Factors Affecting the Dissolution Rate of Sulpiride from Tablets Coated with Polyvinylacetal Diethylaminoacetate, a Gastric-Fluid-Soluble Polymer. II. Effect of Mechanical Destructive Force and Film Coating Strength in the Gastrointestinal Tract

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The bioavailability of sulpiride (SP) from a tablet coated with AEA® (polyvinylacetal diethylaminoacetate), a gastric-fluid-soluble polymer, is very poor in low gastric acidity subjects in the fasting state but improves after food intake. To analyze factors affecting SP bioavailability from AEA® film-coated tablets (AEA® tablets), we prepared AEA® cast film and AEA® tablets and determined the effects of mechanical destructive force and film coating strength in the gastrointestinal (GI) tract on SP dissolution from the tablets. With the paddle method, rapid SP dissolution occurred at pH 4.0 or below but not at pH 5.0 or above. Using the disintegration test method, dissolution at pH 5.0—5.8 markedly increased as the film coating broke due to an increase in the mechanical destructive force and a change in film coating strength. Microscopic observation of AEA® film coating at pH 5.0 supported the marked decrease in the cast film strength observed in pH 5.0 medium with an increase in film swelling. Thus, one important factor affecting AEA® film coating strength is its swelling rate. After food intake, SP bioavailability from AEA® tablet improves, probably due to increased mechanical destructive force with GI motility and decreased film coating strength in GI fluids with increased film swelling in the pH environment after the meal (pH 5.85). This increased SP dissolution rate from AEA® tablet leads to enhanced absorption. We concluded that the increase in mechanical destructive force acting on the tablet after food intake is one of the powerful factors leading to improved drug bioavailability.

Key words AEA®; dissolution rate; film coating strength; film coating swelling; film-coated tablet; sulpiride

Many film-coated tablets are presently available on the market. How film coating agents affect drug bioavailability has been investigated,[1–3] but only a few studies have been done on the influence of gastric-soluble polymers on drug bioavailability from a film-coated tablet.[4] We previously examined the bioavailability in healthy subjects of sulpiride (SP),[5,6] which is very slightly soluble in water, from a commercial tablet coated with AEA® (polyvinylacetal diethylaminoacetate). AEA® is good as a protective coating for hygroscopic drugs due to its low moisture permeability,[7] and some AEA® film-coated tablets (AEA® tablets) are presently 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. Except for our previous study,[8] no work has been done to analyze factors affecting variation in SP bioavailability from AEA® tablets.

A coating made of AEA®, a basic polyelectrolyte, is affected by human gastric acidity because of its pH-dependent dissolution behavior.[5,6] The tablet dissolves rapidly at pH 4 or below but not at pH 5.0 or above. In low gastric acidity subjects, we found[9] the bioavailability to be very poor in the fasting state but significantly better after food intake.

Food intake markedly improves gastrointestinal (GI) motility and changes the physicochemical properties of the GI fluids. SP dissolution from AEA® tablet may be affected by the mechanical destructive force caused by GI motility and the physicochemical properties of the GI fluids after food intake. Of these two factors, the latter was discussed earlier[8]; we found that the ionic strength of GI fluids after food intake was one of the powerful factors affecting bioavailability. In the present work, we examined the mechanical destructive force caused by GI motility.

Another factor which may affect drug bioavailability is the swelling of the AEA® film coating in medium.[7] Hirashima *et al.* reported[10] that the wet strength of sustained release vitamin C film-coated tablet was an important factor affecting breakage of the tablet in the GI tract. Thus, the mechanical destructive force of GI motility and the change in the strength of the AEA® film coating in GI fluids after food intake might influence SP dissolution from AEA® tablet.

