Application of Gel Formation for Taste Masking[1)]

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Masking of the bitter taste from tablets by a water-insoluble gel formed by sodium alginate and bivalent metal was studied. Amiprilose hydrochloride was selected as the model drug with a bitter taste, and its core tablet was prepared. The core tablet was under-coated with sodium alginate and over-coated with calcium gluconate as a bivalent metal, or it was under-coated with calcium gluconate and over-coated with sodium alginate in order to form a gel on the surface of the tablet in the mouth at oral administration. The taste masking was evaluated by the amount of amiprilose hydrochloride released from the tablet. In addition, cross sections of the tablets subjected to a dissolution test were observed by scanning electron microscopy and energy dispersive X-ray microanalysis to evaluate the component distribution of the coated layers and behavior of the drug.

Water-insoluble gel on the surface of the tablet was minimally formed by under-coating with sodium alginate and over-coating with calcium gluconate, and its masking time was 1 min. On the other hand, water-insoluble gel was formed by under-coating with calcium gluconate and over-coating with sodium alginate, and its masking time was relatively long. These results suggest that the gel formation on the surface of tablets by under-coating with calcium gluconate and over-coating with sodium alginate is useful for taste masking of tablets in the mouth at the time of oral administration.

Key words sodium alginate; calcium gluconate; gel; masking; tablet; coating

Techniques for masking the bitter taste of medicines by coating powders, granules, and tablets with a polymer such as ethylcellulose, eudragit®, hydroxypropylmethylcellulose, or hydroxypropylcellulose have been widely employed. Recently, new techniques for taste masking have been reported.[2–5)]

Sodium alginate (ALNa) is a purified substance of natural polysaccharides extracted from marine brown algae with dilute alkaline, and consists of the sodium salt of alginate. Its safety is very high,[6,7)] and it has been widely used as a stabilizer, thickener, dispersing agent, and gelation agent of foods.[8)] In addition, ALNa also has the ability to cause water-insoluble gelation in the presence of bivalent metal ions.[9–14)] Therefore, ALNa has been studied for use in novel drug delivery systems.[15–23)]

In this study, we used ALNa and calcium gluconate (GLCa), as a bivalent metal, and studied the taste masking of a bitter drug by forming a water-insoluble gel on the tablet surface, through the permeation of saliva in the mouth at the time of oral administration.

Experimental

Materials Amiprilose hydrochloride (AP, Greenwich Pharmaceutical Co., Ltd.), an anti-inflammatory drug,[24,25)] was used as the model compound producing a bitter taste. This compound has a high water solubility of 1 g/ml at 20 °C . The following compounds were purchased from commercial sources: povidone (Kollidone® K30, BASF Japan Co., Ltd.) as a binder, microcrystalline cellulose (Avicel® PH-101, Asahi Chemical Industry Co., Ltd.) as a filler, croscarmellose sodium (Ac-Di-Sol®, Asahi Chemical Industry Co., Ltd.) as a disintegrator, magnesium stearate (Taihei Kagaku Sangyo Co., Ltd.) as a lubricant, sodium alginate (AD-3, Kimitsu Chemical Industries Co., Ltd.) and calcium gluconate (Tomita Pharmaceutical Co., Ltd.) as coating agents, and paraffin (SP-3035, Nippon Seiro Co., Ltd.) as a fixing agent for the preparation of a cross-sectioned tablet.

Core Tablet Preparation The formulation and preparation processes of the core tablet are shown in Table 1 and Fig. 1, respectively. AP and povidone were granulated by the addition of water with the high-shear-mixer (Vertical granulator®, FM-VG-10, Powrex Co., Ltd.). The obtained granules were dried at an inlet air temperature of 60 °C with a fluidized bed dryer (LAB-1, Powrex Co., Ltd.) and then passed

Table 1. Formulation of Core Tablet (mg/Tab.)

