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Evaluation and Optimization of Preparative Variables for Controlled-Release Floatable Microspheres Prepared by Poor Solvent Addition Method

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The aim of this study was to evaluate and optimize preparative parameters for floatable theophylline microspheres prepared by the emulsion–solvent evaporation method. A three-factor three-level Box–Behnken design was employed using amount of poor solvent, temperature-increase rate and drug loading as independent factors, and percentage floating at 3 h and time required for 50% drug release as dependent variables. Simultaneous optimization of the parameters for maximum buoyancy and desirable drug release was conducted using a partitioned artificial neural network. A microsphere using 27.6% of drug loading, 0.29°C/min of temperature-increase rate, and 1.7 mL of poor solvent was identified for maximizing buoyancy and sustaining drug release.

Keywords floatable microsphere; sustained release; solvent evaporation; poor solvent addition; optimization; theophylline

INTRODUCTION

Gastroretentive drug delivery systems can be retained in the stomach and assist in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Achieving a prolonged gastric retention time involves floating-type drug delivery systems (Singh & kim, 2000). Both single- and multiple-unit floating systems have been developed; however, multiple-unit systems such as microspheres have an advantage over single-unit systems in that they avoid "all or nothing" gastric emptying. The principle of multiple-unit floating system offers a simple and practical approach to prolonged gastric retention. Two mechanisms, low density and gas generation, are most frequently used in such systems. A low-density system could be achieved by using hollow microspheres with a lower density than that of the gastric content (Kawashima, Niwa, Takeuchi, Hino, & Ito, 1991) or microspheres incorporating a low-density material (Yuasa, Takashima, & Kanaya, 1996). A gas-generating system could be obtained by using pellets containing sodium bicarbonate, which generates carbon dioxide gas in the stomach (Ichikawa, Watanabe, & Miyake, 1991).

Several reports concerning floatable hollow microspheres have been described (El-Kamel, Sokar, Al Gamel, & Naggar, 2001; Kawashima et al., 1991; Stithit, Chen, & Price, 1998; Thanoo, Sunny, & Jayakrishnan, 1993,). But some require a special method to produce the hollow microsphere or provide low yields of product. A conventional method with high product recovery is desired.

In our previous studies dealing with the emulsion–solvent evaporation method, the effects of constant temperature-increase in the solvent evaporation process (the so-called constant temperature-increase method) and poor solvent addition to the dispersed phase (so-called poor solvent addition method) on the drug release property of the microspheres were illustrated (Miyazaki, Onuki, Yakou, & Takayama, 2006; Miyazaki, Yakou, & Takayama, 2007). The constant temperature-increase rate affected the surface characteristics and drug release rate of the microspheres. In brief, a higher rate led to a smoother surface and lower drug release rate. On the contrary, the amount of poor solvent controlled the internal structure of the microspheres and the drug release kinetic. Typically, a larger amount of poor solvent provided a more distinct core-shell structure, resulting in a zero-order drug release kinetic. In addition, several kinds of microspheres remained floating on the fluid for several hours. Therefore, we attempted to modify these techniques for the fabrication of floatable microspheres. Various combinations of temperature-increase rate and amount of poor solvent would provide microspheres with individual floating and drug release behaviors.

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The primary aim of this study was to evaluate the effects of preparative variables on the floating and drug release property of microspheres, considering the contributions of the temperature-increase rate and the amount of poor solvent. The secondary aim was to optimize them for floatable microspheres with a suitable drug release rate. In this formulation, the modulation of drug release rate is also desirable. Thus, it was necessary to simultaneously optimize the processing and formulation variables for both the floating and the drug release behaviors. In this process, we used an artificial neural network (ANN) method compared with conventional multiple linear regression (MLR) analysis.

In this study, model microspheres were prepared from theophylline (TH) and hydrophobically modified dextran propyl dextran mixture ester (PDME). TH was used as a representative drug because sustained-release formulations are desirable because of the short elimination half-life in humans. PDME was selected as a water-insoluble polymer; it is used for contact lenses in the industrial field. Mixtures of acetone and water were used as the dispersed phase and liquid paraffin as the continuous phase. The microspheres were characterized by their particle properties and then analyzed for their floating and drug release behaviors. Finally, the optimal formulation was predicted by simultaneous optimization technique.

