Effect of Polymer Species on Microencapsulation by a Surface Neutralization Method[1)]

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Concerning the new microencapsulation method based on surface neutralization of enteric polymers, the effect of polymer species on microcapsule (MC) properties was studied. First, the encapsulation of crystal aspirin was performed at 40 °C using nine kinds of enteric polymer. It was known that cellulose derivative polymers such as hydroxypropyl methylcellulose acetate succinate (HPMCAS-L, -H), cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HP-55) and carboxymethylethylcellulose (CMEC) produce effective membrane, while synthetic acrylate polymers such as methacrylic acid–methacrylic acid methylester (Eudragit L, S) and methylacrylate–methacrylic acid copolymer (MPM-05) do not.

Then, microencapsulation was performed changing the preparation temperature from 10 to 60 °C for HPMCAS-H, -L, CAP, CMEC and Eudragit S. The polymer content in MCs generally increased by raising the temperature with the exception of HPMCAS-H. In HPMCAS-H, the polymer content was at a maximum around 40 °C. The amount of consumed core aspirin generally increased with the increase of the preparation temperature. As a rule, the amount was the least in polymers which need the least alkali for their dissolution into water. The dissolution depression of aspirin into the JP XI 1st fluid showed various tendencies due to the polymer species. Eudragit S hardly depressed at any preparation temperature. CMEC and HPMCAS-H depressed maximally around 30—50 °C. CAP depressed the most with the increase of the temperature.

In order to elucidate these phenomena, phase separation behaviors were observed for the five polymers at various pHs and temperatures. As a results, the state of the polymer phase around pH 2.0—2.5 concerned well with the properties of the MCs.

Keywords microcapsule; enteric polymer; aqueous coating; aspirin; phase separation; carboxymethylethylcellulose; *in vitro* release

Enteric microcapsules (MCs) are expected to be used as a site specific drug delivery system since they have a drug release free interval until they enter the target site.[2)] We have developed a new and simple microencapsulation method[3)] in the aqueous phase of which the principle is as follows. When crystals of a rarely water-soluble acidic drug is poured into a solution, containing an enteric polymer previously dissolved with the aid of an appropriate amount of alkali, the aqueous phase near the crystal surface changes from alkaline to acidic. Consequently, the dissolved enteric polymer becomes locally insoluble, adheres to the drug surface and forms a seamless film uniformly enveloping the crystals.

In the previous paper,[3)] we used aspirin as the core material and carboxymethylethylcellulose (CMEC) as the enteric polymer. It was known that aspirin could be encapsulated effectively by this method and that the degraded percent during the microencapsulation procedure was few. CMEC dissolves at a rather lower pH among enteric polymers. Meanwhile, the pH change such as from the stomach to the duodenum, from the proximal to the terminal ileum, or others which can be the signal for the beginning of the dissolution phase following the lag phase differs by sites.[4)] For the targeting of the specific site in the gastrointestinal tract, to select a proper polymer which dissolves at the targeting site responding to the pH change at the site is important. The enteric polymers available on the market have various dissolving pHs due to their chemical structures.

Thus, in this work, the microencapsulation of aspirin was performed using various species of enteric polymer in order to know about the applicability of our new method and get basic information about the method.

Experimental

Materials Crystalline aspirin passing through a 32 mesh sieve and remaining on a 42 mesh sieve (particle size: 350—500 μm JP grade) was used. CMEC (Freund Ind. Co., Ltd.), hydroxypropyl methylcellulose acetate succinate (HPMCAS-L, -H, Shinetsu Chem.), hydroxypropyl methylcellulose phthalate (HP-55, Shinetsu Chem.), cellulose acetate phthalate (CAP, Wako Pure Chem.), methacrylic acid–methacrylic acid methyl ester copolymer (Eudragit L, S, Rohm Pharm), methylacrylate–methacrylic acid copolymer (MPM-05, Tanabe Seiyaku) and Shellac (Gifu Shellac) were commercially available and were used without further purification.

Preparation of MCs One hundred milliliters of water and a fixed amount of an enteric polymer were placed in 200 ml beaker. The enteric polymer was dissolved by the addition of a minimum amount of 10% sodium hydroxide solution. The beaker was maintained at a constant temperature (10, 20, 30, 40, 50 or 60 °C) and crystalline aspirin was poured into the solution. The suspension was agitated for 15 min with an agitation paddle at a stirring rate of 400 rpm. The MCs formed were recovered by decantation, washed with water and dried overnight at 40 °C.

