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Optimization of Bilayer Floating Tablet Containing Metoprolol Tartrate as a Model Drug for Gastric Retention

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C. Narendra,[1] M. S. Srinath,[2] and Ganesh Babu[2]

[1]Department of Pharmaceutics, Krupanidhi College of Pharmacy, Bangalore-34, India
[2]Department of Pharmaceutics, Government College of Pharmacy, Bangalore-27, India

ABSTRACT

The purpose of the present study was to develop an optimized gastric floating drug delivery system (GFDDS) containing metoprolol tartrate (MT) as a model drug by the optimization technique. A 2^3 factorial design was employed in formulating the GFDDS with total polymer content-to-drug ratio (X_1), polymer-to-polymer ratio (X_2), and different viscosity grades of hydroxypropyl methyl cellulose (HPMC) (X_3) as independent variables. Four dependent variables were considered: percentage of MT release at 8 hours, $T_{50\%}$, diffusion coefficient, and floating time. The main effect and interaction terms were quantitatively evaluated using a mathematical model. The results indicate that X_1 and X_2 significantly affected the floating time and release properties, but the effect of different viscosity grades of HPMC (K4M and K10M) was nonsignificant. Regression analysis and numerical optimization were performed to identify the best formulation. Fickian release transport was confirmed as the release mechanism from the optimized formulation. The predicted values agreed well with the experimental values, and the results demonstrate the feasibility of the model in the development of GFDDS.

KEYWORDS: Metoprolol tartrate, factorial design, GFDDS, HPMC, bilayered tablet.

INTRODUCTION

Metoprolol tartrate (MT) is a β_1-selective adrenergic blocking agent.[1] When MT conventional tablets are administered with food rather than on an empty stomach, peak plasma concentrations are higher and the extent of absorption of the drug is increased.[2] The maintenance of a constant plasma level of a cardiovascular drug is important in ensuring the desired therapeutic response. Since the half-life of MT is ~3 to 4 hours,[2] multiple doses are needed to maintain a constant plasma concentration for a good therapeutic response and improved patient compliance. It has also been reported that MT absorption in the duodenum and jejunum is directly proportional to the dose availability.[3]

A gastric floating drug delivery system (GFDDS)[4-8] can overcome at least some of these problems and is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments. The GFDDS is able to prolong the retention time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug. The influence of different grades of hydroxypropyl methyl cellulose (HPMC) (K4M and K10M) and Carbopol 934P on the release kinetics and buoyancy was studied in floating and bioadhesive tablets containing captopril as a model drug.[9] Various polymers, including sodium carboxymethylcellulose (SCMC), were investigated for the evaluation of an oral sustained-release floating dosage form of amoxicillin trihydrate; it was reported that SCMC-containing tablets quickly gelled, losing shape and floating on the surface of the dissolution medium.[10]

The objective of this study was to develop an optimized GFDDS containing MT as a model drug—a peroral intragastric floating dosage form having a bulk density lower than that of gastric fluids and remaining buoyant on the stomach contents. To achieve the objective, independent formulation variables such as total polymer content-to-drug ratio, polymer-to-polymer ratio, and different viscosity grades of HPMC (K4M and K10M) were examined. The dependent variables included floating time, percentage of MT release at 8 hours, diffusion coefficient (n), and $T_{50\%}$. Regression analysis was performed to identify the best formulation and to validate the model by comparing the experimental results with the theoretical values of the responses.

MATERIALS AND METHODS

Materials

MT was a gift from Astra Zeneca India Pvt Ltd (Bangalore, India). Methocel k4000 and k10000 cP, sodium carboxymethylcellulose (a high-viscosity polymer of Reliance Cellulose Products Limited, Hydrad, India), and polyvinylpyrrolidone (PVP k30) were supplied by BPRL (Bangalore). Other materials were purchased from commercial sources: soluble starch (Nice Chemicals, Mumbai, India), magnesium

Corresponding Author: C. Narendra, Department of Pharmaceutics, Visveswarapura Institute of Pharmaceutical Sciences, V.V. Puram, Bangalore, 560004, Karnataka, India. Tel: +919845675376; E-mail: narendragcp@rediffmail.com

stearate (Loba Chemicals, Mumbai, India), talc (Reidel India Chemicals, Mumbai, India), sunset yellow (KAPL, Bangalore), di-calcium phosphate (Strides Arco Labs, Bangalore), and Aerosil (Nice Chemicals).

