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Research paper

In vitro evaluation of floating and drug releasing behaviors of hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method

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Abstract

Hollow microspheres (microballoons) floatable in JPX III No.1 solution were developed as a dosage form characterized by excellent buoyant properties in the stomach. Microballoons were prepared by the emulsion solvent diffusion method utilizing enteric acrylic polymers codissolved with drug in a mixture of dichloromethane and ethanol. The release properties of five different drugs exhibiting distinct water solubilities (aspirin, salicylic acid, ethoxybenzamide, indomethacin and riboflavin) entrapped within microballoons were investigated. Buoyancy of the microballoons decreased with increasing drug release rate. In the case of aspirin, salicylic acid and ethoxybenzamide, the drug release profiles of microballoons proved a linear relationships by Higuchi plotting. However, indomethacin and riboflavin release profiles did not follow the Higuchi equation. When the loading amount of riboflavin was higher than the solubility in the mixture of dichloromethane and ethanol, the drug release profiles of the microballoons displayed an initial burst release. The insoluble riboflavin in the mixture of dichloromethane and ethanol adsorbed on to the microballoon surface in the crystal state. Such riboflavin crystals were released preferentially at the initial stage of the release test, which was attributable to the initial burst. In addition, by incorporating a polymer such as hydroxypropylmethylcellulose within the shell of microballoons, the release rate of riboflavin from the microballoons could be controlled while maintaining high buoyancy.

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

1. Introduction

To develop oral drug delivery systems, it is necessary to optimize both the residence time of the system within the gastrointestinal tract and the release rate of the drug from the system. Various attempts have been made to prolong the residence time of the dosage forms within the stomach [1,2]. The prolongation of the gastric residence time (GRT) of delivery devices could be achieved by adhesion to the mucous membranes [3], by preventing their passage through the pylorus [4] or by maintaining them in buoyant fashion in gastric juice [5–7].

With regard to the floating devices, Innuccelli et al. [8–10] reported that an air-contained multiple-unit compartment system showed excellent buoyancy in vitro and prolonged GRT relative to the controls in vivo in the fed state. However, in the fasted state, intragastric buoyancy of the devices did not influence GRT. Yuasa et al. [11] attempted to prepare an intragastric floating and sustained release preparation, which derived its buoyancy from the air trapped in the pores of calcium silicate when these particles were covered with polymer. Murata et al. [12] prepared calcium-induced alginate gel beads that, upon oral administration, were capable of floating on gastric juice. Moreover, Lee et al. [13,14] devised the preparation method of floating microspheres using acrylic resin. Recently, El-Kamel et al. [15] described a floating multiple-unit system for ketoprofen employing Eudragit® S100 alone or a mixture with the permeable Eudragit® RL. Kawashima

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et al. [16] developed hollow microspheres (microballoons) to prolong GRT of the dosage form.

In our previous study the preparation of microballoons was carried out according to the emulsion solvent diffusion method. Buoyant properties and efficiency of drug entrapment within microballoons were optimized.

In the present study, the drug release from microballoons containing five different drugs exhibiting various water solubilities (aspirin, salicylic acid, ethoxybenzamide, indomethacin and riboflavin) was investigated. Additionally, the method to control the drug release rate from the microballoons by mixing other hydrophilic or hydrophobic polymers was investigated.

2. Materials and methods

2.1. Materials

The following drugs were employed (water solubility at room temperature is shown in parentheses): 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). Eudragit® S100, Eudragit® L100, Eudragit® L100-55 (Röhm Pharma GmbH, Germany), ethylcellulose (N-10-F, Shin-etsu Chemical, Japan), hydroxypropylmethylcellulose (TC-5R, Shin-etsu Chemical, Japan) and hydroxypropylmethylcellulosephthalate (HP-55, Shin-etsu Chemical, Japan) were utilized as polymers. 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. [17] as follows: a drug (0.1–1.0 g), polymers (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. A solution of aspirin, salicylic acid, ethoxybenzamide, indomethacin or a suspension of riboflavin was introduced to an aqueous solution of polyvinyl alcohol (0.75 w/v%, 200 ml) at 40 °C, forming an oil-in-water (o/w) type emulsion. The resultant emulsion was stirred, employing a propeller type agitator at 300 rpm. The finely dispersed droplets of the polymer solution of drug were solidified in the aqueous phase via diffusion of the solvent. The dichloromethane that evaporated from the solidified droplet was removed by an aspirator, leaving the cavity of the microsphere filled with water. After agitating the system for 1 h, the resulting polymeric particulate systems were sieved between 500 and 1000 μm and dried overnight at 40 °C to produce microballoons.

2.3. Observation of microballoons

Microballoons were observed using a scanning electron microphotograph (SEM) (JSM-T330A, Nihon Densi, Japan). To investigate the internal morphology, microballoons were divided into two pieces with a knife.

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, polymers and monostearin.

