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Research paper

Physicochemical properties to determine the buoyancy of hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method

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Abstract

Hollow microspheres (microballoons) floatable on JPXIII No.1 solution were developed as a dosage form capable of floating in the stomach. Hollow microspheres were prepared by the emulsion solvent diffusion method using enteric acrylic polymers with drug in a mixture of dichloromethane and ethanol. It was found that preparation temperature determined the formation of cavity inside the microsphere and the surface smoothness, determining the floatability and the drug release rate of the microballoon. The correlation between the buoyancy of microballoons and their physical properties, e.g. apparent density and roundness of microballoons were elucidated. The drug loading efficiency of microballoons with various types of drug was investigated and correlated to the distribution coefficient of drug between dichloromethane and water. The optimum loading amount of riboflavin in the microballoon was found to impart ideal floatable properties to the microballoons. On the other hand, little entrapment was observed for aspirin due to the low distribution coefficient; however, entrapment improved to some extent upon reduction of the pH of the process.

Keywords: Floating controlled drug delivery system; Floating microsphere (microballoon); Emulsion solvent diffusion method; Methacrylic acid copolymer (Eudragit® S100); Buoyancy; Porosity

1. Introduction

Various types of drug delivery systems for oral administration such as drug release rate-controlled delivery systems, time-controlled delivery systems and site-specific delivery systems have been extensively developed. In the cases of rate-controlled and time-controlled delivery systems, sustained drug absorption time is limited to the transit time of the dosage form through the absorption site because, thereafter, the released drug is not absorbed. Thus, when a drug possesses a narrow 'absorption window', design of the sustained release preparation requires both prolongation of gastrointestinal transit of the dosage form and controlled drug release.

A dosage form targeting the gastrointestinal tract is designed to release a drug at a gastrointestinal site. Several gastrointestinal targeting dosage forms [1–3], including intragastric floating systems [4–6], high density systems [1], mucoadhesive systems adhering to the gastric mucosal surface to extend gastric residence time [7], magnetic systems [8], unfoldable extendible or swellable systems [9] and superporous hydrogel systems [10] have been developed. A swellable system must be compressible to a small size and expandable to a sufficiently large size to prevent the transit through the pylorus following oral administration [11].

On the other hand, an intragastric floating system can remain in the stomach, resulting in better drug absorption at the proximal small intestine as well as in the stomach. A hydrodynamically balanced system (HBS) [12,13] was initially described as a floating device with a density lower than that of water. A disadvantage of this system is the high variability of gastrointestinal transit time, due to its all-or-nothing emptying process. Therefore, a multiple-unit

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floating system that can be distributed widely throughout the gastrointestinal tract, providing the possibility of achieving a longer-lasting and more reliable release of drugs, has been sought. Kawashima et al. [14] developed a multiple-unit intragastric floating system involving hollow microspheres (microballoons) with excellent buoyant properties. This gastrointestinal transit-controlled preparation is designed to float on gastric juice with a specific density of less than 1. This property results in delayed transit through the stomach, which could be applicable for a drug absorbed mainly at the proximal small intestine, such as riboflavin.

In the present study, optimum preparation temperature with respect to microballoon cavity formation and factors influencing the buoyancy properties of microballoons were examined. Additionally, five different drugs, which exhibited distinct water solubilities, were tested in terms of entrapment within microballoons. The efficiency of drug entrapment into microballoons and the buoyancy properties of the microballoons were also investigated.

2. Material and method

2.1. Materials

The following drugs were employed (water solubility at room temperature is shown in parenthesis): aspirin (3 mg/ml), salicylic acid (2 mg/ml), ethoxybenzamide (<0.1 mg/ml), indomethacin (<0.1 mg/ml) and riboflavin (0.1 mg/ml). As explained in the previous report [15], Eudragit® S100 (Röhm Pharma GmbH, Germany) was utilized as an enteric polymer soluble at pH > 7.0. Monostearin (Han-i Chemical, Japan) served as a wall membrane-reinforcing agent and polyvinyl alcohol (PVA-120, Kuraray, Japan) functioned as a dispersing agent.