Methods

Experimental Design

A 2-level full-factorial design consists of 8 full-factorial design points; according to the model, 8 experiments were conducted in total. This design generally involves dependent variables Y and independent or controlled variables X_1, X_2, and X_3. The 3 independent formulation variables selected for this study were X_1, total polymer content-to-drug ratio; X_2, polymer-to-polymer ratio; and X_3, polymer grade (HPMC K4M and K10M). The levels of independent variables are shown in Table 1. The dependent variables were Y_1, percentage of MT release at 8 hours; Y_2, $T_{50\%}$; Y_3, diffusion exponent (n); and Y_4, floating time.

Preparation of Bilayer Tablets

The formulations were prepared at random following a 2^3 factorial design. Table 1 shows the level of variables according to experimental design. The preparation process involved 2 steps.

First, drug-loading granules (as an immediate dose) were prepared by mixing MT, starch, PVP, and di-calcium phosphate, using water as a wetting agent. The granules were dried at 60°C for 30 minutes in an oven and then mixed with talc, sunset yellow, and magnesium stearate (the composition is shown in Table 2).

Second, floating granules containing MT (as a sustained dose) were prepared by mixing the drug with the excipients in a formulation as shown in Table 3. The granules were then dried at the conditions listed above. Exactly 0.3 g of floating granules and 0.1 g of drug-loading granules were weighed and compressed into bilayer tablets by a single-punch tablet compression machine (Cadmach, Ahmedabad, India). A flat-faced punch 12 mm in diameter was used for tableting. Each bilayer tablet contained 70 mg (20 mg as loading dose and 50 mg as sustained dose) of MT; the tablets were prepared in 100-tablet batches, and compression was controlled to produce a 5-kg tablet crushing strength.

Table 1. Level of Investigated Variables*

	Independent Variables		
Coded Values	Total Polymer-to-Drug Ratio (X_1)	Polymer-to-Polymer Ratio (X_2)	Polymer Grade (X_3)
–1	1:1	1:1	HPMC K4M
1	4:1	9:1	HPMC K10M

*HPMC indicates hydroxypropyl methyl cellulose.

Table 2. Composition of Drug-Loading Layer of Bilayer Tablet

Composition	Quantity (mg)
Metoprolol tartrate	20
Soluble starch	5
Polyvinylpyrrolidone	4
Magnesium stearate	3
Talc	3
Sunset yellow	2
Di-calcium phosphate	63

In Vitro Evaluation of Bilayer Tablets

Tablets were placed in a 400-mL flask at pH 1.2 maintained at 37°C, and both the time needed to go upward and float on the surface of the fluid and the floating duration (floating time) were determined.[11]

In Vitro Dissolution Studies

The dissolution was performed by using a USP XXII paddle apparatus (Disso 2000, Labindia, Mumbai, India) at a rotational speed of 50 rpm. Exactly 750 mL of simulated gastric fluid (SGF; without enzymes) was used as the dissolution medium and maintained at 37°C ± 1°C. Then, 5 mL of the dissolution medium was taken out at 10 minutes, 20 minutes, 30 minutes, 1 hour, and thereafter every hour for 12 hours. Exactly 5 mL of fresh SGF was added to the dissolution vessel after each withdrawal, to maintain a constant volume. The samples withdrawn were analyzed by using a UV spectrophotometer (Elico model, Mumbai, India) at 275 nm. The amount of drug released was determined from the equation $y = 0.0041x + 0.0013$.

Buoyancy Determination

Buoyancy was determined by using a Westpal balance (Mumbai, India) and a water bath maintained at 37°C ± 1°C.[12] In this process, an optimized formulation was placed in a basket that was immersed in SGF with pH 1.2 at 37°C ± 1°C; the other end of the basket was connected to the balance. The resulting buoyancy was determined by adjusting the balance weight, and a curve was constructed.

