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International Journal of Pharmaceutics 253 (2003) 13–22
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Effect of HPMC and Carbopol on the release and floating properties of Gastric Floating Drug Delivery System using factorial design

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Received 12 March 2002; received in revised form 18 November 2002; accepted 18 November 2002

Abstract

The purpose of this study is to investigate the effect of formulation variables on drug release and floating properties of the delivery system. Hydroxypropyl methylcellulose (HPMC) of different viscosity grades and Carbopol 934P (CP934) were used in formulating the Gastric Floating Drug Delivery System (GFDDS) employing 2 × 3 full factorial design. Main effects and interaction terms of the formulation variables could be evaluated quantitatively by a mathematical model. It was found that both HPMC viscosity, the presence of Carbopol and their interaction had significant impact on the release and floating properties of the delivery system. The decrease in the release rate was observed with an increase in the viscosity of the polymeric system. Polymer with lower viscosity (HPMC K100LV) was shown to be beneficial than higher viscosity polymer (K4M) in improving the floating properties of GFDDS. Incorporation of Carbopol, however, was found to compromise the floating capacity of GFDDS and release rate of calcium. The observed difference in the drug release and the floating properties of GFDDS could be attributed to the difference in the basic properties of three polymers (HPMC K4M, K100LV and CP934) due to their water uptake potential and functional group substitution.

Keywords: HPMC; Carbopol; Floating; Calcium delivery; Factorial design; Moisture uptake

1. Introduction

Calcium supplements have been widely used for the prevention and treatment of osteoporosis and to compensate the daily calcium loss from urine and feces. The need for the dietary intake of calcium is greater for individuals undergoing rapid skeletal growth, such as infants and children, and pregnant and lactating women. Even for healthy adults, normal calcium

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PII: S0378-5173(02)00642-7

losses in urine, feces, and sweat must be balanced by dietary calcium intake or calcium supplement (Heaney et al., 1989; Heaney, 1987; Heaney, 1982; Barger-Lux and Heaney, 1994).

When orally ingested, only about 25–35% of a normal dose of supplemental calcium can be absorbed (Schaafsma, 1997). The incomplete absorption is due to the efficiency of the carrier mediated process (Bronner et al., 1986). Calcium absorption is the sum of a saturable calcium binding protein mediated active transport and a non-saturable concentration gradient dependent passive absorption process. The former process mainly occurs at duodenum and proximal jejunum, and the later occurs predominately in the distal jejunum and ileum (Pansu et al., 1981).

In view of this absorption characteristic, the hypothesis of the current investigation is that if the gastric residence time of a calcium-containing formulation could be prolonged to allow calcium to reach the site of active absorption in a controlled manner, then the oral bioavailability of calcium might thereby be increased. The controlled delivery system for calcium would also be beneficial for patients with hypohydrochloria syndrome, because calcium will be released in a controlled manner.

Combined usage of hydroxypropyl methylcellulose (HPMC) and Carbopol in a mucoadhesive delivery has been reported (Khanna et al., 1997; Anlar et al., 1993) to improve the mucoadhesiveness of the combined system. Marcos et al. (Perez Marcos et al., 1994) studied the potential of combining Carbopol 974P and HPMC K4M using propranolol hydrochloride as a model drug and found that the amount of water imbibed in Carbopol was lower than that by HPMC alone or 1:1 mixture of two polymers. HPMC and CP934 were added extragranularly without exposing the polymers to granulation fluid for compaction purpose (Durrani et al., 1997). However, there has been no study to date designed to evaluate the controlled release and floating properties of the delivery system using the combination of these two polymers.

The objective of this study was to systematically investigate the contribution of several formulation variables on the drug release rate and floating properties of Gastric Floating Drug Delivery System (GFDDS) using calcium carbonate as a model drug.

To achieve this objective, the contribution of two independent formulation variables of the mixed polymeric GFDDS fabricated from a combination of polymers was examined. Independent variables evaluated included different ratios of HPMC K4M and K100LV, and the addition of CP934. The ranges of these formulation variables were chosen based on the results obtained in the preliminary studies conducted in this laboratory. Dependent variables studied included release parameters, i.e. calcium release at 6 h (Rel), time for the release of 50% of calcium ($T_{50\%}$), and floating properties, i.e. Area under floating kinetics curve (AUC_f), and Residual floating force (F_r).

