed materials (microcrystalline cellulose beads, 350—500 μm in diameter), 800 ml of an 80% ethanol solution containing 10% benzoic acid derivatives and 3% binder (polyvinyl acetate) was sprayed by the use of a centrifugal fluidized granulator. The beads were dried at 45 °C for 4 h, and those which passed through a 24 mesh (710 μm) screen and remained on the 30 mesh screen (500 μm) were used as core materials.

Preparation of Microcapsules One hundred milliliters of water and 3 g of enteric polymer were placed in a beaker of 200 ml capacity and an enteric polymer was dissolved by the addition of a definite amount of 1 N sodium hydroxide solution (CMEC 5.6 ml, AS-L 3.1 ml and AS-H 1.6 ml). The pH values of the solutions were 5.5, 5.5 and 6.8 for CMEC, AS-L, and AS-H respectively. The beaker was maintained at a constant temperature (25 °C) and the beads (5 g) were poured into the solution. The suspension was agitated for 15 min at a stirring rate of 400 rpm. As described previously,[3] microencapsulation was completed within 5 min, so a preparation time of 15 min should be enough for this method. The microcapsules produced were recovered by decantation, washed with water and dried at 45 °C for 4 h.

Determination of Single-Nuclear MCs Classification of MCs was carried out by using sieves. The percentage of single-nuclear MCs was estimated as described previously[5] from the percentage of MCs having particle sizes between 500 to 840 μm.

Determination of Drug Content One hundred milligrams of MCs was weighed accurately, then 5 ml of 80% ethanol was added and agitated intensely, and the 1st disintegration test fluid specified in JP XII was added to make exactly 100 ml. The resultant precipitate was removed on filter paper. The 1st fluid was added to 1 ml of filtrate to make exactly 100 ml. Then, benzoic acid derivatives content was determined spectrophotometrically.

Polymer Content in MC (*PC*s) The amount of wall materials (enteric polymer) in MCs should be obtained by determining polymer directly, but it was not easy to find a proper assay method. Therefore, it was calculated by using Eq. 1:

$$PCs(\%) = 100 \cdot (A_{MC} - (A_D + A_B + A_{SM}))/A_{MC} \quad (1)$$

where A_{MC}, A_D, A_B and A_{SM} mean the amount of whole MC, drug, binder and seed material (crystalline cellulose), respectively. A_{MC} was determined by weighing whole MCs obtained after the above microencapsulation procedure. A_D was determined by assaying the benzoic acid derivatives. It was not easy to estimate ($A_B + A_{SM}$), because a proper assay method for polyvinyl acetate or microcrystalline cellulose could not be found. Therefore, it was calculated assuming that all the binder and microcrystalline cellulose used were recovered completely in whole MCs after the microencapsulation procedure. To assure this, we took great care in the recovery procedure of the produced MCs, since the loss of MCs would lead to error in the elucidation of *PC*s.

Determination of pH Profile of Enteric Polymer Solution One hundred milliliters of water and 3 g of enteric polymer were placed in a beaker of 200 ml capacity and each enteric polymer was dissolved by addition of the same amount of 1 N sodium hydroxide as that used in the microencapsulation (CMEC 5.6 ml, AS-L 3.1 ml, AS-H 1.6 ml). The beaker was maintained at a constant temperature (25 °C) and the polymer solution was titrated with 1 N hydrochloric acid while the pH of the titrated solution was measured (pH meter; Horiba F-8DP).

Dissolution Studies MCs of 20 mesh to 30 mesh were used for this study. Dissolution (percent) of drugs from MCs containing 40 mg of benzoic acid derivatives was determined in 900 ml of the 1st or the 2nd disintegration test fluid (JP XII) by the paddle method at an agitation speed of 100 rpm at 37 °C. Permeability constant (P_m) was calculated from the result of the dissolution experiment in the 1st fluid by using Eq. 2.

$$P_m = K_{app} V l_m / (A C_s) \quad (2)$$

where K_{app} is the dissolution rate estimated from the slope of the early linear stage of the dissolution curve, V is the volume of the medium, l_m is the wall thickness calculated according to Koida *et al.*,[3] A is the surface area of microcapsules and C_s is the solubility of each benzoic acid derivative in the 1st fluid.