MATERIALS AND METHODS

Materials

TH was purchased from Kanto Chemical Co., Inc. (Tokyo, Japan) and was used after sieving. The fraction passing through a 100-mesh sieve and remaining on a 200-mesh sieve was used. PDME was donated by Meito Sangyo Co., Ltd. (Nagoya, Japan); it was prepared from dextran (MW 40,000) by substitution of 0.6 mol acetyl, 0.8 mol propyl, 1.4 mol butyl, and 0.16 mol methacrylate per anhydroglucose unit. Liquid paraffin conforming to JP standard was obtained from Iwaki Seiyaku Co., Ltd. (Tokyo, Japan). Sucrose-ester (DKF-10) was generously supplied by Dai-ichi Kogyo Seiyaku Co., Ltd. (Kyoto, Japan) and was used as an emulsifier. Acetone and polyoxyethylene (20) sorbitan monolaurate (Tween 20) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Ultrapure water was supplied by Direct-Q system (Millipore Co., Tokyo, Japan). All other chemicals were of special reagent grade and were used as received.

Experimental Design

A Box–Behnken experimental design was employed to optimize the preparative parameters of a TH microsphere preparation for maximum buoyancy and controlled drug release. The Box–Behnken design was specifically selected because it requires fewer factor combinations than a Central Composite design in cases involving three factors. Table 1 summarizes the independent factors and the levels of experimental units used in the study. Theoretical drug loading (X1), constant temperature-increase rate (X2), and amount of water (X3) were selected as causal factors because these factors were shown in a preliminary study and previous reports (Miyazaki et al., 2006, 2007) to have a significant effect on both buoyancy and drug release. The studies also provided a setting of the levels for each preparative variable. The response variables were percentage of the microspheres floating at 3 h (Y1) and time required for 50% drug release (Y2). A total of 15 runs including triplicate center points were generated (Table 2).

TABLE 1
Independent Factors and their Levels for Box–Behnken Design

	Level		
Factors	–1	0	1
X1: theoretical drug loading (%)	16.7	25.0	33.3
X2: temperature-increase rate (°C/min)	0.25	0.50	1.0
X3: amount of water (mL)	1.0	1.5	2.0

Preparation of Microspheres

Microspheres were prepared according to the experimental design. PDME (7.5 g) was dissolved in 15 mL of a mixture of acetone and water (Table 2). TH (predetermined weight) was then dispersed in the PDME solution under stirrer agitation. The dispersion was poured into agitated liquid paraffin (150 mL) containing DKF-10 (0.75 g) in a vessel settled into a water bath. Following emulsification for 30 min at 20□ in the water bath, the system was heated up to 50°C at the predetermined temperature-increase rate. After allowing the microspheres to settle, the liquid paraffin was decanted off. The microspheres were washed three times with *n*-hexane and then dried under reduced pressure at room temperature overnight. The loading amount of PDME was fixed at a value of 7.5 g/batch.

Evaluation of Microspheres

Recovery of microspheres was determined from the weight ratio of dried microspheres to the loaded amount of TH and PDME.

TH content was analyzed as follows. Approximately 50 mg of microspheres were accurately weighed and dissolved completely in methylene chloride. Samples were filtered with a membrane filter (Millex-LG, Millipore Co., Cork, Ireland, USA) and assayed spectrophotometrically for TH concentration at 274 nm. The polymer did not interfere with the analysis at this wavelength.

The particle size and the distribution of the microspheres were determined by sieving through a set of standard sieves. Each preparation was placed on the uppermost sieve and shaken enough to separate. The fractionized microspheres were weighed to determine the weight distribution. Geometric mean diameter was calculated from the weight distribution for each preparation.

TABLE 2
Experimental Values of Factors and Particle Properties of Microspheres

Formulation Number	Drug Loading (%)	Temperature Increase Rate (°C/min)	Amount of Water (mL)	Product Recovery (%)	Drug Content (%)	Mean Diameter (μm)	Relative Density
1	33.3	1.0	1.5	88.9	33.7	1,096	1.13
2	33.3	0.25	1.5	98.6	35.3	873	0.858
3	16.7	1.0	1.5	92.8	19.7	503	1.09
4	16.7	0.25	1.5	96.3	19.8	405	0.761
5	33.3	0.50	2.0	97.9	35.3	530	0.896
6	33.3	0.50	1.0	93.1	37.3	1282	1.16
7	16.7	0.50	2.0	94.7	16.6	514	1.00
8	16.7	0.50	1.0	93.2	21.8	455	1.09
9	25.0	1.0	2.0	96.9	27.4	702	1.09
10	25.0	1.0	1.0	90.6	20.4	622	1.11
11	25.0	0.25	2.0	97.9	27.7	519	0.914
12	25.0	0.25	1.0	85.9	32.7	583	0.935
13	25.0	0.50	1.5	92.4	29.6	530	1.01
14	25.0	0.50	1.5	96.9	28.7	482	0.990
15	25.0	0.50	1.5	97.6	28.6	572	1.02