2.4.2. Buoyancy

Microballoons (100 mg) were dispersed in JP XIII No.1 solution composed of HCl and NaCl (300 ml, pH 1.2, 37 °C) containing Tween 20 (0.02 w/v%) to simulate gastric fluid. 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).

$$\text{Apparent particle density} = W/V = W/\sum\left(\pi d^3 n/6\right) \quad (1)$$

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

2.4.4. Roundness

Roundness of microballoons was measured by an Image Processing and Analysis System (Q5001W, Leica, Japan). In this system, roundness was calculated according to Eq. (2).

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

where L = circumference of a projective image and S = area of a projective image.

When the roundness of microballoons was close to 1, the microballoons closely resembled spherical particles.

2.4.5. Drug content

Dried microballoons containing a drug were dissolved in a mixture of dichloromethane and ethanol (1:1 v/v) by ultrasonication. The dissolved drug amount 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 of microballoons was calculated according to Eq. (3).

$$\text{Drug content (\%)} = \frac{\text{Weight of drug in microballoons}}{\text{Weight of microballoons recovered}} \times 100 \quad (3)$$

2.4.6. Drug release

The level of drug release from microballoons having diameters of between 500 and 1000 μm was measured by the paddle method at 100 rpm specified in JP XIII as follows. Microballoons (100 mg) were dispersed in JP XIII No.1 solution composed of HCl and NaCl (300 ml, pH 1.2, 37 °C) containing Tween 20 (0.02 w/v%) to simulate gastric fluid or JP XIII No.2 solution composed of NaOH and KH_2PO_4 (300 ml, pH 6.8, 37 °C) containing Tween 80 (0.5 w/v%) to solubilize drugs. The level of the drug release was determined spectrophotometrically employing a UV detector (UV-160A, Shimadzu, Japan).

2.5. Identification of crystalline form of the drug in microballoons

The crystalline form of the drug dispersed in the crust of the microballoons and in the physical mixture of drug and Eudragit® S100 and monostearin was analyzed by X-ray powder diffractometry (XD-3A, Shimadzu, Japan).

3. Results and discussion

3.1. Drug release properties of microballoons

Microballoons were developed as novel delivery systems available for various types of drugs. Microballoons having diameters of between 500 and 1000 μm are characterized by a spherical cavity enclosed within a hard polymer shell, which exhibits thickness of between 100 and 200 μm and contains drug uniformly, 0.88 ± 0.09% ~ 18.87 ± 0.44% (Fig. 1).

Microballoons were formed via an o/w type emulsion; water-insoluble drugs were efficiently entrapped within the shell of microballoons as proved by the absence of drug remaining in aqueous solution after the process. The efficiency of drug entrapment into microballoons could be ascribed to the distribution coefficient between water and dichloromethane under the preparation conditions

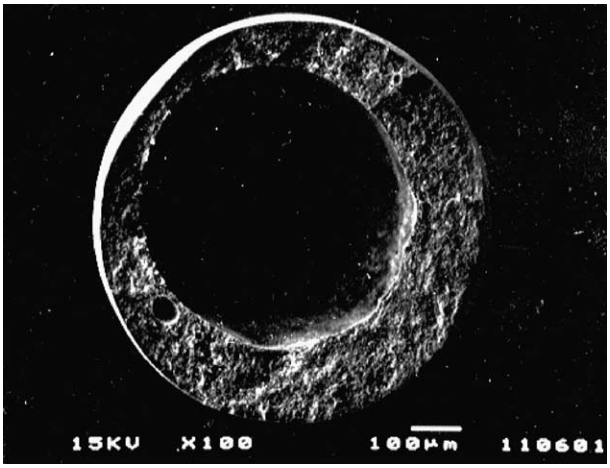

Fig. 1. Scanning electron microphotographs of the cross-section of microballoon. Formulation of organic solution: CH_2Cl_2 8 ml, EtOH 8 ml, riboflavin 0.1 g, Eudragit® S100 1.0 g, monostearin 0.5 g.

as reported in a previous investigation [18]. Buoyancy and drug release from microballoons containing five different drugs exhibiting distinct water solubilities (aspirin, salicylic acid, ethoxybenzamide, indomethacin and riboflavin) in JPXIII No.1 solution with 0.02 w/v% Tween 20 are illustrated in Fig. 2.

Buoyancy of the microballoons decreased with increasing drug release rate. In the case of aspirin, salicylic acid and ethoxybenzamide, the drug release profiles of microballoons were linear when plotted versus the Higuchi equation. These findings indicated that the shell structure of the microballoon was a polymeric matrix containing dispersed drug. Drug release rate was determined by the diffusion of drug from the rigid matrix structure of the shell of the microballoons. However, indomethacin and riboflavin release profiles did not follow the Higuchi equation. When the loading amount of riboflavin was 0.2 g or greater, the drug release profiles of the microballoons exhibited a drug release burst at the initial stage as shown in Fig. 2e. Following the initial burst, riboflavin release became slow and prolonged, indicating that riboflavin release rate was determined by the diffusion of drug from the rigid matrix structure of the shell. In order to explain the initial burst, further investigations were conducted employing scanning electron microphotography and X-ray powder diffraction. Scanning electron microphotographs of aspirin and riboflavin-containing microballoons (loading amount of each drug was 0.2 g) are displayed in Fig. 3.

