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RESEARCH PAPER

Effect of Formulation Variables on the Floating Properties of Gastric Floating Drug Delivery System

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ABSTRACT

Purpose. *To evaluate the contribution of formulation variables on the floating properties of a gastric floating drug delivery system (GFDDS) using a continuous floating monitoring system and statistical experimental design.* ***Methods.*** *A modified continuous floating monitoring system, which consisted of an electric balance interfacing with a PC, was designed to perform the continuous monitoring of floating kinetics of GFDDS. Several formulation variables, such as different types of hydroxypropyl methylcellulose (HPMC), varying HPMC/Carbopol ratio, and addition of magnesium stearate, were evaluated using Taguchi design, and the effects of these variables were subjected to statistical analysis.* ***Results.*** *The continuous floating monitoring system developed was validated, using capsules with different density, and a good correlation between theoretical and experimental values was obtained ($R^2 = 0.9998$), indicating the validity of the*

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setup. The statistical analysis indicated that magnesium stearate had a significant effect on the floating property of GFDDS ($p < 0.05$), and addition of magnesium stearate could significantly improve the floating capacity of the GFDDS. It was found that the HPMC of higher viscosity grade generally exhibited a greater floating capacity, but the effect was not statistically significant. For polymers with the same viscosity, i.e., K4M and E4M, the degree of substitution of the function group did not show any significant contribution. A better floating behavior was achieved at higher HPMC/Carbopol ratio. Carbopol appeared to have a negative effect on the floating behavior of GFDDS. ***Conclusions.*** *It was concluded that by using a validated continuous floating monitoring system, the effect of formulation variables on the floating property of the delivery system and their ranges could be identified. Incorporation of hydrophobic agents, such as magnesium stearate, could significantly improve the floating capacity of the GFDDS.*

Key Words: *Carbopol; Design of experiment; Drug delivery system; Gastric floating; HPMC*

INTRODUCTION

The traditional oral delivery system has certain disadvantages that needed to be overcome, such as the short retention time in the gastrointestinal (GI) tract, protection of GI-labile drugs from the hostile intestine environment, etc. Many attempts have been made in recent years to provide a dosage form with a longer transit time and therefore a more efficient absorption. These approaches include utilization of passage-delaying agents, use of large single-unit dosage forms, development of bioadhesive drug delivery system, and design of "heavy" pellets and floating dosage forms.[1,2] Compared to these approaches, the gastric floating drug delivery system (GFDDS) developed has provided several advantages, as shown by the encouraging results reported earlier.[3–5] Furthermore, the buoyancy action provided by the GFDDS seems to offer a greater safety for clinical uses than some of the above-mentioned approaches. In fact, no adverse effects due to floating devices have been reported to date.

Calcium is a very important element in the maintenance of bone integrity and normal cell function. The mechanism of calcium absorption is a combination of two processes: transporter-mediated active transport, which is saturable, and concentration-dependent passive diffusion, which is non-saturable.[6,7] The active absorption for calcium is known to occur mainly in the duodenum and the upper jejunum segments, where a large amount of calcium-binding protein (CaBP) exist.[7] This site-specificity of calcium absorption has posed a challenge for calcium delivery since the duodenum is the uppermost and shortest segment of the small intestine. Dosage forms, following their gastric emptying, usually pass the duodenum section very quickly, due to the stomach's house-keeping wave.[8] The hypothesis for this research project is that if calcium can be delivered in a controlled manner to the duodenum at a rate that does not exceed the maximum rate of active absorption for calcium, then the oral bioavailability of calcium could be improved. Based on this hypothesis, the GFDDS has been designed in such a way that it should be retained in the stomach for a prolonged period of time, thus maximizing the exposure of calcium to the active absorption site. The floating capacity of the calcium delivery system thus plays an important role in achieving this goal.

In light of this scenario, several prototypes of GFDDS were conceived, with the aid of Taguchi design, which attempt to identify the roles and the potential contribution of the various types of hydroxypropyl methylcellulose (HPMC), varying HPMC/Carbopol ratio, and magnesium stearate. All the experimental results were subjected to statistical analysis, using the SAS program.