Relative density to ultrapure water was determined by liquid displacement method using a pycnometer at 20°C.

Release Test

In vitro drug release studies were carried out at 37 ± 0.5□ in 900 mL of JPXIV 1st fluid (pH 1.2, 0.07 M HCl and 0.0342 M NaCl) with 0.02% (wt/vol) Tween 20 using a standard JPXIV dissolution apparatus with paddle stirrers (100 rpm). Samples (5 mL) were withdrawn from the dissolution vessels at 0.25, 0.5, 1, 2, 4, 6, and 8 h and immediately replaced with an equal volume of the same test fluid. Samples were analyzed spectrophotometrically at 273 nm for TH content after filtration with a membrane filter (Millex-HA, Millipore Co.). The experiments were repeated three times.

Floating Test

Floating studies were conducted in a similar manner to the release test. Typically, fifty microspheres were dispersed into 900 mL of JPXIV 1st fluid with 0.02% (wt/vol) Tween 20 in JPXIV paddle apparatus at 100 rpm. Numbers of floating microspheres were counted by direct observation at 0.5, 1, 2, 3, 4, and 6 h. The rotation of the paddle was briefly stopped during observation and resumed immediately. The experiments were performed in triplicate.

Simultaneous Optimization

Optimization of preparative parameters for floatable microspheres with suitable drug release was performed using a simultaneous optimization technique featuring partitioned ANNs using an extended Kalman filter algorithm (Takayama, Fujikawa, & Nagai, 1999), because a fairly good agreement between observed values and predicted results was previously obtained (Takayama et al., 2000). The mathematical concept for optimization has been detailed elsewhere (Takayama, Fujikawa, Obata, & Morishita, 2003).

At the same time, MLR analysis was conducted for comparison. For selection of the optimal combination of factors, doubly adjusted multiple correlation coefficient with degrees of freedom was used as a judging standard (Wu et al., 2001).

RESULTS

Microsphere Characters

The experimental runs and the particle characters, e.g., product recovery, drug content, mean diameter, and particle density, are summarized in Table 2. Product recovery was found to be good, ranging from 85.9 to 98.6%. Drug content tended to be slightly larger from the theoretical drug loading. All factors had no dominant effect on the mean diameter of the microspheres, varying randomly from 405 to 1282 μm.

Relative density to ultrapure water appears in Table 2 because it is an important characteristic of floatability. The values varied from 0.761 to 1.13 and were not correlated individually with the three independent factors. Generally, formulations having lower density than that of gastric fluid would initially float on the gastric content. The density of gastric fluid is thought to be close to that of water (~1.004 g/cm^3). In this study, several microspheres had a lower density than that of ultrapure water, indicating the probability of floating on the gastric content.

Drug Release Behaviors

The release profiles of TH from all the 15 preparations based on the experimental design are shown in Figures 1 and 2. The cumulative percent released in 8 h ranged from 37% in preparation No.3 to 99% in preparation No. 10. A wide deviation in the release profiles was observed, indicating that they were greatly affected by changes in the level of preparative variables such as drug loading and temperature-increase rate as well as the amount of water.