Fig. 3 illustrates the presence of numerous small pores on the surface of aspirin-containing microballoons, probably arising as a trace of solvent evaporation during the process. Their smooth surface indicated that aspirin was embedded in the shell. Similarly, salicylic acid, ethoxybenzamide and indomethacin-containing microballoons possessed smooth surfaces; moreover, drug particles were not present on the surface. On the other hand, in the case of riboflavin-containing microballoons, the surfaces were covered with

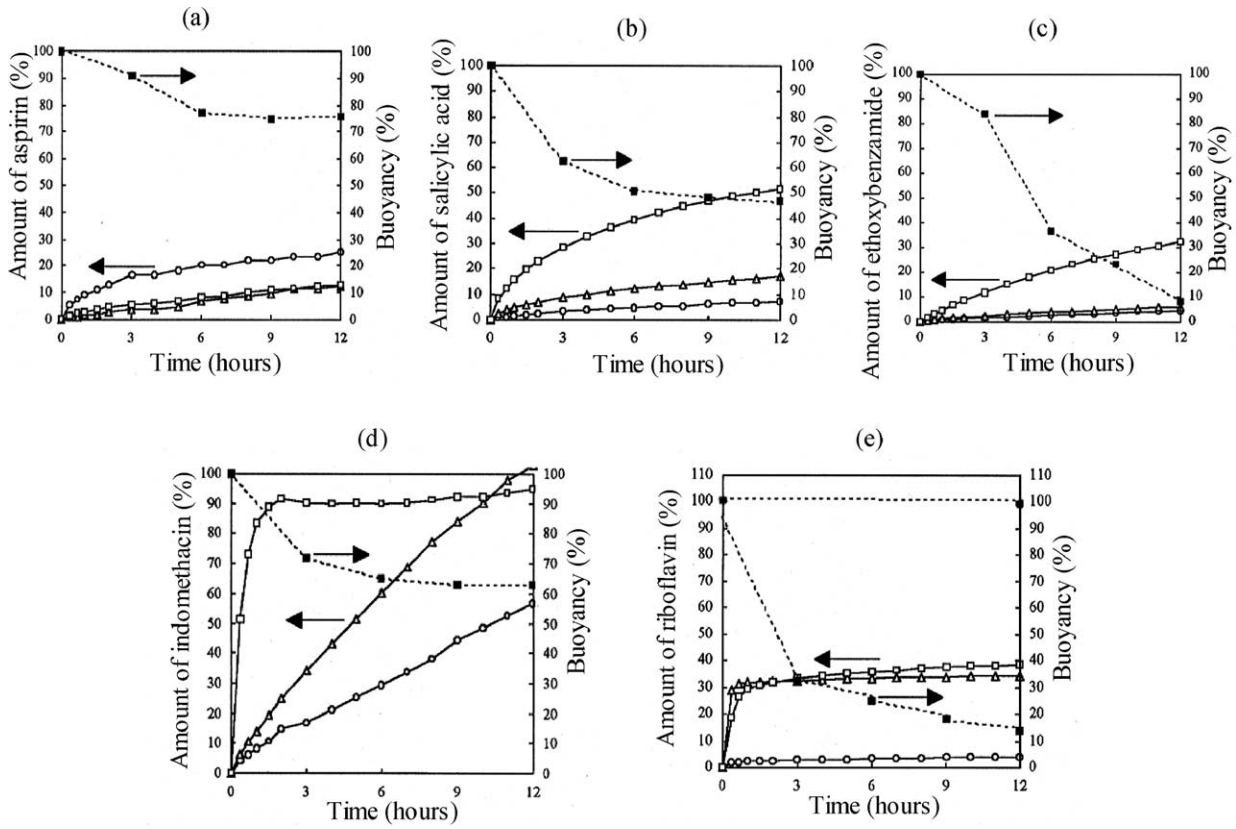

Fig. 2. Buoyancy and drug release from microballoons in JP XIII No.1 solution containing 0.02w/v% Tween 20 (pH1.2). Formulation of organic solution: CH_2Cl_2 8mL, EtOH 8mL, Eudragit® S100 1.0g, monostearin 0.5g. (a) Aspirin (release: ○, 0.2 g; △, 0.5 g; □, 1.0 g; buoyancy: ■, 1.0 g). (b) Salicylic acid (release: ○, 0.2 g; △, 0.5 g; □, 1.0 g; buoyancy: ■, 1.0 g). (c) Ethoxybenzamide (release: ○, 0.1 g; △, 0.2 g; □, 0.5 g; buoyancy: ■, 0.5 g). (d) Indomethacin (release: ○, 0.1 g; △, 0.2 g; □, 0.5 g; buoyancy: ■, 0.5 g). (e) Riboflavin (release: ○, 0.1 g; △, 0.2 g; □, 0.5 g; buoyancy: ●, 0.1 g; ■, 0.5 g). Loading amount of drug is represented in parenthesis.

