Studies on the Development of Intragastric Floating and Sustained Release Preparation. I. Application of Calcium Silicate as a Floating Carrier

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We prepared an intragastric floating preparation using porous calcium silicate (Florite® RE, FLR) as a floating carrier, which has floating ability due to the air included in the pores when they are covered with a polymer, it also has a sustained drug release property. Floating granules were prepared by dropping a 5 or 10% (w/v) ethanol solution of hydroxypropylcellulose (HPC) and ethylcellulose (EC) in 4 different concentration ratios while the FLR was being agitated in a beaker. After the mixture was dried *in vacuo* and sieved, we regarded the granules obtained as primary coated granules (PCG). After drying, the ethanol solution of the polymer was dropped and dried *in vacuo* again, and sieving was carried out to obtain secondary coated granules (SCG). The floating property and surface and inner structures of PCG and SCG were studied. Further, we prepared PCG and SCG including diclofenac sodium (DS) (DS-PCG, DS-SCG) as a model drug, and the drug release profile from these granules was observed. The floating property of SCG was better than that of PCG. A longer floating time was observed with a higher polymer concentration and a lower HPC composition ratio. It was observed by a scanning electron microscope (SEM) and the pore size distribution that more pores of FLR in SCG were covered with polymer than those in PCG. DS-SCG showed a smaller release rate than DS-PCG. These results suggest that FLR is a useful floating carrier for the development of floating and sustained release preparations.

Key words intragastric floating; sustained release; calcium silicate

Recently, many studies have reported on intragastric floating and sustained release preparations[1–3] for the purpose of prolonging both drug effects inside the stomach and the retention of absorption time of a drug in the upper part of small intestine hydrocolloids. For example, preparations[4–6] having floating ability due to carbon dioxide were generated by the reaction of acid and sodium bicarbonate, and a hydrodynamically balanced system (HBS),[7] including a gel-forming polymer, was also proposed.

Calcium silicate, $[2CaO \cdot 3SiO_2 \cdot mSiO_2 \cdot nH_2O \quad (1 < m < 2,\ 2 < n < 3)]$, which has a characteristically porous structure with many pores and a large individual pore volume, has been used as an industrial liquid absorber[8] or a compressive adjuvant of powder.[9] Recently, calcium silicate was approved as a medicinal additive, so it can be widely applied as an absorber of oily drugs[10–12] or as a compressive agent[13–15] for medicine.

In this study, we attempted to prepare an intragastric floating and sustained release preparation which has floating ability resulting from the air trapped in the pores of calcium silicate[16] when they are covered with polymer.

Experimental

Material As a model drug, diclofenac sodium (DS, Takeshima Seiyaku Co., Ltd.), an anti-inflammatory agent, was used. Porous calcium silicate (Florite® RE, FLR, Eisai Co., Ltd.) was used as a floating carrier. Hydroxypropylcellulose L grade (HPC, density = 1.21 g/cm^3) was obtained from Nippon Soda Co., Ltd. Ethylcellulose (EC, density = 1.23 g/cm^3) was purchased from Sinetsu Chemical Industry Co., Ltd.

Preparation of Polymer Coating Solution Five and 10% (w/v) polymer solutions in a 5/95, 10/90, 15/85 and 20/80 composition ratio of HPC and EC were prepared by dissolving them into ethanol. Their viscosities were measured using a Brookfield digital viscometer (Model DV-II+, Kyowa Scientific Co., Ltd.).