MATERIALS AND METHODS

Materials

Calcium carbonate (Lot # A-6-313-24) was received from SmithKline Beecham Consumer

Healthcare (SBCH/Parsippany, NJ). Methocel® K4M, E4M, E5LV, and K100LV, which are commercially available grades of HPMC from Dow Chemicals Co. (Midland, MI), were also supplied by SBCH. Other materials were purchased from commercial sources: citric acid from Sigma Chemical Co. (St. Louis, MO), magnesium stearate from Fisher Scientific Co. (Fairlawn, NJ), hard gelatin capsules (size 000, manufactured by Eli Lilly Co., Indianapolis, IN) from Frontier Co. (Norway, IA).

Continuous Floating Monitoring System

The continuous floating monitoring system was conceived based on the modification of a mucoadhesive force measurement setup.[9] The schematic setup for the system is shown in Fig. 1. A stainless steel basket was connected to a metal string, suspended from a Sartorius electronic balance. The floating object was immersed at a fixed depth into the water bath, which was covered to prevent water evaporation. The upward floating force could be measured by the balance and the data transmitted to an on-line PC through RS-232C interface using a Sarto Wedge program (Sartorious Co., Bohemia, NY). The reading on the balance could be automatically picked up by a LOTUS spreadsheet. The test medium used in floating kinetics measurements was 900 mL simulated gastric fluid (pH 1.2) maintained at 37°C. Data was collected at a 30-sec interval; baseline was recorded and subtracted from each measurement. The dissolution basket had a holder at the bottom in order to measure the downward force.

With capsules of different density, the setup could be validated by comparing the theoretical vs. experimental values. This floating measurement setup can actually be applied to other applications upon modification, such as mucoadhesive and gel strength measurements, which could be done by changing the measuring probe.

Experimental Design

The formulations of GFDDS were conceived using Taguchi design [$L_{16}(4^5)$], because our primary concern is the main effect, i.e., to identify the most influential variable. Taguchi's orthogonal arrays are essentially fractional factorial experiments that allow a simultaneous evaluation of several formulation variables. A full factorial design is clean and straightforward, however, in this case, it would mean $4 \times 4 \times 2 = 32$ experiments without any replication or center points. The experimental design,

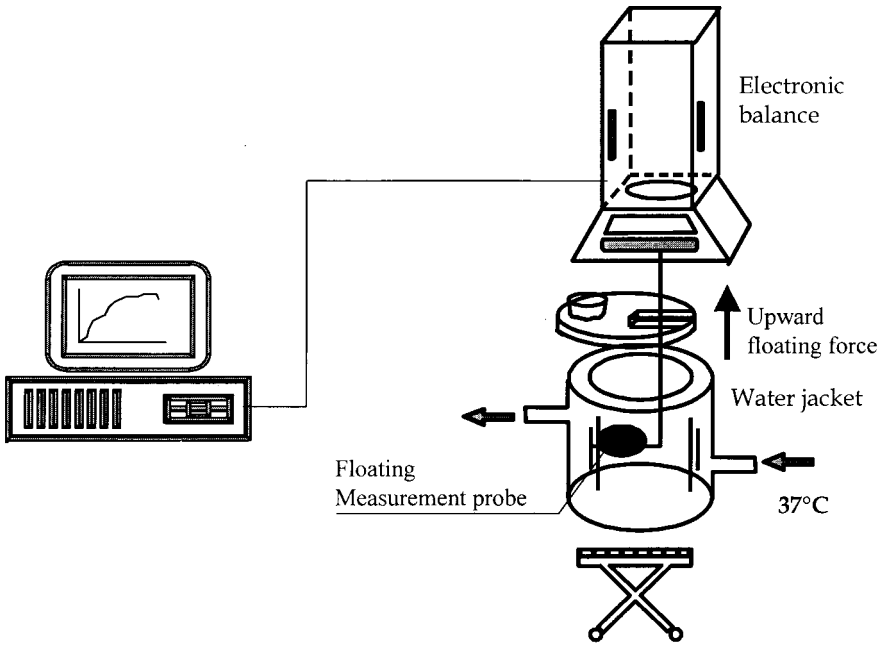

Figure 1. Schematic illustration of setup for continuous floating monitoring system.

