Factors Affecting Dissolution Rate of Sulpiride from Tablets Coated with Polyvinylacetal Diethylaminoacetate, a Gastric-Fluid-Soluble Polymer. I. Effect of Ionic Strength of Gastrointestinal Fluids

Tsuneo HAMAGUCHI,*[,a] Denji SHINKUMA,[a] You YAMANAKA,[a] Masatoshi MIYAKE,[b] Shigeki TAMURA,[b] and Nobuyasu MIZUNO[c]

Department of Pharmacy, Hyogo College of Medicine,[a] 1-1, Mukogawa-cho, Nishinomiya-shi, Hyogo 663, Japan, Technological Development Laboratories, Fujisawa Pharmaceutical Co., Ltd.,[b] 1-6, 2-chome, Kashima, Yodogawa-ku, Osaka 532, Japan, and Faculty of Pharmaceutical Sciences, Mukogawa Women's University,[c] Koshien 9, Nishinomiya-shi, Hyogo 663, Japan. Received December 16, 1994; accepted March 13, 1995

The bioavailability of sulpiride (SP) from a tablet coated with AEA® (polyvinylacetal diethylaminoacetate), used as a gastric-fluid-soluble polymer, is very poor in low gastric acidity subjects in the fasting state but improves after food intake. To analyze the factors affecting SP bioavailability from an AEA® film-coated tablet (AEA® tablet), we prepared AEA® cast film and AEA® tablets and investigated the physicochemical properties of gastrointestinal (GI) fluids affecting the dissolution of the film coating and the dissolution rate of SP from the tablets. The dissolution time of AEA® cast film was shortened with an increase in the ionic strength of the medium, but was delayed by an increase in viscosity and addition of sodium taurocholate to the medium. The AEA® tablet showed rapid dissolution of SP at pH 4 or below but not when the pH was 5.0 or above. In pH 5.0—5.8 media, the SP dissolution rate from the tablet increased as the ionic strength (μ) of the medium rose, reaching maximum at $\mu = 0.3$. Microscopic observations and measurements of film coating thickness revealed that the increased dissolution rate of SP from the tablet with higher ionic strength ($\mu = 0.3$) was due to promotion of the dissolution of the AEA® film coating. Data from pH titration showed that increased ionic strength ($\mu = 0.3$) resulted in higher apparent dissociation, which increased the solubility of AEA® in the medium. We concluded that the ionic strength in GI fluids is one of the factors affecting the bioavailability from AEA® tablet. After food intake, the bioavailability of SP from the tablet improves, probably due to increased apparent dissociation of AEA® caused by an increase in ionic strength from the meal (*ca.* $\mu = 0.3$). This increases the dissolution rate of the film coating and thus, the dissolution rate of SP from the AEA® tablet, leading to enhanced absorption.

Key words AEA®; ionic strength; dissolution rate; film-coated tablet; dissociation; sulpiride

Many film-coated tablets are available on the market, but few studies have been done on how film coating agents affect drug bioavailability.[1,2] We previously examined the bioavailability, in healthy subjects, of commercial film-coated tablets of sulpiride (SP), which is very slightly soluble in water. The tablets coated with AEA® (polyvinylacetal diethylaminoacetate) (AEA® tablets) were markedly affected by human gastric acidity due to their pH-dependent dissolution behavior.[3-5] In low gastric acidity subjects, we found[6] bioavailability to be very poor in the fasting state but markedly improved after food intake. This showed that food intake is an important factor affecting the bioavailability of SP from this tablet.

Food generally includes large amounts of minerals (Na, K, Ca, *etc.*, particularly Na) and carbohydrates, and food intake greatly changes the physicochemical properties of gastrointestinal (GI) fluids such as ionic strength, pH, viscosity and surface tension, and also promotes GI motility. The ionic strength of the experimental meal suspension (pH 5.85) used in our *in vivo* study[6] was estimated to be about 0.33 based on osmotic pressure measurements. An increase in ionic strength of the medium is known to increase dissolution of polyelectrolytes such as AEA®[7] and CAP (cellulose acetatephthalate).[8] However, the dissolution rate of drug from microcapsules coated with a copolymer of dimethylaminoethyl methacrylate and methacrylic acid esters, used as a gastric-fluid-soluble coating in the same manner as AEA®, decreases with an increase in ionic strength.[9] Thus, it is necessary to clarify the effect of ionic strength on SP dissolution from an AEA® tablet. On the other hand, drug dissolution from a sustained-release tablet, which contained granules coated with waxy or polymeric substance, was found to decrease with an increase in the viscosity of the medium.[10] Also, drug dissolution from wax-coated beads could be increased by the addition of gall powder.[11] Thus, the marked changes in ionic strength, viscosity and surface tension caused by food intake may influence the dissolution rate of SP from AEA® tablet, although no such studies have been published. Also, for rational drug therapy, there is a need to elucidate the physicochemical factors of GI fluids which affect drug dissolution from an enteric-coated tablet such as CAP or HPMCP (hydroxypropylmethylcellulose phthalate), particularly the latter which is frequently used in pharmaceutical preparations.

AEA® is good as a protective coating of hygroscopic drugs because of its low moisture permeability,[7] and some AEA® tablets are currently being used in our hospital. The use of AEA® derivatives may be increased in the future if the disadvantages can be resolved, including problems associated with the use of organic solvents in the film coating process and the pH-dependent dissolution behavior. Thus, we need to analyze factors affecting drug bioavailability from AEA® pharmaceutical preparations to develop a rational drug therapy. We know of no work done to analyze factors affecting variation in the bio-

* To whom correspondence should be addressed.

availability of SP from AEA® tablet.

This study was done to analyze the physicochemical factors of GI fluids affecting variation in the bioavailability of SP from AEA® tablet. We prepared AEA® cast film and AEA® tablets with different coating weights to clarify the influence of pH, ionic strength, viscosity and surface tension of GI fluids on dissolution of AEA® cast film, and to determine the effects of ionic strength on the dissolution process of AEA® film coating and the dissolution rate of SP from AEA® tablet. As a reference, an HPMCP film-coated tablet was prepared. We also studied the effects of ionic strength on the apparent dissociation of AEA® in medium and discuss the relationship between the apparent dissociation and solubility of AEA®.

Experimental

Materials SP was supplied by Fujisawa Pharmaceutical Co., Ltd. AEA® was supplied by Sankyo Co., Ltd. HPMC (hydroxypropylmethylcellulose 2910), HPC (hydroxypropylcellulose) and HPMCP 200731 were supplied by Shinetsu Chemical Co., Ltd. All other materials were of reagent grade.