TABLE I. Drugs Used in This Study and Physicochemical Properties of Their Solutions at 25°C

Benzoic acid derivatives	Solubility (mg/ml)	pH_{sat} [a]	pK_a
o-NB	6.1	1.9	2.18
o-CB	1.8	2.4	2.68
SA	2.0	2.5	3.05
AS	5.0	2.6	3.60
m-NB	1.5	2.7	3.24
BA	3.7	2.8	4.06
m-TA	0.7	3.2	4.05
p-HB	9.9	3.0	4.85

a) pH of saturated solution.

Results and Discussion

Properties of MCs Prepared The properties of the MCs of the eight drugs prepared according to the method described in the experimental section are summarized in Table II.

As shown in Table II, the polymer contents in MCs (*PC*s) differed for each polymer. In the case of AS-H, the *PC*s were more than 9% and were the largest among the three polymers. In the case of CMEC, three drugs (BA, *m*-TA, *p*-HB) were not encapsulated and the *PC*s were the smallest among the three polymers with the exceptions of SA and *o*-CB. In the case of AS-L, films were formed with all of the drugs but the *PC*s were much smaller than those with AS-H.

TABLE II. Properties of the MCs Produced

	Polymer content in MCs (*PC*) (%)			Dissolution rate[a] (mg cm^{-3} h^{-1} × 100)			Recovery percent of drugs		
	CMEC	AS-L	AS-H	CMEC	AS-L	AS-H	CMEC	AS-L	AS-H
o-NB	8.9	16.0	19.0	1.6	0.4	1.2	86	89	93
o-CB	5.0	4.0	13.0	1.1	1.1	1.1	86	90	93
SA	5.0	4.2	12.8	1.3	0.7	0.7	80	87	94
AS	4.7	8.0	14.8	2.4	1.3	1.3	77	80	82
m-NB	1.0	4.0	10.0	3.7	1.3	1.4	75	81	84
BA	0	7.0	16.0	8.1	1.6	1.4	77	86	89
m-TA	0	0.4	9.0	1.8	1.1	0.7	90	90	91
p-HB	0	5.0	16.2	16.4	4.4	4.1	60	82	93

a) Dissolution medium: the 1st fluid. Dissolution rate was calculated in the early linear stage.