The present study was done to analyze factors affecting the bioavailability of SP from AEA® tablet. We prepared these tablets with different coating weights and AEA® cast film to determine the influence of the mechanical destructive force of GI motility and the film coating strength after food intake on SP dissolution from AEA® tablet. We also studied the effect of the swelling of AEA® cast film on its strength in medium and discuss the relation of this strength and SP dissolution from the tablet. As a reference, we used an enteric-coated tablet, HPMCP

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(hydroxypropylmethylcellulose phthalate) film-coated tablet (HPMCP tablet), which has high coating strength in the stomach and is used widely in pharmaceutical preparations.

Experimental

Materials SP was supplied by Fujisawa Pharmaceutical Co., Ltd., AEA® by Sankyo Co., Ltd., and HPMCP by Shinetsu Chemical Co., Ltd. All other materials were of reagent grade.

Preparation of Cast Film Each polymer was dissolved in methylene chloride–ethyl alcohol (1 : 1, v/v) at a concentration of 10% (w/v). The film solution (5 ml) was cast in a petri dish (8.9 cm in diameter and 1 cm deep), and the solvent was then allowed to evaporate at room temperature for 5 h. However, AEA® cast film of constant thickness could not be prepared in our laboratory when using the coating solvent (ethyl alcohol–water) for AEA® tablet.

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

Preparation of Film-Coated Tablet A plain tablet from the manufacturing process for commercial SP film-coated tablet (Dogmatil®, 100 mg/tab., lot no. 2060) was used as the core for preparation of film-coated tablets. The coating solutions for AEA® and HPMCP tablets contained AEA® (8% (w/v)) in ethyl alcohol–water (50 : 50, v/v), and HPMCP (8% (w/v)) and cetanol (5% (w/w) to the polymer) in ethyl alcohol–water (80 : 20, v/v), respectively. The solvent composition for AEA® coating was different from that of the solvent for cast film because of problems (poor work environment and solvent remaining in the tablet) with the use of methylene chloride in the film coating process. AEA® tablets with different coating weights (3.12, 6.20, 9.88 mg/tab.) and HPMCP tablets with the usual coating weight (6.54 mg/tab.) were produced with a Hi-coater (Freund, HCT-55). The process conditions 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 to calculate the 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 tablet using a sharp knife, and fragments of the core tablet adhering 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, 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 micrometer. The film coating thicknesses (mean ± S.D.) of AEA® tablets with different coating weights were as follows: 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 and that of the commercial AEA® tablet used in the previous *in vivo* study[8] was 34.4 ± 3.5 μm.

Determination of SP Dissolution Rate from Film-Coated Tablet Dissolution tests were carried out using the disintegration test method and the paddle method according to JP XII. The dissolution media were 900 ml of 1st fluid, pH 4.0 acetate buffer solution (0.1 M), and pH 5.0, 5.8 and 6.5 phosphate buffer solutions (0.05 M). AEA® and HPMCP tablets with holes of different sizes in the film coating (hole diameter (ϕ): 0.73, 1.42, 3.60 mm) were prepared as follows: a circle was drawn in the center of the film-coated tablet surface and the film coating in the circle was carefully removed using a sharp knife. Holes were drilled in both surfaces (the front and the reverse sides) of the film-coated tablet. The T_{50} value, defined as the time required for 50% of SP to dissolve into the dissolution medium, was determined directly from the dissolution profile–time curve.

Measurement of Cast Film Swelling in Medium AEA® and HPMCP cast films, which were prepared as described above, were cut very carefully to 1 cm squares. The cut film was put into 20 ml of medium in a 30-ml glass-stoppered tube, then withdrawn periodically. The dimensions (length, width, thickness) of the cut film were measured, and its swelling was expressed in terms of the percentage of its volume expansion.

Measurement of Cast Film Strength in Medium The apparatus used to measure the strength of cast film in medium is shown in Fig. 1.

