Studies on Production of Higher Functional Pharmaceutical Preparations by Using Various Additives. III.[1] Application of Hollow Glass Beads for Intragastric Floating Granules

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In our previous paper, we developed intragastric floating and sustained release granules using the characteristically porous structure of calcium silicate. In this paper, we investigated the preparation of floating granules using hollow glass beads (GB, density 0.15 g/cm^3) as a carrier and introducing them to the solid dispersion in order to produce a higher floating ability. A 20/5/75 weight ratio of oxprenolol hydrochloride (OXP) as a model drug, hydroxypropylcellulose (HPC) and ethylcellulose (EC) was dissolved in ethanol. Zero, 20, 40, 60 and 80 weight percent of GB to the total weight of OXP, HPC and EC were added to the ethanol solution, and the solvent was then evaporated by rotating the vessel at 50 °C. Several types of solid dispersion which contain suspended and dispersed GB were obtained. The granules having different GB contents were obtained after being dried at 80 °C *in vacuo* and were crushed using a coffee mill for sieving. The density, floating property and drug release profile of the granules were then studied. The density of granules without GB, namely the solid dispersion granules, was 1.18 g/cm^3 and therefore did not have floating properties. The densities of all types of granules containing GB were less than 1 g/cm^3 and these granules floated for a long time in the floating test. It was found that release rates of OXP from granules decreased with decreasing GB content, since the surface area of granules was decreased and a thick layer of solid dispersion was formed. These results suggest that it is possible to prepare floating granules by using GB.

Key words intragastric floating; glass bead; granule

A number of studies have been reported on intragastric floating preparations[2–5] for the purpose of prolonging both drug effects inside the stomach and absorption time of a drug in the upper part of the small intestine. We earlier reported the development of intragastric floating and sustained release granules using porous calcium silicate as a floating carrier.[6] In this report, we studied the possibility of preparation of floating granules having higher floating ability using hollow glass beads (GB) as a carrier and dispersing them into the solid dispersion.

Experimental

Materials Hollow glass beads (glass bubbles®, GB, Sumitomo 3M Co., Ltd., Tokyo) were used as a carrier, with a density (d) of 0.15 g/cm^3. Oxprenolol hydrochloride (OXP, known as a β-adrenaline inhibitor, 1 g of which dissolves in less than 2 ml of water at 37 °C, d=1.20 g/cm^3) was supplied by Nihon Pharmaceutical Industry Co., Ltd., Tokyo. Hydroxypropylcellulose L grade, (HPC, d=1.21 g/cm^3) was obtained from Nippon Soda Co., Ltd., Tokyo. Ethylcellulose (EC, d=1.23 g/cm^3) was supplied by Sin-Etsu Chemical Industry Co., Ltd., Tokyo.

Preparation of Floating Granules The formulation of granules is shown in Table 1. A 20/5/75 weight ratio of OXP, HPC and EC was dissolved in 300 ml of ethanol[7] and GBs were suspended into this solution. Solvent was then evaporated by rotating the vessel at 50 °C. After drying at 80 °C for 16 h *in vacuo*, the residue was crushed using a coffee mill and then sieved. Fractions of 850—1400, 500—850, and 250—500 μm were collected as granule sizes of L, M and S, respectively. L size granules were used in the cases where no description of the granule size was given.

Observation of the Surface of GB Particles and Granules A scanning electron microscope (SEM, Hitachi Ltd., Tokyo, S-2250N) was used to observe the surface of the GB particles and the granules.

Measurement of Density of Granules The density of the granules was determined using an air comparison pycnometer (Toshiba-Beckman Co., Ltd., Tokyo, model 1000) and was calculated from a mean of five determinations.

Floating Test A fixed weight of the granules was immersed in purified water in a vessel maintained at 37 °C. The vessel was then continuously shaken at 37 °C. Particles floating on the surface of the water were recovered by filtration of the supernatant fluid with a filter paper (Toyo Roshi Kaisha, Ltd., type No. 1) at various time intervals, and then dried *in vacuo*. After drying, the particles were weighed. The floating percentage of the granules was calculated using the following equation:

$$\text{floating percentage} = \frac{W_a}{W_b - W_o} \times 100$$

where W_a is the weight of the particles recovered, W_b is the weight of the granules immersed, and W_o is the weight of OXP released at that time.