Specifically, the in vitro release and floating studies of six formulations, prepared according to a 2×3 full factorial design, were performed, using USP type II dissolution apparatus and an online continuous floating monitoring system (Li et al., 2001), respectively. Release and floating parameters were obtained directly from the release and floating kinetics curve. Further regression analysis provided a quantitative relationship between the response and the studied independent variables.

2. Materials and methods

2.1. Materials

Calcium carbonate (Lot #: A-6-313-24) was received from GlaxoSmithKline Consumer Healthcare (GSK, Parsippany, NJ). Methocel® K4M and K100LV, which are commercially available grades of hydroxypropyl methylcellulose from Dow Chemicals Co. (Midland, MI), were also supplied by GSK. Other materials were purchased from the commercial sources: citric acid from Sigma Chemical Co. (St. Louis, MO), CP934 from BFGoodrich, 2000 (Cleveland, OH), magnesium stearate (MgSt) from Fisher Scientific Co. (Fairlawn, NJ), hard gelatin capsules (size 000, manufactured by Eli Lilly Co.) from Frontier Co. (Norway, IA).

2.2. Methods

2.2.1. Experimental design

The formulations were fabricated according to a 2×3 full factorial design, allowing a simultaneous evaluation of two formulation variables and their interactions. The experimental design with corresponding formulations are outlined in Table 1.

Table 1
Composition of GFDDS used in formulation development evaluating the effects of HPMC grades (viscosity) and the presence of Carbopol

Formulation code	Ingredients/capsule				
	Calcium carbonate (mg)	Citric acid (mg)	HPMC K4M/K100LV ratio (K4M/K100LV mg) (X_1)	Carbopol (mg) (X_2)	MgSt (mg)
F1	625	90	0 (0/125)	0	20
F2	625	90	0 (0/125)	40	20
F3	625	90	0.5 (62.5/62.5)	0	20
F4	625	90	0.5 (62.5/62.5)	40	20
F5	625	90	1 (125/0)	0	20
F6	625	90	1 (125/0)	40	20

In this study, fixed amount of calcium carbonate (625 mg), citric acid (90 mg) and magnesium stearate (20 mg) were used; the formulation variables evaluated include:

X_1 HPMC K4M/K100LV ratio (0, 0.5, 1.0);
X_2 absence or presence of CP934 (0, 40).

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

Y_1 percent of calcium release at 6 h (Rel);
Y_2 time for 50% of calcium release from the delivery system ($T_{50\%}$);
Y_3 Area under the floating kinetics curve (AUC_f);
Y_4 Residual floating force (F_r).

2.2.2. Preparation of calcium GFDDS

Calcium carbonate was geometrically mixed with various pharmaceutical excipients except magnesium stearate, in a mortar and pestle for 10 min to achieve a homogeneous blend. Magnesium stearate was added to the blend and mixed for additional 3 min. The final blend was filled into hard gelatin capsules (size 000) manually using slight compression. For each formulation, a total of 10 capsules were prepared for conducting drug release and floating study. Each capsule contained a fixed amount (625 mg) of calcium carbonate.

2.2.3. In vitro characterization of GFDDS

2.2.3.1. Release study. Dissolution studies were conducted using standard USP paddle dissolution apparatus (DT6R/Erweka Instrument Co., Milford, CT). In all the dissolution studies, the paddles were rotated at a speed of 100 rpm in 900 ml simulated gastric fluid (SGF) at 37 ± 0.5 °C. A series of samples (1 ml each) were withdrawn at predetermined intervals for a period of up to 12 h. The samples were filtered and then analyzed by a calcium analyzer (Calcette/Precision Systems Inc., Natick, MA), which uses EGTA solution as a titrant and calcium gluconate and Calcette® reagent cell activator to generate fluorescence. The reaction cell was activated freshly before each set of measurement and the Calcette® was calibrated by a calcium standard solution prior to each use.