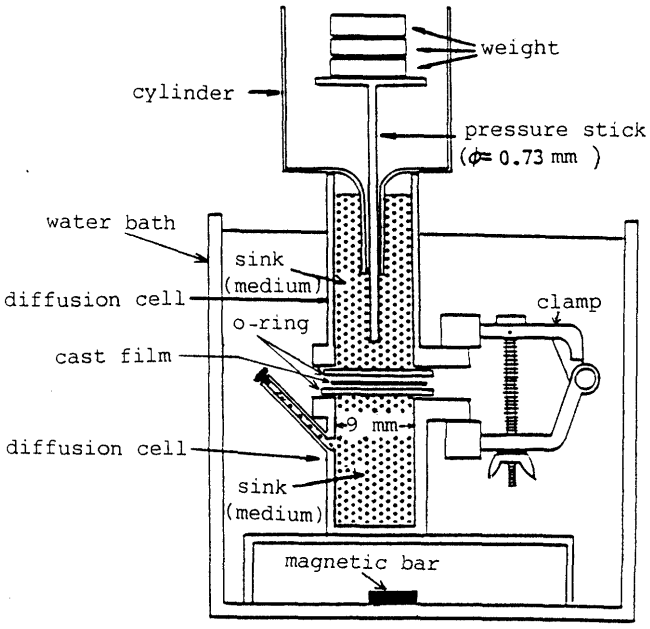

Fig. 1. Schematic Representation of Apparatus for Measuring Strength of Cast Film in Medium

The apparatus consisted of two-compartment diffusion glass cells (9.00 mm i.d.), a pressure stick (0.73 mm o.d.), a clamp, a plastic cylinder, silicon O-rings and a stirred water bath. AEA® and HPMCP cast films, prepared as described above, were cut very carefully to 1.5 cm squares. The cut film was put into 20 ml of medium in a 30-ml glass-stoppered tube, then withdrawn periodically. Next, it was quickly placed between the two compartments of the diffusion glass cells and the fixed clamp, and both glass cells were filled with medium (37 °C) and immersed in the water bath. Weight was applied to the pressure stick until the cut film broke. The strength of the cut film was expressed in terms of the weight needed to break it. The temperature was kept at 37 °C and the media used were pH 5.0 and 6.5 phosphate buffer solutions (0.05 M).

Results and Discussion

Effect of Mechanical Destructive Force on SP Dissolution of AEA® Tablet Food intake improved GI motility which, in turn, increased the mechanical destructive force. A disintegration test method with a strong mechanical destructive force has been found to yield dissolution test results which agree with the bioavailability of chloramphenicol from a tablet.[11] However, this mechanical destructive force is about four times greater than that of the paddle method.[12] We therefore conducted the dissolution test for the AEA® tablet, with the HPMCP tablet as reference, using both the disintegration test method and the paddle method. We used the 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.[5,6,9] The HPMCP tablet used in the test had the usual coating weight (6.54 mg/tab.), which is effective as an enteric coating. The results are shown in Fig. 2.

SP dissolution from the control tablet in both methods was very rapid in the pH range 1.2—6.5 and was not affected by a change in the mechanical destructive force of the dissolution test apparatus. Thus, this control tablet was considered to be suitable as a core for the film-coated tablet.

SP dissolution profiles from AEA® tablet in the paddle method depended on the medium pH because AEA® is a