Table 1

Composition for Formulations of GFDDS Based on Taguchi Design

	Ingredients/Capsule					
			HPMC			
System Code	Ca Carbonate (mg)	Citric Acid (mg)	Grade	(mg)	Carbopol 934P (mg)	Mg Stearate (mg)
T1	625	100	K4M	200	50	0
T2	625	100	K4M	187.5	62.5	25
T3	625	100	K4M	167	83	0
T4	625	100	K4M	125	125	25
T5	625	100	E4M	200	50	0
T6	625	100	E4M	187.5	62.5	25
T7	625	100	E4M	167	83	0
T8	625	100	E4M	125	125	25
T9	625	100	E5LV	200	50	25
T10	625	100	E5LV	187.5	62.5	0
T11	625	100	E5LV	167	83	25
T12	625	100	E5LV	125	125	0
T13	625	100	K100LV	200	50	25
T14	625	100	K100LV	187.5	62.5	0
T15	625	100	K100LV	167	83	25
T16	625	100	K100LV	125	125	0

with corresponding values of each formulation variable is outlined in Table 1. The formulation variables that were evaluated included:

- X_1: HPMC types, including HPMC K4M, E4M, E5LV, and K100LV;
- X_2: HPMC/carbopol ratio, ranging from 4/1, 3/1, 2/1, to 1/1;
- X_3: Magnesium stearate, presence or absence in the delivery system.

In this set of studies, fixed amounts of calcium carbonate (625 mg) and citric acid (100 mg) were used.

The dependent variables that were tested for both sets of studies included the following:

- Y_1: maximum floating force (F_{max});
- Y_2: time to reach the maximum floating force (T_{max});
- Y_3: area under the floating kinetics curve (AUC_f);
- Y_4: residual floating force (F_r).

Preparation of Calcium GFDDS

Calcium carbonate was mixed with various pharmaceutical excipients in a mortar and pestle for 5 min to achieve a homogeneous blend. Magnesium stearate, when used, was added in the final blend and then blended for an additional 3 min. The resultant mixture was filled into hard gelatin capsules (size 000) manually. For each formulation, a total of 10 capsules were prepared, each of which had a fixed amount of calcium carbonate (625 mg).

Statistical Analysis

The results from Taguchi design were analyzed using the SAS program. The mathematical model that PROC REG used is a linear model, which bears the form:

$$Y_i = b_0 + b_1x_1 + b_2x_2 + b_3x_3 + \varepsilon$$

where the Y_i are response variables, the b_j are regression coefficients, and X_1, X_2, and X_3 are the main effects of the formulation variables.

RESULTS AND DISCUSSION

Floating Kinetics Monitoring

In the current study, two approaches that could be used to improve the floating capacity of the

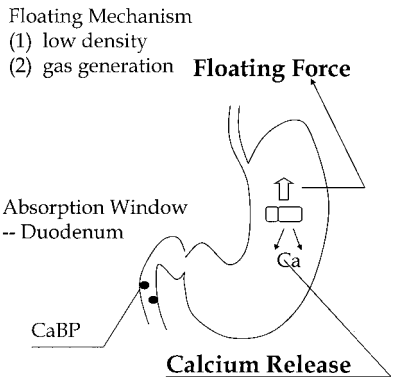

Figure 2. Schematic illustration of approaches for improving floating properties of the delivery system.

delivery system were incorporated (Fig. 2), i.e., low density and gas generation. If a sufficient floating force could be achieved by the combined mechanism, then calcium should be released from the delivery system in a controlled fashion, not oversaturating the active transport—CaBP—existing mainly in the duodenum and upper illeum. Hydroxypropyl methylcellulose is a low-density polymer that has been widely used for this purpose, therefore it was included in the design of the delivery system. Meanwhile, citric acid was also incorporated to utilize the gas generation mechanism, in which citric acid and active calcium carbonate would react to generate carbon dioxide. The floating characteristics of the GFDDS were essential, since they might influence the in vivo behavior of the delivery system. Generally, a higher floating capacity was desired. However, there seemed to be no threshold value for the floating system to remain afloat under a physiological environment,[2] due to the latter's complication.

