Effect of Plasticizer on Microencapsulation with Enteric Polymer by Surface Neutralization Method

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Concerning the microencapsulation method based on surface neutralization of enteric polymers, the effect of plasticizer was studied using methacrylic acid–methacrylic acid methyl ester copolymer (Eudragit S). This did not form an effective film on the surface of particles when used with the general surface neutralization method. Microcapsules (MCs) were prepared by suspending crystal aspirin in aqueous Eudragit S solution containing triethyl citrate (TEC) as plasticizer, and the effects of the preparation conditions on the MC properties were investigated.

The dissolution of aspirin from the MCs prepared at 60 °C in the artificial gastrointestinal fluid (JP XII 1st fluid) was increasingly suppressed as TEC concentration increased. Most effective suppression of the dissolution required a preparation temperature above 40 °C using 40% TEC, and 60 °C using 20% TEC. With the increase in preparation temperature, the polymer content in MCs increased, but the recovery percent of aspirin and the single nuclear percent of MCs decreased. The polymer content in MCs increased with decreasing crystal size of aspirin, while the membrane thickness and permeability constant were almost the same irrespective of crystal size.

The phase separation behaviors of Eudragit S solutions containing TEC were observed at various pHs and temperature and the state of the polymer phase at low pH was recognized to reflect the effect of plasticizer on the microencapsulation.

Keywords microcapsule; enteric polymer; aqueous coating; aspirin; methacrylic acid–methacrylic acid methyl ester copolymer; triethyl citrate

Microcapsules (MCs) of enteric properties are thought to be appropriate as a site specific drug delivery system since they do not release drugs until they enter the target site.[1] We have developed a new and simple microencapsulation method[2] of enteric polymers in aqueous phase the principle of which is as follows. When crystals of a rarely water-soluble acidic drug are 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.

We previously[3] used aspirin as the core material and the microencapsulation was performed with various species of the enteric polymer to learn the applicability of this MC preparation method and obtain basic information about the method. It was known that cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS) and carboxymethylethylcellulose (CMEC) produced effective membranes, while synthetic acrylate polymers such as methacrylic acid–methacrylic acid methylester (Eudragit L and S) and methylacrylate–methacrylic acid copolymer adhered to the aspirin surface, but the resultant MCs did not have enteric properties. This seemed to be due to these polymers having the wrong film formability. The wrong wall formability of Eudragit S was also indicated by Lehmann when it was used for spray coating.[4] He suggested that copolymers of methacrylic acid are brittle substances, so addition of plasticizer is essential to get an effective enteric coating without cracks or splits. The surface neutralization method, however, differs from the spray coating method in its film-forming principle and the effectiveness of plasticizer on the film formation was unknown. Thus, we performed this microencapsulation using plasticizers. As a preliminary experiment, the microencapsulation of aspirin was performed using various enteric polymers such as HPMCAS-H, HPMCAS-L, CMEC, CAP, Eudragit S and Eudragit L with the addition of TEC (40 w/w% of polymers). It was found by microscopic observation that uniform films were formed on the surface of microcapsules in Eudragit S and Eudragit L and that these MCs showed enteric properties by the dissolution test. In the other four polymers there was a great deal of coagulation and the microencapsulations were difficult. As shown previously,[3] the MCs could be obtained without any addition of plasticizer in these four polymers. The coagulation seemed to be caused by the increase of viscosity of the polymer solution with the addition of triethyl citrate (TEC). Thus, in this work, the microencapsulation was performed using Eudragit S and aspirin to determine the effect of plasticizer in detail and to clarify the mechanism of film formation.

Experimental

Materials Crystalline aspirin with particle sizes of 355—500, 250—355 and 150—250 μm were used. Eudragit S (Röhm Pharma) and TEC (Chas, Pfizer & Co., Inc.) were commercially available and were used without further purification.

Film Formability (Cap Method) The film formability of the aqueous polymer solution was evaluated using a diffusion cell consisting of receiver and donor compartments which were separate from each other. The receiver compartment was filled with 20 ml of 8% Eudragit S solution containing 2% plasticizer and the donor compartment was filled with 100 ml of 0.2 M maleic acid solution of which pH was adjusted to 2.5 by the addition of 1 N NaOH. Filter paper (5B; Toyo Roshi Co., Ltd.) was inserted and secured between the compartments. The cell was maintained at 60 °C in a water bath. After standing for 2 h, the film formed by the polymer precipitated on the filter paper was washed with water and dried overnight at 40 °C. The film was visible with the naked eye.