Determination of Osmotic Pressure of a Meal The components of the experimental meal for this study were the same as those of our previous *in vivo* study[6]: 60 g of boiled egg, 130 g of bread, 10 g of margarine, 15 g of processed cheese, 20 g of orange marmalade and 200 ml of water. These components were mixed in a mixer, and 20 ml of the suspension was poured into a 30-ml glass-stoppered centrifuge tube. After shaking for 15 min at 50 rpm and centrifugation, the osmotic pressure of the supernatant was determined with an osmotic pressure meter (Advanced Digimatic Osmometer Model 302). The osmotic pressures of the meal suspension, 0.1 M NaCl, 0.15 M NaCl and 0.3 M NaCl solutions were 605, 179, 275 and 538 mOsm, respectively. The ionic strength of the meal suspension was estimated from the osmotic pressures of the NaCl solutions (0.1 M, 0.15 M (0.9%), 0.3 M), and was *ca.* 0.33 with pH of 5.85.

Preparation of Cast Film Cast films of polymers were prepared by casting solvent with methylene chloride–ethyl alcohol (1 : 1, v/v) into a petri dish 8.9 cm in diameter and 1 cm deep. Each polymer was dissolved in methylene chloride or methylene chloride–ethyl alcohol (1 : 1, v/v) at a concentration of 10% (w/v). The film solution (5 ml) was distributed in the petri dish. After casting, the solution was placed so that the solvent could evaporate at room temperature for 5 h.

Measurement of Cast Film Thickness Cast film thickness was determined at ten different positions on cut film (1.5 × 1.5 cm) using a micrometer, "Peacock" upright dial gauge R1-1A (Ozaki Seisakusho Co., Ltd.). Cast film thicknesses (mean ± S.D.) of AEA®, HPMCP, HPMC and HPC were 70.6 ± 7.2, 64.2 ± 15.6, 66.6 ± 9.2 and 67.6 ± 10.8 μm, respectively.

Preparation of Film-Coated Tablet A plain tablet from the manufacturing process for a commercial SP film-coated tablet (Dogmatil®, 100 mg/tab., lot no. 2060) was used as the core tablet for preparation of the film-coated tablets. The coating solution for the AEA® tablet contained AEA® (8% (w/v)) in ethyl alcohol–water (50 : 50, v/v). AEA® tablets with different coating weights (0.81, 3.12, 6.20, 9.88 mg/tab.) were produced with a Hi-coater (Freund, HCT-55). The coating solution for HPMCP tablet contained HPMCP (8% (w/v)) and cetanol (5% (w/w) to the polymer) in ethyl alcohol–water (80 : 20, v/v). HPMCP film-coated tablet (HPMCP tablet) of usual coating weight (6.54 mg/tab.) with an enteric coating was prepared using the Hi-coater. The process parameters were as follows: spray rates were 40—50 ml/min; inlet air temperature was kept at 45—50 °C; exhaust air temperature was kept at 30—40 °C. Twenty tablets were weighed before and after coating for calculation of mean coating weight. The HPMCP tablets prepared met the requirements of the JP XII disintegration test for enteric-coated tablets.

Measurement of Film Coating Thickness The film coating was peeled from a film-coated tablet using a sharp knife, and fragments of the core tablet which adhered to the film coating were carefully removed using a pincette. These coating films of AEA® and HPMCP were washed in pH 7 buffer solution and the 1st fluid of JP XII, respectively, and dried at 30 °C for 8 h. The film coating was kept in a desiccator at 25 °C for 2 weeks. The thickness of the film coating was determined at six different places using the "Peacock" upright dial gauge R1-1A micrometer. The film coating thicknesses (mean ± S.D.) of AEA® tablets with different coating weights were as follows: 0.81 mg/tab., 17.9 ± 2.5 μm; 3.12 mg/tab., 31.25 ± 1.5 μm; 6.20 mg/tab., 53.0 ± 3.2 μm; 9.88 mg/tab., 82.5 ± 3.9 μm. The film coating thickness (mean ± S.D.) of the HPMCP tablet (6.54 mg/tab.) was 63.4 ± 4.3 μm. The film coating thickness (mean ± S.D.) of the commercial AEA® tablet used in the previous *in vivo* study[6] was 34.4 ± 3.5 μm.

Determination of AEA® Solubility AEA® cast film prepared as described above was cut very carefully to 1 × 1 cm and accurately weighed. The AEA® cut film was placed in a glass vessel containing 200-ml portions of various solutions with stirring until the AEA® cut film no longer dissolved in them. The temperature was kept at 37 °C. The solubility of AEA® in the medium was calculated as the sum of the weight of the AEA® dissolved in the medium.

Measurement of Dissolution Time of Cast Film The measurements of dissolution times of cast films of polymers in media were carried out with a JP XII disintegration test apparatus. Cast films of polymers which were prepared as described above were cut very carefully to 1.5 × 1.5 cm. A thread 10 cm long was attached to one end of the cut film and another thread 10 cm long to the other end. The film was then fixed in the middle point of the glass tube of the basket-rack assembly of the disintegration test apparatus using the threads. The temperature was kept at 37 °C. The media used were 900 ml of 1st fluids ($\mu = 0.03, 0.3, 0.5$), pH 4 acetate buffer solutions (0.1 M; $\mu = 0.07, 0.3, 0.5$), pH 5 phosphate buffer solutions (0.05 M; $\mu = 0.05, 0.3, 0.5$), pH 5.8 phosphate buffer solutions (0.05 M; $\mu = 0.06, 0.3, 0.5$), and pH 6.5 phosphate buffer solutions (0.05 M; $\mu = 0.08, 0.3, 0.5$). Ionic strengths of $\mu = 0.3$ and 0.5 were adjusted with NaCl. The dissolution time of the cast film of the polymer was the time required for the cut film to disappear into the medium.

Determination of Dissolution Rate of SP from Film-Coated Tablet The dissolution test was carried out using the JP XII disintegration test apparatus according to the paddle method. The dissolution media were 900 ml of 1st fluids ($\mu = 0.03, 0.3$), pH 4 acetate buffer solutions (0.1 M; $\mu = 0.07, 0.3$), pH 5 phosphate buffer solutions (0.05 M; $\mu = 0.05, 0.1, 0.3, 0.5, 1.0$), pH 5.8 phosphate buffer solutions (0.05 M; $\mu = 0.06, 0.3$), and pH 6.5 phosphate buffer solutions (0.05 M; $\mu = 0.08, 0.3$). Ionic strengths of the media ($\mu = 0.1, 0.3, 0.5, 1.0$) were adjusted with NaCl. The T_{50} value, defined as the time required for 50% of SP to dissolve in the dissolution medium, was determined directly from the dissolution profile–time curve.

Measurement of Medium Penetration into Tablet A film-coated tablet was put into 5 ml of medium in a test tube, then removed periodically. The medium adhering to its surface was wiped off with a filter paper, and the tablet was weighed. The medium uptake by the film-coated tablet was calculated from the change in weight of the film-coated tablet with time. The temperature was kept at 37 °C. The media used were pH 5 phosphate buffer solutions (0.05 M; $\mu = 0.05, 0.3$) and pH 6.5 phosphate buffer solutions (0.05 M; $\mu = 0.08, 0.3$). The ionic strength of the medium of $\mu = 0.3$ was adjusted with NaCl.