2.2. Preparation of microballoons

Microballoons were prepared by the emulsion solvent diffusion method established by Kawashima et al. [15] as follows: a drug (0.1–1.0 g), Eudragit® S100 (1.0 g) and monostearin (0.5 g) were dissolved or dispersed in a mixture of dichloromethane (8 ml) and ethanol (8 ml) at room temperature. The solution of aspirin, salicylic acid, ethoxybenzamide, indomethacin or suspension of riboflavin was poured into an aqueous solution of polyvinyl alcohol (0.75 w/v%, 200 ml) at various temperatures, 20, 30, 40 and 50°C. Polyvinyl alcohol was added to Sørensen buffer solutions (0.1 M Sodium citrate – 0.1 M HCl, pH 1.24–4.74), when changes in the pH of the aqueous medium were required. The resultant emulsion or suspension was stirred at 300 rpm employing a propeller type agitator for 1 h. Subsequently, the resulting microballoons were sieved between 500 and 1000 μm and dried overnight at 40°C.

2.3. Observation of appearance and cross section of microballoon

Appearance and cross section of microballoon were observed via a scanning electron microphotograph (SEM) (JSM-T330A, Nihon Densi, Japan).

2.4. Measurement of physicochemical properties of microballoons

2.4.1. Recovery

Recovery of microballoons containing a drug was determined by the weight ratio of the dried microballoons to the loading amount of the drug, Eudragit® S100 and monostearin.

2.4.2. Buoyancy

Microballoons (100 mg) were dispersed in JPXIII No. 1 solution (300 ml, pH 1.2, 37°C) containing Tween 20 (0.02 w/v%). The mixture was stirred with a paddle at 100 rpm. After 12 h, the layer of buoyant particles was pipetted and the floating particles were separated by filtration. Particles in the sinking particulate layer were separated by filtration. Both particles types were dried at 40°C overnight. Each weight was measured and buoyancy was determined by the weight ratio of the floating particles to the sum of floating and sinking particles.

2.4.3. Apparent particle density

Apparent particle density was determined by the projective image count method as follows. Microballoons were placed on a glass plate. Heywood diameter and microballoon number were measured by an Image Processing and Analysis System (Q5001W, Leica, Japan). Subsequently, the apparent particle density was calculated according to Eq. (1).

Apparent particle density

$$= W/V = W/\sum(\pi \cdot d^3 \cdot n/6) \quad (1)$$

W, weight of microballoons; V, volume of microballoons; d, Heywood diameter; and n, number of microballoons.

2.4.4. True density

True density of the microballoons was measured by a Helium-Air Pycnometer (No. 1305, Shimadzu, Japan).

2.4.5. Porosity

Porosity of microballoons was calculated according to Eq. (2).

Porosity of microballoons

$$= (1 - \rho_p/\rho_t) \times 100(\%) \quad (2)$$

ρ_p, apparent particle density of microballoons; and ρ_t, true density of microballoons.

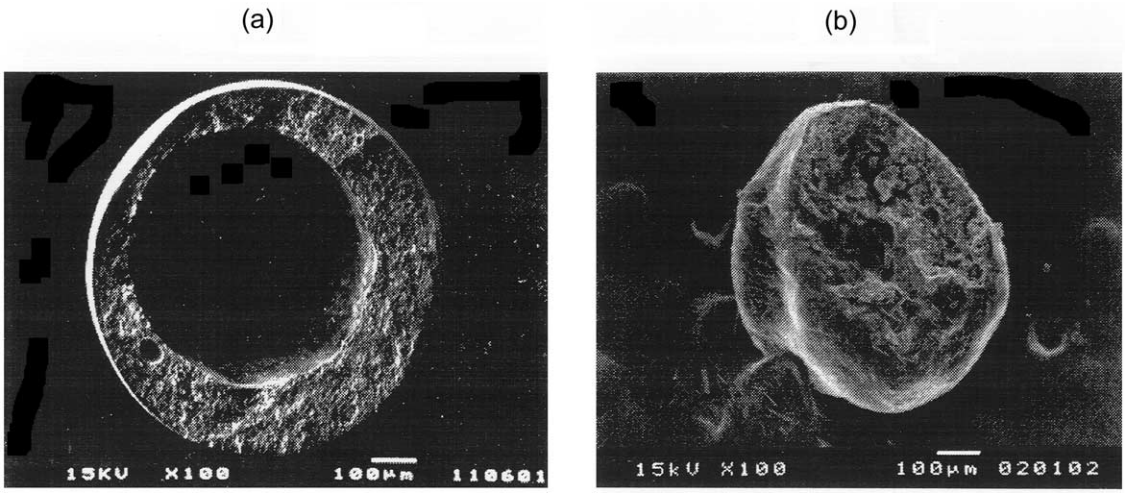

Fig. 1. Scanning electron microphotographs of microballoon cross section. (a) Preparation temperature: 40°C. (b) Preparation temperature: 50°C.