Preparation of Floating Granules without Model Drug The preparation method for floating granules and the apparatus used to prepare them are shown in Figs. 1 and 2, respectively. While 15 g of FLR was being agitated by an agitator at 800 rpm in a 500 ml beaker, HPC–EC solution was dropped by a microtube pump at 2.5—2.8 ml/min. When

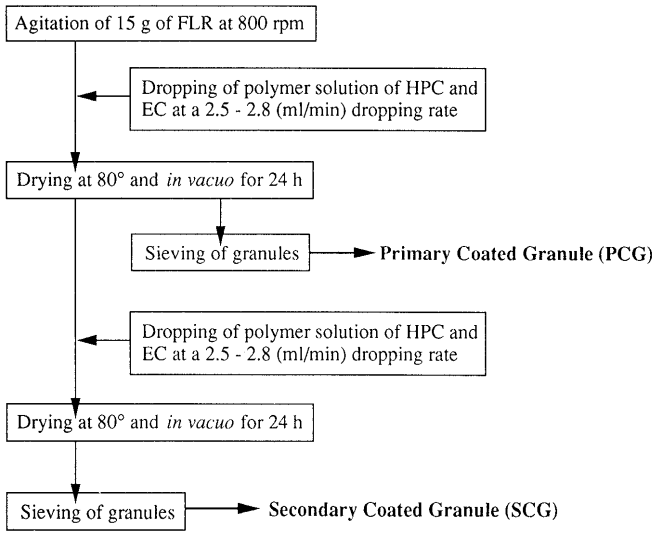

Fig. 1. Preparation Method of Floating Granules

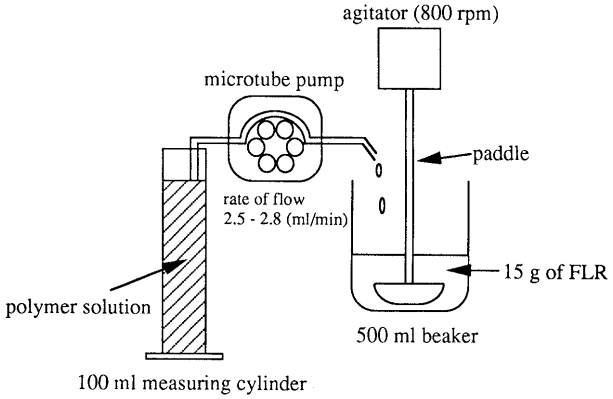

Fig. 2. Apparatus for Granulation

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Table 1. The Viscosity and Volume of Polymer Solution Required for 1 g of FLR in Granulation

HPC/EC	5% (w/v) polymer solution			10% (w/v) polymer solution		
	PCG (ml)	SCG (ml)	Viscosity (m·Pa)	PCG (ml)	SCG (ml)	Viscosity (m·Pa)
5/95	4.3±0.07	8.4±0.07	63.0	4.6±0.08	9.0±0.07	735.5
10/90	4.3±0.05	8.4±0.10	67.9	4.7±0.02	8.9±0.07	865.6
15/85	4.2±0.05	8.5±0.05	70.0	4.6±0.05	8.7±0.13	1007.5
20/80	4.3±0.09	8.4±0.08	79.4	4.5±0.12	8.7±0.05	1278.1

Data represents the mean±S.D. ($n=3$).

a polymer solution was dropped up to a certain volume (±about 1 ml), FLR particles rose up on the wall of the beaker and could no longer be agitated because of the liquid bridges among them. So, this amount was regarded as the end of granulation. After being dried at 80 °C *in vacuo* and sieved (850—1400 μm), primary coated granules (PCG) were obtained. Polymer solution was dropped into unsieved PCG, the coated granules were dried at 80 °C *in vacuo*, and after sieving (850—1400 μm), secondary coated granules (SCG) were obtained.

Preparation of Floating Granule Including Model Drug Fifteen grams of FLR was thrown into 200 ml of 1% (w/v) ethanol solution which had DS dissolved in it, and this solution was ultrasonicated to adsorb the solution inside the pores of FLR while removing the air. After removing the excess ethanol solution by filtration and drying *in vacuo*, FLR powder which had adsorbed DS was obtained. With this FLR powder, including DS, PCS including DS (DS-PCG) and SCG including DS (DS-SCG) were prepared in the same way as above, using a 10% (w/v) polymer solution with a 5/95 composition ratio of HPC and EC.