Measurement of pH Titration Curve of AEA® Aqueous Suspension An aqueous suspension of AEA® (100 mg/ml) was directly subjected to pH titration because of the basic insolubility of the polymer. It takes 3—4 min to reach pH equilibrium, and continuous titration is not possible. Thus, the titration curve was obtained by measuring the equilibrium pH of the AEA® suspension after adding 0.05 N HCl solution to the AEA® suspension using a pH meter (type M-7, Hitachi-Horiba). The media used were distilled water and 0.3 M NaCl solution. The temperature was kept at 25 °C and 37 °C. The apparent pK_a was determined directly from the graph.

Results and Discussion

Factors Affecting Dissolution Time of Cast Polymer Films The effects of changes in physicochemical properties (pH, ionic strength, viscosity and surface tension) of GI fluids on dissolution times of cast films of various polymers were studied. The pH of the medium had markedly different effects on the dissolution times of cast films of various polymers. These results were similar to the descriptions in catalogs of coating agents.[7,12] The dissolution times of cast films of polyelectrolytes such as AEA® and HPMCP depended on the medium pH. The

Table 1. Effect of Ionic Strength on Dissolution Times of Cast Films

pH	Dissolution time (min)														
	AEA®				HPMCP				HPMC			HPC		
	Ionic strength (μ)				Ionic strength (μ)				Ionic strength (μ)			Ionic strength (μ)		
	0.03—0.08	0.1	0.3	0.5	0.03—0.08	0.1	0.3	0.5	0.03—0.08	0.1	0.3	0.03—0.08	0.1	0.3
1.2	5.2±1.1	4.7±1.6	5.5± 2.6	16.3±4.5	240<	240<	240<	240<	4.4±0.6	2.9±0.6	7.2±2.6	33.0±2.9	28.3±2.4	21.3±2.5
4.0	6.9±0.3	4.8±0.3	3.1± 0.1	20.3±2.5	240<	240<	240<	240<	4.3±0.6	4.4±0.4	6.5±0.1	32.9±1.4	15.5±0.2	27.5±5.0
5.0	151.2±7.0	35.6±2.3	23.1± 0.4	240<	240<	240<	240<	240<	5.4±1.7	5.6±0.9	4.8±1.2	29.8±2.7	32.9±4.7	29.2±2.7
5.8	240<	240<	124.9±13.5	240<	130.2±3.9	94.2±6.0	63.8±6.4	29.3±0.7	—	—	—	—	—	—
6.5	240<	240<	240<	240<	15.2±0.4	20.4±2.9	14.9±0.4	14.3±2.9	5.3±0.8	6.9±2.1	5.2±1.1	31.2±1.8	17.5±1.0	26.4±2.9

The dimensions of the cast films were 1.5 cm by 1.5 cm with thicknesses (μm) of : AEA®, 70.6; HPMCP, 64.2; HPMC, 66.6; HPC, 67.6. —, not tested. Each value represents the mean±S.D. of three determinations.

Table 2. Effect of Sucrose Concentration on Dissolution Times of Cast Films

pH	Dissolution time (min)									
	AEA®			HPMCP			HPMC		HPC	
	Sucrose concentration			Sucrose concentration			Sucrose concentration		Sucrose concentration	
	0%	10%	30%	0%	10%	30%	0%	10%	0%	10%
1.2	5.2±1.1	4.3±0.8	4.8±1.1	240<	240<	240<	4.4±0.6	4.4±0.9	33.0±2.9	43.5±2.3
4.0	6.9±0.3	4.7±0.5	16.2±3.9	240<	240<	240<	4.3±0.6	4.4±1.0	32.9±1.4	47.6±2.7
5.0	151.2±7.0	240<	240<	240<	240<	240<	5.4±1.7	4.5±1.2	29.8±2.7	38.5±3.8
6.5	240<	240<	240<	15.2±0.4	18.8±2.2	31.8±1.9	5.3±0.8	4.4±0.3	31.2±1.8	47.6±3.2

The dimensions of the cast films were 1.5 cm by 1.5 cm with thicknesses (μm) of: AEA®, 70.6; HPMCP, 64.2; HPMC, 66.6; HPC, 67.6. Each value represents the mean±S.D. of three determinations.

AEA® cast film dissolved rapidly at pH 4.0 or below but not when the pH was 5.0 or above, indicating that the apparent critical dissolution pH of this film is 5.0. The HPMCP cast film dissolved rapidly at pH 6.5 but not when the pH was 5.8 or below, indicating that its apparent critical dissolution pH is 5.8. In contrast, the dissolution of cellulose derivatives such as HPMC and HPC did not depend on the medium pH.

Table 1 shows that the effect of ionic strength of the medium on the dissolution times of cast films markedly differed among the polymers. The dissolution times of cast films of AEA® and HPMCP were greatly affected by an increase in the ionic strength but those of HPMC and HPC were not. When ionic strength increased to 0.3, the dissolution time of AEA® cast film at pH 5.0 markedly decreased and its apparent critical dissolution pH shifted from pH 5.0 to pH 5.8. However, when the ionic strength increased to 0.5, AEA® cast film did not dissolve at pH 5.0 or above. The variation in dissolution time of the film with ionic strength may have been due to an increase in the apparent dissociation and salting out. Similarly, the dissolution time of HPMCP cast film in pH 5.8 was noticeably shortened when the ionic strength of the medium rose to 0.5. This may have been due to an increase in the apparent dissociation of HPMCP. The effect of ionic strength on the dissolution of HPMCP cast film was similar to that described for CAP cast film.[8]

Table 2 shows the effect of the sucrose concentration of the medium on the dissolution times of cast films of various polymers. An increase clearly delayed the dissolution times of cast films of AEA®, HPMCP and HPC but did not affect that of HPMC cast film, since the viscosity of the medium was increased by an increase in the sucrose concentration of the medium.[10] The delay in the dissolution times of AEA®, HPMCP and HPC cast films may have been due to this increase in medium viscosity.

Table 3 shows that sodium taurocholate in the medium caused a delay of the dissolution time of AEA® cast film but did not affect those of HPMCP and HPMC cast films. The dissolution time of HPC cast film was significantly shortened by the presence of sodium taurocholate in the medium.

Changes in the physicochemical properties of GI fluids affected the dissolution times of HPMC and HPC only slightly or not at all. Thus, drug bioavailability from pharmaceutical preparations coated with these two polymers should not be influenced by physicochemical changes in GI fluids. On the other hand, the dissolution times of AEA® and HPMCP cast films in the region of the apparent critical dissolution pH were affected by these changes. Thus, drug bioavailability from pharmaceutical preparations coated with AEA® and HPMCP can be expected to vary with the physicochemical properties of GI fluids, in the same manner as with pH changes.