2.4.6. Roundness and sphericity

Roundness of microballoons was measured by an Image Processing and Analysis System (Q5001W, Leica, Japan). In the system, roundness was calculated according to Eq. (3).

$$\text{Roundness of microballoons} = L^2/4\pi S \quad (3)$$

L, circumference of a projective image; and S, area of a projective image.

Sphericity was represented by roundness of microballoons. When roundness of microballoons was close to 1, microballoons closely resembled spherical particles.

2.4.7. Drug content and drug recovery

Dried microballoons containing a drug were dissolved in a mixture of dichloromethane and ethanol (1:1 v/v) by ultrasonication. The drug content was measured spectrophotometrically with a UV-detector (UV-160A, Shimadzu, Japan) (aspirin; at 276 nm, salicylic acid; at 304 nm, ethoxybenzamide; at 289 nm, indomethacin; at 350 nm, and riboflavin; at 444 nm). Drug content and recovery of microballoons were calculated according to Eqs. (4) and (5), respectively.

$$\text{Drug content (\%)} = \frac{\text{Weight of drug in microballoons}}{\text{Weight of microballoons recovered}} \times 100 \quad (4)$$

$$\text{Drug recovery (\%)} = \frac{\text{Weight of drug in microballoons}}{\text{Weight of drug loaded in the system}} \times 100 \quad (5)$$

2.4.8. Drug release

The level of the drug release from microballoons exhibiting diameters of between 500 and 1000 μm was measured by the paddle method at 100 rpm, specified in JPXIII as follows. Microballoons (100 mg) were dispersed in JPXIII No. 1 solution (300 ml, pH 1.2, 37°C) containing Tween 20 (0.02 w/v%) and No. 2 solution (300 ml, pH 6.8, 37°C) containing Tween 80 (0.5 w/v%). The amount of the drug release was measured spectrophotometrically employing a UV-detector (UV-160A, Shimadzu, Japan).

3. Results and discussions

3.1. Effects of preparation temperature on the physicochemical properties of microballoons

Microballoons displaying diameters of between 500 and 1000 μm are characterized by a spherical cavity enclosed within a hard polymer shell, which exhibits a thickness of between 100 and 200 μm and uniform drug content (Fig.

Table 1
Riboflavin-containing microballoons prepared at several temperatures

Sample No. (°C)	Microballoons recovery (%)	Riboflavin recovery (%)	Riboflavin content (%)	Buoyancy (%)	Apparent particle density (g/cm^3)	Porosity (%)	Roundness
I (20)	89.9	81.8	5.76 (92.2)[a]	17.0	0.305	71.8	1.25
II (30)	88.9	78.5	5.55 (88.8)	52.9	0.459	57.5	1.23
III (40)	86.0	56.5	4.81 (77.0)	99.3	0.805	25.5	1.18
IV (50)	51.4	39.9	4.94 (79.0)	75.9	0.855	20.8	1.21

[a] Ratio (%) to the theoretical content (6.25%) in microballoons (loading amount of riboflavin: 0.1 g).