Preparation of MCs One hundred milliliters of water, 8 g of Eudragit S and 0.8, 1.6, 2.4 or 3.2 g of TEC (10, 20, 30 or 40% of Eudragit S, respectively) were placed in a 200 ml beaker. Eudragit S was dissolved by the addition of 22 mmol sodium hydroxide solution and pH was adjusted to 7.0. The beaker was maintained at a constant temperature (30, 40, 50

or 60 °C) and 6 g of 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 prepared 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 XII sieves. The single-nuclear percent of MCs was estimated from those having particle sizes of 355—590, 250—425 and 150—300 μm when aspirin with sizes of 355—500, 250—355 and 150—250 μm were used, respectively.

Determination of Aspirin and Polymer Content in MCs Aspirin in the pulverized MCs was dissolved in the 1st fluid of the disintegration test (JP XII). The concentration of aspirin was determined spectrophotometrically at 279 nm. The polymer content in the MCs (%) was estimated by subtracting the aspirin content in the MCs (%) from 100.

Recovery Percent of Aspirin Recovery percent of aspirin was estimated from the following Eq. 1:

$$\text{recovery percent of aspirin} = Y \cdot C_{AS}/A \quad (1)$$

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

Dissolution Measurement Single-nuclear MCs were used for this experiment. Dissolution percent from MCs containing 100 mg of aspirin was determined as previously.[3] Permeability constant (P_m) was calculated from the dissolution experiment in the 1st fluid using Eq. 2:

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

where K_{app} is the dissolution rate constant estimated from the slope of the early linear stage of the dissolution curve, V is the volume of the dissolution medium, l_m is the wall thickness of MCs and was calculated according to Koida *et al.*,[5] A_{MC} is the surface area of MCs and C_s is the solubility of aspirin in the 1st fluid.

Assay of TEC TEC was determined according to Bodmeier and Paeratakul[6] by high performance liquid chromatography (HPLC: a Shimadzu-6A apparatus equipped with a TSKgel ODS-120T column (0.46 i.d. × 25 cm) and a Shimadzu SPD-6A UV monitor (220 nm), mobile phase: 70% methanol, flow rate: 1.0 ml/min).

Observation of Phase Separation Three hundred milligrams of Eudragit S was dispersed in 10 ml of distilled water and dissolved by the addition of 825 μmol sodium hydroxide solution in a 30 ml test tube. The test tube was kept at a constant temperature. Then, the pH was adjusted to the targeted values by 10% HCl. After standing at the same temperature for 2 h, the physical appearance was checked.

Results and Discussion

Comparison of Film Formability of Plasticizers Table I shows the result of a preliminary investigation examining the fitness of four plasticizers with Eudragit S for film formability. In the experiment, pH of the donor solution (about 2.5) was almost the same as the saturated solution of aspirin.[3]

As shown, TEC gave a good film both before and after it was dried, while films by the other plasticizers were brittle, especially after drying. The films of Eudragit S are known to be generally flexible, to be less brittle, to have lower glass transition temperature and thus improved formability with the addition of plasticizer.[7] PEG and triacetin are more hydrophilic than TEC especially at high temperature (the solubility of TEC decreased with the increase in temperature),[8] and their distribution in the polymer phase could be less than TEC, and therefore not enough to form effective film. TEC was the most effective plasticizer among the four and thus was used to study the effect of preparation conditions on the MC properties in the following.

Effect of Plasticizer Amount Figure 1 shows the dissolution profiles of aspirin in the 1st fluid from the MCs preparated at 60 °C with the addition of various amounts of TEC.

With the addition of less than 10% plasticizer, the dissolution of aspirin was hardly suppressed, but with the increase of TEC concentration, especially with an addition of more than 20%, suppression was enhanced. This might be related to the minimum film forming temperature of Eudragit S. Lehmann reported that Eudragit S was a very hard polymer and that minimum film forming temperature without plasticizer could be very high but that this temperature dropped to 60 °C with the addition of 20% TEC.[4] Our result that dissolution was not suppressed by the addition of less than 20% TEC (Fig. 1) apparently coincides with his description. However, this agreement might be viewed as only accidental, since the weight percent of TEC in the polymer phase in this method was not necessarily the same as the polymer solution as described later.