Validation of the Setup

The continuous floating monitoring system consisted of an electronic balance and a PC with an RS-232C cable. In order to validate the setup for this type of measurement, a plastic holder filled with different amounts of polymers was used as a measurement probe. The theoretical floating force was calculated according to Eq. (1) and plotted over the measured floating force. Results are shown in Fig. 3. The theoretical floating force of the tested unit correlated very well with the experimental

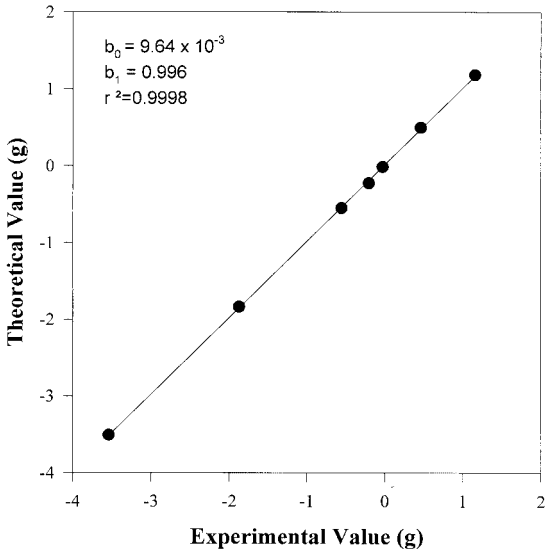

Figure 3. Calibration curve of the on-line continuous floating monitoring system.

values (correlation coefficient = 0.9998, intercept = 0.0096 g), indicating the validity of the setup to measure the floating force of a GFDDS for the negative range measurement.

Characterization of a Typical Floating Kinetic Curve

A typical floating kinetic curve is shown in Fig. 4. The curve was obtained by filling 500 mg of HPMC K100LV into a size 000 capsule. Four parameters were determined from the graph to characterize the floating properties, i.e., F_{max}, T_{max}, F_r, and AUC_f.

These parameters were obtained for each floating measurement and used for statistical data analysis. The overall force that capsules were subjected to was a combination of the upward floating force and the downward gravity force. The physical basis of the floating phenomena of the tested capsule can be expressed as:

$$\begin{aligned} F &= F_{\text{buoyancy}} - F_{\text{gravity}} \\ &= \rho_m g V_c - \rho_c g V_c \\ &= (\rho_m - \rho_c) g V_c \end{aligned} \quad (1)$$

where ρ_m is the density of the floating measurement medium, ρ_c is the density of the test object, and V_c is the volume of the test object.

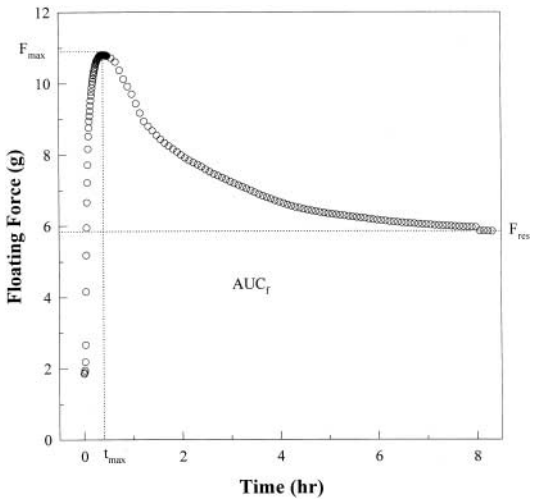

Figure 4. Typical floating kinetics curve of GFDDS, measured by filling 500 mg of HPMC K100LV into a capsule.

From the equation, we know that there are two variables that can influence the overall floating force of the test objects: ρ_c and V_c, namely, density and volume of the test object, corresponding to water uptake of the test object and swelling behavior of the polymeric system.

During the floating measurement experiment, V_c continuously increased due to the swelling of the polymer; ρ_c also increased because of the water uptake into the capsule. The combined effect of these two factors produced a rise in the floating force curve first, which reached a maximum and then declined until an equilibrium was reached. The pattern of the floating curve was determined by the competing mechanism between V_c and ρ_c (Fig. 4).