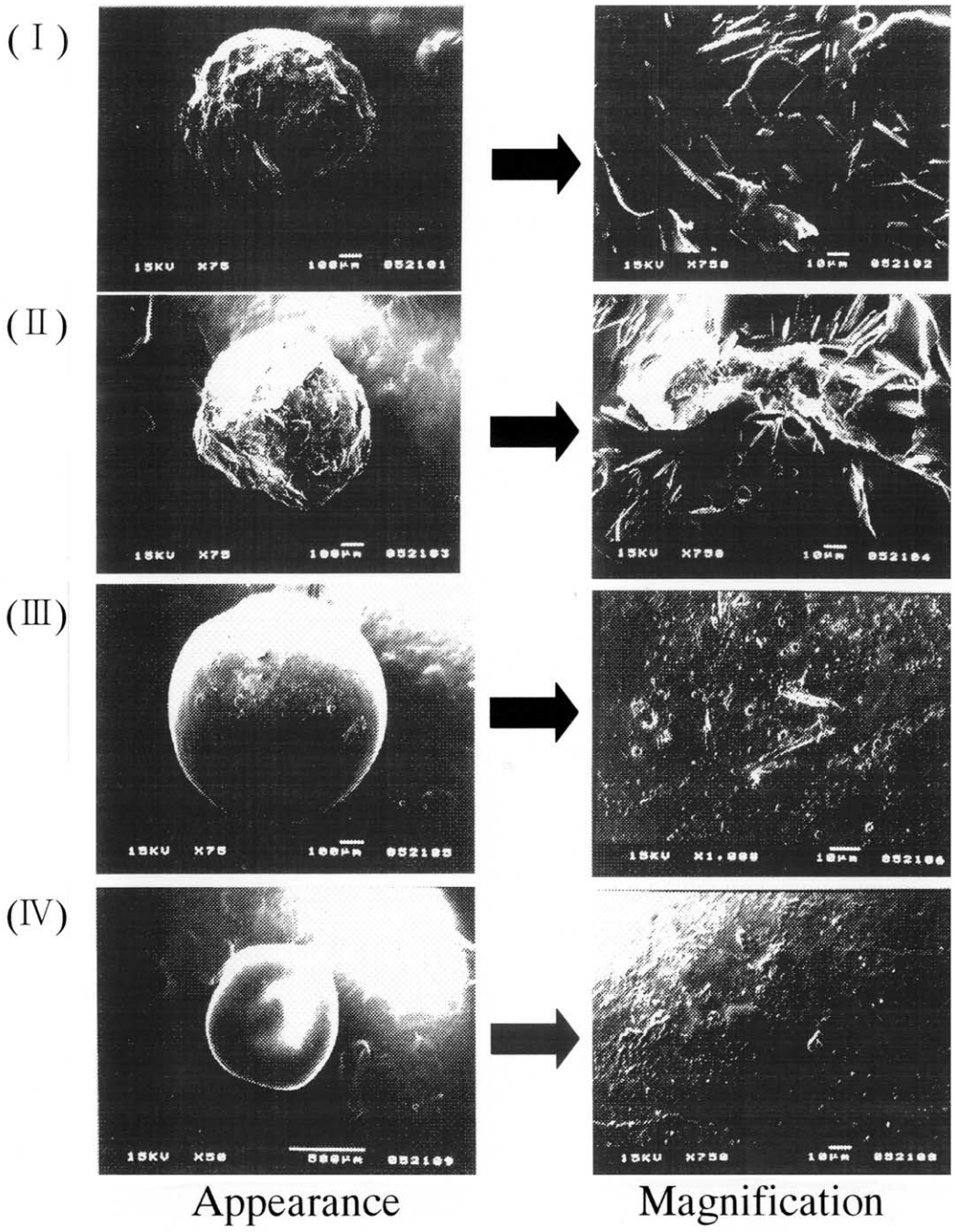

Fig. 2. Scanning electron microphotographs of microballoon appearance. Sample (I), 20°C; sample (II), 30°C; sample (III), 40°C; and sample (IV), 50°C.

1a). The cavity was supposedly formed as follows according to the previous report [15]: a polymer solution and a drug in a mixture of ethanol and dichloromethane were introduced drop-wise to an aqueous solution of polyvinyl alcohol (0.75 w/v%) to form an o/w emulsion. As ethanol diffuses through the aqueous solution, accompanied by simultaneous evaporation of dichloromethane, the solubility of the polymer in the droplet is drastically reduced and educes the coprecipitation of drug and polymer at the interface of the emulsion droplet, forming a solid shell covering the droplet.

Dichloromethane evaporation appeared to be especially related to cavity formation in microballoons. Physicochemical properties of microballoons prepared at several temperatures (20, 30, 40 and 50°C) are presented in Table 1. SEMs of microballoon appearance are shown in Fig. 2. Riboflavin release from microballoons in JPXIII No. 1 solution containing 0.02 w/v% Tween 20 and No. 2 solution containing 0.5 w/v% Tween 80 are illustrated in Fig. 3.