Measurement of Pore Size Distribution in Granules The pore size distribution in the granules was measured by mercury intrusion porosimetry,[8] employing a mercury porosimeter (Quantachrome Co., Autoscan-33). The contact angle of mercury with the samples and the surface tension of mercury were regarded as 140° and 480 dyn/cm, respectively.[9]

Dissolution Study The release behavior of OXP from the granules 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 the dissolution medium. The OXP content in the granules was determined from the absorbance at 283 nm.

Table 1. Formulation of Granules

	GB content (%)				
	0	20	40	60	80
GB	—	20	40	60	80
OXP	20	16	12	8	4
HPC	5	4	3	2	1
EC	75	60	45	30	15

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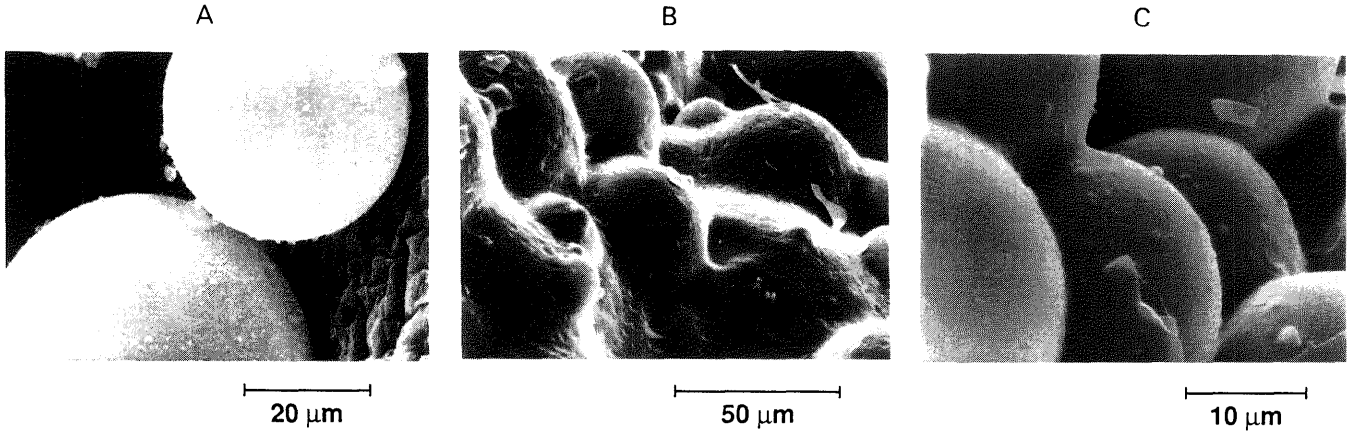

Fig. 1. Scanning Electron Microscopic Photographs of GB Particles and Granules
A, Surface of GB particles; B, Surface of granules with a 20% GB content; C, Surface of granules with a 60% GB content.

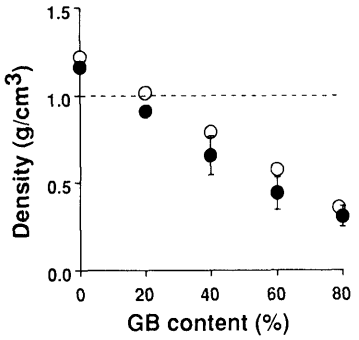

Fig. 2. Effect of GB Content (%) on Density of Granules
○, calculated density; ●, measured density.
Each point represents the mean ± S.D. ($n=3$).

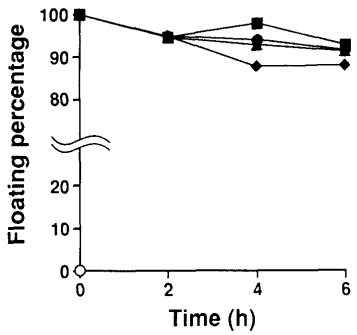

Fig. 3. Effect of GB Content(%) on Floating Percentage of Granules
GB content (%): ○, 0; ●, 20; ■, 40; ▲, 60; ◆, 80.