Release data were fitted to the Power Law (Ritger & Peppas, 1987):

$$\frac{M_t}{M_\infty} = \mathrm{K}t^n \qquad (1)$$

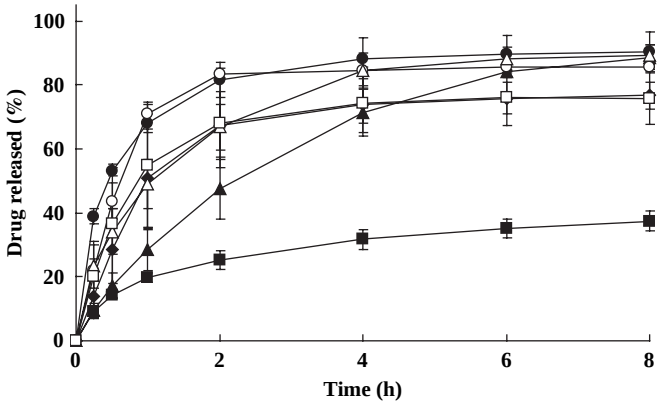

FIGURE 1. Drug release profiles from various microspheres in JPXIV 1st fluid containing 0.02% Tween 20 (pH 1.2). Each point represents the mean ± SD (n = 3). Key: ●, No.1; ▲, No.2; ■, No.3; ◆, No.4; ❍, No.5; △, No.6; □, No.7.

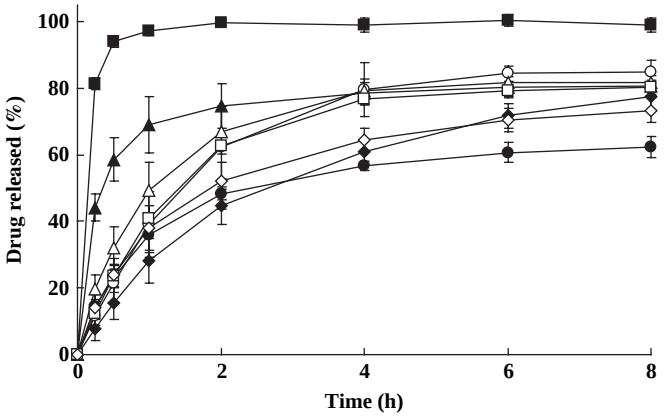

FIGURE 2. Drug release profiles from various microspheres in JPXIV 1st fluid containing 0.02% Tween 20 (pH1.2). Each point represents the mean ± SD (n = 3).Key: ●, No.8; ▲, No.9; ■, No.10; ◆, No.11; ❍, No.12; △, No.13; □, No.14; ◇, No.15.

where M_t/M_∞ represents the fraction of TH released at time t, K is the coefficient constant, and n is the diffusion exponent. The time required for 50% drug release (T50%) was then calculated by the following equation.

$$T50\% = \sqrt[n]{0.5/K} \qquad (2)$$

The results are listed in Table 3. T50% values of many microspheres lay within the preferable range from 0.5 to 1.5 h. The in vitro drug release from TH extended-release granules was defined in Japanese Pharmaceutical Codex (JPC), where values of cumulative percent released with high and low constraints at different time points have been employed as summarized in Table 4. On the basis of JPC, the desirable range of T50% was estimated to be from 0.5 to 1.5 h.

Floating Behaviors

On the basis of the experimental design, the factor combinations yielded different floating characteristics. Floating profiles of the 15 preparations are presented in Figures 3 and 4. Five

TABLE 3
Combinations of Factors and Observed Response Variables

	Factor			Response	
Formulation Number	X1	X2	X3	Y1 (T50%)	Y2 (F3h)
1	1	1	0	0.45	53.3
2	1	−1	0	2.06	97.3
3	−1	1	0	13.6	31.3
4	−1	−1	0	1.17	100
5	1	0	1	0.57	84.0
6	1	0	−1	1.09	58.0
7	−1	0	1	1.01	97.3
8	−1	0	−1	3.26	40.0
9	0	1	1	0.43	48.0
10	0	1	−1	0.02	12.7
11	0	−1	1	2.57	98.7
12	0	−1	−1	1.45	99.3
13	0	0	0	0.78	83.3
14	0	0	0	1.39	72.7
15	0	0	0	2.05	88.7

TABLE 4
Dissolution Test Criteria for Theophylline Extended-Release Granules (200 mg/g)

Time (h)	Amount Dissolved
0.5	Between 20 and 50%
1	Between 40 and 70%
2	more than 75%