Effect of Ionic Strength on Dissolution Rate of SP from AEA® Tablet On the basis of dissolution time data of AEA® cast film, we examined the effect of the ionic strength of GI fluids on the dissolution rate of SP from AEA® tablet. GI motility was promoted by food intake. Also, Ogata *et al.* reported[13] that the bioavailability of chloramphenicol from powder and tablet after food intake agreed with the results of a dissolution test with a strong mechanical destructive force. This led us to conduct the

Table 3. Effect of Sodium Taurocholate on Dissolution Times of Cast Films

pH	Dissolution time (min)							
	AEA®		HPMCP		HPMC		HPC	
	Sodium taurocholate concentration		Sodium taurocholate concentration		Sodium taurocholate concentration		Sodium taurocholate concentration	
	0 mM	10 mM	0 mM	10 mM	0 mM	10 mM	0 mM	10 mM
1.2	5.2±1.1	6.5±0.7	240<	240<	4.4±0.6	4.7±0.5	33.0±2.9	21.1±1.3[a]
4.0	6.9±0.3	7.6±0.8	240<	240<	4.3±0.6	4.1±0.7	32.9±1.4	18.3±1.5[a]
5.0	151.2±7.0	240<	240<	240<	5.4±1.7	3.5±0.5	29.8±2.7	19.6±2.3[a]
5.8	240<	240<	130.2±3.9	127.0±11.1	—	—	—	—
6.5	240<	240<	15.2±0.4	12.7± 0.8	5.3±0.8	6.8±0.7	31.2±1.8	19.0±0.4[a]

The dimensions of the cast films were 1.5 cm by 1.5 cm with thicknesses (μm) of: AEA®, 70.6; HPMCP, 64.2; HPMC, 66.6; HPC, 67.6. *a*) Significantly different from sodium taurocholate concentration of 0 mM, $p<0.05$ (Student's *t*-est). Each value represents the mean±S.D. of three determinations.

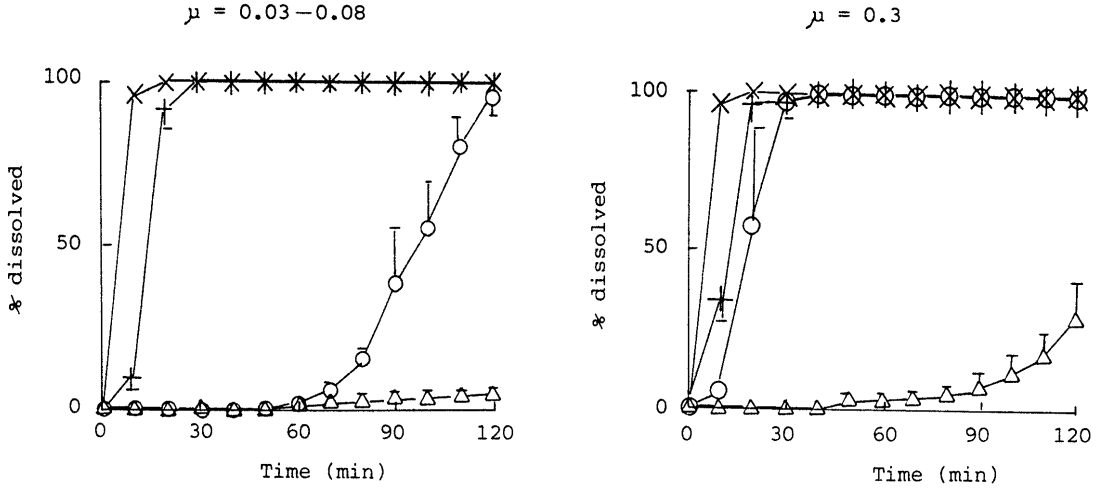

Fig. 1. Effect of Ionic Strength on Dissolution Profiles of Sulpiride from AEA® Film-Coated Tablet Using the Disintegration Test Method with Solutions of Various pH

pH: 1.2, ×; 5.0, +; 5.8, ○; 6.5, △. Coating weight of AEA®: 3.12 mg/tab. Each point represents the mean±S.D. of three determinations.

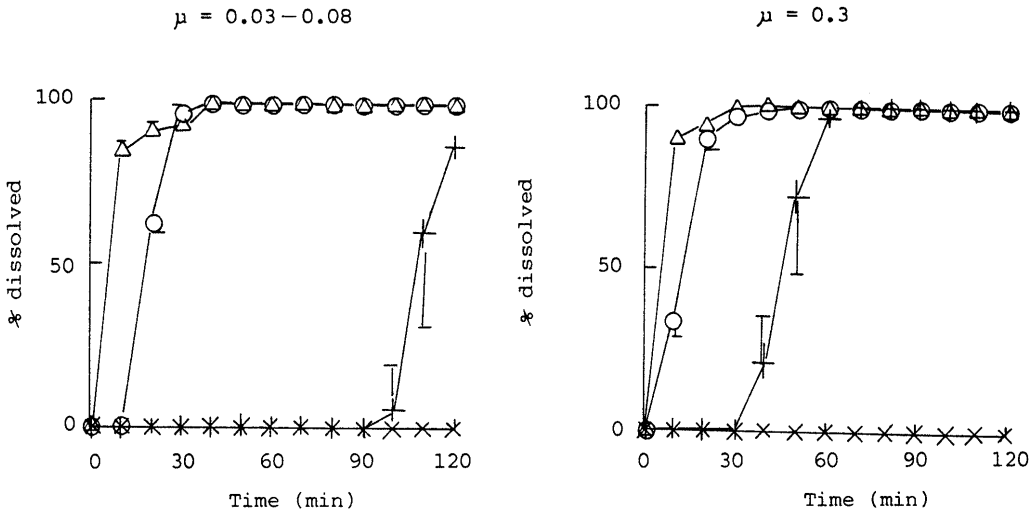

Fig. 2. Effect of Ionic Strength on Dissolution Profiles of Sulpiride from HPMCP Film-Coated Tablet Using the Disintegration Test Method with Solutions of Various pH

pH: 1.2, ×; 5.0, +; 5.8, ○; 6.5, △. Coating weight of HPMCP: 6.54 mg/tab. Each point represents the mean±S.D. of three determinations.

dissolution test for AEA® tablet, with HPMCP tablet as the reference, using a disintegration test method which had a stronger mechanical destructive force than other dissolution test methods.[14]

Figure 1 shows the dissolution profiles of SP from AEA® tablet having a coating weight of 3.12 mg/tab. and a film coating thickness similar to that of the commercial AEA® tablet used in our previous *in vivo* study.[6] Figure 2 shows

the dissolution profiles of SP from HPMCP tablet with the usual coating weight of 6.54 mg/tab., which was effective as an enteric coating.