2.2.3.2. Floating study. In order to provide quantitative measurements of the floating force, an online continuous floating monitoring system, modified from Timmermans et al. (Mesiha and Sidhom, 1995), was designed. The setup consisted of an analytical balance interfaced with a PC via RS232C interface, and the data were collected at an interval of 60 s for up to 8 h (Li et al., 2001, 2002).

Following the calibration of the floating apparatus, one capsule was inserted into the sample holder basket and the holder was then immersed into the simulated gastric fluid (900 ml of 0.1N HCl with 1.8 g of NaCl), maintained at 37 °C by a reaction beaker. All other process variables were kept constant.

2.2.4. Statistical analysis

The results from factorial design were evaluated using SAS program. The mathematical model that PROC REG used is a linear model, which bears the form of Eq. (1)

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 \quad (1)$$

where Y_i is the level of response variables, b_j is the regression coefficient, and, X_1, X_2 and X_{12} represent the main effect of the formulation variables and their interaction.

2.2.5. Moisture uptake of HPMC and Carbopol

Ten milligram each of HPMC and CP934 powder were dried at 40 °C under 0% RH by N_2 stream to a constant weight. The humidity of the chamber was then ramped between 0 and 95% RH. Sorption behavior of the powders was analyzed at 25 °C using a dynamic vapor sorption DVS-1000 instrument (Surface Measurement Systems Ltd., London, UK) instrumented with a Cahn D200 microbalance.

3. Results

Design of experiment (DOE) has been widely used in pharmaceutical field to study the effect of formulation variables and their interactions on response variables (Chu et al., 1991; Garcia Gonzalez et al., 1993). In this study, a 3 × 2 full factorial design (Table 1) was used. The first two formulations contained only HPMC K100LV (viscosity = 100 cP) and the last two formulations contained only HPMC K4M (viscosity = 4000 cP). Formulation F2, F4 and F6, on the other hand, contained CP934 as another agent for gastric retention, which works as a mucoadhesive (Blanco Fuente et al., 1996). The ratio of HPMC to Carbopol was fixed to 3:1.

Table 2
Comparison of various release parameters obtained for formulations (F1–F6) by factorial design

Formulation code	Ca released at 6 h (Rel) (% ± S.D.)	$T_{50\%}$ (h ± S.D.)
F1	97 ± 5	0.12 ± 0.11
F2	90 ± 5	0.20 ± 0.18
F3	88 ± 2	0.23 ± 0.13
F4	86 ± 4	0.43 ± 0.24
F5	78 ± 4	1.84 ± 1.02
F6	47 ± 3	5.47 ± 1.82

The results of calcium release from different formulations, fabricated according to the factorial design, are presented in Figs. 1 and 2. There is a clear difference in the calcium release pattern between the polymers of different viscosity; the fraction of calcium released decreases as the viscosity of GFDDS increases (Fig. 1), while the presence of CP934 appears to decrease the overall calcium release rate from the GFDDS (Fig. 2). The difference in Rel are significant among different formulations F1–F6 (Table 2). And,