Taguchi Design and Data Analysis

Using Taguchi design, many process or formulation variables can be evaluated simultaneously with a relatively small number of experiments. Since we are interested in several different types of polymers, several different HPMC/Carbopol ratios, and adding/not adding magnesium stearate, Taguchi design can check all these non-numerical parameters at once. A typical fractional factorial design could provide only two levels for each variable, and a full factorial design for such an experiment would mean $4 \times 4 \times 2 = 32$ experiments without any center points. However, using Taguchi design, one usually assumes that no interactions are present between the variables. The contribution of the formulation variables was evaluated by an analysis of variance (ANOVA) table. Taguchi design is essentially fractional factorial design and should be considered as a screening type of experiment.[10] The experimental design with the actual amount of each formulation variable is shown in Table 1. Results from the floating measurement for the formulations fabricated from Taguchi design are included in Table 2.

Effect of HPMC Grades on Buoyancy Properties of GFDDS

Buoyancy profiles of GFDDS prepared from various grades of HPMC are illustrated in Fig. 5; numerical values for floating parameters are summarized in Table 3. Comparison of the numeric values and buoyancy profiles of the formulations from different HPMC grades indicates that the magnitude of the floating force for GFDDS fabricated from K4M and E4M (high viscosity, 4000 cPs, $AUC_f \sim 104$ g hr) is generally higher than that from E5LV (low viscosity, 5 cPs, $AUC_f \sim 92.5$ g hr). Floating AUC and residual floating force values of these polymers are in the order K4M~E4M~K100LV > E5LV. Further, the time required to reach the maximum floating force was the shortest for HPMC E5LV (34.5 min), indicating the fastest hydration rate for the low-viscosity polymer. It has been reported that higher molecular weight polymers and slower rates of polymer hydration are usually followed by enhanced floating behavior.[11] The same phenomenon has been observed in the current study: a polymer combination with lower molecular weight (E5LV) has lower floating capacity (Table 3). There appeared to be no significant difference among formulations from K4M, E4M, and K100LV, indicating polymers with viscosity above 100 cPs could form a stable hydrogel layer upon contacting with water. The hydrogel layer therefore formed was strong enough and could inhibit further water penetration into the inside of the capsule, maintaining the floating capacity of the GFDDS. In order to have a stable measurement of the floating force, the measurement was performed under static conditions without any type of hydrodynamic agitation. This could result in a slower erosion of the hydrogel layer as opposed to under agitation, and thus could explain the masked difference between HPMC with viscosity of 4000 and 100 cPs, if any.

Table 2

Comparison of Various Floating Parameters Obtained from Buoyancy Profiles of GFDDS (T1–T16)[a,b] *from Taguchi Design*

System Code	F_{max} (g ± SD)	t_{max} (min ± SD)	F_r (g ± SD)	AUC_f (g hr ± SD)
T1	9.9 ± 0.2	42 ± 5	4.2 ± 1.7	80 ± 18
T2	10.6 ± 0.2	111 ± 18	6.5 ± 0.5	135 ± 5
T3	10.7 ± 0.7	60 ± 7	3.8 ± 0.5	92 ± 8
T4	10.9 ± 0.6	38 ± 3	4.9 ± 0.2	112 ± 3
T5	11.5 ± 0.4	35 ± 3	4.8 ± 0.4	105 ± 5
T6	10.5 ± 0.7	87 ± 2	5.5 ± 0.8	122 ± 12
T7	11.1 ± 0.1	14 ± 4	3.6 ± 0.2	87 ± 5
T8	10.1 ± 0.2	54 ± 4	4.7 ± 0.6	105 ± 10
T9	10.9 ± 0.6	18 ± 3	4.2 ± 0.5	97 ± 9
T10	11.4 ± 0.4	10 ± 2	4.0 ± 0.2	93 ± 2
T11	10.8 ± 0.4	58 ± 17	4.9 ± 1.0	106 ± 14
T12	11.2 ± 0.4	52 ± 6	2.9 ± 0.3	74 ± 6
T13	10.9 ± 0.4	47 ± 8	5.8 ± 0.7	119 ± 9
T14	11.0 ± 0.5	26 ± 5	4.8 ± 0.4	101 ± 8
T15	9.4 ± 0.8	82 ± 8	4.9 ± 1.5	101 ± 20
T16	10.3 ± 0.2	49 ± 12	3.7 ± 0.1	94 ± 3

[a]The time duration for buoyancy studies was 8 hr.
[b]Data were presented as mean ± SD of triplicate experiments.