Floating Test of Granules An aliquot of 0.1 g of granules was immersed in 40 ml of purified water in a vessel maintained at 37 °C. The vessel was then continuously shaken at 37 °C. The granules floating on the surface of water were recovered with a sieve (250 μm sieve opening) at various time intervals. After drying, the granules were weighed. The floating percentage of the granules was defined as the weight ratio of the floating granules against the used granule weight in the floating test.

Measurement of Pore Size Distribution in the FLR Particles, PCG and SCG The pore size distribution in the FLR particles, PCG and SCG, the latter two using a 10% (w/v) polymer solution with a 5/95 composition ratio of HPC and EC, was measured by mercury intrusion porosimetry, employing a mercury porosimeter (Quantachrome Co., Autscan-33).[17] The contact angle of mercury with the samples and the surface tension of mercury were regarded as 140° and 480 dyn/cm, respectively.[18]

Observation of the Surface of FLR Particles, PCG and SCG A scanning electron microscope (SEM, Hitachi Seisakusho Co., Ltd., Type S-2250N) was used to observe the surface of the FLR particles, PCG and SCG, the latter two using a 10% (w/v) polymer solution with a 5/95 composition ratio of HPC and EC.

Dissolution Study The release behavior of DS from DS-PCG and DS-SCG was observed using a flow sampling system (dissolution tester; DT-300, triple flow cell; DTF-359, spectrophotometer; UVIDEC-340, Freund-JASCO) following the paddle method (JP XII) at 100 rpm. Nine hundred milliliters of distilled water at 37±0.5 °C was used as a dissolution medium. The DS content in the granules was determined by spectrophotometry, and the sample weight was defined as the amount of granules containing 15 mg of DS. The quantity of DS was determined by the absorbance at 275 nm.

Results and Discussion

Effects of the Viscosity and Concentration of Polymer Solution on the Amount of Polymer Adsorbed to FLR Particles The viscosity and volume of a polymer solution required for 1 g of FLR in the granulation of each kind of granule are listed in Table 1, and the amount of polymer adsorbed to 1 g of FLR in Table 2. The viscosity of polymer solution increased with increasing polymer concentration. While the viscosity increased with an increasing HPC composition ratio, the volume of polymer solution required for 1 g of FLR in granulation remained nearly identical. At each concentration of polymer solution, its volume required for the granulation of SCG was slightly less than twice as large as that of PCG. The amount of adsorbed polymer showed the same tendency. It suggests that the pore volume decreased because the pores were covered with the polymer layer adsorbed by drying in the granulation of PCG.

Table 2. The Amount of Polymer Adsorbed for 1 g of FLR

HPC/EC	5% (w/v) polymer solution		10% (w/v) polymer solution	
	PCG (mg)	SCG (mg)	PCG (mg)	SCG (mg)
5/95	215.6±5.1	413.3±3.3	457.8±7.7	895.6± 3.8
10/90	215.6±1.9	417.8±1.9	465.6±1.9	888.9±10.2
15/85	214.4±5.1	420.6±6.7	462.2±5.1	870.0±12.0
20/80	214.4±3.8	416.7±4.4	453.3±1.5	874.4± 5.1

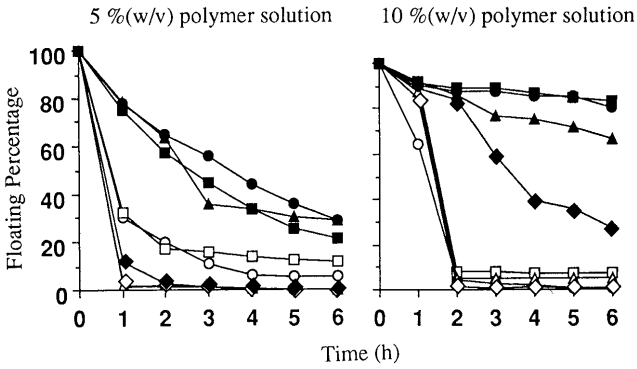

Fig. 3. Effects of Concentration and Composition Ratio of HPC and EC of Polymer Solution on Floating Percentage of PCG and SCG

Ratios of HPC and EC of PCG and SCG: ○, ●; 5/95: □, ■; 10/90: △, ▲; 15/85: ◇, ◆; 20/80.