Curve Fitting of Release Profile

The in vitro dissolution data were fitted to the Korsmeyer and Peppas equation[13]:

$$\frac{M_t}{M_\infty} = kt^n \qquad (1)$$

Table 3. Composition of Floating Layer (mg) as per 2^3 Factorial Design*

	F1	F2	F3	F4	F5	F6	F7	F8
Metoprolol tartrate	50	50	50	50	50	50	50	50
HPMC K4M	25	100	180	45	—	—	—	—
HPMC K10M	—	—	—	—	180	25	45	100
SCMC	25	100	20	5	20	25	5	100

*Each formulation contains 30 mg of microcrystalline cellulose (MCC), 0.75 mg of aerosol, 9 mg of magnesium stearate, and Quantity sufficient (QS) of di-calcium phosphate. HPMC indicates hydroxypropyl methyl cellulose; SCMC, sodium carboxymethylcellulose.

where M_t/M_∞ represents the fraction of drug release at time t, k is the release rate constant, and n is the diffusion coefficient. The entire curve-fitting analysis was performed using GraphPad Prism version 3.02 (GraphPad Software, Inc) and Excel (Microsoft) software.

Results and Discussion

MT's oral bioavailability has been reported to be ~50%,[2] perhaps because of rapid hepatic first-pass metabolism and because MT undergoes degradation in the colon.[14] If the MT dosage form can be retained in the stomach as long as possible, to allow for maximum absorption, MT's bioavailability could be improved. Gastric floating drug delivery is one approach; in it, the GI residence time is prolonged because of the floating behavior. Bilayer tablets were formulated as per a 2^3 factorial design,[15,16] and the factor total polymer content-to-drug ratio was considered to have an important effect on the release from the HPMC matrices,[17] so it was chosen as a response parameter. Different grades of HPMC (K4M and K10M) and SCMC were used as swellable polymers. HPMC was chosen because it is widely used as low-density hydrocolloid system; upon contact with water, a hydrogel layer would be formed to act as a gel boundary for the delivery system, but it would fail to retard the release of drug through the matrix because of its solubility in stomach pH.[18] Various grades of HPMC were reported to have a duration of buoyancy of more than 8 hours in the simulated meal medium, as well as in distilled water.[19] SCMC was used in combination with HPMC to slow the drug release; SCMC's ability to do this may be caused by the low solubility of SCMC at pH 1.2 to 3.[20] Our focus was on the floatability of the dosage form, so the HPMC concentration was increased throughout the experimental design. As stated above, different viscosity grades of HPMC show good floatability, so the viscosity grades were chosen arbitrarily.

Release profiles from the 8 formulations of 2^3 factorial designs are shown in Figure 1 and Figure 2.

It is clear from the figures that the formulations showed biphasic release of MT. In the first phase, the first fraction of the dose (the immediate dose) was released in less than 30 minutes, because of prompt disintegration of the fast-releasing layer and the enhanced rate of dissolution of MT from the system. This behavior was identical for all the

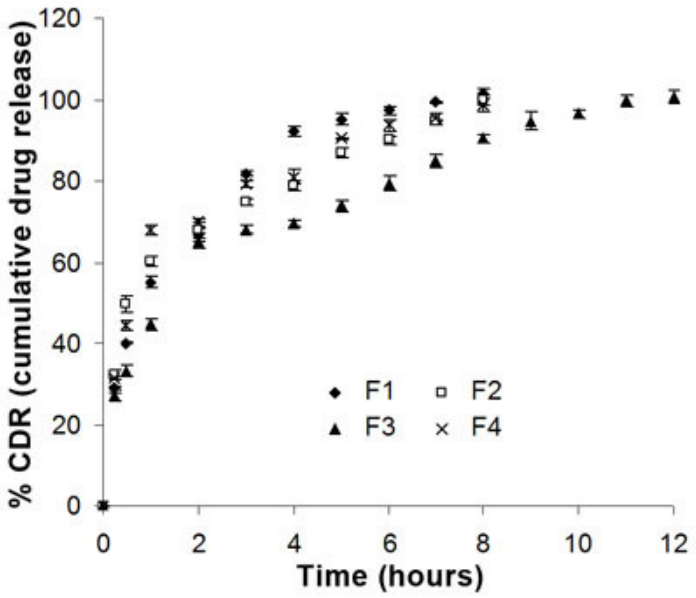

Figure 1. In vitro release profile of metoprolol tartrate from formulations F1 to F4 (n = 3).