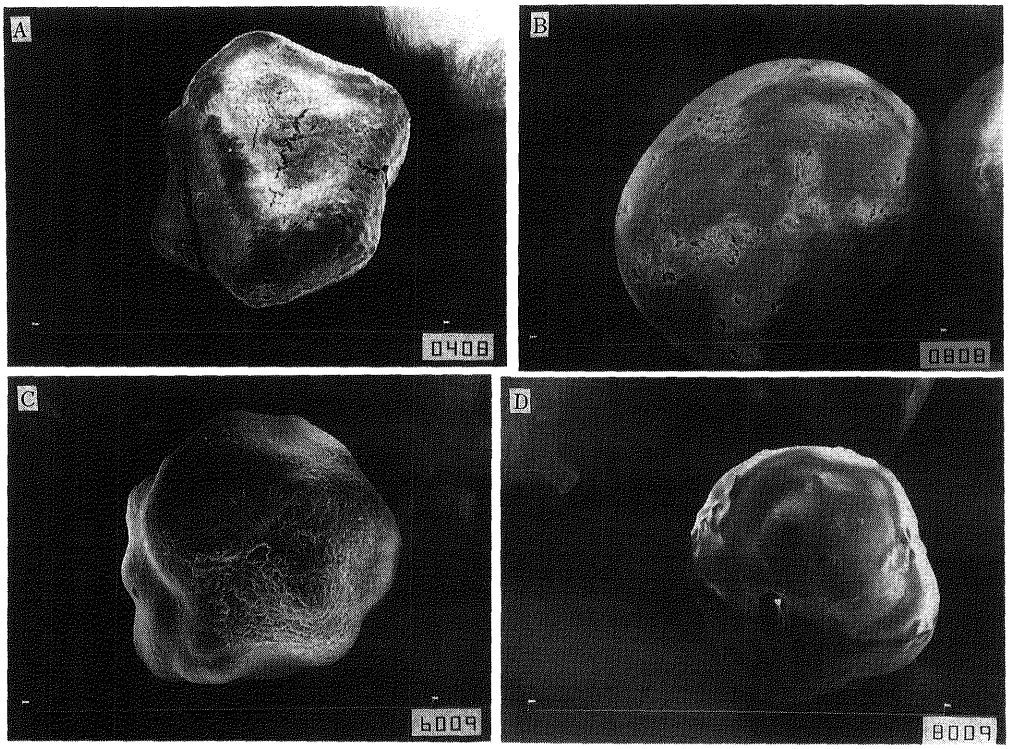

Fig. 1. Scanning Electron Micrographs of Microcapsules Produced
A: BA and CMEC. B: BA and AS-L. C: BA and AS-H. D: *o*-NB and CMEC.

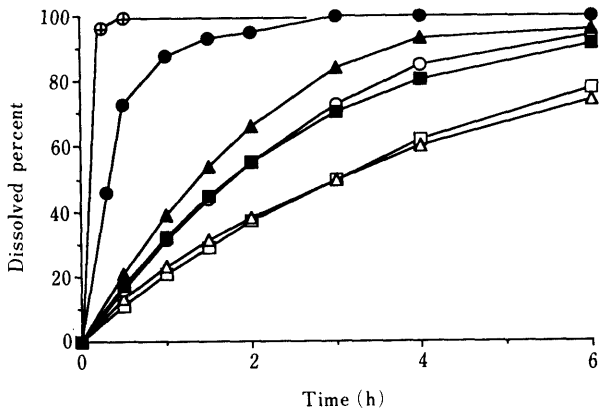

Fig. 2. Dissolution Percent of SA and BA in the 1st Fluid from MCs
Open symbols are for SA and closed symbols are for BA. □, ■, AS-H; △, ▲, AS-L; ○, ●, CMEC; ⊕, core.

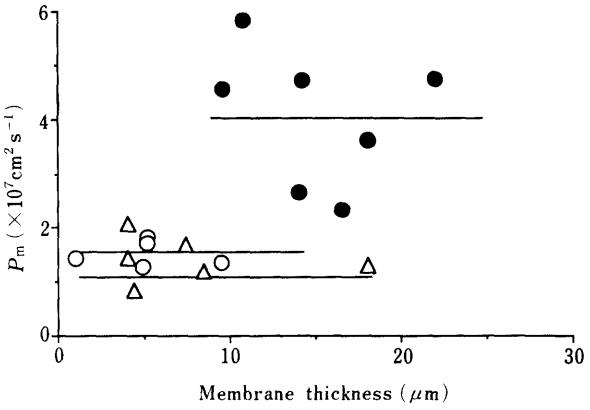

Fig. 3. Plots of Permeability Constant against Membrane Thickness
●, AS-H; △, AS-L; ○, CMEC.

Figure 1 shows some examples of scanning electron micrographs of the MCs. It can be seen that a film (A) was not formed with CMEC, but films were formed with AS-L and AS-H when BA beads were used (B and C). However, films were formed with CMEC if other beads such as *o*-NB were used (D).

The dissolutions of the drugs in the 2nd fluid from the MCs were rapid ($t_{50} < 10$ min) in all cases, while they were delayed in the 1st fluid and the rate differed from MC to MC preparation.

In Fig. 2, typical data on dissolution in the 1st fluid are shown for the MCs of SA and BA. From the initial linear parts of the curves, values of dissolution rate, k_{app}, were calculated for all the MCs, and are summarized in Table II.