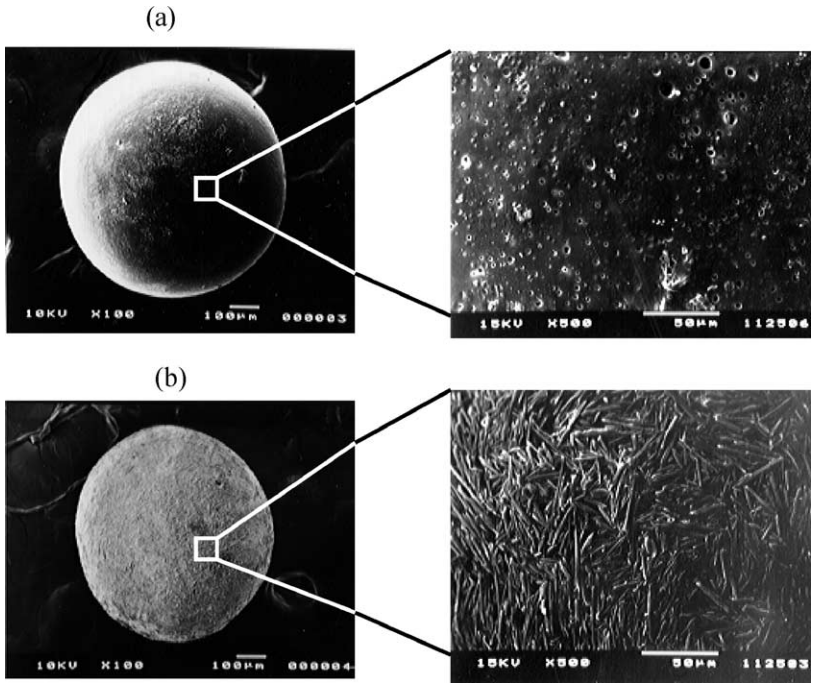

Fig. 3. Scanning electron microphotographs of microballoons. (a) Aspirin. (b) Riboflavin.

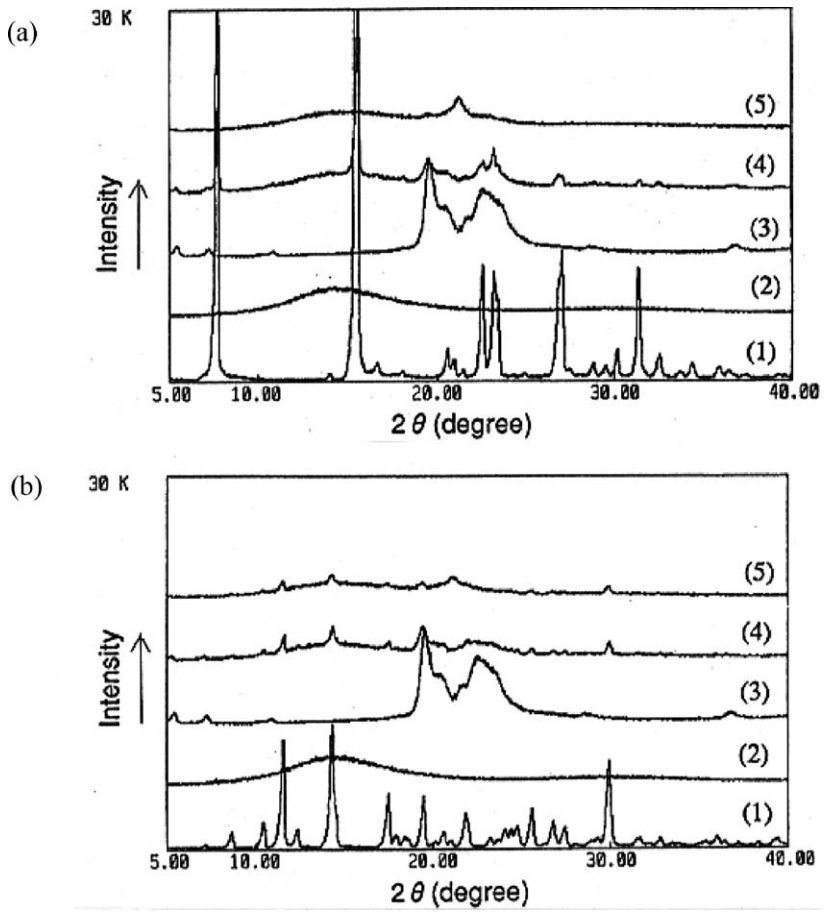

Fig. 4. X-Ray powder diffraction patterns. (a) Aspirin. (b) Riboflavin. (1) Drug. (2) Eudragit® S100. (3) Monostearin. (4) Physical mixture (Drug: Eudragit® S100: Monostearin = 2:10:5). (5) Microballoons.

needle-like particles. X-ray powder diffraction patterns of aspirin or riboflavin-containing microballoons are displayed in Fig. 4. The component ratio of the physical mixture was identical to those of microballoons; namely, the drug/Eudragit® S100/monostearin ratio was 2:10:5.