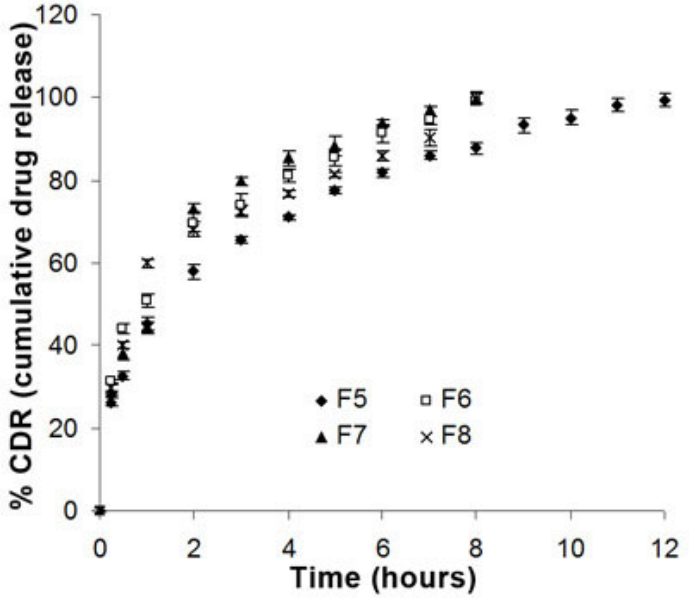

Figure 2. In vitro release profile of metoprolol tartrate from formulations F5 to F8 (n = 3).

Table 4. Curve-Fitting Data of Release Rate Profile and Floating Time Obtained for Formulations (F1-F8) by Factorial Design

Formulation Code	Y_1 Metoprolol Tartrate Release at 8 Hours (%)	Y_2 $T_{50\%}$ (hours)	Y_3 Diffusion Coefficient (n)	Y_4 Floating Time (hours)	R^2
F1	101.31 ± 2.11	1.32 ± 0.03	0.35 ± 0.02	8.45 ± 0.35	0.99
F2	99.97 ± 0.99	1.82 ± 0.06	0.29 ± 0.01	14.83 ± 0.41	0.97
F3	90.33 ± 0.70	2.55 ± 0.04	0.43 ± 0.07	22.23 ± 0.29	0.95
F4	98.70 ± 2.23	1.35 ± 0.04	0.25 ± 0.02	10.07 ± 0.32	0.97
F5	87.72 ± 1.54	2.61 ± 0.07	0.44 ± 0.01	23.21 ± 0.28	0.93
F6	99.03 ± 0.98	1.95 ± 0.05	0.29 ± 0.01	8.23 ± 0.34	0.98
F7	99.48 ± 2.77	1.63 ± 0.08	0.34 ± 0.03	10.37 ± 0.35	0.97
F8	99.87 ± 2.10	1.99 ± 0.01	0.29 ± 0.02	15.41 ± 0.44	0.98

formulations. After the release of the first fraction, the release of the sustained dose (the floating layer) depended upon the HPMC:SCMC ratio and the viscosity grades of HPMC. Formulation F1, which contained the lowest polymer concentration, could not control the release for long, possibly because of the poor strength of the matrix. For formulations F2, F4, F6, F7, and F8, the drug release from the system was 99% within 8 hours. But formulations F3 and F5, which contained a high polymer concentration of HPMC, were able to keep their integrity and therefore showed good control of the drug dissolution process, with a slower release rate for a longer period of time.