The surface states of MCs observed with a scanning electron microscope revealed that many large cracks were generated in the MCs prepared without TEC (Fig. 2A), and this was consistent with the previous results.[3] Meanwhile, the surfaces were smooth and well covered by the polymers with the increased TEC added to Eudragit S solution (Fig. 2B—D).

Effect of Microencapsulation Temperature In Fig. 3, the dissolution profiles of aspirin in the 1st fluid from the MCs prepared with the addition of 20% and 40% TEC at various temperatures are shown.

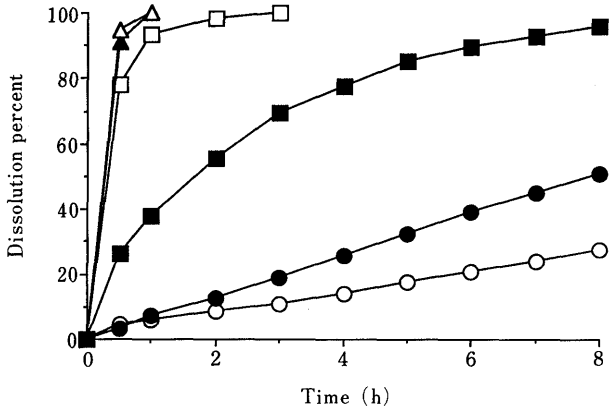

Fig. 1. Dissolution Profiles of Aspirin in the 1st Fluid from MCs Prepared at 60 °C with Varied TEC Concentrations

△, without TEC; ▲, 5%; □, 10%; ■, 20%; ●, 30%; ○, 40%. The value of each symbol is the percent of TEC of the amount of Eudragit S.

TABLE I. Comparison of Film Formability of Eudragit S with Four Plasticizers

Plasticizer	Without plasticizer	PEG 400	PEG 6000	Triacetin	TEC
Before drying	Whitish, many cracks	Whitish, some cracks	Whitish, some cracks	Whitish, some cracks	Transparent, no cracks
After drying	Whitish, many cracks	Whitish, many cracks	Whitish, many cracks	Whitish, many cracks	Transparent, no cracks

Evaluation: by cap method, at 60 °C. PEG, polyethylene glycol.