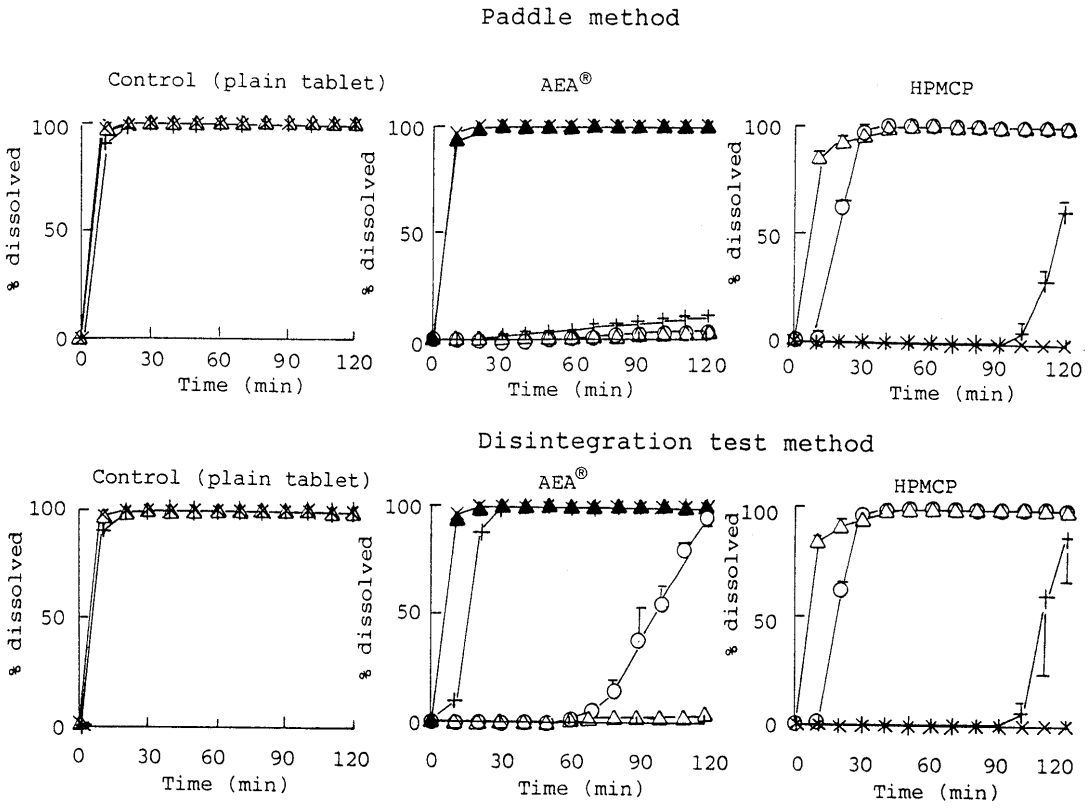

Fig. 2. Effect of Mechanical Destructive Force of Dissolution Apparatus on Dissolution Profiles of Sulpiride from AEA® and HPMCP Film-Coated Tablets in Solutions of Various pH

Dissolution medium pH: ×, 1.2; ▲, 4.0; +, 5.0; ○, 5.8; △, 6.5. Coating weight (mg/tab.): AEA®, 3.12; HPMCP, 6.54. The control tablet was a plain tablet used as the core when preparing the film-coated tablet. Each point represents the mean ± S.D. of three determinations.

basic polyelectrolyte with an apparent pK_a of 4.85.[8] Dissolution was very rapid at pH 4.0 or below but markedly delayed at pH 5.0 or above, and thus the apparent critical dissolution pH (the lowest pH at which the AEA® tablet remained undissolved) was 5.0. SP dissolution patterns at pH 5.0 or above showed an apparent zero-order rate. In the disintegration test method, SP dissolution from the AEA® tablet markedly increased at pH 5.0 and pH 5.8 due to tablet disintegration. But the mechanical destructive force effect on the dissolution was not recognized at pH 6.5 as the tablet remained intact, indicating that it varied with the pH of the medium. This may have been due to a change in the strength of the film coating based on its physicochemical property in the medium.

The dissolution profiles of SP from HPMCP tablet in the paddle method depended on the medium pH as HPMCP is an acidic polyelectrolyte. SP dissolution from the HPMCP tablet was very rapid at pH 5.8 or above but markedly delayed at pH 5.0 or below. At pH 5.0, the dissolution pattern in the paddle method was related to tablet disintegration. The dissolution test results for the HPMCP tablet in the disintegration test method were almost the same as those in the paddle method, indicating that an increase in the mechanical destructive force does not affect SP dissolution from it.