Using the k_{app} values, the P_m values were estimated and are plotted against the wall thickness in Fig. 3. The P_m values of MCs prepared using CMEC and AS-L were very similar even though the wall thickness of the MCs differed widely. This phenomenon is consistent with the finding of Koida *et al.*[3] that the P_m values of aspirin MCs prepared by using CMEC were almost the same, irrespective of the wall thickness. However, the P_ms in AS-H were much larger than those in CMEC and AS-L and varied very widely. The larger P_ms mean that the wall membranes of AS-H were less compact than those with CMEC or AS-L. This may be ascribed to the precipitation behavior of polymers with acidic drugs. Thus, the polymer solutions used for the microencapsulation (pH 6.8, 5.5 and 5.5 and α values of 0.00, 0.29 and 0.05 for AS-H, AS-L and CMEC, respectively) were titrated with 1 N HCl. The pH changes were shown against α in Fig. 4. Here, α value means the

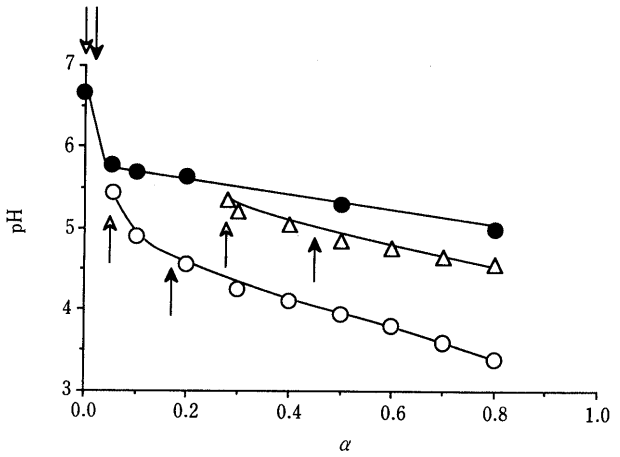

Fig. 4. pH Change of the Microencapsulation Medium against Equivalency Ratio of Hydrogen Ion to Acidic Groups (α) when Titrated with 1 N HCl Solution

↑ and ↑ indicate the point before adding 1 N HCl and that at which polymer began to precipitate. 0.1α corresponded to 0.16, 0.43 and 0.59 ml of 1 N HCl for AS-H, AS-L and CMEC, respectively. ●, AS-H; △, AS-L; ○, CMEC.

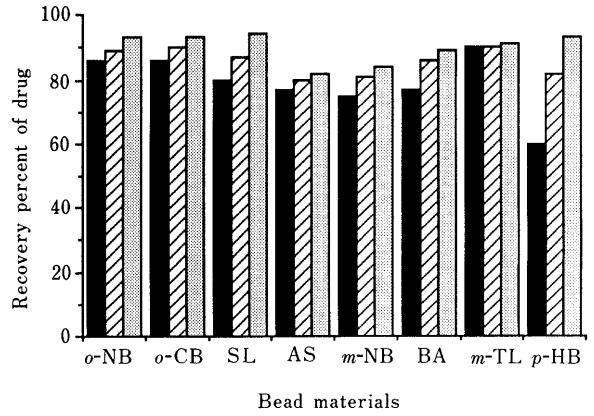

Fig. 5. Recovery Percent of Drugs in MCs

▨, AS-H; ▨, AS-L; ■, CMEC.

equivalency ratio of hydrogen ion to acidic groups of polymer, calculated as

$$\alpha=(E_{HCl}+E_{PA}-E_{NaOH})/E_{PA} \quad (3)$$

where E_{HCl}, E_{PA} and E_{NaOH} mean the equivalency of HCl added to the polymer solution, that of NaOH used to dissolve the polymer and that of acidic group of the polymer. Titrations were also carried out using 0.1 N HCl and 0.01 N HCl, but the pH was dependent only on α and not on the concentration of titrant, so the α values determined with 1 N HCl are shown in Fig. 4.

The polymers were precipitated from each polymer solution by adding 0.05, 0.6 and 0.8 ml of 1 N HCl and the corresponding α values (denoted as α_ps and indicated by closed arrows in Fig. 4) were evaluated as 0.03, 0.43 and 0.18 for AS-H, AS-L and CMEC, respectively. The P_m values in AS-H (Fig. 3) may be highest because the time for wall formation was not enough to produce compact and uniform walls, since AS-H precipitated with the smallest amount of acid as shown in Fig. 4.