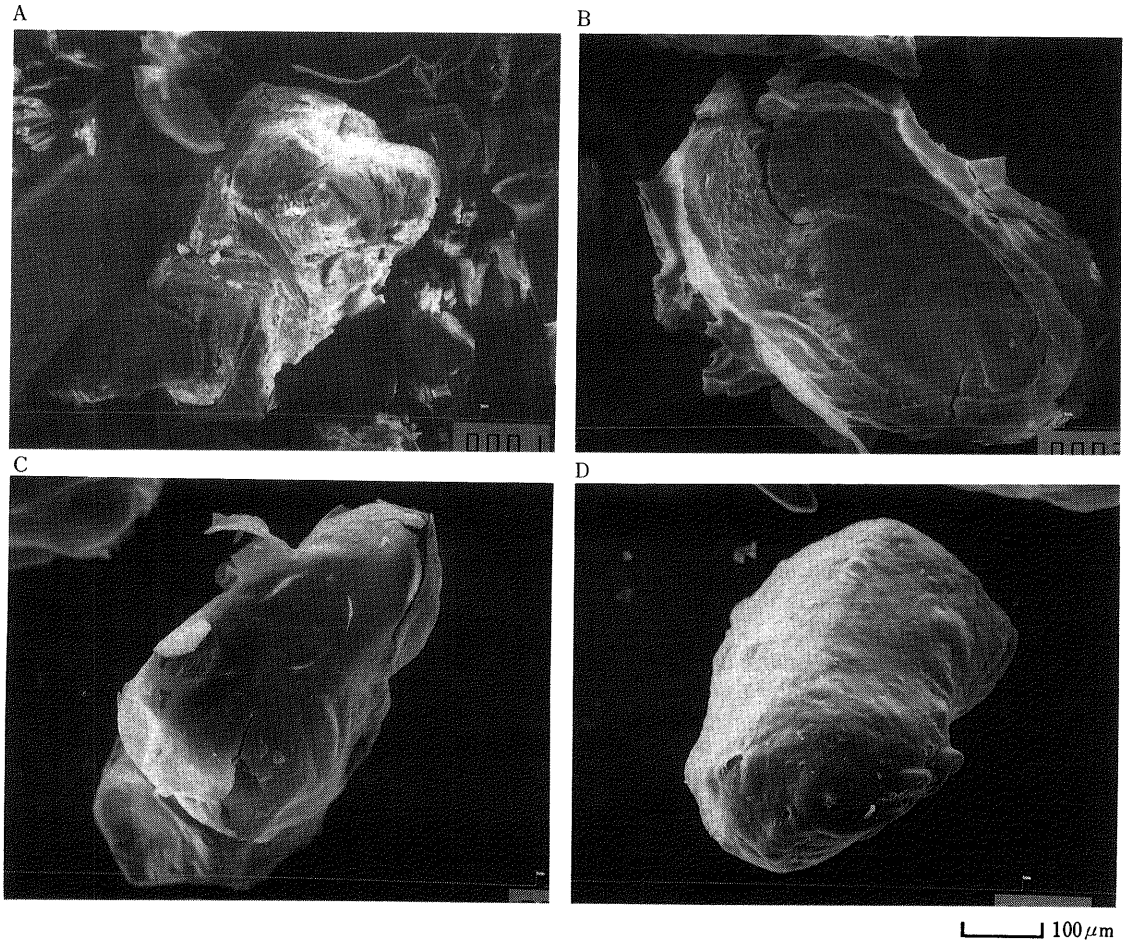

Fig. 2. Scanning Electron Microphotographs of MCs Prepared Using Eudragit S with Various TEC Concentrations
A, 0%; B, 10%; C, 20%; D, 40%.

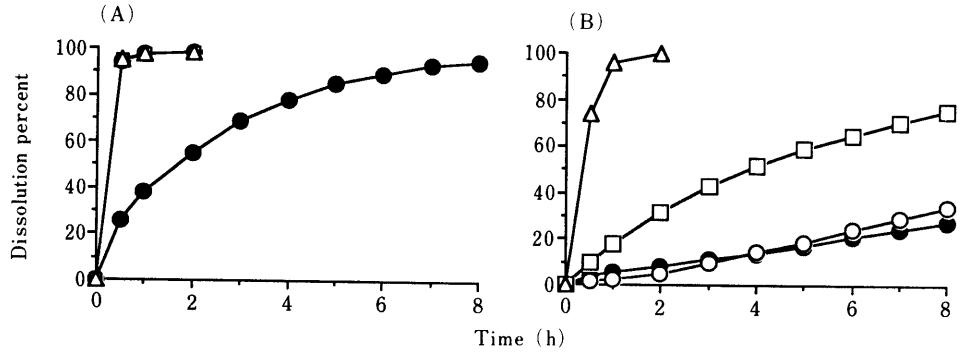

Fig. 3. Dissolution Profiles of Aspirin in the 1st Fluid from the MCs Prepared at Various Temperatures with Additions of 20% (A) and 40% TEC (B)
△, 30 °C; □, 40 °C; ○, 50 °C; ●, 60 °C.

As shown, the preparation temperature should be raised to over 60 °C in 20% TEC and to over 40 °C in 40% TEC to suppress the dissolution effectively. This suggests that the film forming temperature was lowered to 60 °C by the addition of 20% TEC, and to 40 °C by the addition of 40% TEC in this microencapsulation method.

In the case of ordinary spray coating, most of the plasticizer remains in the film and the proportion of the amount of plasticizer to the polymer in the film is almost the same as that of the coating solution.[8] However, in this method, the proportions of the ingredients in the film can be changed from that of the initial polymer solutions since not all of the polymer and the plasticizer are necessarily used for the film formation. Thus, the distribution of TEC in the microencapsulation medium was measured. That is, the aqueous solution dissolving 8 g of Eudragit S and 3.2 g of TEC in 100 ml of water was added to 22 ml of 1 N HCl to make Eudragit S precipitate. The equivalent of HCl added was equal to that of NaOH used to solubilize the polymer. The pH value of supernatant measured after the addition of HCl was about 4 and most of the carboxylic groups were considered to be undissociated. Then, the TEC concentration in the supernatant was determined. The amount of TEC in the aqueous phase was found to be