Granule	Amiprilose HCl	200
	Povidone	6
Powder	Microcrystalline cellulose	85
	Croscarmellose sodium	8
	Magnesium stearate	1
	Total weight	300

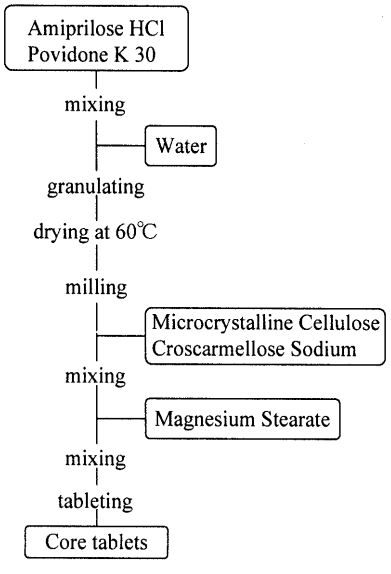

Fig. 1. Preparation Process of Core Tablets

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through the screen of a mill (Power mill P-3S, Dalton Co., Ltd.). The milled granules were mixed with filler, disintegrator, and lubricant in a V-shaped mixer (V-30, Tokuju Kousakusho Co., Ltd.) to make a powder mixture for tableting. The powder mixture was compressed into a core tablet weighing 300 mg with a rotary tableting machine (Cleanpress Correct 12HUK, Kikusui Seisakusho Co., Ltd.).

Coating Tablet Preparation In the case of mixture with ALNa and GLCa aqueous solutions, it was difficult to spray the mixed solution on the tablet because of its gel formation. Therefore, the tablets were coated with ALNa and GLCa separately. Formulations of an over-coating layer (OCL) of GLCa and an under-coating layer (UCL) of ALNa are shown in Table 2, and those of OCL of ALNa and UCL of GLCa are shown in Table 3. Machine settings for applying ALNa and GLCa coats are shown in Table 4. Each layer of the tablet was coated with 5% and 5—5.5% aqueous solution of ALNa and GLCa, respectively, by the use of a coating machine (HCT-MINI, Freund Industrial Co., Ltd.). In order to shorten the coating time, a high concentration of GLCa aqueous solution at 50 °C was used. Coated weights of the layers were 10% of the core tablet weight.

Dissolution Test The dissolution test of the coated tablet was carried out according to the JP XII paddle method at 50 rpm, with the tablet in 900 ml of purified water at 37 °C. Test solution was removed at appropriate time intervals. The concentration of AP in the solution was determined by HPLC equipped with a refractive index detector (ERC-7520, Shimadzu Seisakusho Co., Ltd.). In this study, masking time was regarded as the lag time before AP was released from the tablet.

Observation of External View of Tablet Photographs of an external view of the coated tablet and of the tablet removed at appropriate times in the dissolution test were taken with a camera equipped with a macro lens (F50, AF Micro Nikkor 60 mm, Nikon Co., Ltd.).

Observation of Cross-Sectioned Tablets Coated tablets were removed at appropriate times in the dissolution test and then dried under reduced pressure at 60 °C overnight. The dried tablet was sunken into melted paraffin and then cooled. The tablet fixed with the paraffin was cut with a cutter. The resulting cross section of the tablet was observed, and photographs were taken with a scanning electron microscope (S-2250N, Hitachi Seisakusho Co., Ltd.). Cross sections of tablets were also observed with an energy dispersive X-ray microanalyzer (EMAX-5770EDX, Horiba Seisakusho Co., Ltd.). The distribution of AP, ALNa, and GLCa in the tablet was indicated as the elements chlorine, sodium, and calcium, respectively.

Table 2. Weight Ratio of Over Coatimg Layer (OCL)-Calcium Gluconate (GLCa)/Under Coating Layer (UCL)-Sodium Alginate (ALNa) in Coating Layers

OCL-GLCa	7	5	3	0
UCL-ALNa	3	5	7	10

Table 3. Weight Ratio of OCL-ALNa/UCL-GLCa in Coating Layers

OCL-ALNa	7	5	3	0
UCL-GLCa	3	5	7	10

Table 4. Settings for Coating Machine Operation

Condition	ALNa	GLCa
Flow rate of fluid (g/min)	1.2—1.6	1.1—2.0
Temperature of fluid (°C)	R.T.	50
Spray air pressure (kg/cm^2)	1.0	1.0
Inlet air temperature (°C)	77—83	80—83
Outlet air temperature (°C)	49—50	49—54
Pan speed (rpm)	16	14—16
Amount of charged tablets (g)	250	216—250