Preparation at 20 or 30°C provided porous microspheres having higher porosity with a surface so rough as to crumble upon touching (Fig. 2). Although the respective apparent particle densities of the resulting microballoons were low,

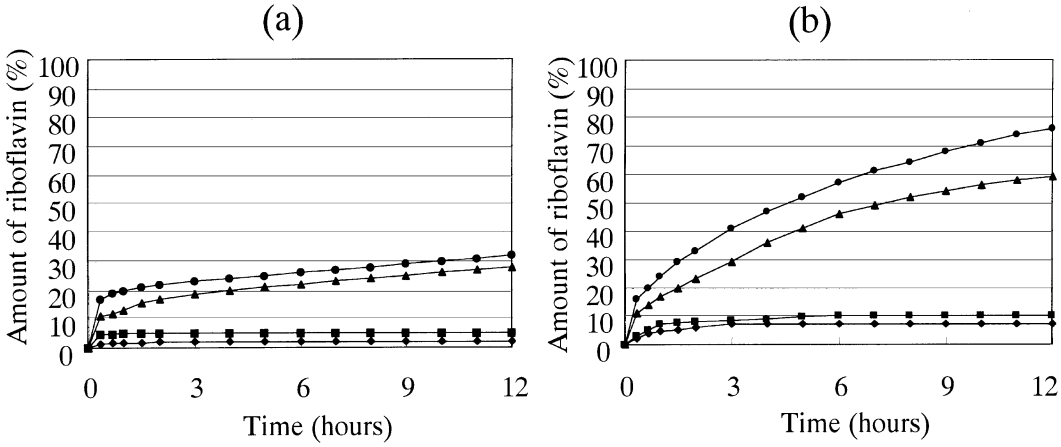

Fig. 3. Riboflavin release from microballoons. (a) JPXIII No. 1 solution (pH 1.2). (b) JPXIII No. 2 solution (pH 6.8). ●, sample (I); ▲, sample (II); ■, sample (III); and ◆, sample (IV).

both buoyancies were low probably due to the easy penetration of JPXIII No.1 solution through the porous surface (Table 1).

The roundness of microballoons prepared at 40°C was close to 1; moreover, surfaces were less rough than those of microballoons prepared at 20 or 30°C. As shown in Fig. 3, the amount of riboflavin released from microballoons prepared at 40 or 50°C was small, which was attributable to the limited penetration of JPXIII Nos. 1 and 2 solution as a result of the smooth surfaces of the microballoons. Fig. 2 illustrates the presence of numerous small pores on the surface of microballoons prepared at 40°C, probably arising as a trace of solvent evaporation.

Microballoons prepared at 50°C exhibited no hollow nature as depicted in Fig. 1b; however, a single large depression occurred on the surface. The microballoons possessed high apparent particle density and low buoyancy due to the absence of a cavity as described in Table 1. Few traces of evaporation were observed on the surface, which was attributable to the rapid evaporation of dichloromethane at temperatures beyond the boiling point (40.2°C). At 40°C, polymers and the drug were coprecipitated and the shell was formed by the diffusion of ethanol into the aqueous solution and simultaneous evaporation of dichloromethane. In contrast, microballoons prepared at 50°C demonstrated a single large depression at the surface, which was a consequence of rapid evaporation of dichloromethane.

As previously noted, physicochemical properties (buoyancy, apparent particle density and sphericity) of microballoons varied according to the rate of dichloromethane evaporation in the emulsion solvent diffusion method. A slow rate of evaporation led to formation of porous microspheres as dichloromethane remained in the droplets preventing formation of a hard polymer shell. On the other hand, a rapid rate of evaporation provided microspheres exhibiting a single large depression due to the drastic evaporation of dichloromethane.

Microballoons shells were conveniently formed by gradual coprecipitation of drug and polymers, as well as successive evaporation of the inner solvent. Gradual evaporation of dichloromethane at 40°C appeared necessary for cavity formation in microballoons.

3.2. Floating behavior of microballoons

Apparent particle density of microballoons containing no drug prepared at 40°C was measured in order to examine the relationship between the apparent particle density and buoyancy.