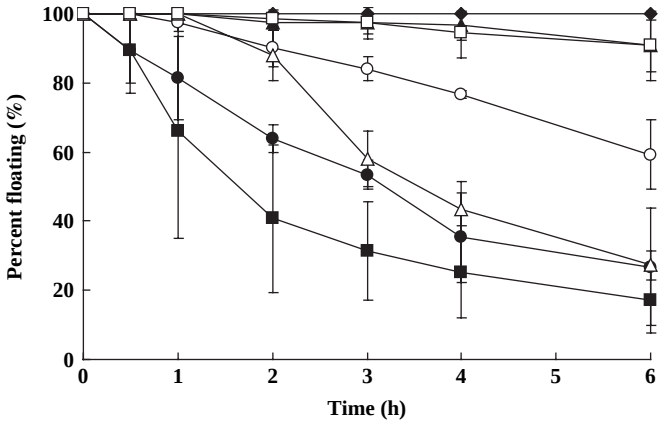

FIGURE 3. Floating profiles of various microspheres in JPXIV 1st fluid containing 0.02% Tween 20. Each point represents the mean ± SD (n = 3). Key: ●, No.1; ▲, No.2; ■, No.3; ◆, No.4; ❍, No.5; △, No.6; □, No.7.

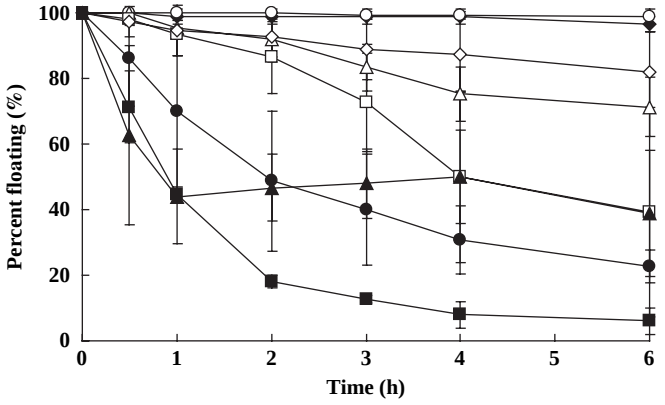

FIGURE 4. Floating profiles of various microspheres in JPXIV 1st fluid containing 0.02% Tween 20. Each point represents the mean ± SD (n = 3). Key: ●, No.8; ▲, No.9; ■, No.10; ◆, No.11; ❍, No.12; △, No.13; □, No.14; ◇, No.15.

preparations (No. 1, 2, 7, 11, 12) showed at least 90% floating at 6 h. Percent floating at 6 h varied from 6 to 100%, indicating appropriate design to evaluate the preparative variables.

Floatability was represented as percentage floating at 3 h (F3h) as summarized in Table 3, because previous radiographical studies (Kawashima et al., 1991) proved that hollow microspheres orally administrated to humans were dispersed in the upper part of stomach and retained there for 3 h against peristaltic movements. In addition, a wide deviation from 12.7 to 100 was observed in the values of F3h. In previous reports, no response variable corresponding to floatability was included in the objective of formulation optimization owing to little variation in floating test data.

Multi-Objective Simultaneous Optimization

The multi-objective simultaneous optimization method incorporating a partitioned ANN described earlier was applied

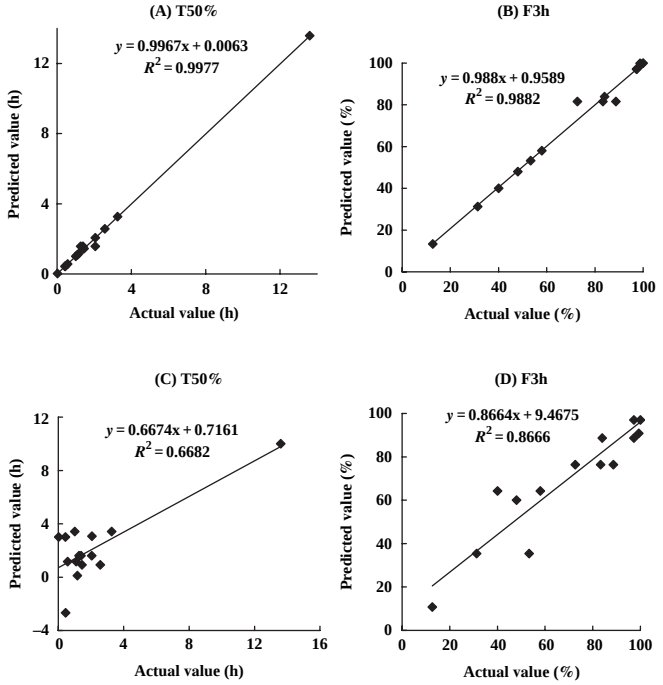

FIGURE 5. Correlation between the actual and predicted values in T50% (a, c) and F3h (b, d). Key: (a, b) artificial neural network, (c, d) multiple linear regression.