Results and Discussion

Release Profiles of AP from Tablets Figure 2 shows the release profiles of AP for the core tablet, and for the tablet over-coated with GLCa and under-coated with ALNa, which was prepared according to the formulation shown in Table 2. Dissolution of the core tablet began immediately, whereas the masking times for the coated tablets were about 1 min and did not vary according to the weight ratio of OCL/UCL. The rate of release of AP from the various coated tablets was almost the same as that from the core tablet. Figure 3 shows the release profiles of AP for the core tablet and the tablets over-coated with ALNa and under-coated with GLCa, which were prepared according to the formulation shown in Table 3. In this case, the rates were different depending on the weight ratio of OCL/UCL, in the rank order of 7/3 > 5/5 > 3/7. In the case of tablets over-coated with ALNa and under-coated with GLCa, with weight ratios of 5/5 and 3/7, the release rates of AP after the lag time were slower than that of the core tablet. These results suggests that these gel formations are applicable to sustained-release drug delivery. The rate of AP release from the tablet singly coated with GLCa was smaller than that from the one singly coated with ALNa (*cf.* "◇" in

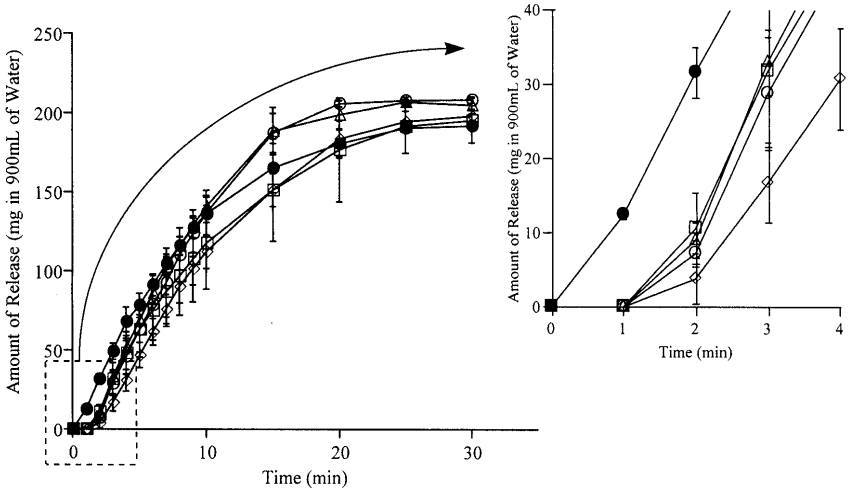

Fig. 2. Release Profiles of AP from Core Tablet and Tablets Coated with OCL-GLCa and UCL-ALNa

Weight ratio of OCL/UCL: ●, core tablet; ○, 7/3; △, 5/5; □, 3/7; ◇, 0/10. Each point represents the mean ± S.D. (n = 3).

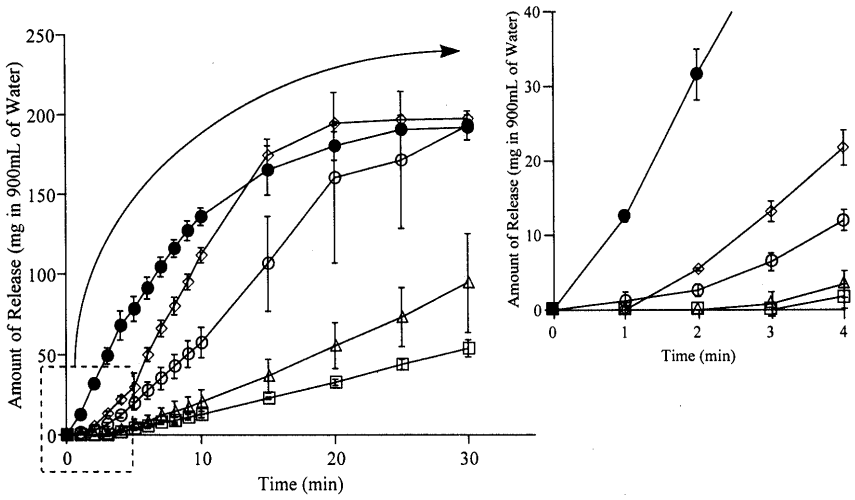

Fig. 3. Release Profiles of AP from Core Tablet and Tablets Coated with OCL-ALNa and UCL-GLCa

Weight ratio of OCL/UCL: ●, core tablet; ○, 7/3; △, 5/5; □, 3/7; ◇, 0/10. Each point represents the mean ± S.D. ($n=3$).