Effects of the Concentration and Composition Ratio of Polymer Solution on the Floating Property of Granules Figure 3 shows the results of the floating test of granules which were prepared with a 5 or 10% (w/v) polymer solution. In the case of the preparations using 5% (w/v) polymer solution, while each PCG showed a low floating percentage after 1 h, SCG showed a high floating percentage (70—80%) after 1 h, except when using a 20/80 composition ratio of HPC and EC, and then in each case the floating percentage gradually decreased. On the other hand, in the case of the preparations using 10% (w/v) polymer solution, the floating percentage of each PCG significantly decreased after 2 h. The floating percentage of SCG was higher than that of PCG, and also showed a tendency to decrease with an increasing HPC ratio in the polymer solution. Especially, the floating percentage of

SCG using a 20/80 composition ratio of HPC and EC remarkably decreased. This suggests that the density of the granules increased because water permeated into the pores of FLR as HPC eroded, since HPC begins to erode slightly when the HPC ratio of the HPC–EC matrix system is over 15%.[19] These results show that it is possible to create a high floating property with SCG using a 10% (w/v) polymer solution which has high viscosity.

The Surface State and Internal Structure of FLR Particles, PCG and SCG The pore size distributions of FLR particles, PCG and SCG are shown in Fig. 4. Figure 4a is represented in frequency curves and Fig. 4b in cumulative curves. It is observed from Fig. 4a that FLR had many pores with diameters of about 0.15 and 12 μm, which are considered to be intraparticle pores and interparticle pores, respectively. In Fig. 4b, PCG and SCG showed a decreased volume of intraparticle and interparticle pores. This may have been caused by the FLR particles being covered with polymer, with liquid bridges formed once the polymer solution was adsorbed. It is possible that the decrease in pore volume was caused by the mechanical breakage of pores when the FLR particles were agitated. However, we certified that there was no significant difference ($p<0.05$) when we measured the change in pore volume of FLR particles several 5 min periods of agitation for 30 min. Figure 5 shows SEM views of the surfaces of the FLR particles, PCG and SCG. In Fig. 5A, FLR appears as petal structures because of the scaly crystals of calcium silicate which form many of the pores. With PCG, the adsorption of polymer was observed to the extent that it was still possible to observe petal structures (Fig. 5B), whereas with SCG, the area of pores of FLR covered with a polymer increased, showing that a lot of pores were covered with polymer in secondary granulation. On the basis of these results, the formation processes for PCG and SCG as shown in Fig. 6 were considered. In the primary coating process, because the viscosity of the polymer solution is high (Table 1) and the contact angle is large, the polymer may cover the upper part of the pores of FLR when it is adsorbed, as shown in B. After drying *in vacuo*, the polymer layer may be formed, including air in the pores of FLR, as shown in