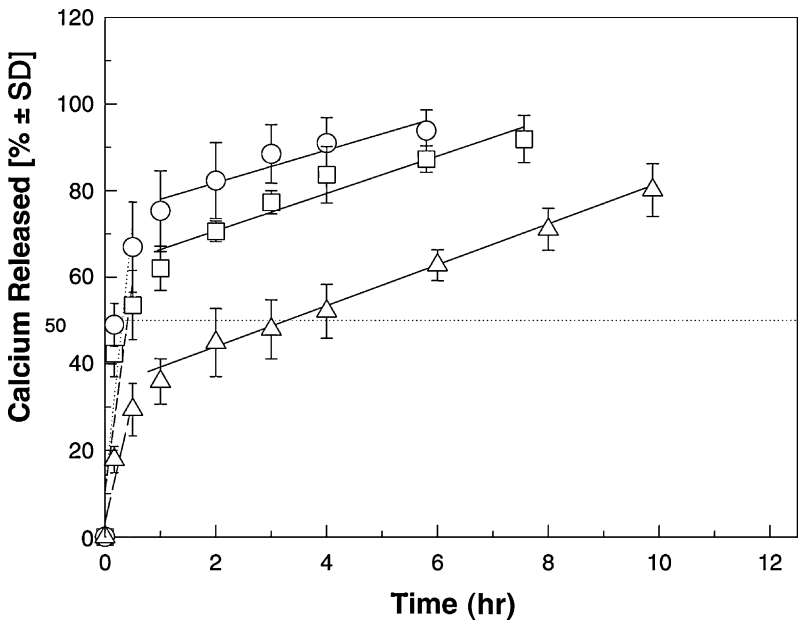

Fig. 1. Effect of HPMC grades (different viscosity) on the release of calcium from formulations F1–F6 (○, K100LV; □, K4M and K100LV; △, K4M; $n = 6$).

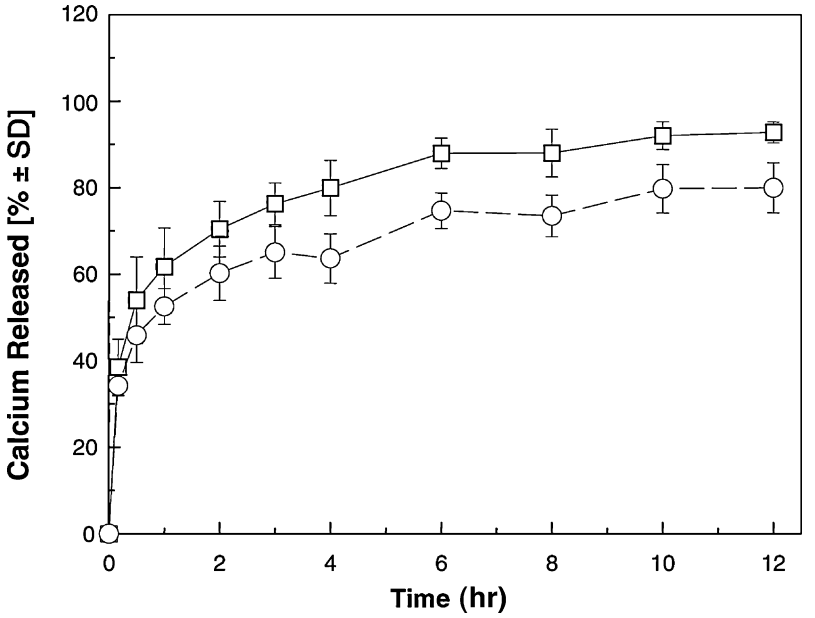

Fig. 2. Effect of presence or absence of CP934 on the dissolution profiles of calcium from formulations F1–F6 (□, no CP934; ○, with CP934; $n = 9$).

the mean values of $T_{50\%}$ increased from 0.12 to 5.47 h (Table 2).

Furthermore, the calcium release appears to exhibit two phases. The apparent release rates of calcium from these two phases are estimated by linear regression of the separate sets of points on the profile. As can be seen from Fig. 3, there is a significant difference in the burst effect from formulations fabricated from polymers with different viscosity ($P < 0.01$). However, the differences observed for the second phase of the release curve were non-significant. This may suggest that the initial burst effect is followed by the completion of a stable gel layer which, in turn, controls the release of calcium from the delivery system.

Results of the floating properties of the GFDDS are presented in Figs. 4 and 5. There appears to be some difference in AUC_f and F_r for systems fabricated by using HPMC K4M, K100LV and their mixture (Fig. 4). The difference is significant between HPMC K4M/K100LV ratios 0 versus 1.0 and 0.5 versus 1.0 ($P < 0.05$), while is not significant between HPMC K4M/K100LV ratios 0 versus 0.5 ($P < 0.05$). However, the presence of CP934 does make a significant difference ($P < 0.05$, Fig. 5). The values for F_r and AUC_f, summarized in Table 3, appear to suggest a decrease in the values of F_r and AUC_f as the viscosity of the polymeric system increases.

ANOVA test of the release and floating properties of formulations indicated that K4M/K100LV ratio, presence of CP934 and their interaction are significant in terms of calcium release properties ($P < 0.01$). The same variables are also found to be significant for AUC_f and F_r values with $P < 0.01$ (Tables 3 and 4).