In the case of aspirin-containing microballoons, aspirin existed completely in the amorphous state in the shell of microballoons, which was indicated by the characteristic peakless patterns of the X-ray diffraction. On the other hand, in the case of riboflavin-containing microballoons, original crystals were present, as indicated by characteristic peak patterns of the X-ray diffraction. As previously noted, the surfaces of riboflavin-containing microballoons were covered with needle-like crystals. Therefore, the initial burst was attributed to the dissolution of riboflavin crystals present on the surfaces at release test in JPXIII No.1 solution supplemented with 0.02 w/v% Tween 20. In addition, buoyancy of riboflavin-containing microballoons rapidly decreased due to the initial burst. This was because many macropores were left on the surface through which the dissolution medium easily penetrated with reducing buoyancy after dissolving the crystals. When the loading amount of riboflavin was 0.1 g, the initial burst was not observed. Fig. 5 displays scanning electron microphotographs of microballoons (loading amount of riboflavin: 0.1, 0.2, 0.5 and 1.0 g).

In cases where the loading amount of riboflavin was 0.1 g, numerous small pores were observed on the surfaces of microballoons; moreover, original crystals were not present. In contrast, when the loading amount was 0.2 g or greater, the surfaces were covered with needle-like particles. X-ray powder diffraction patterns of riboflavin-containing microballoons (loading amount of riboflavin: 0.1, 0.2 and 0.5 g) and riboflavin powder are presented in Fig. 6.

When the loading amount of riboflavin was 0.1 g, riboflavin existed completely in the amorphous state in the shell of microballoons, as indicated by characteristic peakless patterns of the X-ray diffraction. On the other hand, in cases where the loading amount was 0.2 g or greater, the original crystals were present, as indicated by characteristic peak patterns of the X-ray diffraction. When the loading amount of riboflavin was 0.2 g or greater, riboflavin was incompletely dissolved in a mixture of dichloromethane and ethanol (1:1 v/v). Therefore, the insoluble riboflavin was adsorbed on the microballoon surface in the crystal state. Riboflavin crystals adsorbed on microballoon surfaces were released at the beginning of the release test, which was attributable to the initial burst.

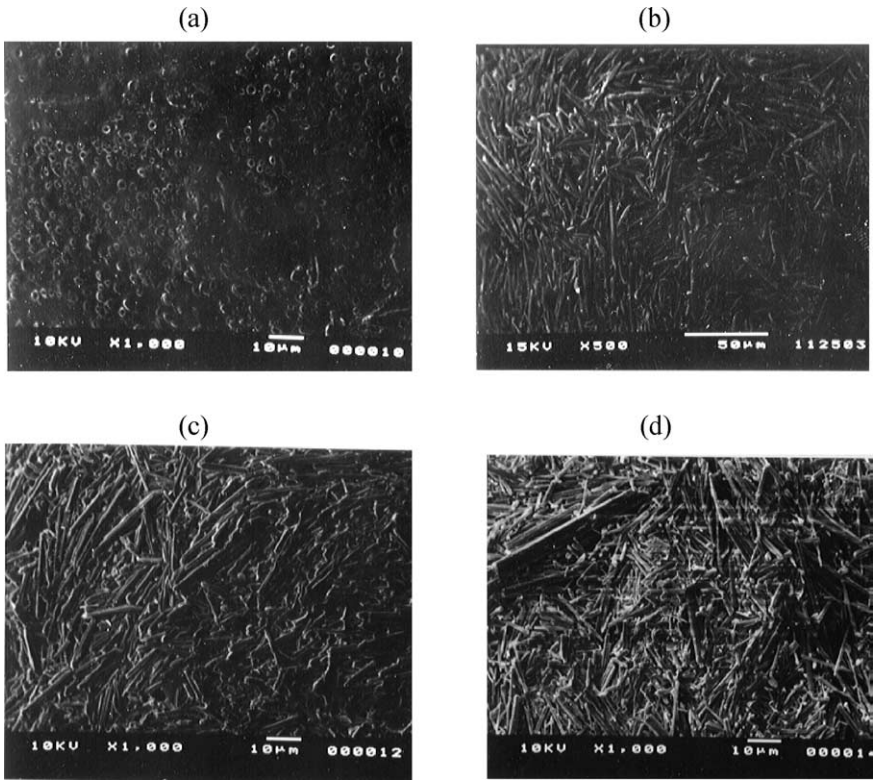

Fig. 5. Scanning electron microphotographs of appearance of microballoons. (a) Riboflavin 0.1 g. (b) Riboflavin 0.2 g. (c) Riboflavin 0.5 g. (d) Riboflavin 1.0 g.

3.2. Control of drug release by mixing polymers

When the loading amount of riboflavin was 0.1 g, the initial burst was not observed; moreover, little riboflavin was released from microballoons in JPXIII No.1 solution containing 0.02 w/v% Tween 20. This phenomenon appeared to afford low bioavailability for a drug absorbed mainly at the proximal small intestine, such as riboflavin. Thus, in order to modulate the drug release rate from the microballoons, they were prepared by mixing hydrophilic or hydrophobic polymer in Eudragit® S100.