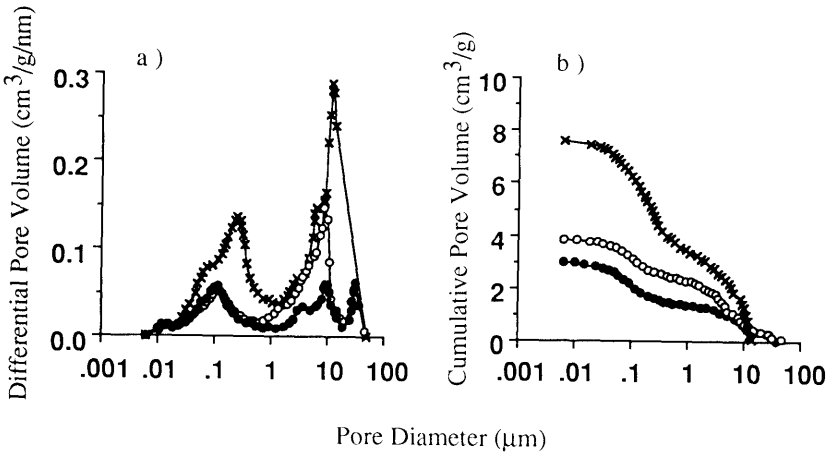

Fig. 4. Pore Size Distributions of FLR Particles, PCG and SCG

a) Differential pore volume, b) cumulative pore volume. ×, FLR particles; ○, PCG; ●, SCG. These granules were prepared with a 10% (w/v) polymer solution with a 5/95 composition ratio of HPC and EC.

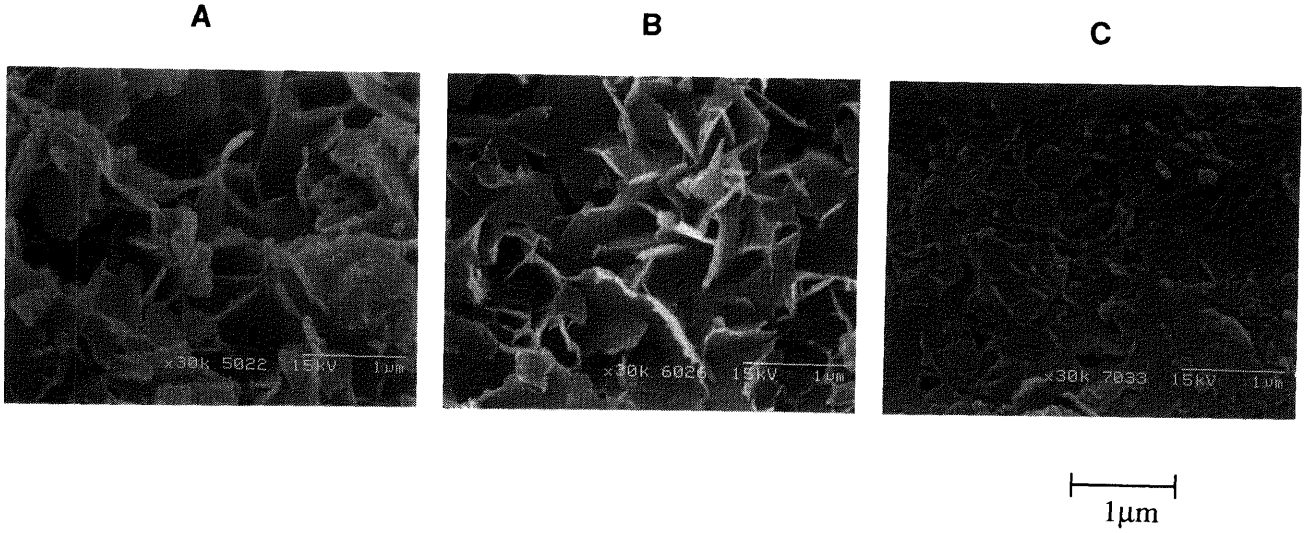

Fig. 5. Scanning Electron Microscopic Views of FLR Particles, PCG and SCG (×30000)

A, FLR particles; B, PCG; C, SCG. These granules were prepared with a 10% polymer solution with a 5/95 composition ratio of HPC and EC.