Moisture uptake of the polymers used in this investigation are illustrated in Fig. 6. All three polymers, which picked up significant amount of water during the absorption profile, exhibited a slight hysteresis. While the moisture absorption curves of HPMC K4M

Table 3
Comparison of various floating parameters obtained from buoyancy profiles of GFDDSs (F1–F6) from full factorial design

Formulation code	F_r (g)	AUC_f (g h)
F1	6.37(0.18)	54.1(2.3)
F2	3.57(0.55)	40.8(4.8)
F3	4.95(0.41)	46.7(4.5)
F4	4.21(0.33)	45.4(2.6)
F5	3.61(0.25)	37.2(0.7)
F6	3.42(0.18)	38.8(1.8)

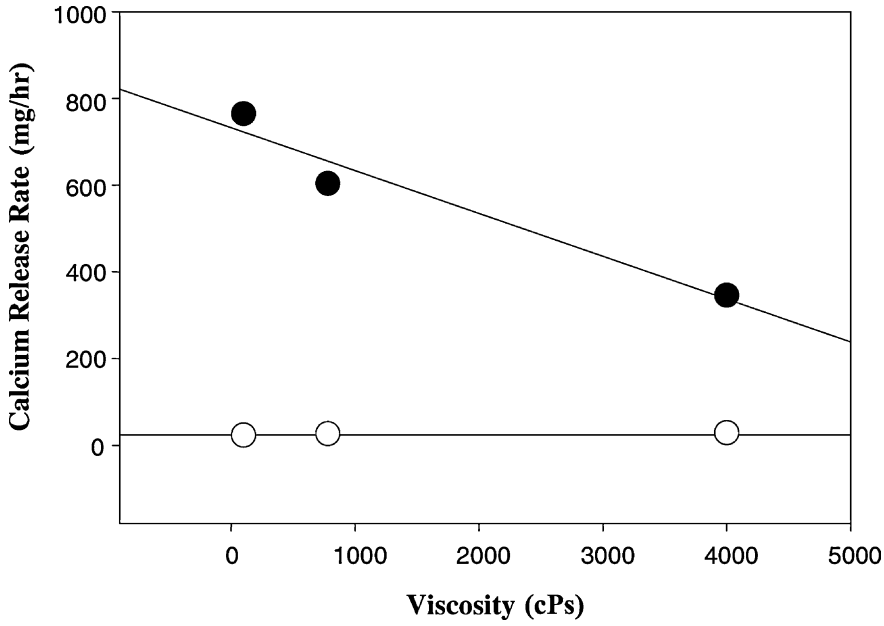

Fig. 3. Effect of viscosity of the polymeric system on the apparent release rate of calcium from the two phases (●, phase I; ○, phase II).

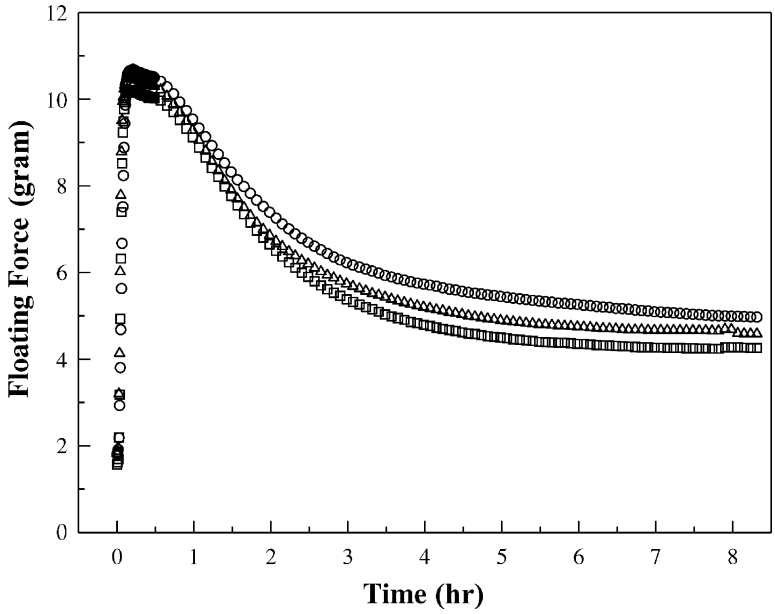

Fig. 4. Buoyancy profiles of GFDDS prepared from different grades of HPMC for formulations F1–F6 (○, K100LV; △, K4M and K100LV; □, K4M; $n = 6$).