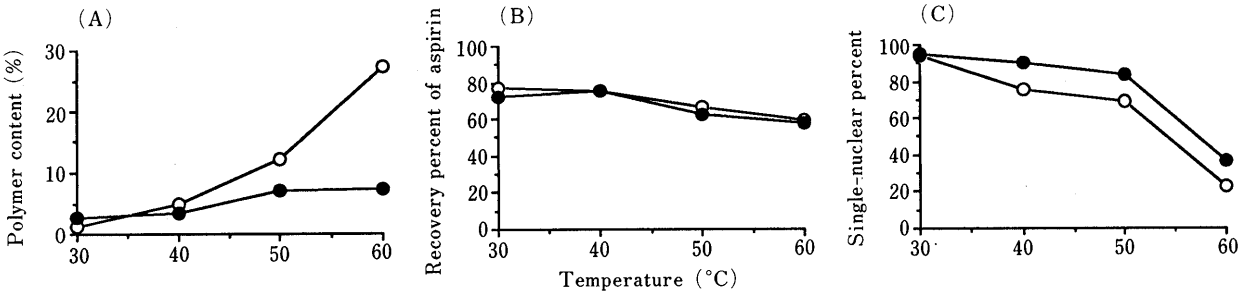

Fig. 4. Influence of Microencapsulation Temperature on Polymer Content in MCs (A), Recovery Percent of Aspirin (B) and Single-Nuclear Percent of MCs (C)

●, 20% TEC; ○, 40% TEC.

reduced to 75% of the initial amount, and thus 25% of the TEC was presumed to be distributed in the polymer phase. In this experiment, most of the polymer was precipitated, therefore, the weight percent of TEC against the polymer seemed to be only 10% in the precipitated polymer phase. In practical microencapsulation, the weight percent of TEC in the film seems nearly equal to this 10%. This value seems much smaller than that described by Lehmann: that 20% TEC was necessary to reduce film forming temperature to 60 °C. But he reported that water acted as a temporary plasticizer in the formation of anionic acrylic latex polymer film.[4] Nakagami *et al.* also reported that the glass transition temperature of free films was decreased not only by the incorporation of the plasticizer but also by the absorption of moisture.[9] Therefore, the film forming temperature in an aqueous dispersion system such as this method might be lowered with less plasticizer compared with the dry polymer. Water could interact with the polar groups of the polymer chains and weaken the intramolecular attraction between the polymer segments.

In Fig. 4, the polymer contents in MCs (A), the recovery percent of aspirin in MCs (B) and the single-nuclear percent of MCs (C) are shown against the preparation temperature.

As shown in Fig. 4A, the polymer contents in MCs increased as the microencapsulation temperature increased. The general increasing tendency could be caused by the cohesive force of the enteric polymer, the dissolving amount and the release rate of aspirin increasing with the increase of temperature. The fairly large difference in polymer content between 40% TEC and 20% TEC over 50 °C (Fig. 4A) is considered to reflect the change of polymer phase: a gel like polymer phase (Pg) was attained at about 45 °C in 40% TEC while it was attained at about 55 °C in 20% TEC as shown later (Fig. 6). The recovery percent of aspirin in MCs decreased with the increase of temperature (Fig. 4B). The coagulation extent increased as the microencapsulation temperature increased and was extreme at 60 °C but decreased greatly at below 50 °C (Fig. 4C).

Permeability Constants Determined for MCs of Various Particle Size Figure 5 shows the dissolution profiles of aspirin in the 1st fluid from the MCs prepared using aspirin of various particle sizes.

Each MC gave zero order-like profiles regardless of the core size. The dissolution was further suppressed as crystal size increased. Using the zero order dissolution rate constants, K_{app}s, the permeability constants, P_ms, were calculated using Eq. 2 and are shown in Table II.