to the prediction of processing and formulation variables for TH microsphere, which had a desired drug release rate and floatability. The factor combinations (summarized in Table 2) and the observed responses (summarized in Table 3) for the 15 preparations are used as a training data set. The numbers of units in the hidden layer of the optimal ANN model were determined to be 4 and 3 for T50% and F3h, respectively, by using Akaike's information criterion as a judging index. Figure 5 shows the correlation between actual value (experimental value) and predicted value, not only by the ANN but also by the MLR for comparison. A good linear correlation was shown in both T50% and F3h of the ANN model in contrast to those of the MLR. Moreover, the accuracies of the ANN and the MLR model were evaluated by use of the mean bias and the mean accuracy defined in Equations (3) and (4), respectively.

$$B_m = \frac{\sum_{i=1}^{n} \left| X_p - X_t \right| / X_t}{n} \times 100 \tag{3}$$

$$A_m = \frac{\sum_{i=1}^{n} (X_p - X_t) / X_t}{n} \times 100 \tag{4}$$

where B_m is the percentage mean bias, A_m is the percentage mean accuracy, X_p is the predicted value of response variables, X_t is the actual value of response variables, and n is the number of experiments. In the ANN model, the B_m and A_m for T50% were calculated to be −0.81 and 0.29%, and the B_m and A_m for F3h were −0.51 and 1.9%, respectively. On the contrary, in the MLR model, the B_m and A_m for T50% were determined to be −1004.2 and 1128.5%, and the B_m and A_m for F3h were −2.20 and 14.4%, respectively. These results indicated that the ANN model had a better predictability compared with the conventional MLR method.

Response Surfaces

The ANN provided a response surface describing the effects of processing and formulation variables on final product characteristics. Figure 6 shows the response surfaces of T50% predicted by the ANN as a function of X2 (temperature-increase rate) and X3 (amount of water) at a constant value of X1 (drug loading). Non-linear relationships between the factors and the response variables were represented well with the response surfaces. Upon comparison with (a), (b), and (c) in Figure 6, it was evident that the factor with maximum influence on the drug release was the drug to polymer ratio, and that the influence of X2 and X3 was altered with changes of drug loading. At 17% of drug loading (Figure 6a), the increase in X2 and X3 led to an increase in Y1 (T50%), consistent with previous reports (Miyazaki et al., 2006, 2007). At higher drug loadings (Figures 6b and c), however, the effect of water amount was small. This was because that the thickness of the wall or matrix of the microsphere was very important for drug dissolution. Many previous studies mentioned that drug release rates were controlled by changing the ratio of drug to polymer in the microsphere. However, the change in the ratio is often accompanied by difficulties such as low product recovery, alternation of size, and so on. In contrast, these results showed that the drug release rate could be controlled by the temperature-increase rate and the amount of water without any difficulties at the lower level of drug loading.

Figure 7 shows the response surfaces of F3h predicted by the ANN as a function of X2 (temperature-increase rate) and X3 (amount of water) at a constant value of X1 (drug loading). In contrast to drug release, the influence of X1 was relatively small. This is because the wall thickness of the microsphere is less important for buoyancy. On the contrary, the floatability was controlled mainly by the temperature-increase rate. The buoyancy decreased with increasing X2. On the whole, faster evaporation caused a reduction in percent floating. The amount of water was important in the case of higher temperature-increase rate (Figures 7b and c). At the lower level of X3, e.g., less than 1.3 mL, the value of F3h was very small.

Contributions

The dependent and independent variables were related using surface response plots. Contributions of the factors were estimated by surface response plots using a contribution index (Fujikawa, Takayama, & Nagai, 1998). Table 5 summarizes the contribution indices. With respect to Y1 (T50%), the contribution index of X1 was found to be 55.8%, showing a large value as expected. The contributions of X2 and X3 were at the same level.