Physicochemical properties of riboflavin-containing microballoons prepared using mixed polymers are presented in Table 1. Scanning electron microphotographs of

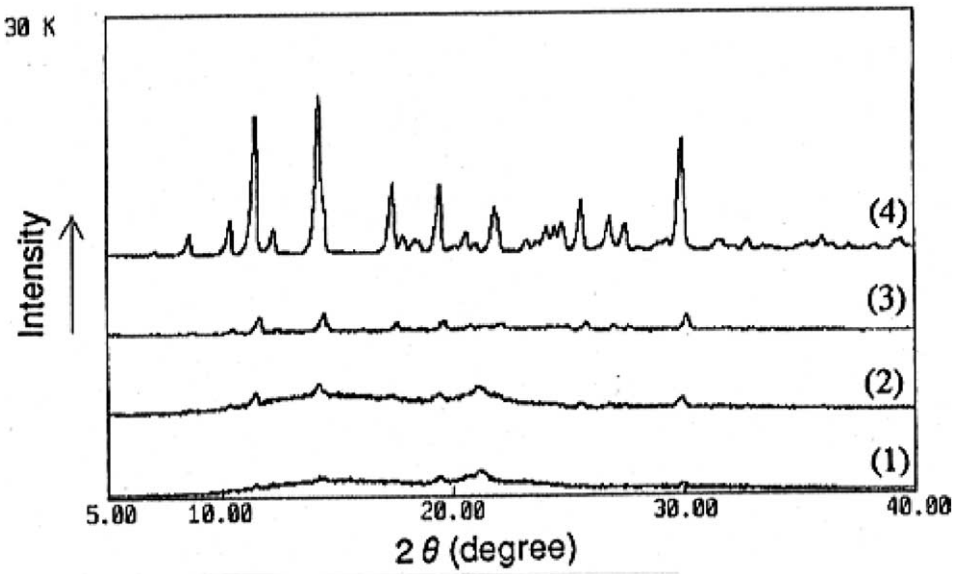

Fig. 6. X-ray powder diffraction patterns of riboflavin-containing microballoons and riboflavin powder. (1) Riboflavin 0.1 g. (2) Riboflavin 0.2 g. (3) Riboflavin 0.5 g. (4) Riboflavin powder.

Table 1
Physicochemical properties of riboflavin-containing microballoons

Sample	Apparent particle density (g/cm^3)	Buoyancy (%)	Percent released[a] (%)		Roundness
			20 min	12 h	
S100/L100 = 9:1	0.401	72.6	4.8	22.9	1.41
S100/L100-55 = 9:1	0.656	61.3	3.5	43.3	1.61
S100/HPMCP = 9:1	0.474	88.4	2.4	4.3	1.28
S100/HPMC = 9:1	1.029	93.6	1.7	21.1	1.11
S100/EC = 9:1	0.957	96.4	6.8	8.2	1.24

[a] Percent released: JPXIII. No. 1 solution containing 0.02% Tween 20 (pH 1.2); S100/Eudragit® S100; L100: Eudragit® L100; L100-55: Eudragit® L100-55; HPMCP, hydroxypropylmethylcellulosephthalate; HPMC, hydroxypropylmethylcellulose; EC, ethylcellulose.

microballoons and plots of riboflavin release from microballoons in JP XIII No.1 solution supplemented with 0.02 w/v% Tween 20 (pH 1.2) are displayed in Figs. 7 and 8, respectively.

The roundness of microballoons prepared upon mixing Eudragit® L100 in Eudragit® S100 exhibited relatively high values due to the rough surfaces as observed by SEM. The amount of riboflavin released from microballoons prepared by mixing Eudragit® L100-55 was high, probably due to the facilitated penetration of JPXIII No. 1 solution in the microballoon. In the case of hydroxypropylmethylcellulosephthalate (HPMCP), buoyancy was high and the amount of riboflavin released was low, due to poor penetration of JPXIII No.1 solution through the smooth rigid surfaces of microballoon.

In the case of hydroxypropylmethylcellulose (HPMC), irrespective of high apparent particle density, buoyancy was high. HPMC was considerably soluble and gelled in JPXIII No.1 solution. Additionally, roundness of microballoons possessing smooth surfaces was close to 1. Thus, buoyancy appeared to be high due to the difficulty in penetration of JPXIII No.1 solution through the rigid smooth surfaces.