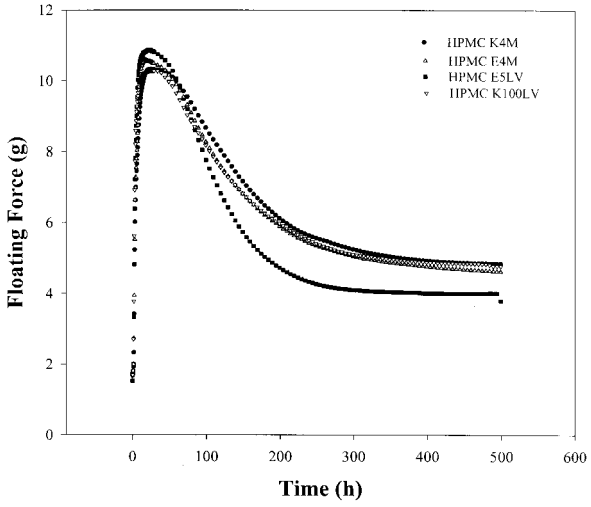

Figure 5. Effect of HPMC grades on the floating properties of GFDDS by Taguchi design.

The difference between HPMC K and E types of polymers is in the degree of substitution of the function group. The number of substitute groups on the anhydroglucose units of cellulose can be designated by weight percent or by the average number of substitute groups attached to the ring, a concept known to cellulose chemists as "degree of substitution" (DS). In the methocel E and methocel K cellulose ether products, methoxyl substitution is still the major constituent (Table 4). Molar substitution reports the number of moles of hydroxypropyl groups per mole of anhydroglucose.

As can be seen from Table 4, HPMC K grade has less methoxyl substitution than HPMC E grade (22% vs. 29%), and the difference in hydroxypropyl substitution between K and E grades was not significant (8.1% vs. 8.5%). Overall, the HPMC K grade is more hydrophilic. The general properties of different HPMC polymer grades are available in the Methocel Cellulose Ethers Technical Handbook.[12] In this case, the difference in substitution between the two grades does not contribute to a difference in the floating properties between HPMC K4M and E4M, which are two different types of HPMC with the same viscosity.

Effect of HPMC/Carbopol Ratio

Mucoadhesive polymer (e.g., carbopol 934P) has been widely used in the drug delivery field.[13,14] Carbopol was incorporated here to introduce another

Table 3

Comparison of Floating Parameters Among Formulations Fabricated from Different Types of Polymers[a]

	F_{max} (g)	t_{max} (min)	F_r (g)	AUC_f (g hr)
K4M	10.525	62.75	4.85	104.75
E4M	10.8	47.5	4.65	104.75
E5LV	11.075	34.5	4	92.5
K100LV	10.4	51	4.8	103.75

[a]Reported as mean values from all formulations from K4M (T1–4), E4M (T5–8), E5LV (T9–12), and K100LV (T13–16), respectively.

Table 4

Comparison Between Substitution of Different Types of HPMC Polymers[a]

Product	Methoxyl Degree of Substitution	Methoxyl (%)	Hydroxypropyl Molar Substitution	Hydroxypropyl (%)
Methocel E	1.9	29	0.23	8.5
Methocel K	1.4	22	0.21	8.1

[a]Dow Chemical Handbook.[12]

gastroretentive mechanism, i.e., mucoadhesion. Carbopol is insoluble in water and artificial gastric fluid, but soluble in artificial intestinal fluid. This is due to its ionizable –COOH group. When exposed to water, carbopol becomes viscous and thus tends to bind the mixed polymeric system together, resulting in a reduced erosion of GFDDS. The effect of HPMC/Carbopol ratio on the mucoadhesive force[15,16] has been reported in the literature and is not the focus of current study. It has been shown by Anlar et al.[16] that the adhesion force of HPMC K100M and Carbopol is weakest at HPMC K100M/Carbopol ratio of 1:1. However, there has not been any report on the floating capacity of the delivery system by combining these two polymers together.