The results indicated that the pH is the main factor affecting SP dissolution from the AEA® tablet. In the pH range 5.0—5.8, the apparent critical dissolution pH region, the dissolution is affected by the mechanical destructive force of the dissolution test apparatus. Since the meal suspension pH was 5.85,[8] the gastric fluid pH after food intake in low gastric acidity subjects could be expected to range between 5.0 and 6.0. Thus, the increase in the mechanical destructive force acting on the AEA® tablet after food intake in low gastric acidity subjects is a powerful factor improving SP bioavailability, in addition to the ionic strength of GI fluids reported previously.[9] In the HPMCP tablet, the main factor affecting SP dissolution is the pH of the medium, not the mechanical destructive force of the dissolution test apparatus, indicating that this enteric-coated tablet is difficult to break down in the stomach after food intake and can protect a drug against decomposition in the acidic environment of the stomach.

Effect of Mechanical Destructive Force on SP Dissolution from AEA® Tablets with Different Coating Weights The effect of the mechanical destructive force on SP dissolution from a film-coated tablet markedly differed between AEA® tablet (3.12 mg/tab.) and HPMCP tablet (6.54 mg/tab.). This may have resulted from a difference in the strength of the AEA® film coating due to a lesser coating weight of the tablet compared to that of the HPMCP tablet or a characteristic of AEA® in the medium. To learn the influence of the mechanical destructive force of the dissolution test apparatus on SP dissolution from AEA® tablet when its coating weight increases, we examined the effect of coating weight on SP dissolution from this tablet using the disintegration test method and the paddle method at pH 5.0. As shown in Fig. 3, SP dissolution in both methods decreased with an increase in

the coating weight. However, even AEA® tablets with large coating weights (6.20, 9.88 mg/tab.) readily disintegrated with a great increase in dissolution when the mechanical destructive force of the dissolution test apparatus was increased. This suggested that the strengths of the AEA® tablets with large coating weights at pH 5.0 may be low, possibly due to some characteristic of AEA® in the medium.

The results indicated that increasing the mechanical destructive force of the dissolution test apparatus affected SP dissolution from AEA® tablet (3.12 mg/tab.) at pH 5.0—5.8 but not that from HPMCP tablet (6.54 mg/tab.) at pH 5.0. The difference in effects was not due to the difference in the coating weights but possibly to the different characteristics of the two film coatings in medium.

Effect of Film Coating Breakage on SP Dissolution from AEA® Tablet In the disintegration test method, the marked increase in SP dissolution from AEA® tablet at pH 5.0—5.8 may have been due to breaking of the film coating. To determine the effect of the breakage, we prepared AEA® tablets with holes of different sizes (hole diameters (ϕ): 0.73, 1.42, 3.60 mm) in the film coating and studied the effect of partial breakage on SP dissolution from the tablets, with the HPMCP tablet as reference, using the paddle method at pH 5.0.

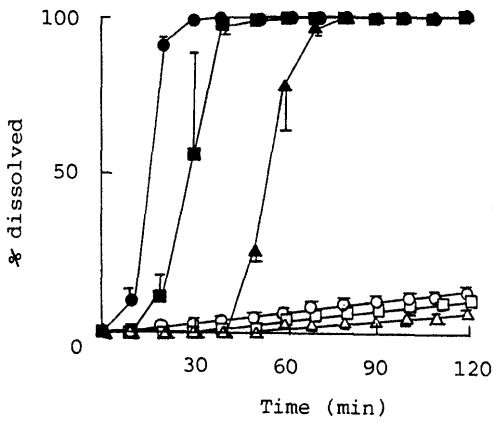

Fig. 3. Effect of Coating Weight on Dissolution Profiles of Sulpiridefrom AEA® Film-Coated Tablet in pH 5.0 Buffer Solution Using the Paddle Method and the Disintegration Test Method

Dissolution method: paddle method, open symbols; disintegration test method, closed symbols. Coating weight of AEA® (mg/tab.): ○, 3.12; □, 6.20; △, 9.88. Each point represents the mean ± S.D. of three determinations.