In the case of ethylcellulose (EC), many needle-like particles were present on the surface. The release profiles of the microballoons exhibited a burst (6.8%) of riboflavin during the initial stage (for 20 min), followed by a plateau pattern for 12 h. In addition, buoyancy appeared to be high as a consequence of hydrophobic properties of the EC polymer. Consequently, mixing hydrophilic polymers such

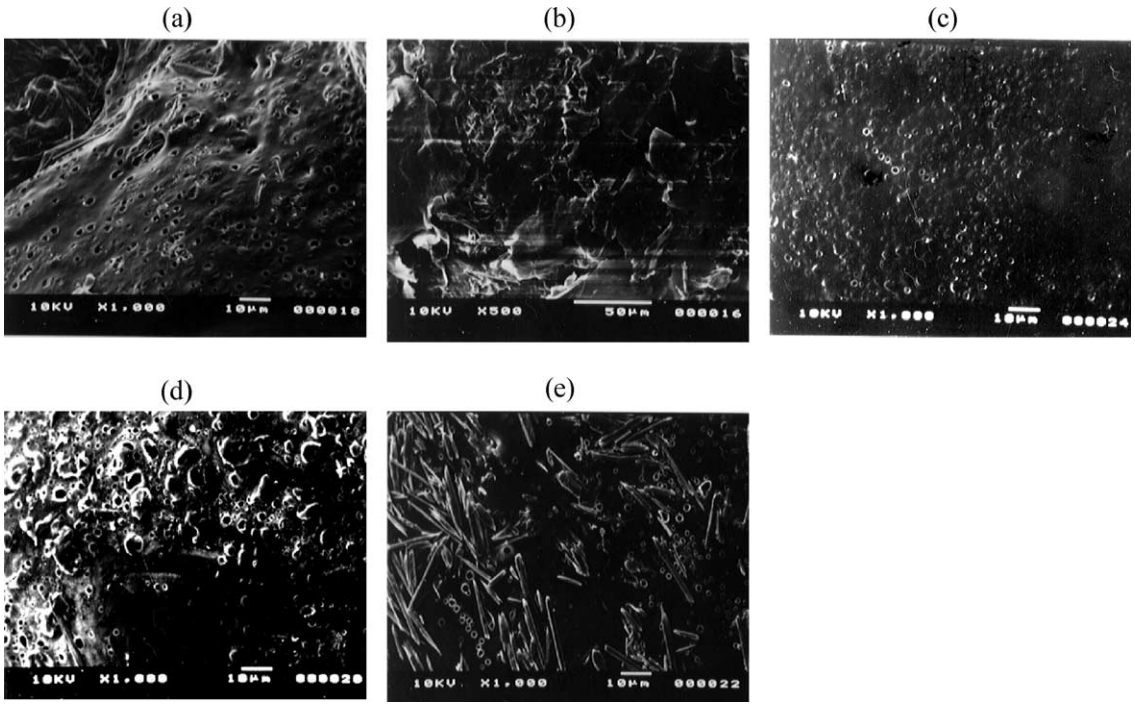

Fig. 7. Scanning electron microphotographs of microballoons. (a) S100/L100 = 9:1. (b) S100/L100-55 = 9:1. (c) S100/HPMCP = 9:1. (d) S100/HPMC = 9:1. (e) S100/EC = 9:1.

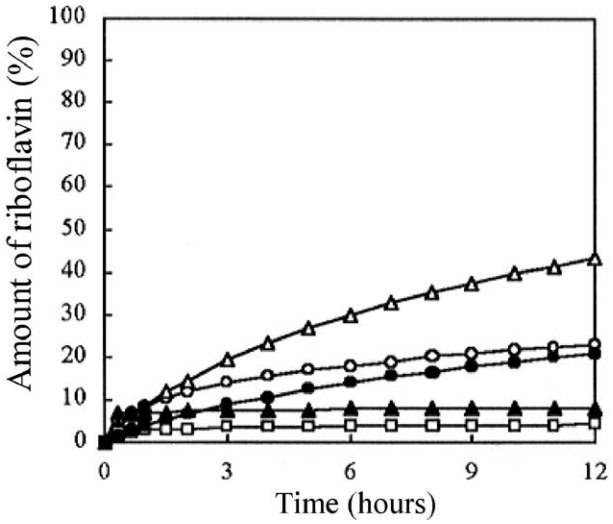

Fig. 8. Riboflavin release from microballoons in JP XIII No.1 solution containing 0.02 w/v% Tween 20 (pH 1.2). ○, S100/L100 = 9:1; △, S100/L100-55 = 9:1; □, S100/HPMCP = 9:1; ●, S100/HPMC = 9:1; and ▲, S100/EC = 9:1.

Table 2
Physiochemical properties of riboflavin-containing microballoons

Sample	Microballoons recovery (%)	Buoyancy (%)	Percent released[a] (%)	
			pH1.2	pH6.8
S100/HPMC = 10:0	87.5	99.2	4.2	5.9
S100/HPMC = 9:1	90.3	93.6	25.0	100.1
S100/HPMC = 8:2	86.3	62.7	46.8	97.1
S100/HPMC = 7:3	77.3	38.0	77.1	100.6
S100/HPMC = 6:4	87.3	38.2	89.3	103.6

[a] Percent released: amount of riboflavin (%) after 12 h; S100, Eudragit®, S100; HPMC, hydroxypropylmethylcellulose.

as Eudragit® L100, Eudragit® L100-55 or HPMC in the shell of microballoons afforded elevated riboflavin release from microballoons. In conclusion, the drug release property and buoyancy of microballoons could be determined by apparent particle density, surface topography and wettability of microballoons.