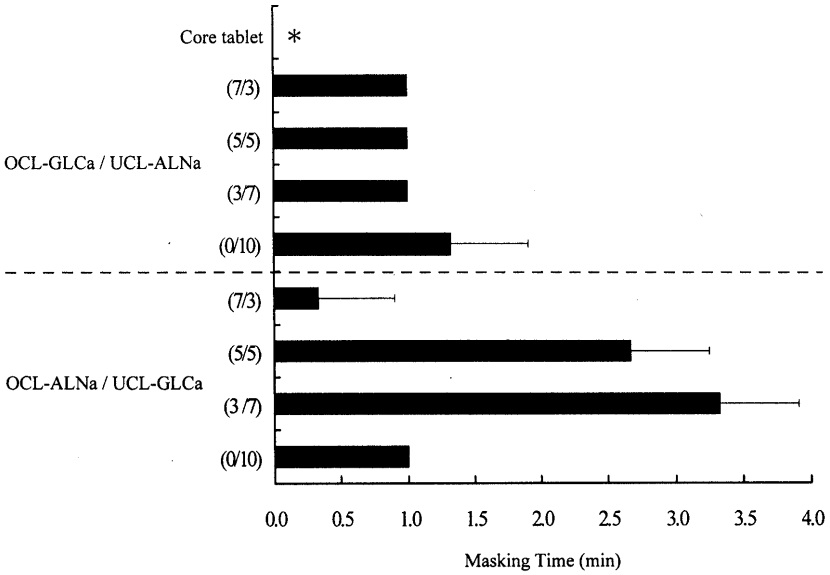

Fig. 4. Masking Time in Various Coated Tablets

*: masking time was not observed. Each column represents the mean ± S.D. ($n=3$).

Figs. 2, 3).

Figure 4 shows the masking time of the core tablet and of the various coated tablets. For the core tablet, there was no masking time, whereas a masking time of 1 min was observed for tablets over-coated with GLCa and under-coated with ALNa. However, the reason why the same masking time was observed for these tablets has yet to be clarified. In the tablets over-coated with ALNa and under-coated with GLCa, the masking time was remarkably increased as the weight ratio of the under layer of GLCa increased. For the tablet singly coated with ALNa or GLCa weight ratio of 0/10 in the upper and lower parts of the graph, each masking time was about 1 min.

External View of Tablet and Component Distribution of Cross-Sectioned Tablet Figure 5 shows the external view of a tablet over-coated with GLCa and under-coated with ALNa, which had a weight ratio of 7/3, as well as the internal structure and composition distribution in this tablet when it was removed during the dissolution test and cross-sectioned. In composition distribution before the dissolution test, GLCa, indicated as the element calcium (red) was recognized in the over layer, and ALNa, indicated as the element sodium (blue) was recognized in the under layer. Inside the coating layers, AP, indicated as the element chlorine (green) was observed. The masking time of this tablet was about 1 min. At 1 min after the dissolution test started, a thin coating barely adhering to the core tablet was observed. In the composition distribution of the tablet, the over layer of GLCa had become thin and coarse. In addition, the under layer of ALNa was no longer observable, but AP, ALNa, and GLCa were found intermingled at the surface of the tablet. Thus, a water-insoluble gel layer had formed at the surface, and AP had started to diffuse through the gel layer. At 3 min after the start of the dissolution test, no coating layer was observed in the optical photograph, and only AP was observed by X-ray microanalysis. These