In Fig. 5, the recovery percent of the drugs in MCs are shown for each polymer. The recovery was in the order

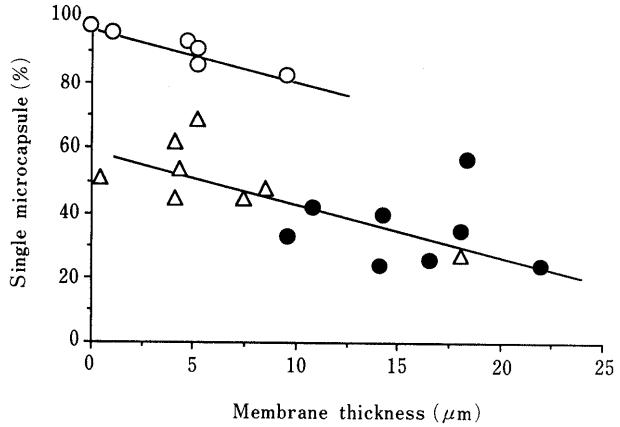

Fig. 6. Plots of Single Nuclear Percent of MC against the Membrane Thickness

●, AS-H; △, AS-L; ○, CMEC.

AS-H > AS-L > CMEC for all of the drugs. This seems to correspond to the order of the amount of hydrogen chloride necessary to precipitate the polymer from the microencapsulation medium: AS-H < AS-L < CMEC (Fig. 4). In almost all cases, the recovery of drugs was more than 80%, but it was about 60% in the combination of *p*-HB and CMEC. This low value is considered to be caused by the weak acidity and the high solubility of *p*-HB together with the low precipitation pH to CMEC (Fig. 4).

The amounts (%) of single-nuclear MCs are plotted against membrane thickness for each polymer in Fig. 6.

As shown, the values decreased as the membrane thickness increased for all the polymers. It is interesting that the membrane thicknesses of AS-H and AS-L fell on the same line while those of CMEC fell on a different higher line. This means that coagulation of MCs was minor in the case of CMEC, but rather large with AS-L and AS-H. The great difference between CMEC and the two ASs is considered to arise from differences in the polymer properties, such as viscosity, adhesiveness, diffusion rate in a diffusion layer and so on.

Factors Affecting Microencapsulation Efficiency As the encapsulation principle of this method is based on polymer precipitation due to the alteration of the acidity around beads, physical properties of the drug affecting the acidity of the solution seemed to influence the microencapsulation efficacy. Such properties may include solubility, pH of a saturated solution, pK_a, diffusion constant, apparent dissolution rate constant of each drug and so on. However, diffusion constants would not differ very much since the molecular weights do not differ greatly. Therefore, if the thickness of the diffusion layer is supposed not to vary greatly among the drugs, the apparent dissolution rate constants, k, defined by the Noyes–Whitney equation ($dc/dt=k(C_s-C)=DS/Vl(C_s-C)$,[7] where D is the diffusion constant of the drug, S is the surface area of the beads, V is the volume of the dissolution medium and l is the thickness of the diffusion layer) may not differ greatly among the drugs, since they were spheronized to have the same surface area. In Fig. 7 the *PC*s, an index of microencapsulation efficiency, of all the MCs are plotted against the solubility (A) and the pH of saturated solution of each drug (B).

As shown, the *PC*s seemed to increase a little with the increase of solubility in AS-H, but there is no clear relation to the solubility in AS-L and CMEC (Fig. 7A). They generally decreased as the pH of the saturated solution increased, but the regression lines were different for the individual polymers (Fig. 7B).

The principle of this microencapsulation is based on the acid-base equilibrium shown in Eqs. 4 and 5, which offers a way to predict the microencapsulation efficiency mathematically.

$$HD \rightleftharpoons D^- + H^+ \quad (4)$$

$$P^- + H^+ \rightleftharpoons HP \quad (5)$$

where P^- and HP mean the dissociated and undissociated anions of polymer and D^- and HD are the dissociated and undissociated drug, respectively.

The solid drug dissolves in the aqueous phase and then partly dissociates into anion and hydrogen ion. A part of the dissociated polymer anion associates with hydrogen ion and the increase of HP precipitates the polymer to form a film enveloping the beads. The difference in the microencapsulation efficiency among polymers seems to be clearly understandable on the basis of Eqs. 4 and 5.