3.3. Riboflavin release from microballoons prepared by mixing HPMC with Eudragit® S100

It was found that the drug release rate and buoyancy of microballoons prepared by coformulating HPMC was relatively improved due to gelation in JPXIII No.1 solution. Therefore, the effect of HPMC mixing ratio on physicochemical properties and drug releasing behaviors of the microballoons were investigated as shown in Table 2 and Fig. 9.

Although the recovery of microballoons appeared unchanged by HPMC ratio, the buoyancy decreased with increasing HPMC ratio. These results were attributable to the conversion of spherical microballoons to needle-like particles possessing no hollow structure. In addition, the JPXIII No. 1 solution can readily penetrate into microballoons due to the increased dissolution of HPMC in the solution. The amount of riboflavin released from microballoons in JPXIII No. 1 solution containing 0.02 w/v% Tween 20 (pH 1.2) increased with increasing HPMC ratio. This behavior was explained by the increased contact area of particles with the medium due to the poor buoyancy associated with increased HPMC ratio. The amount of riboflavin released from microballoons in JP XIII No. 2 solution supplemented with 0.5 w/v% Tween 80 (pH 6.8) significantly increased in association with increased HPMC ratio.

In conclusion, a recommendable preparation formulation of microballoon to increase the bioavailability of riboflavin

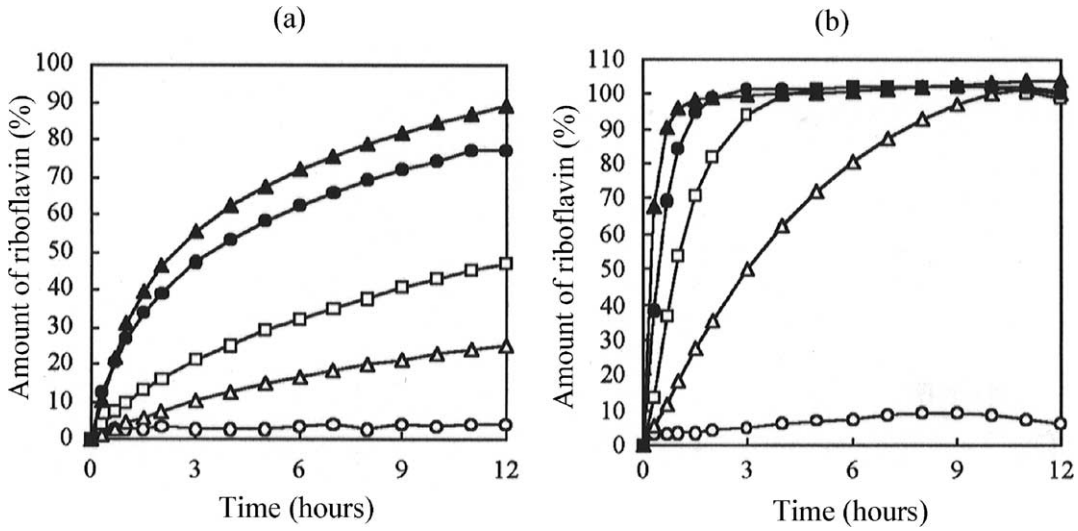

Fig. 9. Riboflavin release from microballoons. (a) JP XIII No.1 solution (pH 1.2). (b) JP XIII No.2 solution (pH 6.8). ○, S100/HPMC = 10:0; △, S100/HPMC = 9:1; □, S100/HPMC = 8:2; ●, S100/HPMC = 7:3; and ▲, S100/HPMC = 6:4.

absorbed mainly at the proximal small intestine (pH 4–6.5) was riboflavin 0.1 g, Eudragit® S100 0.9 g, HPMC 0.1 g and monostearin 0.5 g due to their desired drug release and floatable properties.

4. Conclusion

Hollow microspheres (microballoons) with enteric acrylic polymers such as Eudragit® S100 floatable in JPXIII No. 1 solution were successfully prepared by the emulsion solvent diffusion method. Five different drugs exhibiting distinct water solubilities such as aspirin, salicylic acid, ethoxybenzamide, indomethacin and riboflavin, could be enclosed in the shell of microballoon forming a matrix-like structure. The drug dispersed in the shell as an amorphous or crystalline state, depending upon the loading amount of drug, was released following Higuchi kinetics or some other method, respectively. The crystalline drug adsorbed on the surface of microballoon caused an initial burst release. The buoyancy of microballoons decreased with increasing drug release rate. By coformulating mixed polymer, the drug release and buoyancy of microballoons were modified depending upon their apparent density, surface topography and wettability.

Upon incorporation of hydrophilic polymers such as HPMC in the shell of microballoons, the amount of riboflavin released from microballoons could be enhanced. Riboflavin released properties of the microballoons were influenced by the pH of the release test solution; the amount of riboflavin released from microballoons in JP XIII No. 2 solution (pH 6.8) significantly increased in association with increased HPMC ratio. A preparation formulation of microballoon to increase the amount of riboflavin released from microballoons maintaining high buoyancy could be provided; riboflavin 0.1 g, Eudragit® S100 0.9 g, HPMC 0.1 g and monostearin 0.5 g.

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