3.2.1. Relationship between buoyancy, apparent particle density and porosity

Apparent particle density, porosity and buoyancy of microballoons containing no drug of less than 500 μm, between 500 and 1000 μm and in excess 1000 μm in diameter were measured. The particle sizes of microballoons were closely correlated to apparent particle density, porosity and buoyancy as displayed in Fig. 4.

Apparent particle density of microballoons decreased in the following order: less than 500 μm, between 500 and

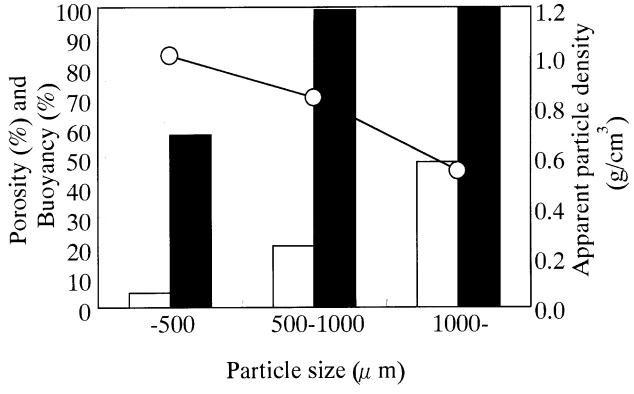

Fig. 4. Relationship between particle size and physicochemical properties of microballoons. □, porosity (%); ■, buoyancy (%) and -○-, apparent particle density (g/cm^3).

Table 2
Physicochemical properties of riboflavin-containing microballoons

Amount of riboflavin (g)[a]	Riboflavin recovery (%)	Riboflavin content (%)	Buoyancy (%)	Apparent particle density (g/cm^3)	True density (g/cm^3)	Porosity (%)
0	0	0 (0)[b]	99.2	0.841	1.062	20.8
0.1	56.5	4.81 (77.0)	99.3	0.805	1.081	25.5
0.2	53.8	6.94 (59.0)	17.1	0.781	1.105	29.3
0.5	50.7	14.07 (56.3)	13.8	0.613	1.144	46.4
1.0	41.4	18.53 (46.3)	18.6	0.594	1.153	48.5

[a] Amount of riboflavin loaded in the process.
[b] Ratio (%) to the theoretical content in microballoons.

1000 μm and greater than 1000 μm in diameter. Porosity of microballoons increased as cavity volume increased in the identical order. In this case, buoyancy of microballoons increased as well.

The particle size of microballoons could be controlled by the droplet size of emulsion after the solution of Eudragit® S100 and monostearin was poured into an aqueous solution of polyvinyl alcohol. In large emulsion droplets, a greater amount of ethanol and dichloromethane were entrapped. The larger cavity appeared to be formed by the diffusion of ethanol into the aqueous solution and simultaneous evaporation of dichloromethane.

3.2.2. Relationship between the buoyancy of microballoons and the loading amount of riboflavin

Apparent particle density, porosity and buoyancy of microballoons prepared at several loading amounts of riboflavin were measured. In accordance with the loading amount of riboflavin (i.e. 0, 0.1, 0.2, 0.5 and 1.0 g), riboflavin content, buoyancy, apparent particle density and porosity of the resulting microballoons varied distinctly as presented in Table 2 and Fig. 5.

When the loading amount was 0.2 g or greater, the buoyancy of the microballoons largely decreased, accompanied by increased porosity. The reason for increase in porosity was not correlated to the increasing cavity volume; rather, it was attributed to the elevation of the riboflavin load. Upon an increase in loading amount, the uniform polymer shell of microballoons was unable to form; consequently, a large number of needle-like particles were generated. Furthermore, the JPXIII No. 1 solution can readily penetrate microballoons through the rough surfaces, affording reduced buoyancy. Thus, in the case of drug-entrapped microballoons, the buoyancy of these microballoons appeared to be more greatly affected by surface roughness than by the apparent particle density. In instances where the loading amount of riboflavin was 0.2 g or greater, riboflavin was not completely dissolved in a mixture of dichloromethane and ethanol. Riboflavin in the suspension was trapped within the uniform polymer shell of microballoons; as a result, rigidity of the shell decreased.