Classification of Single-Nuclear MCs The classification of MCs was carried out using JP sieves. The percentage of single nuclear MCs was estimated from MCs having diameters from 350 to 590 μm.

Determination of Aspirin and Polymer Content in MCs Single nuclear MCs (350 to 590 μm) were pulverized and aspirin in the pulverized MCs was dissolved in the 1st fluid of the disintegration test (JP XI). The concentration of aspirin was determined spectrophotometrically at 279 nm. The polymer content (%) in MCs was estimated by subtracting the aspirin content percent in the MCs from 100.

Recovery of Aspirin Recovery of aspirin was estimated from the following equation

$$\text{recovery of aspirin (\%)} = Y \times C_{AS}/A$$

where Y is the yield of MCs (g), C_{AS} is the aspirin content (%) in MCs and A is the amount of aspirin (g) used for the microencapsulation.

Dissolution Measurement Single nuclear MCs (350 to 590 μm) were used for this experiment. Dissolution percent from MCs containing 100 mg of aspirin was determined using an auto sampler (Toyama Sangyo Co., Ltd.) in 900 ml of the 1st disintegration test fluids (JP XI) by the paddle method at 37 °C and an agitation speed of 100 rpm. As aspirin might degrade to salicylic acid during the dissolution test, the wavelength of 279 nm was selected to determine the amount of released aspirin. Aspirin and salicylic acid show the same molar extinction coefficient at this wavelength in the 1st fluid.

Observation of Phase Separation Three hundred milligrams of each enteric polymer was dispersed in 10 ml of distilled water and was dissolved

by the addition of a minimum amount of 10% NaOH solution in a 30 ml test tube. The test tube was kept at a constant temperature. Then the pH was adjusted to the aimed values by the use of 10% HCl. After standing at the temperature for 2 h, the physical appearance was visually observed.

The percent of the precipitated volume was determined as $(H_P/L) \times 100$, where H_P is the height of the precipitated phase and L is the whole height.

Measurement of Viscosity[5] Three grams of each polymer were dissolved by the addition of 10% NaOH solution and adjusted to pH 7. Then, distilled water was added to make 30 ml of an aqueous polymer solution. Viscosities of the above solutions were measured using a viscometer, Visconic Type E (Tokyo Keiki Co., Ltd.), at the rotation speed of 100 rpm.

Results and Discussion

Microencapsulation by Use of Various Enteric Polymers Table I shows the properties of the nine polymers used in this study and those of the MCs prepared using these polymers at 40 °C.

As shown, cellulose derivatives (CMEC, HPMCAS-L, -H, HP-55 and CAP) produced effective membranes as known from the relatively less dissolution percents of aspirin into the 1st fluid. Synthetic acrylate polymers (Eudragit L and S) adhered on the aspirin surface, but the resultant MCs did not show good enteric properties. MPM-05 and Shellac were difficult to use since serious coagulation of MCs occurred.

TABLE I. Enteric Polymers Used in This Study and Properties of MC Prepared at 40 °C Using Each Polymer

Polymer species	Polymer properties		MC properties	
	$(pH)_{min}$ [a]	A_{NaOH} [b] (mmol)	Polymer content (%)	Dissolved %[c] at 240 min
CMEC	5.0	15.0	30	29.6
HPMCAS-L	5.0	8.3	24	43.6
HPMCAS-H	7.0	5.0	51	25.7
HP-55	5.5	16.8	14	84.5
CAP	5.7	22.0	42	35.0
Eudragit L	6.0	16.0	22	100
Eudragit S	7.0	22.0	30	90.0
MPM-05	5.0	18.5	Seriously coagulated	
Shellac	7.0	5.0	Seriously coagulated	

In the microencapsulation, 6 g of aspirin and 8 g of enteric polymer were used. *a*) The lowest pH at which each polymer dissolves. *b*) The amount of NaOH necessary to dissolve 8 g of each polymer. *c*) Percent of dissolved aspirin with dissolution test into the 1st fluid after 240 min.

A comparison of the polymer contents between the MCs prepared by using an analogous polymer group as HPMCAS-L and -H or Eudragit L and S reveals that the polymer content is higher in the polymer of which $(pH)_{min}$ is higher. This should reflect that polymer precipitation on aspirin is easier as the difference between the $(pH)_{min}$ of a polymer and the pH of an aqueous solution near the aspirin particles is wider. (The pH of the solution near the aspirin is presumed to be similar to the pH of saturated aspirin solution (about 2.3 at 40 °C)). However, this relation was not consistant when polymer groups differed as is shown in that the polymer content prepared using HPMCAS-H was greater than that prepared using Eudragit S although their $(pH)_{min}$s were identical. For this, other factors such as monomer properties, molecular weight or high order structure of each polymer would be of concern.