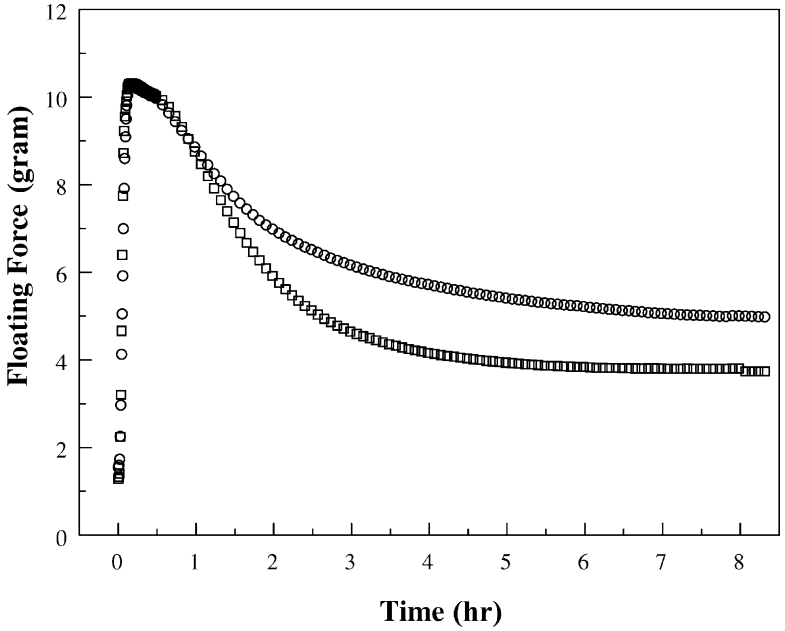

Fig. 5. Buoyancy profiles of GFDDS prepared from formulations F1–F6 with and without CP934 (○, without CP934; □, with CP934; $n = 9$).

Table 4
ANOVA table for different floating parameters from full factorial design

Source	d.f.	Sum square	Mean square	F value	Probability
$Release_{6h}$ (%)					$R^2 = 0.9648$
X_1	2	2941.71	1471.86	104.24	0.0001
X_2	1	933.26	933.26	66.14	0.0001
$X_1 \times X_2$	2	767.03	383.52	27.18	0.0001
$T_{50\%}$ (min)					$R^2 = 0.8807$
X_1	2	46.51	23.25	31.05	0.0001
X_2	1	7.61	7.61	10.17	0.0078
$X_1 \times X_2$	2	12.18	6.09	8.13	0.0059
F_r (g)					$R^2 = 0.9063$
X_1	1	9.36	9.36	55.50	0.0001
X_2	1	8.00	8.00	47.42	0.0001
$X_1 \times X_2$	1	3.20	3.20	18.99	0.0008
AUC_f (g h)					$R^2 = 0.8674$
X_1	1	918.75	918.75	45.12	0.0001
X_2	1	470.22	470.22	23.09	0.0003
$X_1 \times X_2$	1	252.08	252.08	12.38	0.0038