With respect to Y2 (F3h), the contribution index of X2 was 62.1%. The buoyancy was found to be significantly affected by

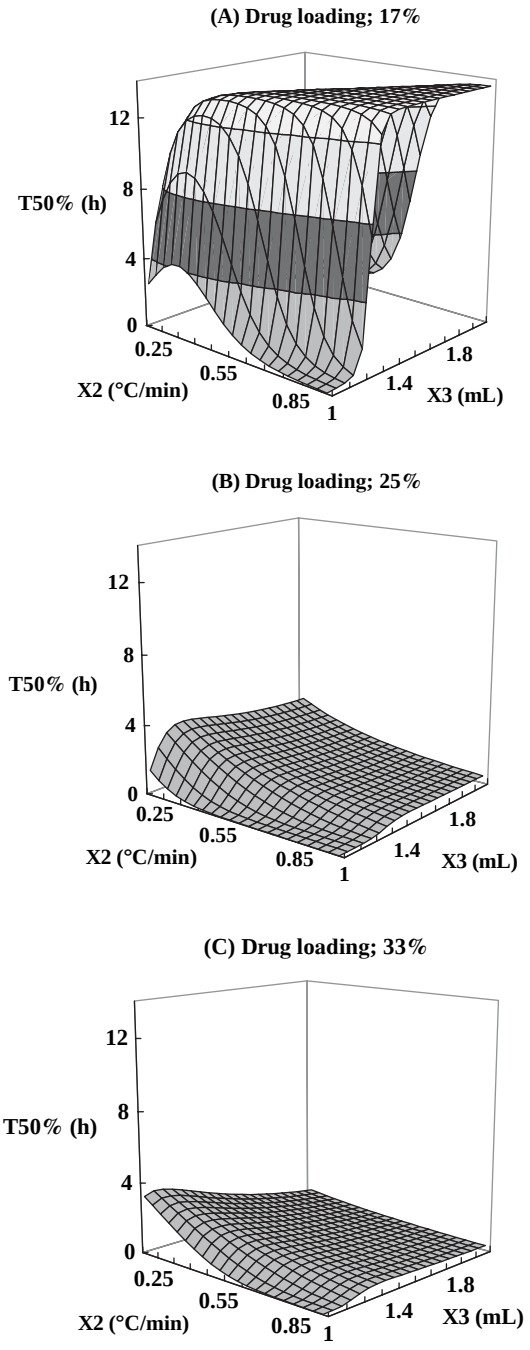

FIGURE 6. Response surface plot showing the effect of temperature-increase rate (X2) and amount of water (X3) on T50% (Y1).

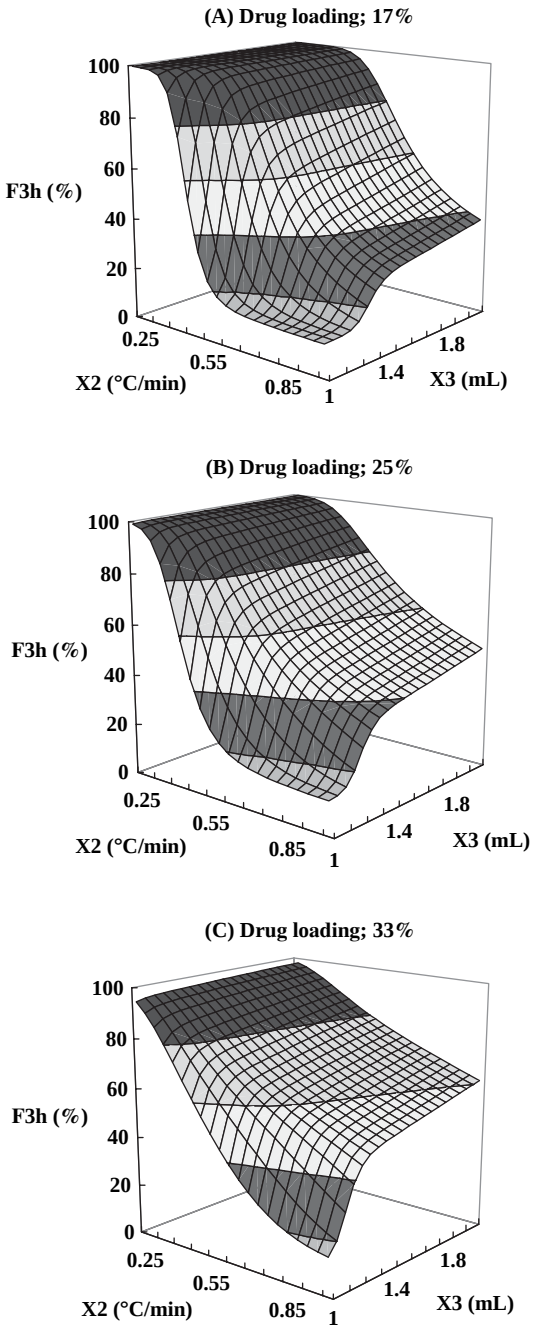

FIGURE 7. Response surface plot showing the effect of temperature-increase rate (X2) and amount of water (X3) on F3h (Y2).