The first phase of the drug release profile depended on the concentration of the drug in the upper layer as an immediate dose and hence followed first-order release kinetics. In the second phase of the release (1-8 hours), the data were fitted to Equation 1 and the diffusion coefficient was found to be 0.25 to 0.44 (Table 4). Based on the n value, the mechanism of MT release from the floating layer followed Fickian transport.[21]

The results obtained from the experiment were statistically analyzed for response variables by using Design Expert 6.05 version (Stat-Ease Inc., Minneapolis, Minnesota). The design was evaluated by a factorial linear interactive first-order model:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 \quad (2)$$

The regression coefficients for each term in the regression model are summarized in Table 5, and the analysis of variance (ANOVA) information is shown in Table 6.

Table 5. Regression Coefficients for the Responses

$Y_1 = 97.05 - 2.58X_1 - 2.99X_2 - 2.45X_1X_2$
$Y_2 = 1.90 + 0.34X_1 + 0.13X_2 + 0.20X_1X_2$
$Y_3 = 0.34 + 0.027X_1 + 0.030X_2 + 0.042X_1X_2 + 0.020X_2X_3$
$Y_4 = 14.10 + 4.82X_1 + 2.37\ X_2 + 1.43\ X_1X_2$

Effect of Formulation Variables on Release Properties

In the case of Y_1 (percentage of MT release at 8 hours), coefficients b_1 and b_2 were found to be significant, with an interaction of b_{12}. In Table 5, we can see only negative coefficients; when the total polymer content-to-drug ratio (X_1) increased, MT release at 8 hours decreased. Similar results were reported earlier: as the polymer concentration in the matrix increases, the release rate decreases.[22] The relationship between variables was further elucidated using contour plots. The effects of X_1 and X_2 on Y_1 at a fixed level of X_3 (HPMC K4M) are given in Figure 3. At low levels of X_2, Y_1 did not show any significant changes when X_1 increased from the –1 level to the +1 level. But the same Y_1 decreased from 98.39% to 89.98% when the total polymer content-to-drug ratio (X_1) was increased and the polymer-to-polymer ratio (X_2) was kept at the highest level. For the higher grade of HPMC (K10M) (Figure 4), as the

Table 6. Analysis of Variance Table for Dependent Variables From Full Factorial Design*

Source	df	Sum Square	Mean Square	F Value	Prob > F
Metoprolol tartrate release at 8 hours (%) $R^2 = 0.9648$					
X_1	1	53.20	53.20	33.70	0.0044
X_2	1	71.70	71.70	45.42	0.0025
X_{12}	1	48.17	48.17	30.51	0.0052
$T_{50\%}$ (hours) $R^2 = 0.8466$					
X_1	1	0.92	0.92	14.57	0.0188
X_2	1	0.14	0.14	2.21	0.2111
X_{12}	1	0.34	0.34	5.30	0.0828
Diffusion coefficient (n) $R^2 = 0.9926$					
X_1	1	0.0060	0.0060	48.40	0.0200
X_2	1	0.0072	0.0072	57.60	0.0169
X_{12}	1	0.0140	0.0140	115.60	0.0085
X_{23}	1	0.0032	0.0032	25.60	0.0369
Floating time (hours) $R^2 = 0.9971$					
X_1	1	185.86	185.86	1036.00	0.0001
X_2	1	44.94	44.94	250.47	0.0001
X_{12}	1	16.36	16.36	91.19	0.0007

*Prob > F less than .05 indicate model terms are significant.