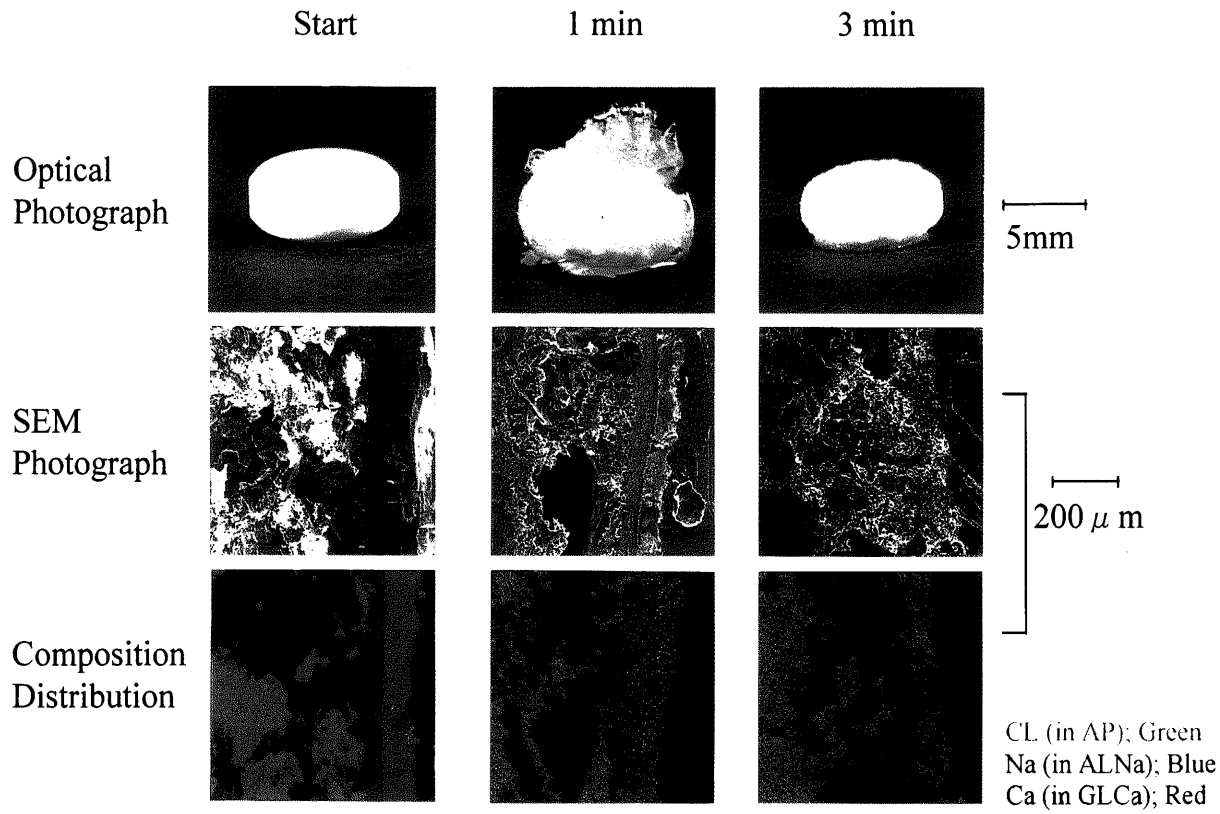

Fig. 5. External View of Tablet Coated with OCL-GLCa/UCL-ALNa = 7/3 and Internal Structure and Composition Distribution of Tablet Removed during the Dissolution Test and Cross-Sectioned