The surface states of MCs observed with a scanning electron microscope reveals that the surfaces were smooth and well covered in HPMCAS-H (Fig. 1A), CMEC, HP-55 and CAP. Meanwhile, the naked crystals or many large cracks were observed in the MCs of Eudragit L, S (Fig. 1B) or Shellac and the resultant MCs hardly showed enteric properties (Table I).

Effect of Microencapsulation Temperature As previously shown, the MC properties produced using CMEC were affected greatly by the preparation temperature. The most effective wall was produced at about 40 °C, although wall materials increased with the increase of preparation temperature between 10—60 °C. Thus, microencapsulation was performed at a temperature between 10 °C to 60 °C using CMEC, HPMCAS-L, -H, Eudragit S or CAP and the properties of MCs were compared.

In Fig. 2, the dissolution patterns of aspirin in the 1st fluid from the MCs prepared at various temperatures were shown for HPMCAS-H, -L and Eudragit S for examples.

HPMCAS-L showed first order-like patterns regardless of the preparation temperature. These tendencies were the same as CMEC and CAP (not shown). HPMCAS-H gave

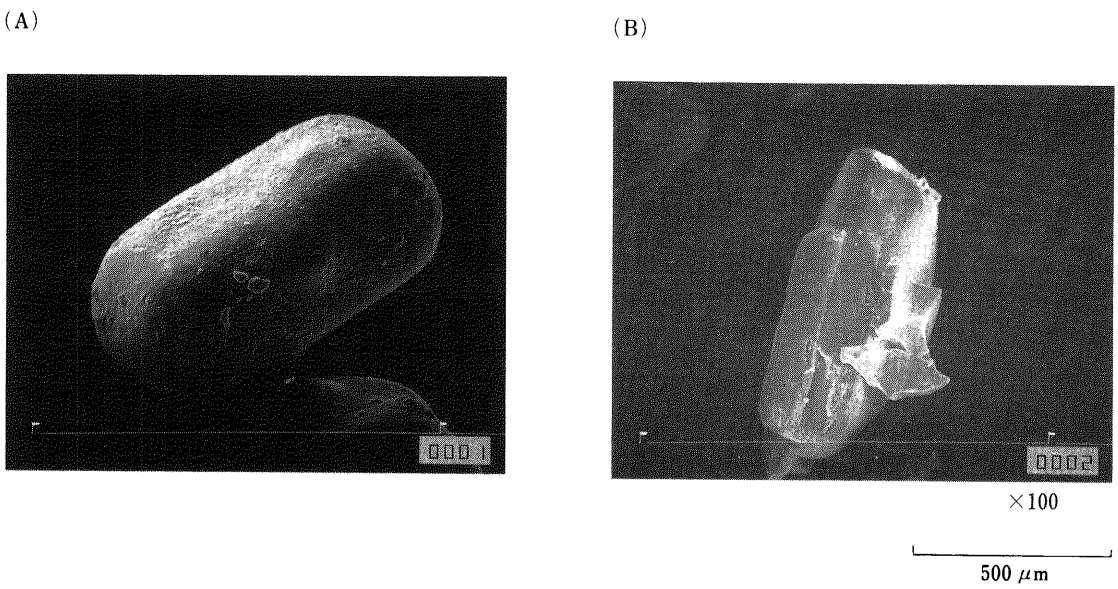

Fig. 1. The Scanning Electron Microphotographs of the MCs Prepared Using HPMCAS-H (A) and Eudragit S (B)

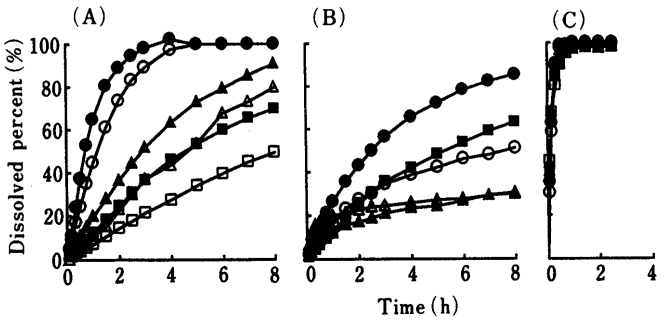

Fig. 2. Dissolution of Aspirin in the 1st Fluid from MCs Prepared at Various Temperatures Using HPMCAS-L (A), -H (B) or Eudragit S (C)
●, 10 °C; ○, 20 °C; ▲, 30 °C; △, 40 °C; ■, 50 °C; □, 60 °C.