Results and Discussion

Observation of the Surface of GB Particles and Granules Figure 1 shows SEM photographs of the surface of the GB particles and granules. The GB particle is a spherical particle with a mean diameter of about 30 μm, as shown in Fig. 1A. As shown in Fig. 1B, GB particles in granules with a 20% GB content, *i.e.* granules containing 80% solid dispersion, were buried in the matrix, and a thick layer of the solid dispersion was formed. However, in granules with a 60% GB content, *i.e.* granules containing 40% solid dispersion, the matrix was mainly affixed to the points of contact between the GB particles.

Floating Property of Granules Figure 2 shows the densities of the granules measured by using an air comparison pycnometer and calculated by using the true densities of the constituent materials. The measured and calculated densities were approximate values. In all granule types, the measured density was slightly lower than the calculated value. It is thought that this is because air bubbles were incorporated into the granules when the solvent was evaporated. In all granules with greater than 20% of GB, the measured density was less than 1 g/cm^3, thus they are expected to have floating properties. Therefore the floating property of the granules was studied by the floating test and results are shown in Fig. 3. Granules without GB, whose density was higher than 1 g/cm^3, sank immediately, and thus had no ability to float. On the other hand, granules with GB showed a high floating percentage (90—95%) at 6 h from the start of the experiment. The floating percentage showed a tendency to decrease with increasing GB content in the granules. It is thought that this occurred because the amount of crushed GB particles and solid dispersion particles with crushed GB, (made using a coffee mill) increased with increasing GB content. Thus most of the fractured surfaces in the granules were occupied by GB particles due to the decreased amount of solid dispersion forming bridges between the GB particles.

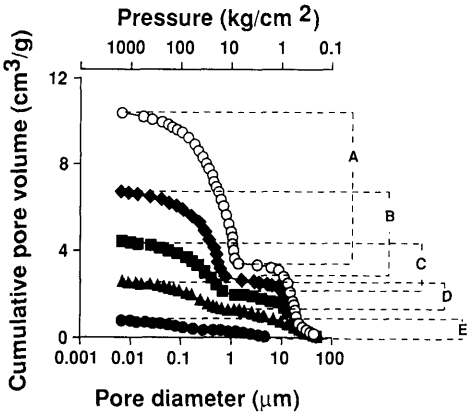

Fig. 4. Pore Size Distribution in GB Particles and Granules
○, GB particles. GB content (%) in granules: ●, 20; ▲, 40; ■, 60; ◆, 80.

Internal Structure of Granules Figure 4 shows the pore

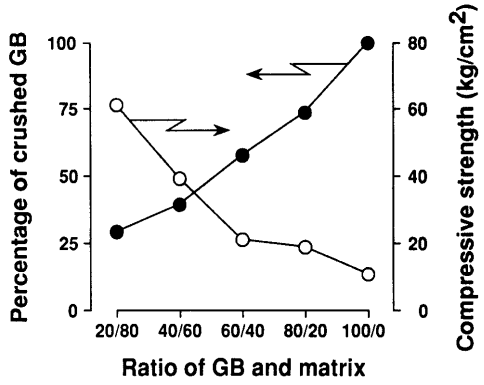

Fig. 5. Percentage of Crushed GB and Compressive Strength of GB in Granules

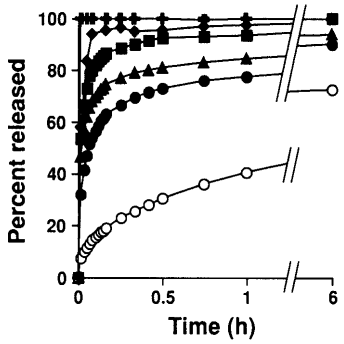

Fig. 6. Effect of GB Content (%) on Percentage of OXP Released from Granules

+, OXP powder. GB content (%): ○, 0; ●, 20; ▲, 40; ■, 60; ◆, 80.