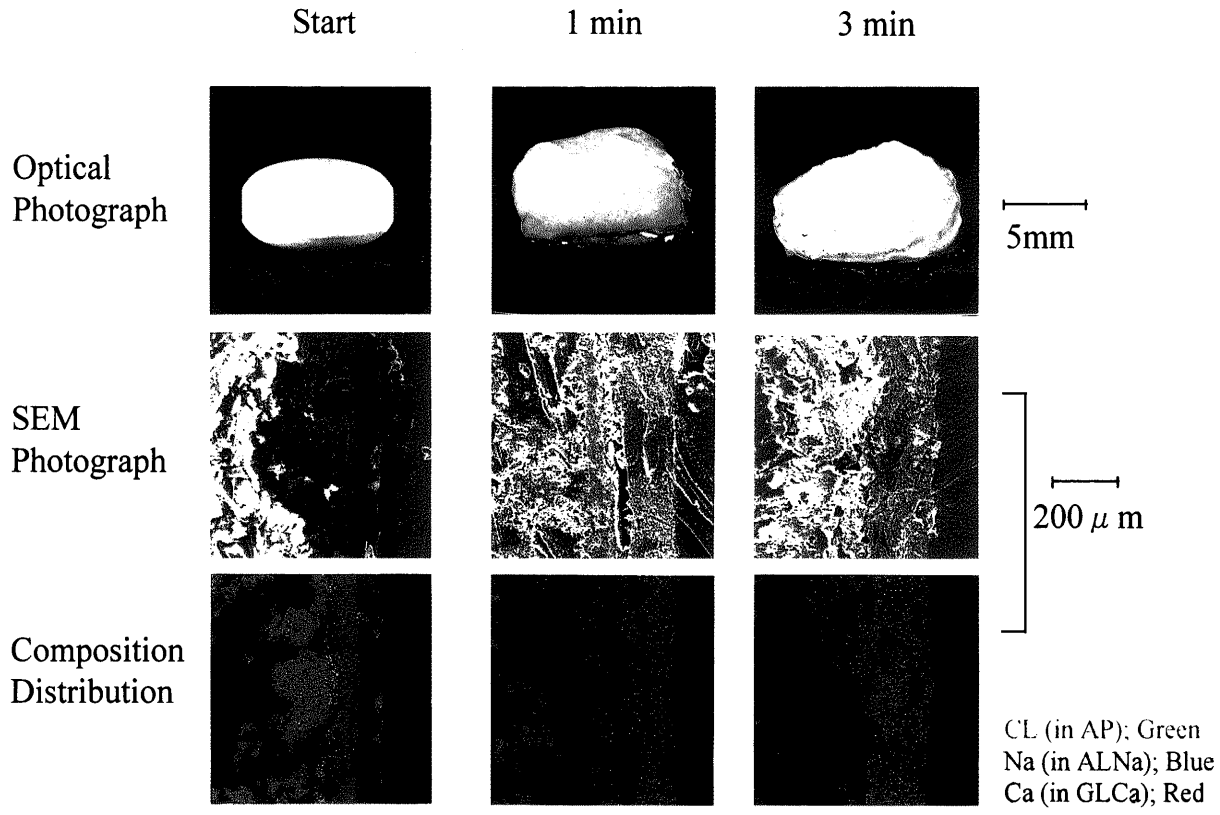

Fig. 6. External View of Tablet Coated with OCL-ALNa/UCL-GLCa = 7/3 and Internal Structure and Composition Distribution of Tablet Removed during the Dissolution Test and Cross-Sectioned