In order to evaluate the effect of incorporation of Carbopol on the floating properties of GFDDS, Carbopol was included in GFDDS in a different ratio to HPMC: HPMC is a hydrophilic polymer and Carbopol is a water-insoluble but water-swellable polymer; HPMC is a neutral polymer and Carbopol is, on the other hand, a large, cross-linked polymer with molecular weight $\sim 2 \times 10^6$ Da and free carboxylic acid groups. Under the tested condition (pH 1.2), the swelling of HPMC should not be affected by the pH, since its driving force for swelling arises from the water–polymer thermodynamic mixing contribution to the overall free energy.[17] Meanwhile for Carbopol, since the pH is below the pK_a of the polymer, the swelling is due to the uncharged –COOH group that hydrates by forming hydrogen bonds with the imbibing water, thus extending the polymer chains.[18] The swelling of these two polymers should contribute partially to the floating behavior of the current delivery system.

The effects of HPMC/Carbopol ratio on the buoyancy properties of GFDDS prepared from various grades of HPMC are summarized in Table 5. A comparison between the floating parameters (F_r and AUC_f) showed that a better floating property was achieved at higher HPMC/Carbopol ratio, 4/1 vs. 2/1 (92.5 > 89.5, 108 > 103.5 g hr) and 3/1 vs. 1/1 (128.5 > 108.5, 97 > 84 g hr). This result demonstrates that incorporation of Carbopol has a negative effect on the floating behavior of the delivery system. From ANOVA (Table 6), there was a statistically significant difference for the residual floating force at different HPMC/Carbopol ratios. The negative effect of Carbopol on the floating properties of the delivery system could be explained by the swelling phenomenon of the two polymers. As stated above, pH 1.2 is not the most favorable condition for the swelling of Carbopol to form hydrogel.

Table 5

Comparison of Floating Parameters Among Formulations Fabricated from Different HPMC/Carbopol Ratios

HPMC/Carbopol[a] (K4M, E4M)	F_{max} (g)	t_{max} (min)	F_r (g)	AUC_f (g hr)
4/1 no MgSt	10.7	38.5	4.5	92.5
2/1 no MgSt	10.9	37	3.7	89.5
3/1 MgSt	10.55	99	6	128.5
1/1 MgSt	10.5	46	4.8	108.5
HPMC/Carbopol[b] (K100LV, E5LV)	F_{max} (g)	t_{max} (min)	F_r (g)	AUC_f (g hr)
4/1 MgSt	10.9	32.5	5	108
2/1 MgSt	10.1	70	4.9	103.5
3/1 no MgSt	11.2	18	4.4	97
1/1 no MgSt	10.75	50.5	3.3	84

Reported as mean values from all formulations fabricated from HPMC/carbopol ratio:
[a]4/1 no MgSt T1, T5), 2/1 no MgSt (T2, T6), 3/1 MgSt (T3, T7), 1/1 MgSt (T4, T8);
[b]4/1 MgSt (T9, T13), 2/1 MgSt (T10, T14), 3/1 no MgSt (T11, T15), 1/1 no MgSt (T12, T16).

Table 6

ANOVA Table for Different Floating Parameters from Taguchi Design

Source	DF	Sum Square	Mean Square	F Value	$Pr > F$
F_{max} (g)					$R^2 = 0.4276$
HPMC Grade	3	1.09	0.36	1.08	0.4093
HPMC/Carbopol Ratio	3	0.35	0.12	0.34	0.7939
Mg Stearate	1	0.56	0.56	1.69	0.2302
t_{max} (min)					$R^2 = 0.4879$
HPMC Grade	3	1622	541	0.75	0.5509
HPMC/Carbopol Ratio	3	1173	391	0.54	0.6654
Mg Stearate	1	2678	2678	3.73	0.0896
F_r (g)					$R^2 = 0.8749$
HPMC Grade	3	1.85	0.62	3.22	0.0824
HPMC/Carbopol Ratio	3	3.09	1.03	5.39	0.0254
Mg Stearate	1	5.76	5.76	30.12	0.0006
AUC_f (g hr)					$R^2 = 0.8182$
HPMC Grade	3	109	36	1.76	0.2315
HPMC/Carbopol Ratio	3	189	63	3.07	0.0912
Mg Stearate	1	441	441	21.51	0.0017

It has been reported by Slovin and Robinson[19] that under pH 1.2, the extent of Carbopol 974P swelling is less than that of HPMC in vitro. This difference in swelling would translate into a difference in V_c [Eq. (1)]. Adding a less-swellable polymer carbopol would therefore negatively affect the floating behavior of the delivery system.