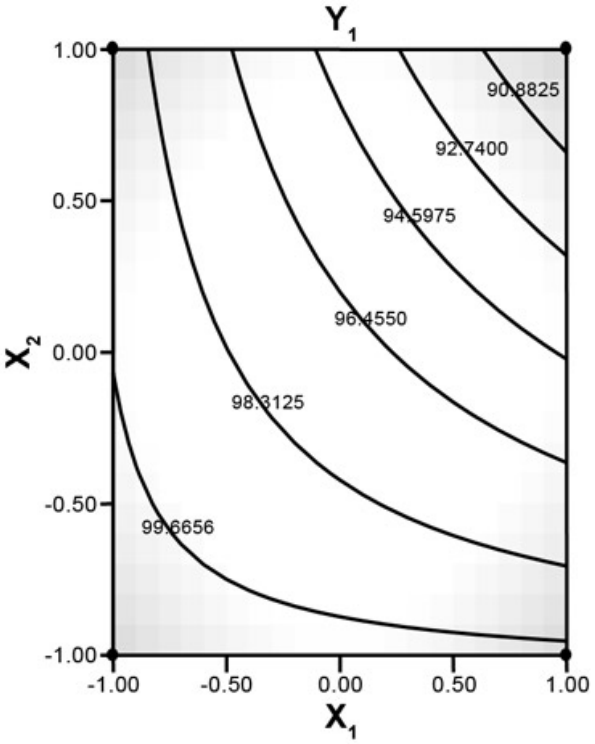

Figure 3. Contour plot showing the effect of total polymer content-to-drug ratio (X_1) and polymer-to-polymer ratio (X_2) on percentage of metoprolol tartrate release at 8 hours (Y_1), for HPMC K4M. HPMC indicates hydroxypropyl methyl cellulose.

total polymer content-to-drug ratio (X_1) increased, the release decreased from 99.63% to 88.83% because the polymer-to-polymer ratio (X_2) was kept at a higher level. This finding was due to the increased strength of the gel layer; the drug diffusion was controlled by the penetration of liquid through the gel layer. The ANOVA analysis for $T_{50\%}$ (Y_2) is shown in Table 6; only coefficient b_1 was found to be significant, with an F value of 14.57 ($P = .0188$). In almost all the formulations, 30% to 40% of MT was released rapidly within 30 minutes of the experiment (Figures 1 and 2), corresponding to low $T_{50\%}$ values of expected desired range of 2 to 3 hours. When the total polymer content-to-drug ratio (X_1) values were increased, the $T_{50\%}$ values showed an increase in coefficient value of 0.34 (Table 5), which may have been due to slower water uptake (the water diffusion and release rate also slowed). The model term for Y_3 (diffusion coefficient) was found to be significant, with an F value of 53.36 ($P < .0185$). In this case, the coefficients b_1 and b_2 and the interaction b_{12} were found to be significant. As the variables X_1 and X_2 increased, the diffusion coefficient also increased, which may have been due to the fact that increased polymer loading increased the strength and viscosity of the gel layer, which in turn delayed the water diffusion into the core of the tablet, leading to uniform drug release. Such behavior may be closely related to the porosity and tortuosity of the gel barrier. Because of the

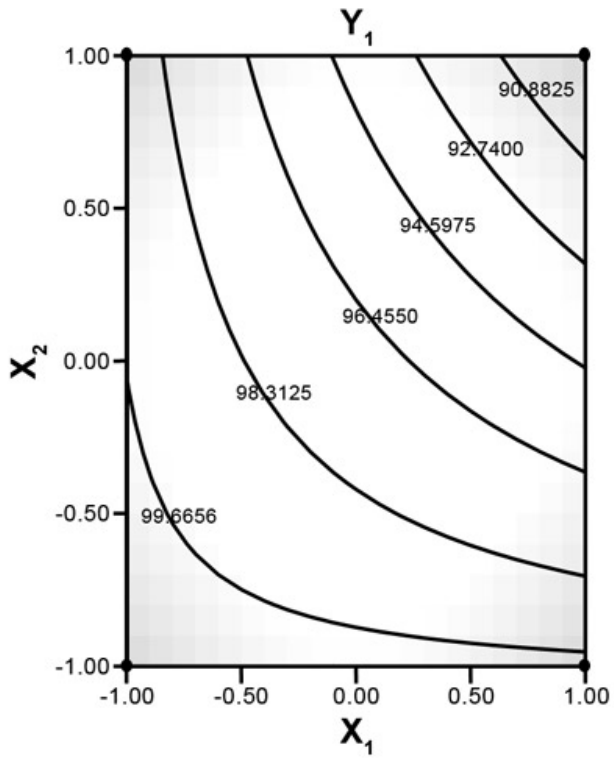

Figure 4. Contour plot showing the effect of total polymer content-to-drug ratio (X_1) and polymer-to-polymer ratio (X_2) on percentage of metoprolol tartrate release at 8 hours (Y_1), for HPMC K10M. HPMC indicates hydroxypropyl methyl cellulose.