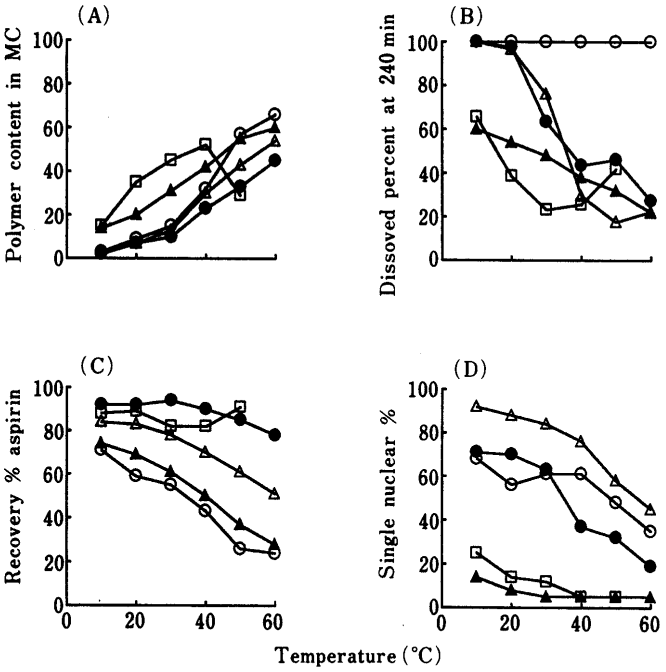

Fig. 3. Influence of the Microencapsulation Temperature on Polymer Content in MCs (A), Dissolved Percent at 240 min in the 1st Fluid (B), Recovery Percent of Aspirin as Microcapsules (C) and Single Nuclear Percentage of MCs (D)
□, HPMCAS-H; ●, HPMCAS-L; △, CMEC; ○, Eudragit S; ▲, CAP.

a first order-like pattern at 10 °C. However, the dissolution from the MCs prepared at 30 °C and 40 °C increased rapidly until 20% and thereafter hardly changed for several hours. These very slow release rates presumably reflected that the polymer films of these MCs are very dense and aspirin could not permeate through them easily. The initial rapid stage might be caused from the MCs having some small cracks or water channels in the films. The dissolution of aspirin should be very little from the MCs enveloped completely with the polymer and this resulted in the least increase in the dissolution rates after the rapid dissolution.

In the case of Eudragit S, almost all of the aspirin dissolved out very rapidly. The MCs prepared with this polymer were apt to have cracks on their surface (Fig. 1B). This could be due to their wrong film forming ability since the use of a plasticizer with the polymer could improve the enteric properties of the produced MCs.[6] Wrong wall forming ability of copolymers of methacrylic acid as Eudragit L or S was also indicated by Lehmann by means of spray coating.[7] He suggests that large amounts of

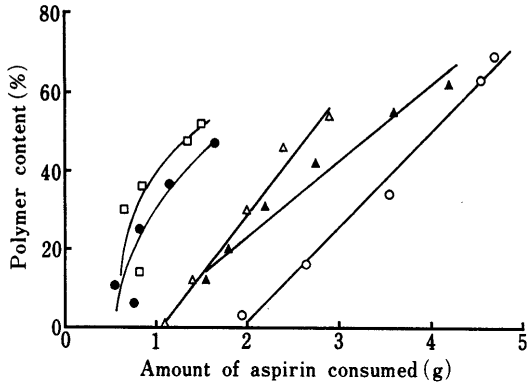

Fig. 4. Relation between Polymer Contents in MCs and Amount of Aspirin Consumed during Microencapsulation
□, HPMCAS-H; ●, HPMCAS-L; △, CMEC; ○, Eudragit S; ▲, CAP.

plasticizing agents or in combination with soft polymer dispersions are necessary for good film formation when the polymers of such high minimum film-forming temperatures are used.

In Fig. 3, polymer contents in MCs (A), dissolution rates at 240 min in the 1st fluid (B), recovery percent of aspirin (C) and percent of single nuclear MCs (D) were shown against the preparation temperature.