This interesting finding led us to believe that one has to be cautious when incorporating Carbopol as another gastroretentive mechanism, since it would compromise the floating behavior of the delivery system, although it has been reported as an effective mucoadhesive agent.[15,16] Interested readers can refer to some excellent reviews in the literature on mucoadhesive systems.[20,21]

Effect of Magnesium Stearate

The effect of magnesium stearate on the buoyancy profile of GFDDS is displayed in Fig. 6, which

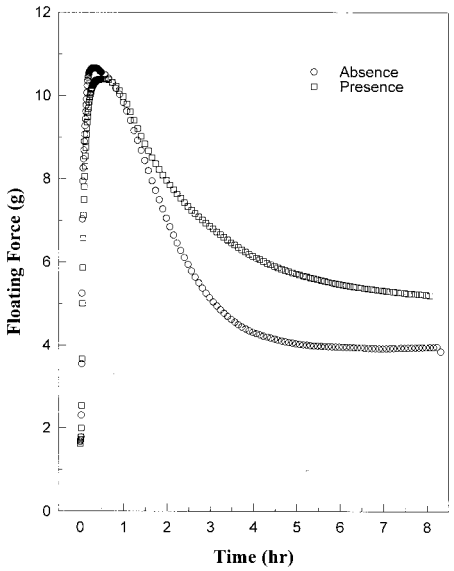

Figure 6. Effect of magnesium stearate on the floating properties of GFDDS by Taguchi design.

clearly shows that the buoyancy property of GFDDS is improved by the presence of magnesium stearate. The same conclusion can be obtained from Table 5, in which formulations with magnesium stearate all exhibit an improved floating behavior compared with formulations without magnesium stearate. The beneficial effect of magnesium stearate on the buoyancy properties of the GFDDS is probably due to the hydrophobic nature of the magnesium stearate.[2] Water uptake and penetration through the delivery system are significantly slowed down by the addition of magnesium stearate, thus improving the buoyancy properties of GFDDS.

ANOVA Test

The ANOVA table of the effects of the three formulation variables on the floating properties of GFDDS is summarized in Table 6. Magnesium stearate had a statistically significant effect on the floating property of calcium GFDDS for both F_r and AUC_f ($p < 0.05$), which represented the overall floating capacity of a GFDDS. This is the same conclusion we could obtain from Fig. 6 and Table 5. Results obtained from SAS analysis of buoyancy parameters indicated that the HPMC/Carbopol ratio was significant for F_r at the 0.05 level. A higher HPMC/Carbopol ratio was generally preferred for the maximization of floating capacity. High-viscosity grade (K4M and E4M) HPMC provided slightly better floating properties than low-viscosity grade (E5LV) HPMC. However, the effect was not statistically significant. The lack of significance for the test variables F_{max} and T_{max} was due to the relative homogeneity of the obtained data.

CONCLUSIONS

The continuous floating monitoring system was developed and validated, and was found to be very useful in characterizing the in vitro floating behavior of a GFDDS. A typical floating kinetic curve with four floating parameters identified, F_{max}, T_{max}, AUC_f, and F_r, was used to record the floating kinetics of the GFDDS. Among these parameters, AUC_f and F_r were found to be the most important. Statistical experimental design was employed in order to identify the most influential formulation variables on the floating properties of the GFDDS. An ANOVA test on the results from these experimental designs demonstrated that the hydrophobic agent, magnesium stearate, could significantly improve the floating capacity of the delivery system. A high-viscosity polymer had a beneficial effect on the floating properties of the GFDDS. Different types of polymers with the same viscosity, i.e., K4M and E4M, on the other hand, did not demonstrate any significant impact on the floating properties of the GFDDS. Carbopol, although it could introduce another gastroretentive mechanism into the delivery system, was found to have a negative impact on its floating behavior.

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