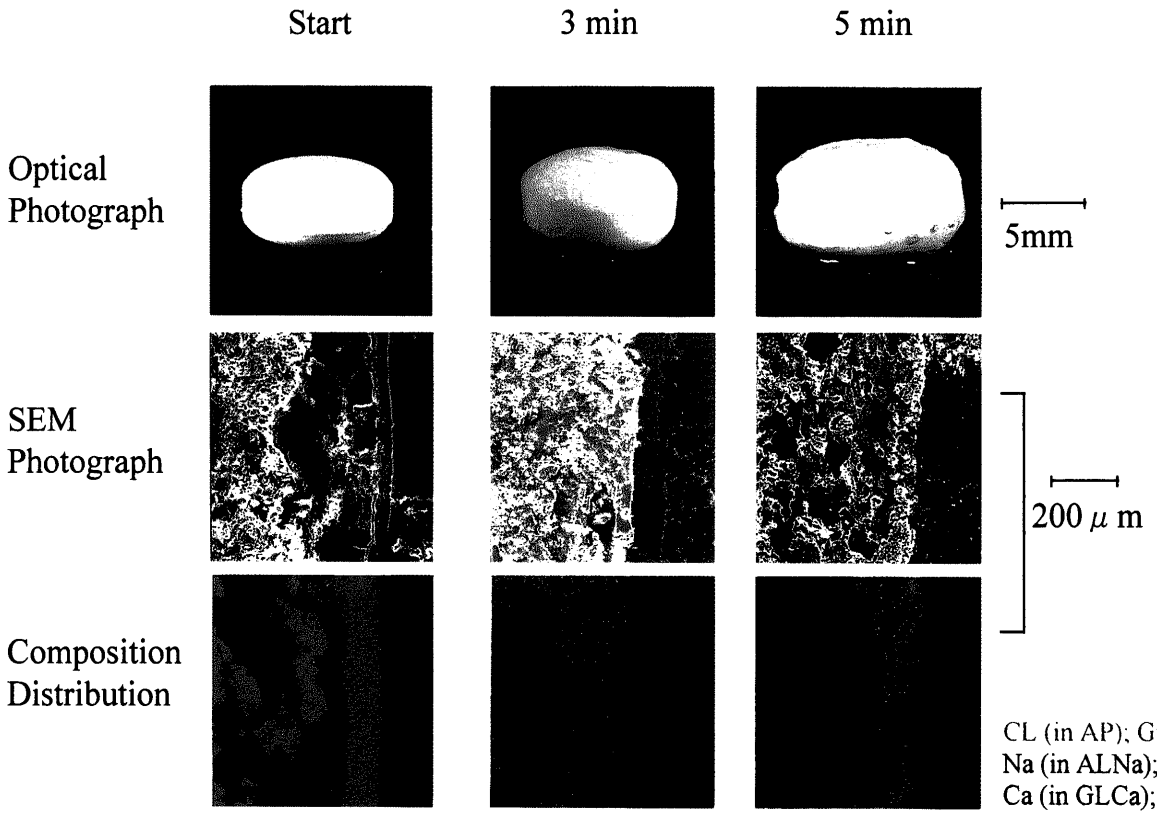

Fig. 7. External View of Tablet Coated with OCL-ALNa/UCL-GLCa = 3/7 and Internal Structure and Composition Distribution of Tablet Removed during the Dissolution Test and Cross-Sectioned

results suggest that a long masking time was not attained by over-coating with GLCa and under-coating with ALNa because GLCa had dissolved in the test fluid before the water-insoluble gel was properly formed.

Figure 6 shows the same changes in a tablet over-coated with ALNa and under-coated with GLCa, which had a weight ratio of 7/3. The masking time of this tablet was about 20 s. At 1 min, an extremely large, swollen gel layer was observed on the surface of the tablet. In terms of composition distribution, the over layer of ALNa was not detectable, and AP was observed to have passed through the GLCa layer and reached the surface of the tablet. These results suggest that an extremely coarse gel layer had formed by this time. At 3 min, the coating layer was more swollen than that at 1 min, and the composition distribution indicated that the GLCa layer had become even more coarse and that GLCa had already been released.

Figure 7 shows the same changes in a tablet over-coated with ALNa and under-coated with GLCa, but having a weight ratio of 3/7. The masking time of this tablet was the longest found in this study, *i.e.*, 3.3 min. In the optical photograph taken at 3 min, a swollen gel layer was observed, and this layer was thinner than that of the comparable tablet over-coated with GLCa and under-coated with ALNa. Based on composition distribution, AP was scarcely observed in the part of the gel layer where GLCa was localized. Thus, AP had not yet diffused into the gel layer from the part of the core tablet adjoining the gel layer, because a thin and dense gel layer had formed to retard the entry of water from outside the tablet. Analysis of composition distribution at 5 min showed the amount of AP to be extremely decreased just beneath the GLCa layer, that is, in the core tablet.

Conclusions

In the case of the tablet over-coated with GLCa and under-coated with ALNa, only a slight water-insoluble gel was formed, and a long masking time was not found because the rate of GLCa release into the test fluid was extremely high. However, when the tablet was over-coated with ALNa and under-coated with GLCa, the masking time was prolonged with increasing amounts of GLCa because of the greater availability of GLCa to cause the formation of a water-insoluble gel. These results suggest that the gel formation on the surface of tablets by under-coating with GLCa and over-coating with ALNa is useful for taste masking of tablets in the mouth at the time of oral administration.

References and Notes

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