As can be seen from Fig. 1, the dissolution profile of SP from AEA® tablet depended on the medium pH, with dissolution being very fast at pH 5.0 or below but markedly delayed at pH 5.8 or above due to the long lag time of SP dissolution. When ionic strength increased to 0.3, SP dissolution from AEA® tablet notably increased at pH 5.0 and 5.8, and a promotion at pH 6.5 began after 90 min due to shortening of the lag time of SP dissolution. The dissolution of SP from HPMCP tablet depended on the medium pH, and a similar ionic strength effect was observed on the dissolution rate of SP from this tablet (Fig. 2). These results agreed well with those obtained from AEA® and HPMCP cast films as shown in Table 1. Thus, the lag times of SP dissolutions from the two types of tablets were materially shortened by an increase in ionic strength of the medium.

Our results show that the dissolution rates of SP from AEA® and HPMCP tablets were definitely affected by the pH and ionic strength of the medium. The effect of ionic strength on SP dissolution from film-coated tablet was determined by a dissolution test using the paddle method[14] which has a weaker mechanical destructive force than the disintegration test method (Figs. 3, 4). In medium of $\mu=0.05$—0.06, the dissolution rate of SP from AEA® tablet markedly decreased at pH 5.0 or above and its dissolution profile showed an apparent zero-order rate (Fig. 3A). The dissolution rate of SP from AEA® tablet in pH 5.0 increased when the medium ionic strength increased from 0.05 to 0.3 (Fig. 3B), and the percent dissolved during 1 h was 98% in medium of $\mu=0.3$ compared with 5.9% in medium of $\mu=0.05$; about 14% SP was dissolved after 1 h in medium of $\mu=0.5$. Therefore, the dissolution rate of SP from AEA® tablet in pH 5.0 reached maximum when the ionic strength was 0.3 (Fig. 3B). A similar ionic strength effect was observed for HPMCP tablet, and the dissolution pattern was found to be related to the disintegration of HPMCP film coating (Fig. 4B). The dissolution rate of SP from HPMCP tablet in pH 5.0 reached maximum when the ionic strength was 0.5.

Thus, the ionic strength of the medium contributed to shortening the lag time of dissolution of the HPMCP tablet when the ionic strength rose from 0.05 to 0.5 and also to

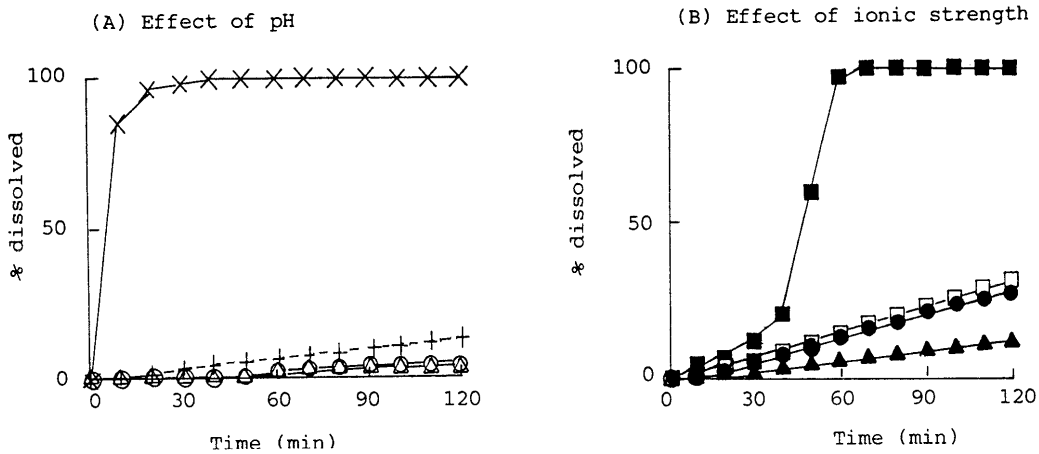

Fig. 3. Effect of pH (A) and Ionic Strength (B) on Dissolution Profiles of Sulpiride from AEA® Film-Coated Tablet Using the Paddle Method

pH: 1.2, ×; 5.0, +; 5.8, ○; 6.5, △. Ionic strength (μ): 0.05, ▲; 0.1, ●; 0.3, ■, 0.5, □. Coating weight of AEA®: 3.12 mg/tab. Each point represents the mean of three determinations.

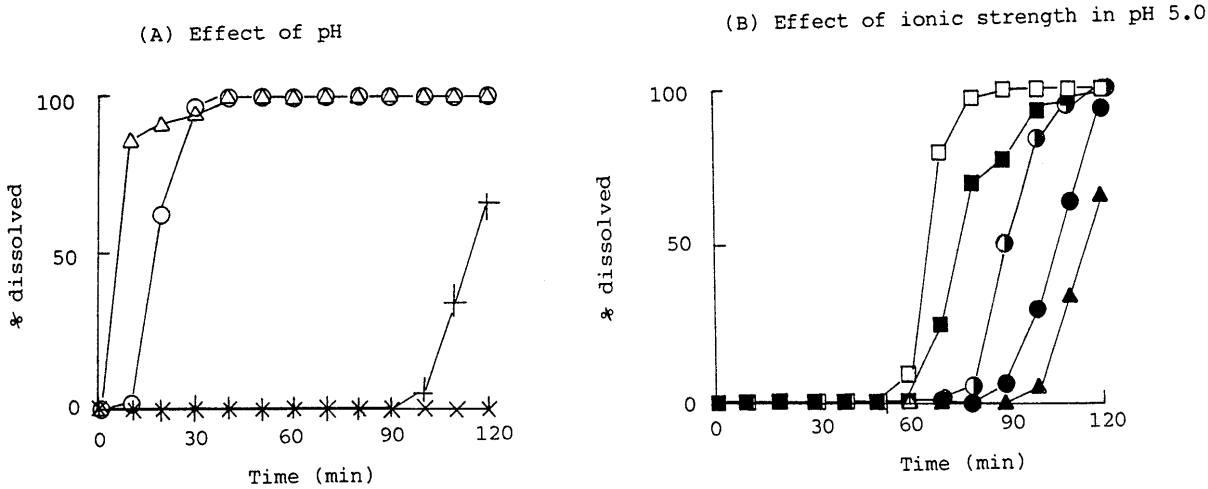

Fig. 4. Effect of pH (A) and Ionic Strength (B) on Dissolution Profiles of Sulpiride from HPMCP Film-Coated Tablet Using the Paddle Method

pH: 1.2, ×; 5.0, +; 5.8, ○; 6.5, △. Ionic strength (μ): 0.05, ▲; 0.1, ●; 0.3, ■; 0.5, □; 1.0, ◑. Coating weight of HPMCP: 6.54 mg/tab. Each point represents the mean of three determinations.

increasing the dissolution rate of SP from AEA® tablet when the ionic strength rose from 0.05 to 0.3. The effect of the mechanical destructive force on SP dissolution from film-coated tablet differed between AEA® and HPMCP tablets; it did not affect the dissolution from HPMCP tablet but markedly increased that from AEA® tablet. Clearly, the dissolution rate of SP from AEA® tablet was increased by increases in the mechanical destructive force and ionic strength of the medium ($\mu=0.3$) in the same manner as with the pH changes. Also, in the case of HPMCP tablets, the factors affecting SP dissolution were pH and the ionic strength of the medium. Since the meal suspension pH was 5.85, the gastric fluid pH after food intake in low gastric acidity subjects could be expected to range between 5.0 and 6.0. Thus, our results indicated that the bioavailabilities of AEA® and HPMCP tablets in apparent critical dissolution pH values vary greatly with the ionic strength of the meal ingested.