Figure 4 shows that the effect of partial breakage of the film coating on SP dissolution from a film-coated tablet markedly differed between the two types of tablets. The increases in SP dissolution from AEA® tablets with hole diameters of 0.73 and 1.42 mm were small because the two tablets did not disintegrate during the 120 min. Although SP dissolution from the AEA® tablet with the largest hole diameter ($\phi = 3.60$ mm) notably increased, the shell of the film coating did not disintegrate and remained intact after 120 min. On the other hand, SP dissolution from the HPMCP tablet with a hole increased with the hole diameter due to tablet disintegration. Thus, large breakage of the film coating was clearly important in the marked increase in SP dissolution from AEA® tablet at pH 5.0.

The results indicated that, in the disintegration test method, the marked dissolution increase from AEA® tablet at pH 5.0—5.8 (Figs. 2, 3) at which the AEA® film coating does not dissolve, is probably due to large breakage of the film coating, and the very slight increase in dissolution at pH 6.5 results because the film coating remains intact. These results thus suggested that the strength of the film coating at pH 5.0—5.8 may be lower than that at pH 6.5.

Physicochemical Properties of AEA® Film Coating in Medium In the disintegration test method, SP dissolution from AEA® tablet at pH 5.0—5.8 markedly increased with large breakage of the film coating, but the dissolution at pH 6.5 did not increase when the film coating was intact (Fig. 2). This marked difference in dissolution may have been due to a change in the AEA® film coating strength in medium based on its physicochemical properties. AEA® is also known to swell in medium,[7] and this may influence its coating strength. The physicochemical properties of AEA® film coating in medium were studied by evaluating the strength and swelling of cast film, using HPMCP cast film as a reference. We also measured the strength and swelling of AEA® and HPMCP film coatings in medium.

The strength–time profiles of Fig. 5 show that the AEA® cast film strength varied with the medium pH, decreasing

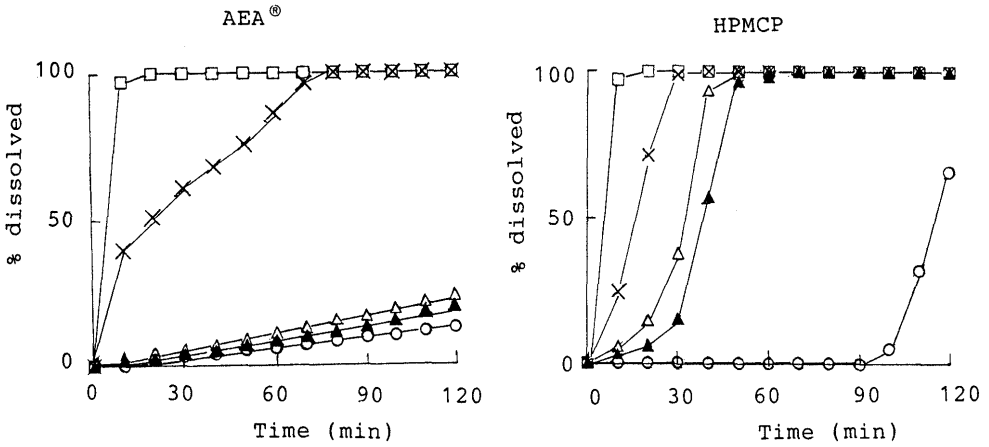

Fig. 4. Effect of Holes of Different Sizes in the Film Coating on Dissolution Profiles of Sulpiride from AEA® and HPMCP Film-Coated Tablets in pH 5.0 Buffer Solution Using the Paddle Method

Hole diameter (mm): ○, 0; ▲, 0.73; △, 1.42; ×, 3.60; □, control tablet (plain tablet). Coating weight (mg/tab.): AEA®, 3.12; HPMCP, 6.54. Each point represents the mean of three determinations.