As shown in Fig. 3A, the polymer contents increased as the microencapsulation temperature increased with the exception of HPMCAS-H. The general increasing tendency could be caused by that the cohesive force of the enteric polymer, the release rate and dissolving amount of aspirin increased with the increase of temperature. The decrease in polymer content of the MCs prepared with HPMCAS-H at 50 °C was probably caused by the change of the polymer properties as shown later in the phase diagram (Fig. 5) or the increase in the viscosity of the bulk solutions (Fig. 6). At 60 °C, microencapsulation was impossible with this polymer since the polymer solution got twisted around the stirring bar presumably due to the Weissenberg effect.[8]

Figure 3B shows that the efficiency of the enteric coating differed by each polymer. Dissolutions were not depressed with Eudragit S at any temperature. They were hardly depressed at a low temperature with CMEC and HPMCAS-L and the depression extent was the most at around 50 °C in the former while it increased almost monotonously with the temperature in the latter. The dissolution was depressed fairly well even at a low temperature with CAP and HPMCAS-H, and the depression extent increased monotonously with the increase in temperature in the former, while it became maximum around 30 °C in the latter.

As shown in Fig. 3C, the recovery percents of aspirin in MCs decreased as the microencapsulation temperature increased when Eudragit S, CMEC or CAP was used. The recovery percents were more than 80% at all the preparation temperatures when HPMCAS-L or -H was used.

As known from Fig. 3D, coagulation increased as the temperature increased in all the polymers. The coagulation was the least with CMEC, while it was very severe with HPMCAS-H or CAP.

In Fig. 4, the relation between the polymer contents in MCs and the amount of aspirin consumed during the microencapsulation was plotted. Polymer contents in-

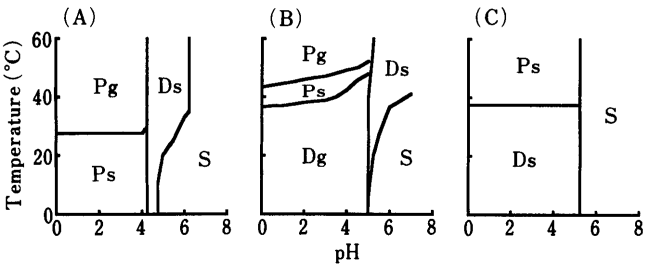

Fig. 5. Phase Diagram of Polymer Solution at Various Temperatures and pHs

A, HMPCAS-L; B, HMPCAS-H; C, Eudragit-S. Region Pg: Phase separation occurred. Polymer phase was viscous and hard gel. Aqueous phase was transparent. Region Ps: Phase separation occurred. Polymer phase was viscous and soft gel. Aqueous phase was transparent. Region Dg: Viscous and soft gel-like dispersion. Region Ds: Cloudy dispersion. Region S: Transparent aqueous solution.

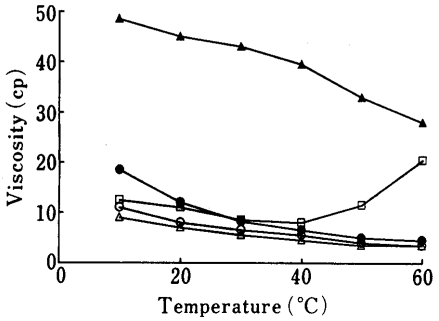

Fig. 6. Viscosity of Polymer Solutions (10%) at Various Temperature at pH 7

□, HPMCAS-H; ●, HPMCAS-L; △, CMEC; ○, Eudragit S; ▲, CAP.

TABLE II. Percent of Precipitated Volume from Each Polymer Solution after Two Hours at pH 2

	Temperature (°C)					
	10	20	30	40	50	60
CMEC	100	100	100	95	85	63
Eudragit S	100	100	85	77	70	60
HPMCAS-L	70	50	11	11	11	11
HPMCAS-H	100	100	100	75	10	10
CAP	70	70	70	70	70	70

creased linearly with the amount of the consumed aspirin in CMEC, Eudragit S and CAP and a fairly large amount of aspirin was necessary to increase wall thickness in them. As shown in Table I, these polymers required much alkali to dissolve them. While, in the case of HPMCAS-L and -H, the polymer contents in MCs increased greatly with a small change of the consumed aspirin. These polymers do not need much alkali to dissolve them (Table I) and could precipitate easily with a less acidic drug.

Phase Diagram of Each Polymer To understand the above difference in the microencapsulation with each polymer, phase separation phenomena were observed at various pHs and temperatures for some polymers.