In the paddle method, which inflicts a weak mechanical destructive force, the dissolution profiles of SP from AEA® tablet at pH 5.0 or above showed an apparent zero-order rate (Fig. 3A), indicating that the medium was able to penetrate into the tablet. The change in film structure affecting the penetration rate of medium into AEA® tablet would therefore affect the dissolution rate of SP from it. Also, the dissolution time of AEA® cast film was shortened by an increase in ionic strength (Table 1). Thus, the increase in the SP dissolution rate from AEA® tablet with rising ionic strength may have been due to a change in film structure, such as a decrease in film thickness caused by dissolution of the AEA® film coating.

Effect of Change in Film Structure on Dissolution Rate of SP from AEA® Tablet To clarify the effect of differences in film structure, such as thickness, on the dissolution rate of SP, we prepared AEA® tablets with different coating weights and examined the effect of ionic strength on SP dissolution rates from them and the medium uptake by the tablet in pH 5.0 buffer solutions with $\mu=0.05$ and 0.3. The results of the dissolution test are shown in Fig. 5. In medium of $\mu=0.05$, the dissolution percentages for AEA® tablets with coating weights of 0.81, 3.12, 6.20, and 9.88 mg/tab. after 2 h were about 25, 13, 10 and 6%, respectively. In medium of $\mu=0.3$, the T_{50} values for AEA® tablets with coating weights of 0.81, 3.12, 6.20 and 9.88 mg/tab.were 33, 47, 52 and 68 min, respectively. Thus, the dissolution rate of SP from AEA® tablet was notably enhanced by an increase in ionic strength. Also, these rates in pH 5.0 buffer solutions of $\mu=0.05$ and 0.3 decreased with an increase in the coating weight of AEA®. These results indicated that the dissolution rate of SP from AEA® tablet is closely related to film thickness.

The results of the medium penetration test are shown in Fig. 6. The medium uptake by AEA® tablet (3.12, 9.88 mg/tab.) increased with an increase in the ionic strength of the medium. The rate for a tablet with a low coating weight was greater than that with a high one, and the amount of medium penetration into AEA® tablet with low coating weight was saturated after 20—30 min. Observations from the medium penetration test revealed that AEA® tablets with coating weights of 3.12 and 9.88 mg/tab. had become larger after 60-min immersion

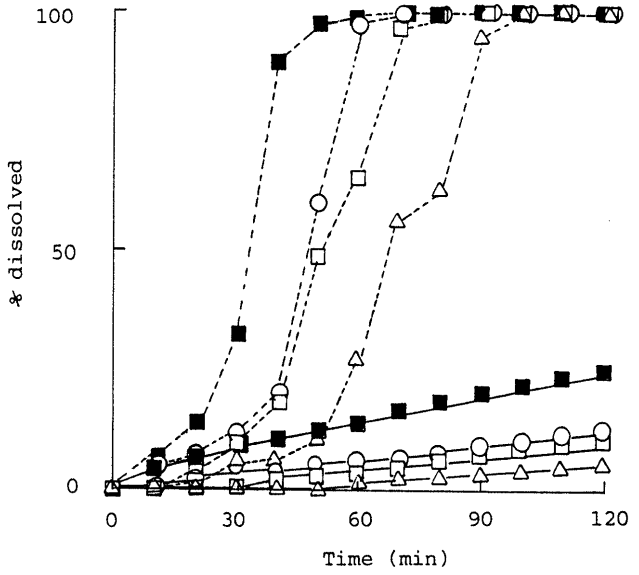

Fig. 5. Effect of Ionic Strength on Dissolution Profiles of Sulpiride from AEA® Film-Coated Tablets with Various Coating Weights Using the Paddle Method with pH 5.0 Buffer Solution

Coating weight of AEA® (mg/tab.): 0.81, ■; 3.12, ○; 6.20, □; 9.88, △. Ionic strength (μ): 0.05, ——; 0.3, – – –. Each point represents the mean of three determinations.

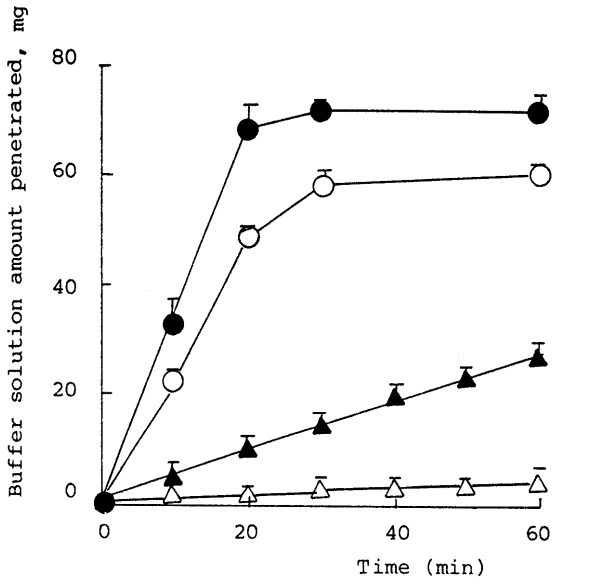

Fig. 6. Effect of Ionic Strength on the Medium Uptake by AEA® Film-Coated Tablet in pH 5.0 Buffer Solution at 37 °C

Ionic strength (μ): 0.05, open symbols; 0.3, closed symbols. Coating weight of AEA® (mg/tab.): 3.12, ○; 9.88, △. Each point represents the mean ± S.D. of three determinations.

in medium of $\mu=0.3$ than tablets in medium of $\mu=0.05$. Medium penetration profiles of AEA® tablets with coating weights of 3.12 and 9.88 mg/tab. showed that water transfer into both tablets was an apparent zero-order process in a similar manner to the dissolution rate of SP from AEA® tablets until both tablets disintegrated (Fig. 5). In contrast, water transfer into HPMCP tablet did not occur even after 60-min immersion in pH 5.0 buffer solutions of $\mu=0.05$ and 0.3 (data not given). These results indicated that the penetration rate of medium into AEA® tablet notably increases with an increase in ionic strength and suggested that water transfer into the tablet occurs

through the pores of the film coating.