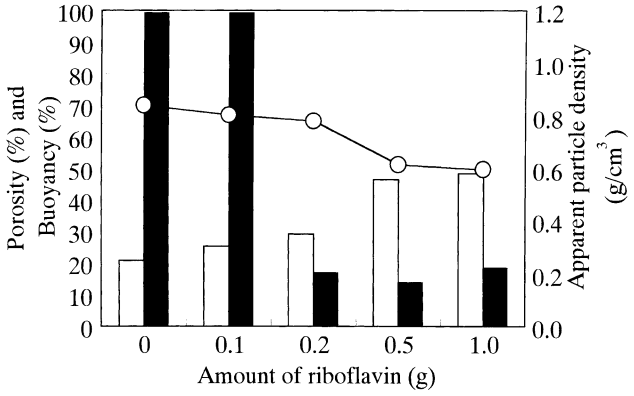

Fig. 5. Relationship between physicochemical properties of microballoons and amount of riboflavin loaded in the process. □, porosity (%); ■, buoyancy (%) and -○-, apparent particle density (g/cm^3).

3.2.3. Relationship between buoyancy, apparent particle density and sphericity

Sphericity in drug-containing microballoons possessing smooth surfaces was expectedly high. In this case, roundness was close to 1. In contrast, needle-like particles characterized by a high degree of roundness exhibited very rough surfaces. Thus, surface roughness appeared to be denoted by roundness. Apparent particle density, roundness and buoyancy of several microballoons were measured (Fig. 6).

In cases where microballoons possessed identical degrees of roundness, the buoyancy of the microballoons increased, accompanied by decreased apparent particle density. In instances where microballoons demonstrated identical apparent particle density, when roundness was close to 1, microballoon buoyancy increased. This observation was attributable to the poor ability of the JPXIII No. 1 solution to penetrate the spherical microballoons due to the smooth surfaces. Thus, the factors influencing the buoyant properties of microballoons were apparent particle density and roundness. Furthermore, roundness appeared to be a suitable index for roughness of microballoon surfaces.

3.3. Drug entrapment into microballoons

Entrapment of five different drugs, exhibiting distinct water solubilities, into microballoons was examined in Table 3. Recovery of indomethacin and ethoxybenzamide

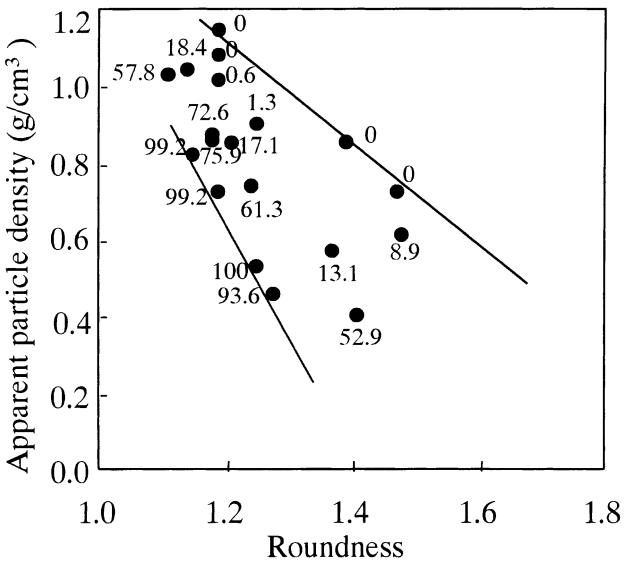

Fig. 6. Relationship between buoyancy, apparent particle density and roundness. Buoyancy (%) is shown in figures.

with high distribution coefficient between dichloromethane and water during the entrapment process was 89 and 37%, respectively. On the other hand, both aspirin and salicylic acid, characterized by low distribution coefficient, were little entrapped (6 and 14%, respectively) due to the transfer of those compounds to the aqueous solution during the process. In the case of aspirin, reduction of pH during the process improved recovery from 2.7 to 8.8% via an increase in the distribution coefficient (Table 4). In these instances, efficiency of drug entrapment into microballoons could be ascribed to the distribution coefficient under preparation conditions. When the distribution coefficient was high, efficiency of drug entrapment into microballoons was elevated. This phenomenon was due to the lack of retention of drugs with low distribution coefficient in the emulsion droplet aqueous solution during the process, which led to reduced entrapment into microballoons.