The appearance of the polymer phase could be classified with three phases, S, D and P. The polymers were completely dissolved and the solution were transparent in S. Polymers dispersed uniformly in D. Further, the polymer appearances in D could be divided into two phase in HPMCAS-H (Fig. 5B) and CMEC (not shown). They were cloudy and had less viscous dispersion in a higher pH but were fairly viscous and had gel-like dispersion in a lower pH. We denoted the former as Ds and the latter as Dg, respectively.

In region P, polymers precipitated and a clear aqueous phase and a polymer rich phase were observed. Precipitated volumes became constant within 2 h and did not change thereafter.

In Table II, percents of precipitated volumes determined at pH 2 were shown. Since the pH of the saturated solution of aspirin was about 2.6 at 20 °C and 2.1 at 60 °C, the state of the polymers at pH 2 is presumed to reflect the state of the polymers near the aspirin crystals during the microencapsulation procedure. As is known from the small precipitation volume, HPMCAS-L and -H consisted of a very condensed polymer phase at a higher temperature. The precipitated polymers were very viscous and hard gels. Thus, such a region was denoted as Pg in the phase diagram in Fig. 5. At the lower temperature, the precipitated volume % was large and the polymer phase was less viscous and appeared like soft gels. The region was denoted as Ps.

In Fig. 6, viscosities of these polymer solutions at pH 7 were shown at various temperatures. This viscosity should reflect the polymer solutions in phase S and the situation before the microencapsulation was started.

The intermolecular force between polymers is presumed to be larger in the order of the region Pg > Ps > Dg > Ds > S. The increase of the force could also contribute to the increase in the polymer contents at a higher temperature (Fig. 3A) in addition to the increase in comsumed aspirin (Fig. 3C).

In the case of HPMCAS-L, precipitation occurred below pH 4. But the polymer phase appeared to be different between above and below 30 °C (Fig. 5A). At a higher temperature, the polymer phase was more condensed (Table II) and had gel-like hard precipitation. At a lower temperature, it had soft precipitation. Since the pH around aspirin crystals is supposed to be 2—2.5, the phase transition of the polymer at the microencapsulation procedure would be: $T<30$ °C: S→Ds→Ps, $T>30$ °C: S→Ds→Pg. The sudden decrease in the dissolution rate at around 30 °C (Fig. 2B) presumably corresponded to this phase transition.

The possible phase transition of HPMCAS-H during the microencapsulation would be (Fig. 5B): $T<10$ °C: S→Dg, $10\,°C<T<35\,°C$: S→Ds→Dg, $35\,°C<T<45\,°C$: S→Ds→Ps, $45\,°C<T$: Ds→Pg. The difference in the ending phase around 40 °C (Dg and Ps) presumably led to the highest polymer contents in MCs (Fig. 3A) and the greatest dissolution depression (Fig. 3B) at 40 °C. At more than 40 °C, the polymer phase was Pg and serious coagulation was presumably due to the too viscous properties of this phase.

The phase transition of CMEC during microencapsulation was presumed to proceed as follows from its phase diagram.[3] $T<40$ °C: S→Ds→Dg, $40\,°C<T<50\,°C$: S→Ds→Ps, $50\,°C<T$: S→Ds→Ps→Pg.

The rapid increase in the dissolution depression from 30 °C to 40 °C (Fig. 3B) presumably reflects that the ending phase of the polymer was Ps or Pg at more than 40 °C while it was Dg below 40 °C.

In Eudragit S, Pg of Dg did not appear (Fig. 3C). Even in Ds, the polymer phase was not so viscous as others. The low viscosity of Ds suggests that the side chain of a polymer

is scarcely entangled with the side chain of another polymer. The adhesion force of the polymer to the drug, which depends on the chemical and physical interactions between polymer and surface,[9] is also presumably weak.

In the case of CAP, phase transition differed from others and was very simple. The polymer phase changed from S to Pg around pH 4.5 at any temperature (not shown) and phase D was not observed at any pH and temperature. The monotonous increase in the polymer content in MCs (Fig. 3A), monotonous depression of dissolution (Fig. 3B) and recovery percent (Fig. 3C) would reflect this monotone phase transition.

As described in the above, CMEC and HPMCAS-L seemed to be useful for this method since dissolution depression, recovery % of aspirin and coagulation extent were comparatively good among the polymers used. HPMCAS-H had much advantage in forming an effective wall even at low temperature, consumed less aspirin and had good dissolution depression, though, unfortunately, the coagulating was serious. By means of some further device, it may be possible to use this polymer for this method. The study is now being performed.

References and Notes

1) A part of this work was presented at the Japanese–United States Congress of Pharmaceutical Sciences, Honolulu, Hawaii, December, 1987.
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