Next, to clarify the effect of ionic strength of the medium on the film coating structure of AEA® tablet, we examined the effects of ionic strength on surface structure and film thickness of a tablet with a coating weight of 3.12 mg/tab. Figure 7 is a photograph of the surface of the tablet immersed in pH 5.0 buffer solutions of $\mu=0.05$ and 0.3. The coating surface was markedly affected by the increase in ionic strength (Fig. 7). It became translucent when immersed in medium of $\mu=0.3$ but not in medium of $\mu=0.05$. Figure 8 shows film thickness profiles of the tablet immersed in pH 5.0 and 6.5 buffer solutions of $\mu=0.05$ and 0.3. The mean film coating thickness of the tablet after 60-min immersion in pH 5.0 buffer solutions were 30.9 and 24.0 μm, respectively. The thickness in pH 6.5 buffer solution was not affected by the ionic strength.

At pH 6.5, AEA® film coating did not dissolve, nor was dissolution promoted by an increase in ionic strength. However, at the apparent critical dissolution pH value, dissolution was enhanced by an increase in ionic strength, and consequently film coating thickness decreased and the film coating tended to expand; this resulted in facilitation of water transfer through the film coating with an increase in the SP dissolution rate.

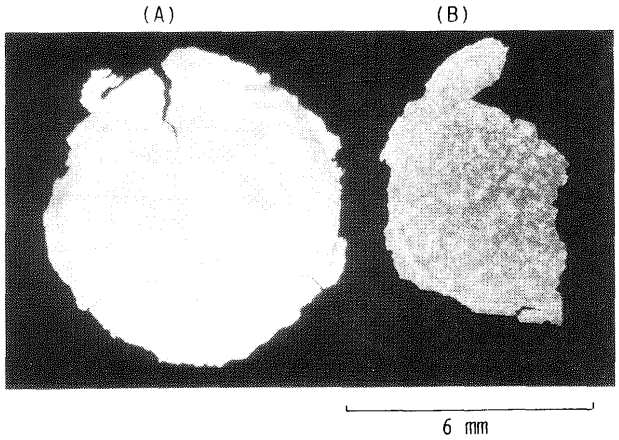

Fig. 7. Photograph of the Surface of AEA® Film-Coated Tablets Immersed in pH 5 Buffer Solutions of Different Ionic Strengths at 37 °C for 1 h

Ionic strength (μ): A, 0.05; B, 0.3.

Effect of Ionic Strength on Physicochemical Properties of AEA® The thickness of AEA® film coating in pH 5.0 decreased with an increase in ionic strength (Fig. 8). Also, on the basis of the dissolution time data, when ionic strength was increased to 0.3, the dissolution time of AEA® cast film in pH 5.0 was shortened and its apparent critical dissolution pH value shifted from pH 5.0 to 5.8 (Table 1). These results suggested that the apparent dissociation of AEA® varied with the medium ionic strength. To learn the effect of ionic strength on the dissolution rate of AEA® in the medium, the effects of ionic strength on AEA® physicochemical properties such as dissociation and solubility were examined.

pH titration of AEA® aqueous suspensions was measured to determine the electrolyte property of the diethylamino group in AEA®. This was done using AEA® aqueous suspensions (1 mg/ml) since AEA® did not dissolve in water at room temperature. Figure 9 shows that the apparent dissociation of AEA® at 25 °C and 37 °C increased with increasing ionic strength of the medium. The apparent pK_a values of AEA® in water without and with NaCl at 37 °C were 4.85 and 6.1, respectively. Therefore, in pH 5.8 buffer solution of $\mu=0.3$, the dissociated form of the diethylamino groups of AEA® increased and the solubility of AEA® in medium increased, resulting in an increase in the dissolution rate of the AEA® film coating. Additionally, it became clear that the dissolution rate of AEA® in medium was increased by a decrease in temperature. The marked increase in the apparent dissociation of AEA® on addition of NaCl was probably due to shielding of the charge of diethylamino groups in AEA®.[15] Thus, our results indicated that the apparent dissociation of AEA® is an important factor affecting the dissolution rate of the AEA® film coating.

As shown in Table 4, the solubility of AEA® was markedly affected by ionic strength and temperature; in water with 0.1 M NaCl ($\mu=0.1$) it was about 1/5 that in water. This effect was probably due to phase separation, or salting out. In pH 5.0 buffer solution, the solubility of AEA® varied with the concentration of added NaCl: when ionic strength increased from 0.05 to 0.3, its solubility

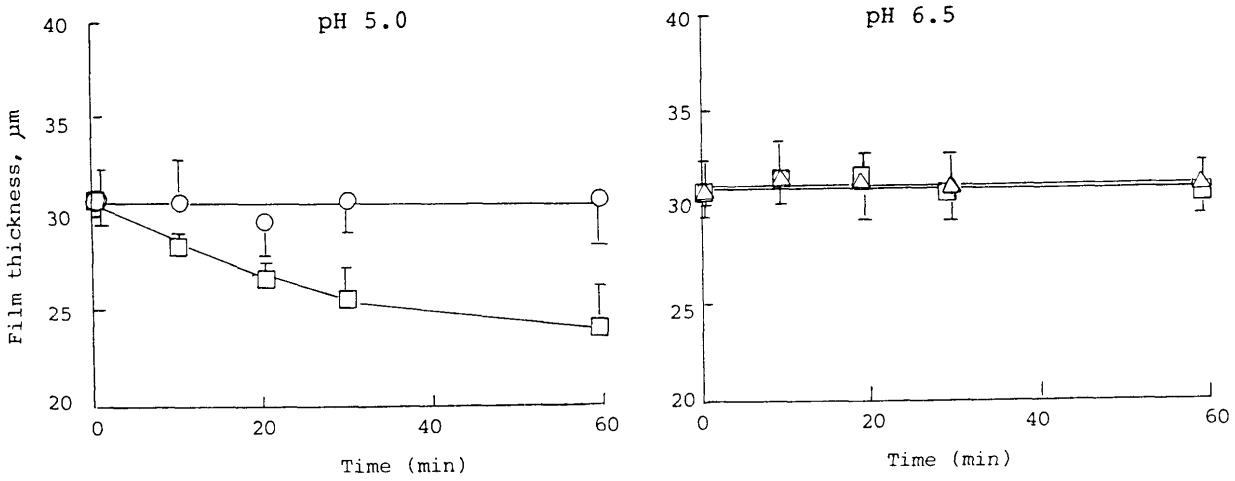

Fig. 8. Effect of Ionic Strength on Film Thickness of AEA® Film-Coated Tablet in pH 5.0 and 6.5 Buffer Solutions at 37 °C

Ionic strength (μ): 0.05, ○; 0.08, △; 0.3, □. Each point represents the mean ± S.D. of three determinations.