The polymer content in MCs increased with the decrease

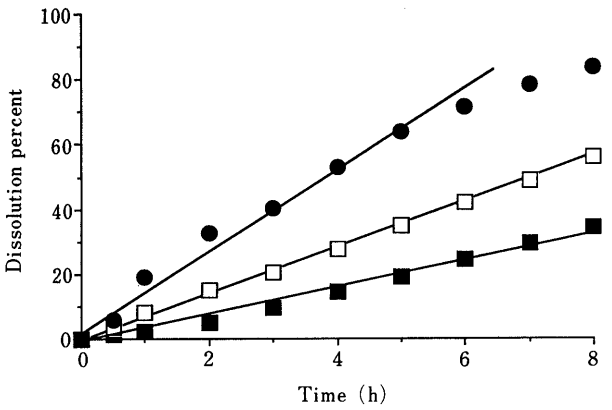

Fig. 5. Dissolution Profiles of Aspirin in the 1st Fluid from the MCs Prepared Using Various Sized Particles of Aspirin with the Addition of 40% TEC at 50 °C

■, 355—500 μm; □, 250—350 μm; ●, 150—250 μm.

Table II. Polymer Content in MC, Membrane Thickness and P_m Values of MCs Prepared Using Aspirin Particles of Various Sizes

Particle size (μm)	Polymer content (%)	Membrane thickness (μm)	P_m ($\times 10^8$ cm^2 s^{-1})
150—250	25.7	10.3	1.4
250—350	17.8	10.1	1.6
355—500	12.1	9.3	1.5

of crystal size but the membrane thickness and permeability constants were almost the same irrespective of crystal size. The same P_ms of the three MCs seemed to suggest that the films produced were fairly tough since the difference of the curvature due to the difference in particle sizes did not have much effect on the film properties. Bhagat *et al.* indicated that the coating technique using a chemical reaction at the surface enabled uniform coating of all particles,[10] while Fukumori *et al.* reported that the release rates of drug from MCs prepared by spray coating with Wurster equipment were strongly dependent on the particle size of the product.[11] The feasibility of such uniform coating is considered to be one of the major advantages of this microencapsulation method.

Consideration of the Role of Plasticizer The phase separation behaviors were observed earlier[3] for the aqueous solutions of various enteric polymers by changing their pHs and temperatures. The state of the polymer phase around pH 2.0—2.5 was known to be closely concerned with the properties of the produced MCs. Thus, the phase separation

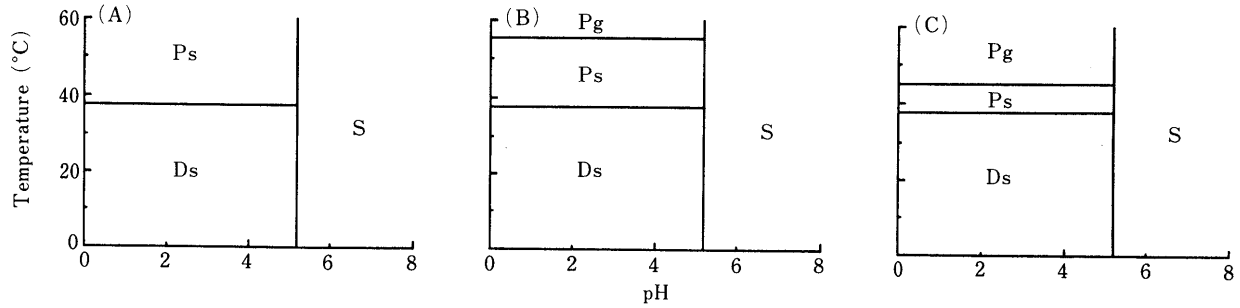

Fig. 6. Phase Diagram of Eudragit S Solution at Various Temperatures and pHs

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 Ds: cloudy dispersion. Region S: transparent aqueous solution.