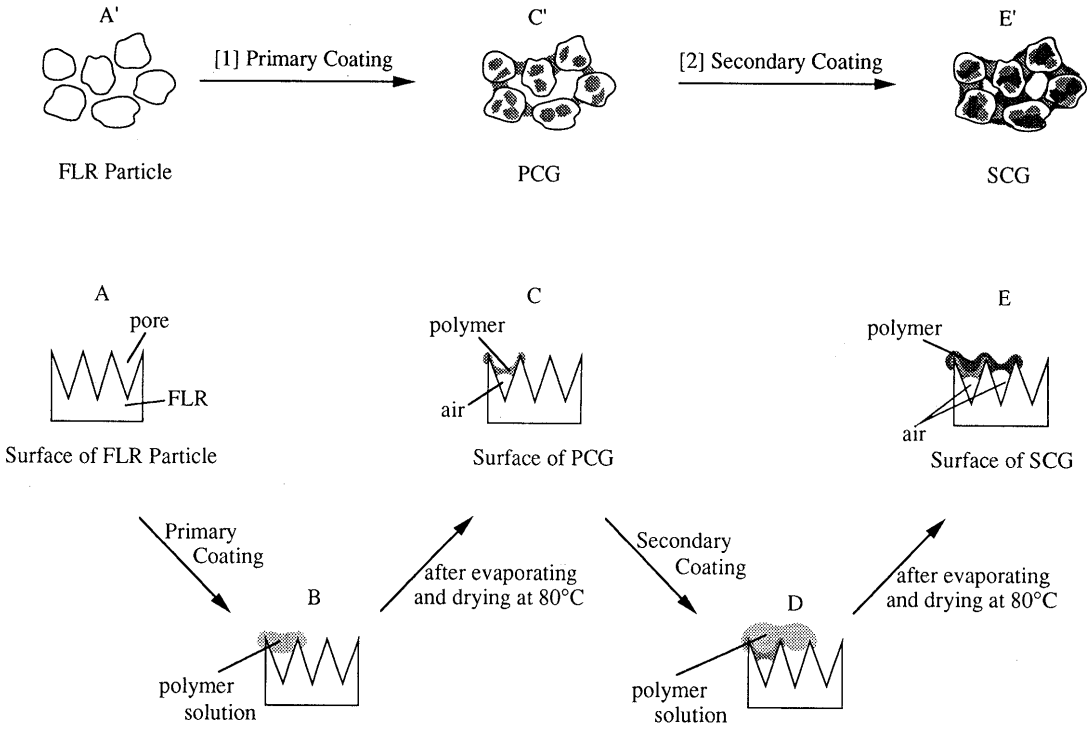

Fig. 6. Proposed Schemes of the Formation Process of PCG and SCG

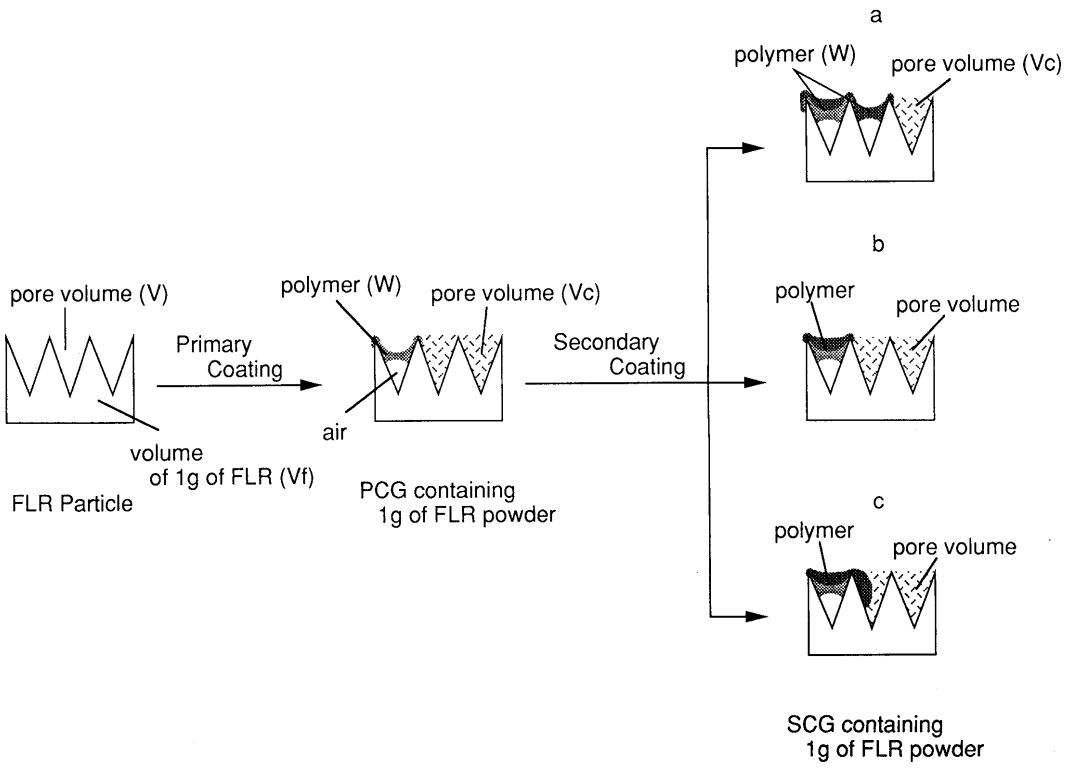

Fig. 7. Calculation Method for the Apparent Density of Coated Granules

C. The polymer solution also acts as a binder, and therefore, PCG may form polymer bridges between FLR particles when they are prepared, as shown in C'. In the secondary coating process, when the polymer solution drops into PCG, it may be adsorbed on the polymer layer formed during primary coating, and on the upper part of the pores which had not been covered in primary coating, as shown in D. After drying *in vacuo*, SCG may cover more pores and form a thicker layer than C when they are prepared, as shown in E. It is thought that if PCG and SCG are prepared according to this coating process, the decrease in pore volume, as measured with a mercury porosimeter, occurs because the intraparticle and interparticle pores of FLR in the granules are covered with a polymer. It could be considered that this decrease explains the increase in the apparent volume of the granules shown

in Fig. 7. Therefore, the apparent densities of PCG and SCG were calculated according to the following equations.

$$\rho=(1+W)/\{V_f+(V-V_c)\}$$