size distribution of GB particles and granules with GB. In GB particles, pores with mean diameters of about 20 μm and less than 1.5 μm were observed. It is considered that pores with a mean diameter of about 20 μm are interparticle pores. In granules with GB, cumulative pore volume decreased with decreasing GB content. This may be due to an increase in the amount of solid dispersion filling the interparticle pores among GB particles with low GB content. The pores with a mean diameter of less than 1.5 μm were presumed to be caused by crushed GB because the pressure of mercury at the measurement exceeded about 18 kg/cm^2, which is the compressive strength of GB.[10] The mean diameter of pores in GB particles made from crushed GB decreased with decreasing GB content. Figure 5 shows the relationship between GB content and the percentage of crushed GB and the compressive strength of GB in the granules. The pressure of mercury at the rising point on the plot in Fig. 4 was considered to be the compressive strength. The percentage of crushed GB in each type of granule was calculated by B/A × 100, C/A × 100, D/A × 100, E/A × 100 in Fig. 4, respectively, where A is the volume of the pores made by crushed GB in the case of GB alone, and B, C, D and E are the volume of the pores made by crushed GB in each type of granule. It was observed that the percentage of crushed GB decreased with increasing ratio of solid dispersion, due to the decreased GB content in the granules, whereas the compressive strength of the GB increased. These results suggest that the compressive strength of GB increased because the GB

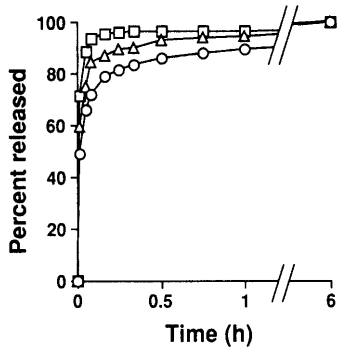

Fig. 7. Effect of Particle Size of Granules on Percentage of OXP Released from Granules

Particle size of granules: ○, L (850—1400 μm); △, M (500—850 μm); □, S (250—500 μm).

particles were covered with a thicker layer of solid dispersion.

Release Profile of OXP from Granules The release profile of OXP powder and OXP from granules is shown in Fig. 6. The percentage of released OXP powder reached nearly 100% about 1 min after initiation, because OXP powder is an extremely water soluble medicine. Release rates of OXP from granules decreased with decreasing GB content. This may be explained as follows; the surface area of solid dispersion exposed to the dissolution medium per unit weight of granule decreased with decreasing GB content in the granules, since a thicker layer of the solid dispersion was formed, as shown in Fig. 1. This means a decrease in the number of OXP molecules on the surface of the solid dispersion. Thus, OXP released by diffusion through the HPC hydrogel layer in the solid dispersion increases with decreasing GB content in the granules.[11] Figure 7 shows the release profile of OXP from granules with different particle sizes (size L, M and S) in granules with 40% GB. The release rate of OXP was larger with the smaller granule size, since the specific surface area is larger with the smaller size granule. Moreover, the floating percentage was about 90% for all sizes after 6 h from initiation, and no effect of granule size on floating ability was observed. In our previous paper,[12] we reported that the pH of the dissolution medium on the release profile of OXP from the solid dispersion had no effect. Therefore, the release profile of OXP from the floating granules should not be affected by pH of the dissolution medium.

Conclusion

These results suggest that it is possible to prepare intragastric floating granules using hollow glass beads as a floating carrier and dispersing them into the solid dispersion. Furthermore, it has been clarified that the release rate of a drug from the granules can be controlled by changing the ratio of the solid dispersion and GB, as well as the size of the granules.

References and Notes

1) We designate this article as Part III of "Studies on Production of Higher Functional Pharmaceutical Preparations by Using Various Additives"; Parts I and II of the series are "Application of Calcium Silicate for Medicinal Preparation.I" published in *Chem. Pharm. Bull.*, **42**, 2327—2331 (1994) and "Studies on the Development of

Intragastric Floating Preparation. I" published in *Chem. Pharm. Bull.*, **44**, 1361—1366 (1996), respectively.
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