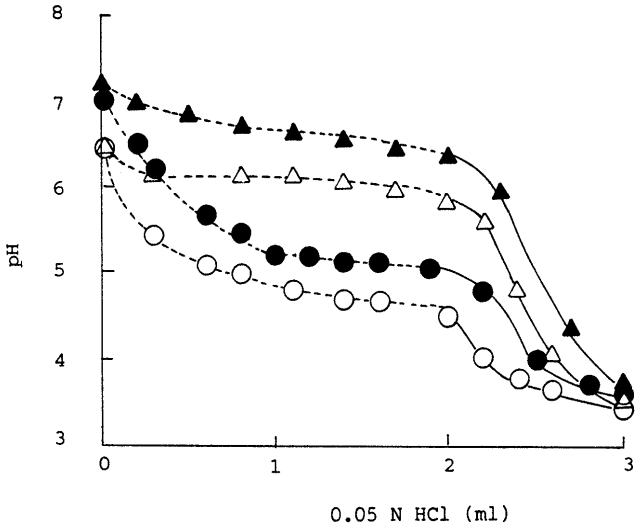

Fig. 9. Effect of Ionic Strength on pH Titration Curves of AEA® Aqueous Suspensions at 25 °C and 37 °C

Temperature: 25 °C, closed symbols; 37 °C, open symbols. Ionic strength of suspension medium (μ): 0, ○; 0.3, △. AEA® concentration: 0.1 g/100 ml. Solubility pattern of AEA®: soluble, ——; insoluble, – – –.

Table 4. Solubility of AEA® in Various Solutions with Different Ionic Strengths at 7 °C and 37 °C

Solvent	Solubility (mg/ml)
Water ($\mu=0$)[a]	1.65
Water ($\mu=0.1$)[a]	0.30
Water ($\mu=0$)[b]	<0.01
pH 5 phosphate buffer solution ($\mu=0.05$)[b]	0.22
pH 5 phosphate buffer solution ($\mu=0.3$)[b]	2.69
pH 5 phosphate buffer solution ($\mu=0.5$)[b]	0.34

Temperature: *a*) 7 °C; *b*) 37 °C. Ionic strength (μ) of solvent was adjusted with NaCl.

increased about 12-fold because of the increase in the apparent dissociation of AEA® (Fig. 9), while when the ionic strength increased from 0.3 to 0.5, its solubility in medium of $\mu=0.5$ decreased to 1/8 that in medium of $\mu=0.3$ due to salting out.

The results indicated that the apparent dissociation of AEA® varies with the concentration of added NaCl, which changes the dissolution rate of AEA® in the medium. The apparent dissociation of AEA® was a major factor affecting the dissolution rate of AEA® in medium when the ionic strength of the medium was 0.3. Salting out was also a major factor affecting the dissolution rate of AEA® in medium when the ionic strength was 0.5.

Conclusions

The dissolution time of AEA® cast film was affected by the physicochemical properties of GI fluids. It was shortened by an increase in ionic strength of the medium but was delayed by an increase in viscosity and addition of sodium taurocholate to the medium. The dissolution rate of SP from AEA® tablet was found to vary with the ionic strength of GI fluids as well as pH. The dissolution rate of SP from AEA® tablet markedly increased with an increase in the ionic strength of the medium. When the ionic strength was 0.3, its dissolution rate reached maximum due to change in the dissolution rate of the AEA® film coating.

The physicochemical properties of AEA® were affected by the medium ionic strength. An increase in the apparent dissociation of AEA® due to an increase in the medium ionic strength ($\mu=0.3$) increased the solubility of AEA® in medium, resulting in an increasing dissolution rate of the AEA® film coating, and then in an increased dissolution rate of SP from AEA® tablet. When ionic strength rose to 0.5, the solubility of AEA® in the medium decreased due to the salting out effect, resulting in a decreased dissolution rate of the AEA® film coating and a decreased dissolution rate of SP from AEA® tablet.

Our results showed that the increase in bioavailability after food intake (*ca.* $\mu=0.3$) in low gastric acidity subjects resulted from an increase in the dissolution rate of SP from AEA® tablet due to a rise in the ionic strength of the GI fluids; this seems to be an important factor affecting the dissolution rate of drug from tablet coated with polyelectrolyte. We recommend that the dissolution medium, such as the 1st and 2nd fluids for dissolution tests of tablet coated with polyelectrolyte, be taken into account when varying the ionic strength of GI fluids.

References and Notes

1) Ogata H., Aoyagi N., Kaniwa N., Shibazaki T., Ejima E., Takagishi Y., Ogura T., Tomita K., Inoue S., Zaizen M., *Int. J. Pharmaceut.*, **23**, 277 (1985).
2) Aoyagi N., Ogata H., Kaniwa N., Koibuchi M., Shibazaki T., Ejima A., Mizobe M., Kohno K., Samejima M., *Chem. Pharm. Bull.*, **34**, 281 (1986).
3) Shinkuma D., Hamaguchi T., Kobayashi M., Yamanaka Y., Mizuno N., *Yakuzaigaku*, **48**, 106 (1988).
4) Shinkuma D., Hamaguchi T., Kobayashi M., Yamanaka Y., Mizuno N., *Int. J. Clin. Pharmacol. Ther. Toxicol.*, **27**, 499 (1989).
5) Shinkuma D., Hamaguchi T., Kobayashi M., Yamanaka Y., Mizuno N., *Int. J. Clin. Pharmacol. Ther. Toxicol.*, **28**, 440 (1990).
6) Shinkuma D., Hamaguchi T., Kobayashi M., Yamanaka Y., Mizuno N., *Int. J. Clin. Pharmacol. Ther. Toxicol.*, **29**, 303 (1991).
7) "Catalog of AEA, Sankyo," Sankyo K. K., Tokyo, 1987, pp. 6—7.
8) Hayashi M., Nagai T., Nogami H., *Chem. Pharm. Bull.*, **18**, 2350 (1970).
9) Sjoqvist R., Nyqvist H., Sjovall J., Westerlund D., *J. Microencapsulation*, **2**, 123 (1985).
10) Mizuno N., Shimizu C., Morita E., Shinkuma D., Yamanaka Y., *Yakuzaigaku*, **43**, 209 (1983).
11) Tomida Y., Yokohama S., Maki M., Toguchi H., Shimamoto T., *J. Takeda Res. Lab.*, **36**, 83 (1977).
12) "Catalog of HPMCP," Shinetsu Chemical Co., Ltd., Tokyo, 1991, p. 2.
13) Ogata H., Shibazaki T., Inoue T., Ejima A., *J. Pharm. Sci.*, **68**, 712 (1979).
14) Ogata H., Shibazaki T., Inoue T., Ejima A., *J. Pharm. Sci.*, **68**, 708 (1979).
15) Armand J. Y., Magnard F., Bouzon J., Rollet J., Taverdet J. L., Vergnaud J. M., *Int. J. Pharmaceut.*, **40**, 33 (1987).