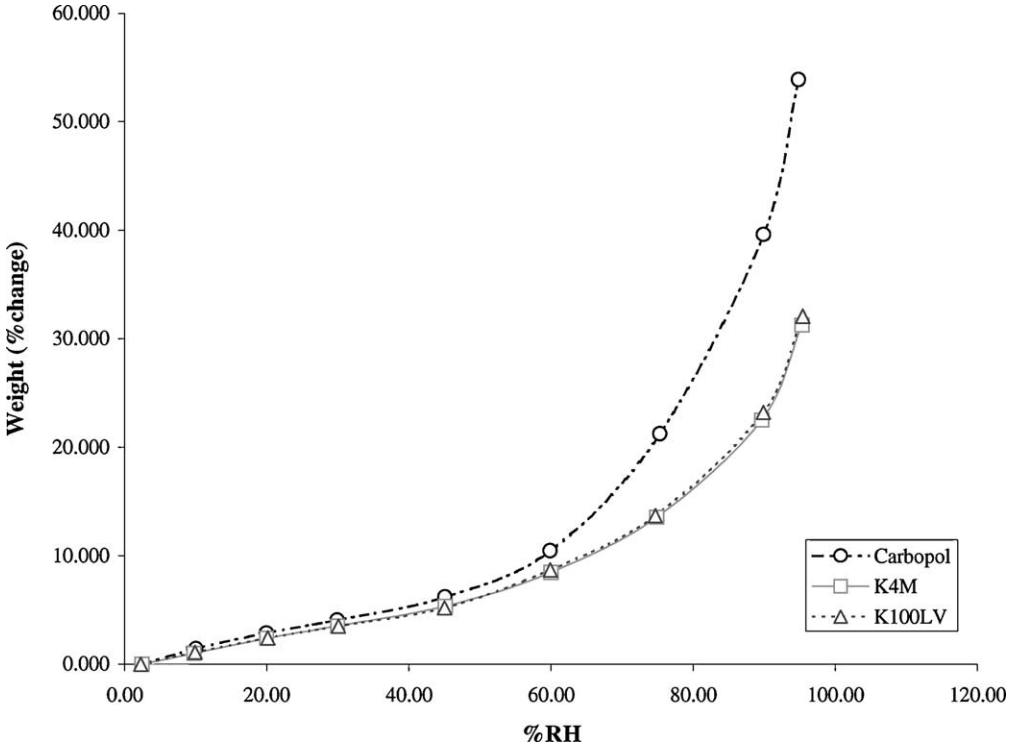

Fig. 6. Effect of presence or absence of CP934 on the floating profiles of GFDDS Fig. 6. Moisture uptake profile of HPMC K4M, K100LV and CP934 (○, Carbopol; □, K4M; △, K100LV; $n = 9$).

and K100LV are almost identical, the curve of CP934 exhibited higher moisture uptake compared with cellulose derived polymer.

4. Discussion

4.1. Release properties of delivery system

There has been considerable interest in using different grades of HPMC in controlled release drug delivery system (Perez Marcos et al., 1994; Sirkia et al., 1993; Colombo et al., 1999; Dortunc and Gunal, 1997) due to their hydrophilic nature and fast hydration. It has been reported (Mesiha and Sidhom, 1995) that polymers of different viscosity grades can yield different drug absorption.

The release profiles of formulations F1–F6, prepared by using HPMC K4M, K100LV and their 1:1 mixture, are illustrated in Fig. 1. The release profiles appear to be bi-phasic with initial burst effect (less than 30 min) followed by a polymer-controlled slower release in the second phase. The difference in burst effect of the initial time is a result of difference in the viscosity of the polymers. The viscosity of HPMC K4M, K100LV is 4000 and 100 cP, respectively, viscosity of their mixture could be obtained by empirical equation (Eq. (2)) presented as follows:

$$V_b{}^{1/8} = F_1 V_1{}^{1/8} + F_2 V_2{}^{1/8} \quad (2)$$

where V_b is the viscosity of the polymeric mixture; F_1 and F_2 are the fraction of the polymers and V_1 and V_2 are the viscosity of the two polymers, respectively as described in Methocel® handbook (Dow Chemical Co, 1996). In this study the viscosity of a mixture of 1:1 mixture of HPMC K4M and K100LV is determined to be 780 cP.

As can be seen from Fig. 1, polymeric system with low viscosity polymer (HPMC K100LV) yielded a faster initial burst effect. Dortunc and Gunal (1997)

has reported that increased viscosity resulted in a corresponding decrease in the drug release. Similar results were reported by Wan et al., in which they have demonstrated that HPMC with higher viscosity resulted in thicker gel layer formation (Wan et al., 1995). On the other hand, the apparent drug release rate observed in the second phase from HPMC K4M, K100LV and their mixture are quite similar, with a slight variability in value from 23.6 to 27.1 mg/h. The difference in the apparent release rate is illustrated in Fig. 3. As indicated above, once the gel layer of the polymeric system is formed, there appears to be no difference in release rate from the delivery system.