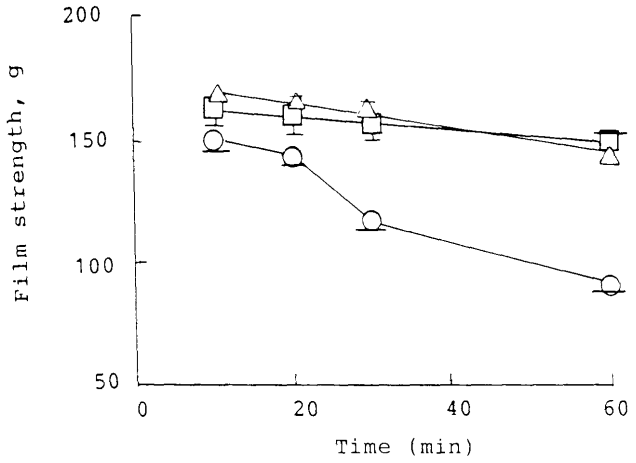

Fig. 5. Strength of AEA® and HPMCP Cast Films in pH 5.0 and 6.5 Buffer Solutions at 37 °C with Time

AEA® cast film: ○, pH 5.0; □, pH 6.5. HPMCP cast film: △, pH 5.0. Length, width and thickness of the AEA® and HPMCP cast films are 10, 10, and 0.070 mm and 10, 10, and 0.064 mm, respectively. Each point represents the mean ± S.D. of three determinations.

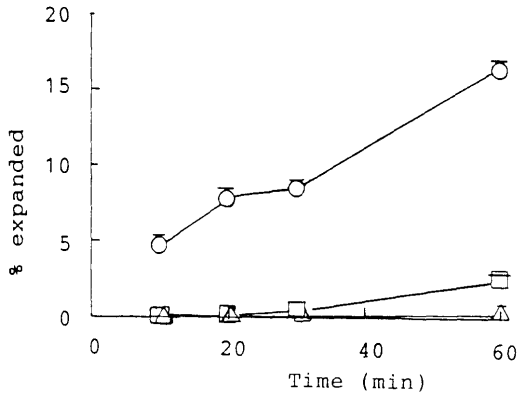

Fig. 6. Swelling of AEA® and HPMCP Cast Films in pH 5.0 and 6.5 Buffer Solutions at 37 °C with Time

AEA® cast film: ○, pH 5.0; □, pH 6.5. HPMCP cast film: △, pH 5.0. Length, width and thickness of the AEA® and HPMCP cast films are 10, 10, and 0.070 mm and 10, 10, and 0.064 mm, respectively. Each point represents the mean ± S.D. of three determinations.

markedly at pH 5.0 but only slightly at pH 6.5. The strength of HPMCP in pH 5.0 decreased slightly. These results agreed well with those of dissolution tests of AEA® and HPMCP tablets in the disintegration test method. Thus, the marked increase in SP dissolution from AEA® tablet at pH 5.0—5.8 in the disintegration test method is due to a significant decrease in the strength of the film coating.

The expansion–time profiles in Fig. 6 of AEA® and HPMCP cast films in medium show that AEA® cast film expansion varied with the medium pH, increasing greatly at pH 5.0 but only slightly at pH 6.5; HPMCP cast film expanded slightly at pH 5.0. The AEA® cast film thus swells at pH 5.0 but not at pH 6.5, probably because of the hydration caused by the electrolyte property of the diethylamino groups of AEA® (pK_a 4.85)[8] in medium. The results of the swelling and strength tests of cast films in medium indicated that AEA® cast film strength in medium decreases as the swelling increases, suggesting the importance of the swelling rate. Martin[13] has stated that the forces responsible for the mechanical strength of a