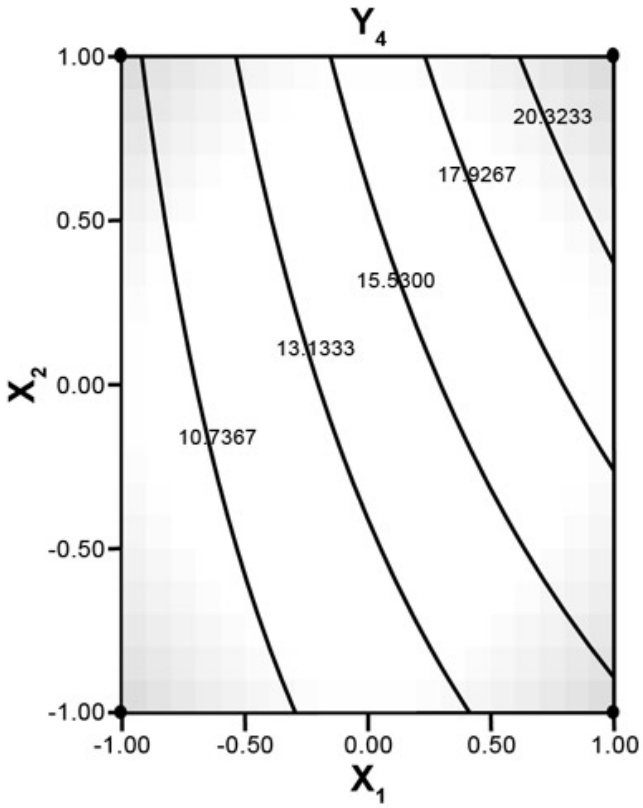

Figure 5. Contour plot showing the effect of total polymer content-to-drug ratio (X_1) and polymer-to-polymer (X_2) ratio on response floating time (Y_4).

Table 7. Composition of Optimized Formulations*

Composition	Drug Loading Layer (mg)	Floating Layer (mg)	
		Optimized Formulation 1	Optimized Formulation 2
Metoprolol tartrate	20	50	50
Starch soluble	5	—	—
PVP	4	—	—
HPMC K4M	—	180	—
HPMC K10M	—	—	180
SCMC	—	20	20
MCC	—	30	30
Aerosil	—	0.75	0.75
Magnesium stearate	3	9	9
Talc	3	—	—
Sunset yellow	2	—	—
Di-calcium phosphate	63	10.25	10.25

*PVP indicates polyvinylpyrrolidone; HPMC, hydroxypropyl methyl cellulose; SCMC, sodium carboxymethylcellulose; MCC, microcrystalline cellulose.

high viscous gel layer, more resistance to erosion was observed and these matrices could maintain the integrity of the tablet for up to 10 hours. At a later stage (after 12 hours of dissolution studies), the water diffusion increased, leading to disintegration and erosion of the tablet.

Effect of Formulation Variables on Floating Time

The coefficients found to be significant for percentage MT release at 8 hours were also found to be significant for floating time (Y_4) (Table 5). As the factor X_1 increased, the floating time also increased; a similar linear positive effect was also observed by increasing the HPMC-to-SCMC ratio. The polymer grade was found to be nonsignificant, indicating that the floating time was not influenced by the HPMC grade (K4M or K10M). The contour plot in Figure 5 shows an interaction between X_1 and X_2 and the F value of 91.19 ($P < .0007$) from Table 6. At a higher level of polymer-to-polymer ratio (X_2), the floating time increased from 10.33 hours to 22.20 hours when the total polymer content-to-drug ratio (X_1) was increased from –1 to +1. At a lower level of polymer-to-polymer ratio (X_2), there was a significant increase in floating time from 8.48 hours to 15.16 hours when X_1 was increased from –1 to +1. For all the formulations, the time required for the tablets to go from the bottom to the top of a beaker containing pH 1.2 at 37°C ± 1°C was found to be under 30 minutes. Once the tablets (F3 and F4) came up to the surface, they remained buoyant for up to 24 hours, during which the tablets lost their integrity and the size of the swollen matrix gel drastically reduced because of disintegration and erosion. In fact, the floating time (buoyancy) of the tablets is governed by both (1) the swelling (hydration) of the hydrocolloid particles on the tablets' surface when the tablets contact the gastric fluids, which in turn results in an increase in the bulk volume; and (2) the presence of the internal voids in the dry center of the tablet (porosity). These 2 factors are essential for the tablet to acquire a bulk density of less than 1 and remain buoyant on the gastric fluid.[23]