However, the microencapsulation process should be very complicated, since dissolution of acidic drug, dissociation of drug molecule into H^+ and D^-, neutralization and precipitation of polymer, adhesion of polymer on beads and so on occur in the diffusion layer built up around the beads when they are poured into aqueous polymer solution. The amounts of the molecular forms of each compound and the velocity of mass transport in each process should greatly affect the microencapsulation efficiency, and further, both of them seem to change continuously with the progress of microencapsulation. For example, the drug dissolution rate from beads is presumed to be reduced with time due to the wall produced, or the immigration and precipitation of polymer may be reduced with time due to the increase of the viscosity around beads as the polymer precipitates. Thus, it is difficult to establish a mathematical model which can completely describe the whole microencapsulation process.

Therefore, we considered the initial stage of the microencapsulation and made the following assumptions.

1) The aqueous phase contacting the surface of beads is saturated with drug and the drug concentration linearly decreases in the diffusion layer and becomes zero in the bulk phase. 2) Polymer concentration and sodium ion concentration (derived from sodium hydroxide used to dissolve polymer beforehand) are uniform in the whole aqueous phase. 3) The change of the bead diameter is negligibly small during microencapsulation.

Then, at point a X in the diffusion layer, Eqs. 6, 7 and 8 apply to the drug.

$$K_a = (H^+)_x(D^-)_x/(HD)_x \quad (6)$$

$$C_{Dx} = (HD)_x + (D^-)_x \quad (7)$$

$$(D^-)_x = K_a C_{Dx}/((H^+)_x + K_a) \quad (8)$$

where K_a is the dissociation constant of the drug, and (H^+), (D^-), (HD) and C_D are the normality of hydrogen ion, drug ion, undissociated drug and total drug, respectively. The subscript X indicates the position in the diffusion layer.

Defining the dissociation constant of polymers is very

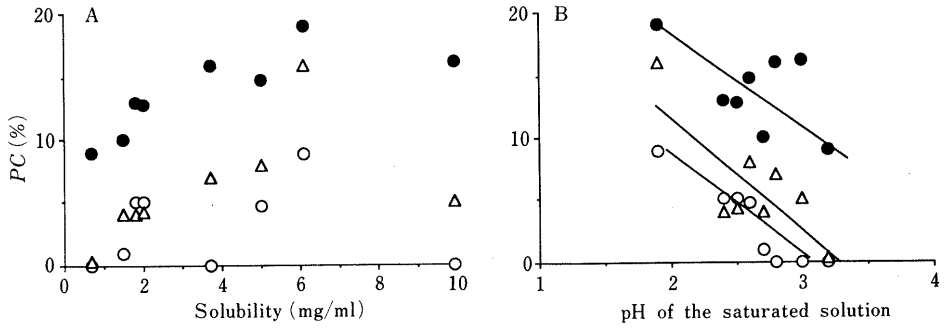

Fig. 7. Plots of Polymer Content in MCs against Solubility of Benzoic Acid Derivatives (A) and the pH of Saturated Solution of Them (B)
●, AS-H; △, AS-L; ○, CMEC.

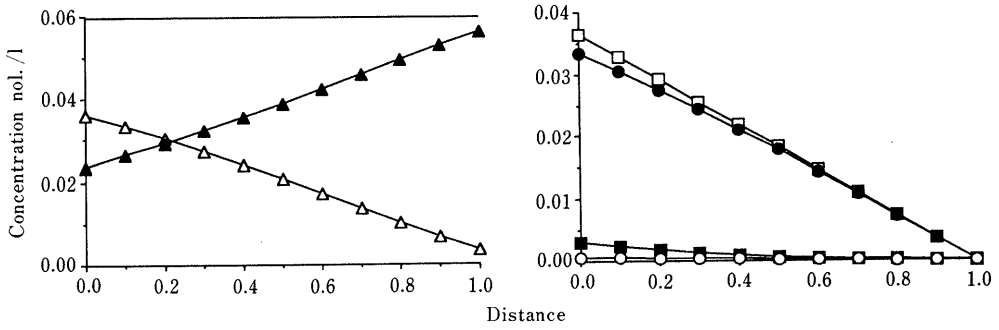

Fig. 8. Distribution of Various Molecules or Ions in the Diffusion Layer Calculated on the Basis of Eqs. 9, 11 and 13 for the Microencapsulation of *o*-NB with CMEC
—, C_p; △, HP; ▲, P^-; □, C_D; ●, D^-; ■, HD; ○, H^+.