where ρ is apparent density of the coated granule, V_f is the real volume of 1 g of FLR, V is the pore volume in 1 g of FLR, V_c is the pore volume in coated granules containing 1 g of FLR, and W is the weight of polymer adsorbed in the coated granule containing 1 g of FLR. The results are shown in Fig. 8. The apparent densities of PCG and SCG were lower than 1 (g/cm^3), and so they have the ability to float. Those of SCG were higher than those of PCG. The change in apparent volume with decreasing V_c occurred only slightly, probably because the polymer layers in SCG were formed as shown in Fig. 7b and 7c rather than in Fig. 7a. No change in density was observed with the different composition ratios of HPC and EC of the polymer solution, which may be attributed to nearly the same densities of HPC and EC. These results show that the granules which have a floating ability are prepared by involving the air into the pores with a polymer solution of high viscosity. Therefore, we prepared granules including DS and studied the floating ability and the release property of DS from these granules.

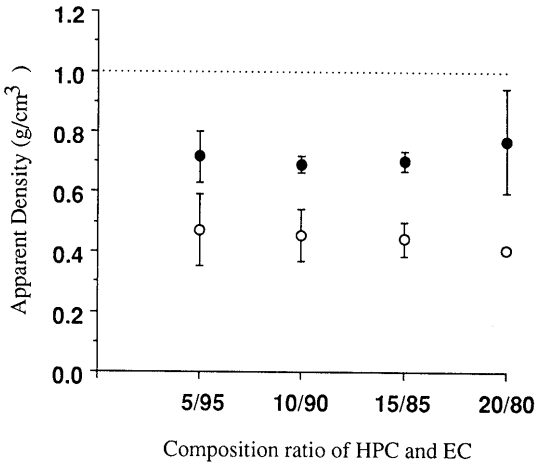

Fig. 8. Effects of Composition Ratios of HPC and EC on Apparent Densities of PCG and SCG

○, PCG; ●, SCG. Each value presents the mean±S.D. of three experiments.