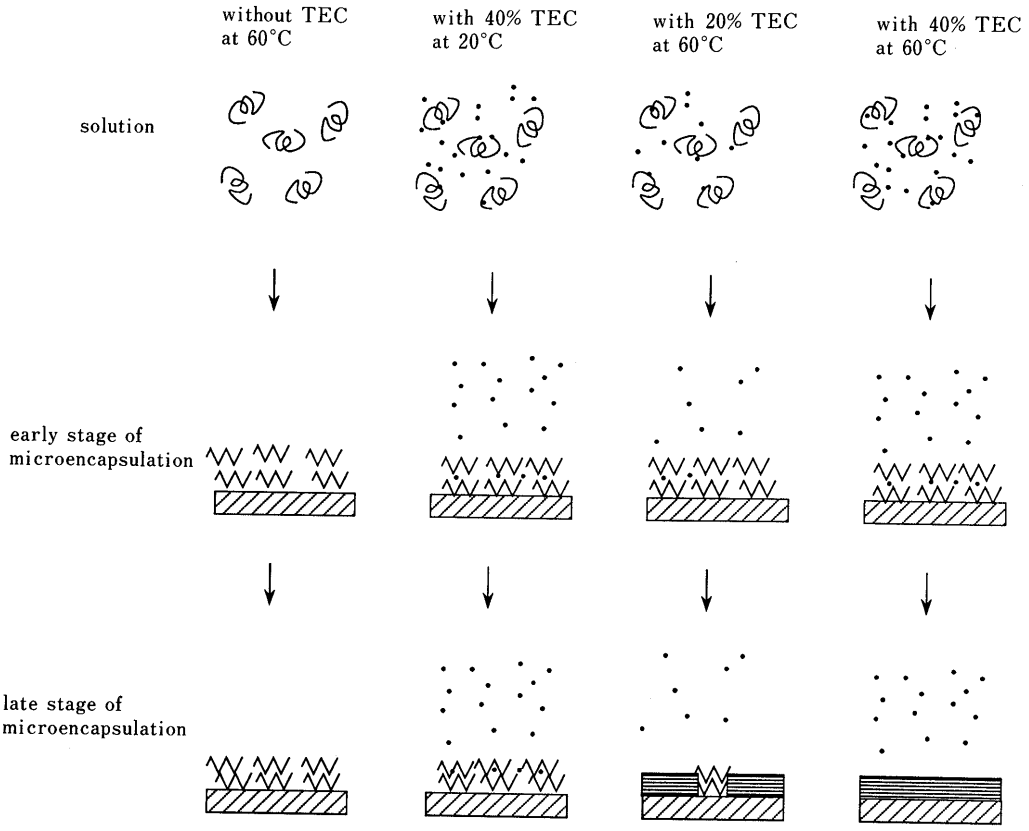

Fig. 7. Schematic Representation of the Film Forming Process of Eudragit S When MCs are Prepared by This Method with or without the Addition of TEC

▨, aspirin; ·, TEC; ⌒, solubilized Eudragit S; ∿, precipitated Eudragit S; ▤, film formed Eudragit S.

behaviors were observed for Eudragit S solutions to which TEC (40 and 20%) had been added compared to without TEC addition.

The appearance of the polymer phase could be classified into three phases, S, D and P. The polymer was completely dissolved and the solution was transparent in S; the polymer was not dissolved but dispersed uniformly in D; and the polymer was precipitated and a clear aqueous phase and a polymer rich phase were observed in P.

When pH was less than 5.2, the polymer solutions were separated; the polymer rich phase was very viscous and like hard gels at more than 55 °C with the addition of 20% TEC (Fig. 6B) and at more than 45 °C with 40% TEC (Fig. 6C). Such a region was denoted as Pg in the phase diagram. At 38—45 °C or at 38—55 °C with the addition of 40% TEC or 20% TEC, the polymer phase was less viscous and appeared like soft gels; this region was denoted as Ps. Without TEC, the Pg phase was not observed even at high temperature and low pH (Fig. 6A).

Figure 7 shows a schematic representation of the film forming process for Eudragit S in coexistence with TEC.

Without the plasticizer, Eudragit S adheres to the aspirin surface but it is difficult for the polymer to form a seamless film since the film forming temperature is high. With the addition of TEC to the Eudragit S solution, a part of TEC is precipitated together with Eudragit S on the core. It is, however, impossible to form an effective film at 20 °C even with the addition of 40% TEC. When temperature is increased but TEC is insufficient (as in the case of 60 °C and 20% TEC), film is partly formed but the polymer is still apt to have cracks. With enough plasticizer and raising the temperature to above that required for film forming

(as in the case of 60 °C with 40% TEC), the precipitated polymer can form a continuous film and consequently lead to microcapsules of good enteric properties. As shown in Fig. 3, the dissolution of aspirin was suppressed by the preparation at 60 °C or above 40 °C with the addition of 20% TEC and 40% TEC, respectively. Such temperature was nearly that at which the polymer phase changed to Pg. Therefore, the Pg phase seemed to produce "the film formed Eudragit S," while Ps and Ds phases seemed to result in "the precipitated Eudragit S."

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