the temperature-increase rate. Kawashima et al. (1991) reported that the rapid removal of solvent from the emulsion droplets leads to polymer precipitation at the interface, thus making them hollow. In this case, the rapid evaporation of acetone from the dispersion produces cavities and pores in the microspheres, which render them hollow and cause them to float. However, the floatability of the microspheres was not correlated linearly with their relative density (summarized in Table 2). In general, the floatability is affected by various factors such as porosity and water repellency. Therefore, the floatability was not defined by the relative density of the microsphere alone.

TABLE 5
Contribution Index (%) of Independent Factors to Each Response Variable

	*T*50%	F3h
X1: theoretical drug loading	55.8 ± 1.0	13.5 ± 0.2
X2: temperature-increase rate	22.2 ± 1.4	62.1 ± 0.8
X3: amount of water	22.0 ± 1.4	24.4 ± 0.9

The values are represented as the mean ± SD (n = 5).

Optimization

The optimization of the controlled release floatable microspheres was performed according to the generalized distance function method (Takayama & Nagai, 1991).

In the floating dosage forms, maximization of the buoyancy (F3h) would be favorable because it indicated a longer gastric retention. At the same time, sustained release of drug is desirable. As described earlier, the TH extended release granules have specific drug dissolution requirements as summarized in Table 4. Thus, a certain constraint was applied on *T*50%, that is, maximum within 1.5 h. For example, to identify the optimal formulation and processing parameters for a TH microsphere with maximum F3h and maximum *T*50% (within 1.5 h), optimization was carried out. The optimization result indicated a setting of drug loading (27.6%), temperature-increase rate (0.29□/min), and amount of water (1.7 mL). The model predicted a 1.50-h *T*50% and 98.7% floating at 3 h. The optimized microsphere prepared according to the predicted optimum formulation and process conditions demonstrated 1.54 h *T*50% and 96.7% floating, which were close to the predicted values. These results demonstrated that the simultaneous optimization technique incorporating ANN is useful for the evaluation and prediction of the formulation and processing variables.

DISCUSSION

Development of controlled-release floatable TH microspheres was achieved by use of both the poor solvent addition method and the constant temperature-increase method. The floatable TH microspheres were prepared by these methods, wherein the rapid evaporation of good solvent helped to form the core-shell structure or cavities in the matrix under poor solvent-existing conditions. In addition, the systematic approach allowed us to evaluate the preparative parameters for the controlled-release floatable microspheres. Microspheres with desirable drug release and floating properties for TH were thus successfully developed using the emulsion–solvent evaporation

process, optimizing preparative parameters by a multi-objective simultaneous optimization technique.

Various approaches and technologies are available to achieve controlled release floatable systems in multiple-unit form. Kawashima et al. (1991) prepared hollow microspheres, so-called microballoons, with a drug loaded in their outer shells by an emulsion–solvent diffusion method. Drug release rates were controlled by changing the ratio of polymer to drug in the microballoon. In producing the microballoon, however, the polymer concentration in the solvent is important. With an increasing concentration of polymer solution, the product recovery of microballoons decreased drastically. Moreover, Sato, Kawashima, Takeuchi, and Yamamoto (2004) mentioned that the relationship between drug release rate and buoyancy of the microballoons was a "Trade-off," requiring selection of an appropriate balance.

In contrast, drug release rate and buoyancy could be improved at the same time using the present method. Furthermore, both the desired time period for floating and the rate of drug release would be modulated by levels of the preparative variables. In addition, high product recovery was obtained over a wide range of preparative variables. Ease of manufacture also gave an advantage on this method.

In this study, optimization was conducted only for TH as an example. The objective values of response variables, however, can be changed to suit for other drugs. In conclusion, the current emulsion–solvent evaporation procedure is a promising method to prepare multiple-unit floating drug delivery systems.

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