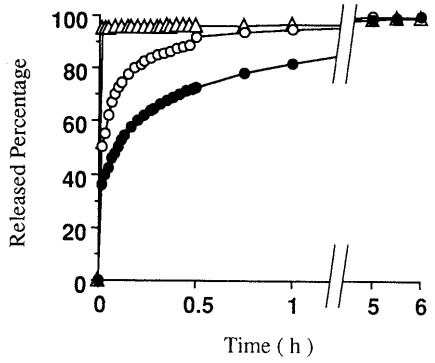

Fig. 9. Release Profiles of DS from DS-PCG and DS-SCG

△, DS powder; ○, DS-PCG; ●, DS-SCG.

The Floating Ability and Release Profile of DS from DS-PCG and DS-SCG Figure 9 shows the release profiles of DS from DS-PCG and DS-SCG. The released percentage of DS powder reached nearly 100% after about 1 min from the start. DS-PCG and DS-SCG showed sustained release profiles, and the release rate of DS from DS-SCG was smaller than that from DS-PCG. The initial high release rates of DS from DS-PCG and DS-SCG were attributed to the dissolution of DS from that part of the pores uncovered with polymer. The relation between the floating percentage of primary and secondary coated granules and the released percentage of DS from each is shown in Fig. 10. In primary coating, the floating percentage of DS-PCG appeared to be more than 80%, whereas that of PCG was very low after 2 h from the start. It was found that the preliminary adsorption of a drug to FLR particles caused a marked increase in the floating percentage. The amounts of polymer adsorbed in the preparation of DS-PCG and DS-SCG were almost equal to those of PCG and SCG. However, it is not clear why the floating percentage improved when the drug was included in the primary coating. The released percentage of DS from DS-PCG reached almost 100% after about 3 h. On the other hand, in secondary coating, the floating percentage of DS-SCG and SCG were nearly the same. The release behavior of DS from DS-SCG showed a sustained release, and about 100% of DS was released after 6 h from the start.

Conclusions

It is possible to prepare an intragastric floating and sustained release preparation using FLR as the floating carrier by covering the pores of the FLR adsorbing a drug

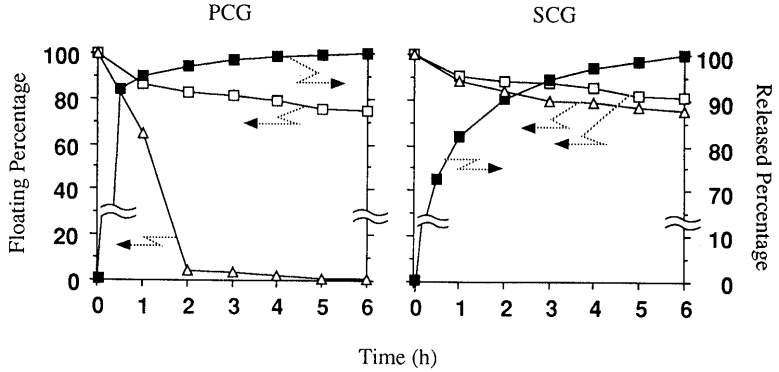

Fig. 10. Relationship between the Floating Percentage of Granules and the Release Profiles of DS from PCG and SCG

△, floating percentage of granules without DS; □, floating percentage of granules containing DS; ■, released percentage of granules containing DS.

with a polymer composed of HPC and EC and involving the air into the pores. Furthermore, the floating ability of the granules and the release rate of a drug from the granules can be controlled by changing the amount of added polymer as well as the composition ratio of the HPC and EC of the polymer solution.

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