complicated, since one polymer molecule has many dissociation phases and the dissociation constant differs with α. However, the microencapsulation process in this method is considered to be affected by many other factors as described above, and the precise dissociation constants of the polymer, even if they could be determined, would not be very helpful to understand the microencapsulation process clearly. Thus, in this study, the dissociation constants of polymers were approximated as constants irrespective of α for convenience. Then,

$$K_p=(H^+)_x(P^-)_x/(HP)_x \tag{9}$$

$$C_p=(P^-)_x+(HP)_x \tag{10}$$

$$(P^-)_x=K_pC_p/((H^+)_x+K_p) \tag{11}$$

where K_p is the dissociation constant of the polymer, and C_p is the normality of total polymer.

As the solution is electrically neutral,

$$(Na^+)_x+(H^+)_x=(D^-)_x+(P^-)_x \tag{12}$$

where (Na^+) is normality of sodium ion added beforehand to dissolve the polymer in the preparation ((OH^-) should be negligibly small compared to (H^+)).

By substitution of Eqs. 8 and 11 into Eq. 12 and rearrangement, the following equation is obtained.

$$(H^+)_x^3+(K_a+K_p+(Na^+)_x)(H^+)_x^2 +(K_aK_p+(Na^+)_xK_a+(Na^+)_xK_p-(K_aC_{Dx}+K_pC_p))(H^+)_x +(Na^+)K_aK_p-K_aK_p(C_{Dx})-K_aK_pC_p=0 \tag{13}$$

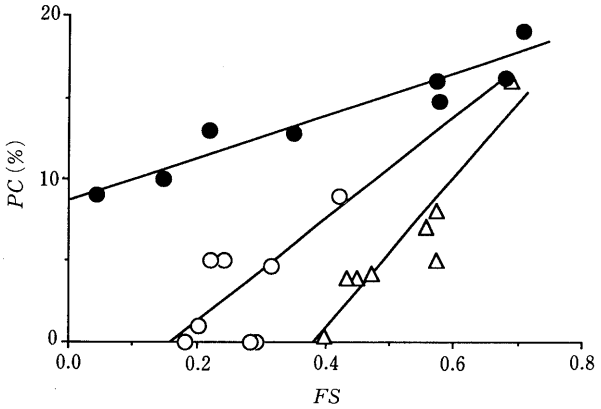

Fig. 9. Plots of Polymer Content in MCs (*PC*) against *FS* Values Defined in Eq. 15

●, AS-H; △, AS-L; ○, CMEC.

In Eq. 13, K_a, $(Na^+)_x$ and C_p are constant through the diffusion layer and are known, and C_{Dx} can be calculated, due to the assumption, as

$$C_{Dx}=C_s \quad (1-X/l) \tag{14}$$

where l is the length of the diffusion layer.

As for the dissociation constants of polymers, we regarded the pH of the polymer solution at $\alpha=0.5$ as their pK_p values. Thus, the pK_p values of CMEC, AS-L and AS-H were estimated from Fig. 4 as 4.0, 4.9 and 5.3, respectively.

$(H^+)_x$ could be obtained by solving Eq. 13 using the above parameters. Then $(P^-)_x$ and $(HP)_x$ could be calculated from Eqs. 11 and 9, respectively. In Fig. 8, C_{Dx}, $(H^+)_x$, $(HD)_x$, $(D^-)_x$, $(HP)_x$, $(P^-)_x$ and C_p calculated for the case of *o*-NB and CMEC combination as above are shown as an example.

If $(HP)_x$ increases in the diffusion layer, the amount of the precipitating polymer is considered to increase. Thus, the ratio of $(HP)_x$ to whole polymer concentration (to remove the effect of polymer concentration in each solution), $(HP)_x/C_p$, was calculated at each point X, which is the Xth point from the surface when the diffusion layer is devided into numerous small parts with the same length. Then, *FS* defined by Eq. 15 was numerically calculated by the trapezoidal method.

$$FS=\int_0^1((HP)_x/C_p)dx \tag{15}$$

FS means the fraction of the polymer acidic group associated with hydrogen ion in the whole diffusion layer. The *PC*s experimentally determined were plotted against *FS* in Fig. 9.