Optimization

The polynomial equations generated for the dependent and independent variables are shown in Table 5. The process was optimized for the response Y_1 to Y_4, and the optimized formulation was arrived at by maximizing the floating time, the percentage of MT release at 8 hours, and the $T_{50\%}$ to obtain the desired levels of X_1 to X_3. The results from the optimization clarified the optimum settings for the bilayer floating tablets with a high total polymer content-to-drug ratio (1:4) and polymer-to-polymer ratio (1:9). The results also illustrate that the HPMC viscosity grade, whether K4M or K10M, did not influence the floating time. To verify the reproducibility, a new formulation (the composition of the

Table 8. Comparison Between the Experimental and Predicted Values for the Most Probable Optimal Formulations

Dependent Variable	Optimized Formulation 1		Optimized Formulation 2	
	Experimental	Predicted	Experimental	Predicted
Metoprolol tartrate release at 8 hours (%)	87.36 ± 2.67	89.72	85.53 ± 3.94	88.57
$T_{50\%}$ (hours)	2.42 ± 0.51	2.58	2.89 ± 0.32	2.56
Diffusion coefficient (n)	0.39 ± 0.11	0.42	0.42 ± 0.09	0.44
Floating time (hours)	21.5 ± 1.00	22.72	22.5 ± 1.15	22.56

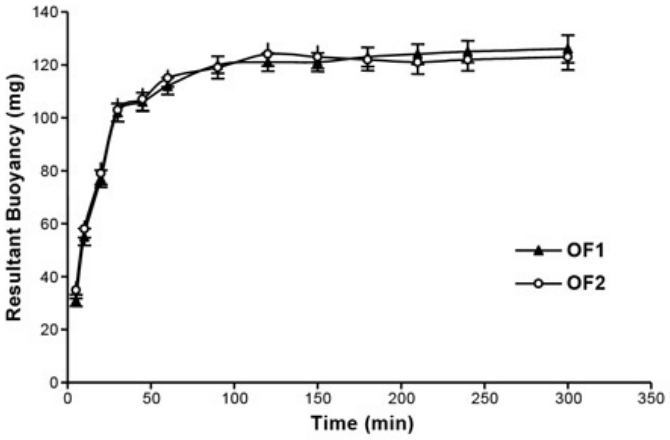

Figure 6. Time buoyancy kinetics curve of OFs. OF indicates optimized formulation.

optimized formulations is shown in Table 7) was prepared according to the predicted levels and evaluated. The results (Table 8) showed a good relationship between the experimental and predicted values, which confirms the practicability of the model. From the floating kinetics curve in Figure 6, the buoyancy generated by the tablets was 102 ± 3.4 mg and 103 ± 4.4 mg, respectively, for optimized formulations OF1 and OF2 within 30 minutes, a sufficient buoyancy for the whole tablet to go up to the surface and float for a long period.[12]

CONCLUSIONS

This article discussed a positive application of a computer optimization technique for the development of a bilayer GFDDS in which polymer (HPMC) viscosity grade (K4M or K10M) did not significantly affect the floating and release properties. However, the factor total polymer content-to-drug ratio and the polymer-to-polymer ratio did significantly affect the studied dependent variables. The dosage form can control the release, avoid dose dumping, and extend the duration of action of a drug with prolonged floating time. This dosage form holds promise for further in vivo studies, which can be extrapolated for the development of other delivery systems.

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