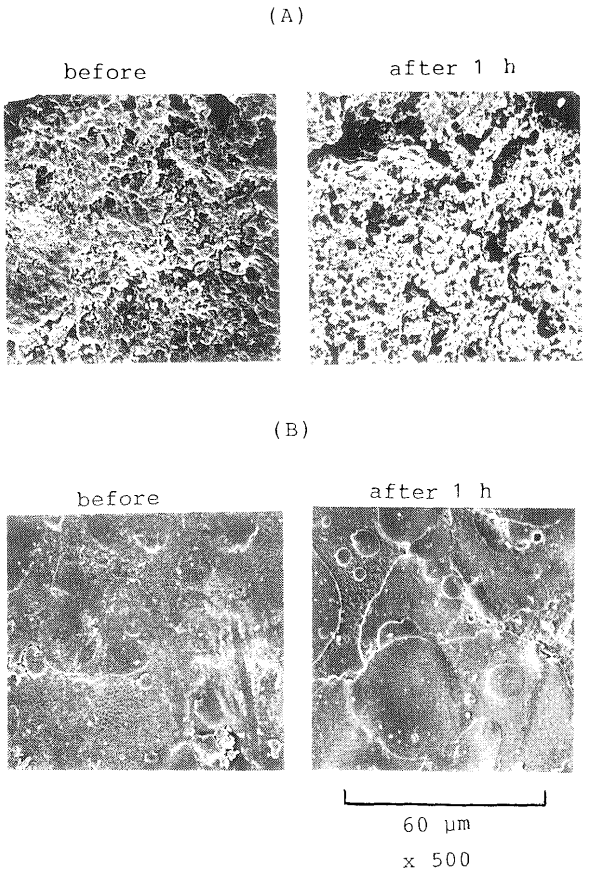

Fig. 7. Scanning Electron Micrographs of Surfaces of AEA® (A) and HPMCP (B) Film-Coated Tablets Immersed in pH 5.0 Buffer Solution at 37 °C for 1 h

Coating weight (mg/tab.): AEA®, 3.12; HPMCP, 6.54.

solid polymeric object are the secondary valence forces between adjacent polymer chains rather than the primary valence forces joining together the backbone atoms of single chains. Thus, the decrease in the strength of the AEA® film coating after swelling is probably due to a decrease in the secondary valence forces between adjacent AEA® chains caused by the hydration.

We attempted to determine the strength and swelling of the film coatings of AEA® (3.12 mg/tab.) and HPMCP (6.54 mg/tab.) tablets in medium, but the film coatings (*ca.* $\phi = 7.0$ mm) were too small for the film strength test apparatus (Fig. 1). We thus resorted to scanning electron micrographs, as shown in Fig. 7. After 60-min immersion of the two types of tablets in pH 5.0, there were marked differences in surface structures between them. The AEA® film coating had become rough and porous, while that of the HPMCP film coating was smooth and not porous. The rough AEA® structure had notably increased understood without repeating compared to that before the immersion, indicating that the AEA® film coating markedly swells at pH 5.0.

Our results indicated that the strength of the AEA® film coating in medium markedly varies with the medium pH and that factors affecting it include the swelling rate based on the pK_a of AEA®.

Conclusion

Using the paddle method with a weak mechanical

destructive force, the AEA® tablet showed SP dissolution that was rapid at pH 4.0 or below but notably delayed at pH 5.0 or above. With the disintegration test method with a strong mechanical destructive force, the SP dissolution markedly increased at pH 5.0—5.8 but decreased at pH 6.5.

The strength of the AEA® cast film varied with the medium pH, decreasing markedly at pH 5.0 but only slightly at pH 6.5. The strength decreased as the swelling increased, showing the swelling rate to be an important factor. Microscopic observations of the AEA® film coating at pH 5.0 supported the results that the AEA® cast film swelled at this pH. Thus, the decrease in strength of the AEA® film coating at pH 5.0 was due to the increase in its swelling rate based on the pK_a of AEA® (4.85). These results indicated that, in the disintegration test method, the marked dissolution increase at pH 5.0—5.8 was due to large breakage of the film coating caused by increased mechanical destructive force and a decrease in the strength of the AEA® film coating in medium.

The increase in the mechanical destructive force acting on AEA® tablet after food intake in low gastric acidity subjects is thus a powerful factor in improving drug bioavailability. This together with the film coating strength in medium at pH 5.0—5.8 are important determinants affecting SP dissolution from AEA® tablet. We recommend that the dissolution test for tablets coated with polyelectrolyte, such as AEA® with a pH-dependent swelling characteristic, be taken into account together with variation in the mechanical destructive force of GI motility and the film coating strength of the tablet in GI fluids.

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