As shown, *PC* values increased as *FS* increases, though each polymer showed a different dependency on *FS*. In the case of AS-L and CMEC, *PC*s were zero until the *FS* values became about 0.4 or 0.2, respectively. These values were very close to α_p of each polymer (Fig. 4) at which each polymer began to precipitate. Both *FS* and α_p are intrinsic parameters of each polymer and can be determined independently of microencapsulation. Thus, in Fig. 10A, *PC*s values experimentally determined are plotted against $(FS-\alpha_p)$.

As shown in Fig. 10A, all of the *PC*s seemed to be plotted on the same curve but the cases of BA-CMEC and *p*-HB-CMEC deviated from the curve. *PC*s increased very rapidly when $(FS-\alpha_p)$ was small but the rate of increase became smaller as $(FS-\alpha_p)$ increased. This seemed to reflect the fact that polymer walls were formed rapidly in the case

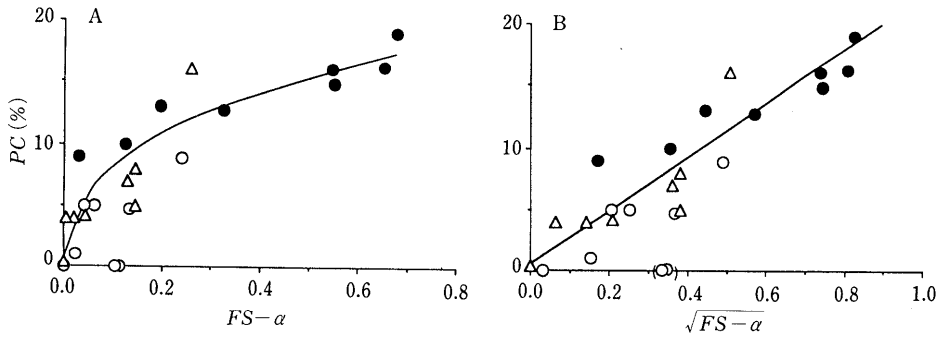

Fig. 10. Plot of *PC*s against $(FS-\alpha_p)$ (A) and $\sqrt{(FS-\alpha_p)}$ (B)

●, AS-H; △, AS-L; ○, CMEC. PCs of BA-CMEC and *p*-HB-CMEC are enclosed in brackets ( ).

of high ($FS-\alpha_p$) and further wall increase was prevented, since the wall formed should act as a barrier to drug dissolution from the core, and interfere with further reaction between hydrogen ion and polymer.

In Fig. 10B the *PC*s are plotted against the root of ($FS-\alpha_p$). As shown, fairly good linearity was obtained. The regression line was statistically calculated by the least squares method as,

$$PC=20.5\cdot\sqrt{(FS-\alpha_p)}+0.04 \qquad (r=0.849) \tag{16}$$

The deviation of BA-CMEC and *p*-HB-CMEC in Fig. 10 may be explained as follows. As shown in Table II, BA and *p*-HB have rather high pK_a values. Therefore, larger amounts of these drugs should dissolve to lower the pH around the bead surface. In the cases of AS-H and AS-L, the polymers seemed to be precipitated by even weak acidity produced by BA or *p*-HB, since their pK_p values were much higher than that of CMEC. However, in the case of CMEC, such weak acidity was not enough to produce the film wall around the beads. In this case, a greater amount of the drugs should have dissolved from the beads to lower the pH around the surface, and consequently, the drug dissolution should have been faster. Such fast dissolution might have been accompanied with a marked change in the surface state, as can be presumed from the lower recovery percent (especially in the case of *p*-HB, Fig. 5). Therefore, in such cases the assumptions used to derive the mathematical model may not hold. Thus, the regression curve in Fig. 10B was recalculated after exclusion of these two cases as,

$$PC=20.7\cdot\sqrt{(FS-\alpha_p)}+0.7 \qquad (r=0.913) \tag{17}$$

The high *r* value shows that Eq. 17 can predict the *PC* values from the intrinsic properties of the polymer and drug and is useful to identify suitable combinations of drug and enteric polymer.

References and Notes

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