Fig. 2 demonstrates the effect of CP934 on the release of calcium from GFDDS. It appears that the incorporation of CP934 decreased the release of calcium from the GFDDS by 1.26-fold. Carbopol is insoluble in water and simulated gastric fluid, under the test condition (pH = 1.2). And, the swelling behavior of the Carbopol is attributed to the uncharged –COOH group that get hydrated by forming hydrogen bonds with the imbibing water and, therefore, extending the polymer chain (Mortazavi, 1995). Formulations without CP934 exhibited a much higher burst effect, likely due to the fact that CP934 is a cross-linked polymer with high molecular weight ($\sim 2 \times 10^6$ Da) and viscosity, and, when contacted with water, it would swell and hold water inside its microgel network. This particular property may partially be responsible for the retarded release of calcium from the GFDDS. The experiments have demonstrated that 30–70% of calcium would be held in the slow release portion of the dosage form. The resultant gradual delivery of calcium to the intestine theoretically would enhance absorption (Heaney, 1987). This should be evaluated in a future bioavailability study.

4.2. Floating properties of delivery system

As illustrated in Fig. 3, GFDDS prepared by using HPMC K4M exhibited lower floating properties compared to GFDDS prepared by using K100LV. However, the difference between different floating curves of different polymeric system is small. This can be attributed to the identical moisture profile for HPMC K4M and K100LV (Fig. 6). While there is a similar water uptake rate, the increase in density of the GFDDS (ρ_c) will be comparable, resulting in a similar change in floating capacity of the GFDDS (F), i.e. Eq. (3)

$$F = F_{\text{buoyancy}} - F_{\text{gravity}} = (\rho_w - \rho_c) g V_c \tag{3}$$

where ρ_c, V_c is the density and volume of capsule, ρ_w is density of water.

Results in Fig. 4 demonstrate that incorporation of CP934 has a negative effect on the floating behavior of the delivery system. This can be explained by the moisture isotherm of CP934 (Fig. 6), which illustrates that CP934 has a much higher moisture absorption curve compared to cellulose-based HPMC. The moisture gain for CP934 is significantly higher compared to moisture gain for HPMC (55% weight gain for CP934 versus ~33% for HPMC at RH of 95%); this results in a dramatic increase in the density of the GFDDS (ρ_c, Eq. (5) above) which, in turn, shows a corresponding decrease in the floating capacity of GFDDS.

4.3. Moisture uptake of HPMC K4M, K100LV and CP934

Fig. 6 illustrates the similar moisture absorbing isotherm for HPMC K4M and K100LV, while the moisture absorbing isotherm curve for CP934 is much steeper under identical conditions. The relationship between chemical potential (μ), water activity (a_w) and relative humidity (RH) in moisture isotherm study are illustrated in Eqs. (4) and (5):

$$\mu = \mu^0 + RT \ln a_w = \mu^0 + RT \ln \frac{P}{P^0} \tag{4}$$

$$\text{RH} = 100 \times \frac{P}{P^0} \tag{5}$$

which suggest that equilibrium at certain RH is an indirect indication of the chemical potential of the water in the system (Kontny and Zografi, 1995), which could be translated into the water activity in the polymeric system. CP934, a polyacrylic acid based system, appears to have a much stronger solid–water interaction compared with HPMC, a cellulose-based polymer. This is an interesting way of looking at the water–polymer interaction and a recent study (Sacchetti, 1998) has elaborated the thermodynamic analysis of the moisture sorption isotherm, in which activities, chemical potentials, and free energy are calculated for water–solid systems.

5. Conclusions

Overall, this study concludes that viscosity is a major factor affecting the release and floating properties of the GFDDS. The higher viscosity seems to inhibit the initial burst effect of calcium release from the GFDDS; however, it does not seem to affect the calcium release rate thereafter. Carbopol, however, is found to compromise the release and floating properties of GFDDS. Although it might provide other gastric retentive mechanisms to maintain the GFDDS in the GI tract, it might not be a good candidate to be included in gastric floating delivery system.

Acknowledgements

The authors would like to thank Park-Davis chair endowment for providing pre-doctoral fellowship to Dr. Shoufeng Li and GlaxoSmithKline Consumer Healthcare for providing funding support for this project.

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