In suspensions, such as for riboflavin, irrespective of its low distribution coefficient, recovery was high, 54%. When the loading amount of riboflavin was 0.2 g or greater, riboflavin was incompletely dissolved in a mixture of dichloromethane and ethanol. Riboflavin in the suspension

Table 4
Relationship between drug recovery, pH and distribution coefficient

Drug recovery (%)	8.8	8.6	8.0	5.5	2.7
pH	1.24	2.04	2.88	3.80	4.47
Distribution coefficient[a]	1.98	1.95	1.92	1.10	0.73

[a] Distribution coefficient = Drug concentration in dichloromethane/Drug concentration in an aqueous solution.

efficiently trapped within the microballoon shell with matrix of precipitated polymers. Consequently, recovery of riboflavin was elevated. Moreover, rigidity of the shell decreased and buoyancy of the microballoons largely decreased due to the heterogeneous polymer shell of microballoons co-mixed with riboflavin.

Thus, the optimum loading amount of riboflavin appeared to be 0.1 g, as at that point, buoyancy of the microballoons attained its highest level.

4. Conclusion

Microballoons, as a potential floating intragastric system, were produced by the emulsion solvent diffusion method. Microballoons prepared at 40°C were hollow and buoyant. In contrast, microballoons prepared at 50°C were not hollow, resulting in poor buoyancy. Drug release rate from the microballoon prepared at 40 or 50°C was sufficiently reduced and prolonged. This phenomenon was attributable to the limited penetration of dissolution medium as a result of the smooth surfaces of the microballoons. Moreover, microballoons prepared at 20 or 30°C were so brittle as to crumble upon touching. Although apparent particle densities of the microballoons were low, the buoyancy was low probably due to the ready penetration of JPXIII No. 1 solution via the porous surface. The increased penetration of medium into the microballoons promoted their drug release rates. Thus, gradual evaporation of dicloromethane appeared necessary for microballoon cavity formation. The preparation method involving the introduction of the solution or suspension into an aqueous solution of polyvinyl alcohol at 40°C is ideal for production of hollow, buoyant microballoons.

When the roundness of microballoons was close to 1,

Table 3
Efficiency of drug entrapment into microballoons at 40°C

Drugs	Solubility (mg/ml)[a]	Distribution coefficient[b]	Drug content (%)	Drug recovery (%)	Buoyancy (%)[c]
Aspirin	3	1.7	0.88 (7.5)[d]	6.3	99.1
Salicylic acid	2	1.3	2.87 (24.4)	13.8	99.7
Ethoxybenzamide	<0.1	67	5.97 (49.2)	36.5	94.3
lndomethacin	<0.1	60	11.12 (94.6)	88.5	98.7
Riboflavin	0.1	0.7	6.94 (59.0)	53.8	17.1

[a] Solubility (water) at 20 ± 5°C.
[b] Distribution coefficient = Drug concentration in dichloromethane/Drug concentration in an aqueous solution.
[c] Particle size: 500–1000 μm.
[d] Ratio (%) to the theoretical content (11.76%) in microballoons (loading amount of a drug: 0.2 g).

microballoons were spherical particles with smooth surfaces. The buoyancy of the microballoons with smooth surfaces appeared to increase as the JPXIII No. 1 solution was scarcely able to penetrate the microballoons. Therefore, factors influencing buoyant properties of microballoons were apparent particle density and roundness; additionally, roundness appeared to be a suitable index for microballoon surface roughness.

Upon drug dissolution in the mixture of dichloromethane and ethanol, efficiency of drug entrapment into microballoons could be ascribed to the distribution coefficient. When the distribution coefficient was high, efficiency of drug entrapment into microballoons increased.

In the case of suspensions, such as for riboflavin, irrespective of its low distribution coefficient, recovery was high as insoluble riboflavin in the suspension was efficiently entrapped within the shell of microballoons with the polymer matrix. The optimum loading amount of riboflavin appeared to be 0.1 g; at this level, buoyancy of the microballoons was highest. Thus, optimum loading amount appeared to differ in accordance with the drug properties.

Microballoons obtained via this method could constitute a novel drug delivery system floating in the stomach. The pharmacokinetic profile of riboflavin-containing microballoons in humans will be reported in a subsequent report.

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