Development and In Vitro Evaluation of an Oral Floating Matrix Tablet Formulation of Diltiazem Hydrochloride

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ABSTRACT

The purpose of this research was to prepare a floating drug delivery system of diltiazem hydrochloride (DTZ). Floating matrix tablets of DTZ were developed to prolong gastric residence time and increase its bioavailability. Rapid gastrointestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose. The tablets were prepared by direct compression technique, using polymers such as hydroxypropylmethylcellulose (HPMC, Methocel K100M CR), Compritol 888 ATO, alone or in combination and other standard excipients. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of sodium bicarbonate and succinic acid on drug release profile and floating properties were investigated. A 3^2 factorial design was applied to systematically optimize the drug release profile. The amounts of Methocel K100M CR (X_1) and Compritol 888 ATO (X_2) were selected as independent variables. The time required for 50% (t_{50}) and 85% (t_{85}) drug dissolution were selected as dependent variables. The results of factorial design indicated that a high level of both Methocel K100M CR (X_1) and Compritol 888 ATO (X_2) favors the preparation of floating controlled release of DTZ tablets. Comparable release profiles between the commercial product and the designed system were obtained. The linear regression analysis and model fitting showed that all these formulations followed Korsmeyer and Peppas model, which had a higher value of correlation coefficient (*r*). While tablet hardness had little or no effect on the release kinetics and was found to be a determining factor with regards to the buoyancy of the tablets.

KEYWORDS: Diltiazem hydrochloride, gastroretentive, floating drug delivery, controlled release.

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INTRODUCTION

Retention of drug delivery systems in the stomach prolongs overall gastrointestinal transit time and improves the oral bioavailability of the drugs that are having site-specific absorption from the stomach or upper part of the small intestine. Therefore different approaches have been proposed to retain the dosage form in the stomach including bioadhesive systems,[1] swelling and expanding systems,[2,3] floating systems,[4,5] and delayed gastric emptying devices.[6] The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.

Diltiazem hydrochloride (DTZ) is a calcium channel blocker belonging to the benzothiazepine family. It is widely prescribed for the treatment of hypertension and angina.[7] DTZ undergoes an extensive biotransformation, mainly through cytochrome P-450 CYP3A,[8] which results in less than 4% of its oral dose being excreted unchanged in urine.[9] Bioavailability of DTZ is ~30% to 40% owing to an important first pass metabolism.[7,9,10] It has an elimination half-life of 3.5 hours and has an absorption zone from the upper intestinal tract.[9,10] Efficacy of the administered dose may get diminished due to incomplete drug release from the device above the absorption zone.[11] DTZ requires multiple daily drug dosage in order to maintain adequate plasma concentrations. Therefore, it is a suitable model candidate for gastroretentive formulation. The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability.[12] High solubility of DTZ was a major challenge in designing its controlled drug delivery system. In this study, Methocel K100M CR was used as a swelling as well as a release-retarding polymer. Compritol 888 ATO[13] chemically known as glyceryl behenate, a hydrophobic polymer is used as a matrix-forming controlled release polymer. Because high water soluability of the DTZ results in hydration of matrix prepared with Methocel K100M CR alone, thereby resulting in variability in the release profiles of DTZ. To minimize the hydration rate of the matrix and variability in the release profiles, Compritol 888 ATO was tried in combination with Methocel K100M CR. The formulations were

optimized with 3^2 factorial design for desired acceptance criteria (ie, floating lag time is of less than 5 minutes; floating duration of 24 hours; $t_{50\%}$, between 10 and 12 hours; and $t_{85\%}$, between 20 and 25 hours).

In context of the above principles, a strong need was recognized for the development of a dosage form to deliver DTZ in the stomach and to increase the efficiency of the drug, providing controlled release action. The present investigation applied a systematic balance between floating lag time, floating duration, and in vitro drug release for the development of gastroretentive dosage forms of DTZ suitable for a once-daily formulation with improved bioavailability.

Materials and Methods

Materials

Methocel K100M CR and Compritol 888 ATO were kindly supplied by Colorcon Asia Pvt Ltd (Goa, India). DTZ was a gift sample from Cipla Ltd (Mumbai, India). Sodium bicarbonate, succinic acid, talc, and magnesium stearate were purchased from S. D. Fine Chemicals Ltd (Mumbai, India). All other ingredients were of analytical grade.

Methods

Preparation of Diltiazem Hydrochloride Floating Matrix Tablets

DTZ, Methocel K100M CR, and Compritol 888 ATO were passed through sieve No. 80 separately. The drug was mixed with the polymers and other ingredients in weight proportion as mentioned in Table 1. The powder blend was then lubricated with magnesium stearate (2% wt/wt) and talc (2% wt/wt), and this lubricated blend was compressed into tablets using 12.5-mm flat-face round tooling on a single punch tablet machine (Cadmach, Ahmedabad, India). The compression force was adjusted to obtain tablets with hardness in range of 5 to 6 kg/cm^2. The formulations of the preliminary trial batches H1 to H9 and C1 to C5 are shown in Table 1. Formula C5 has the same composition as that of C3, but it was prepared by melt granulation[14] in order to evaluate the effect of the melt granulation method on the release of the drug. Compritol 888 was melted at 50°C, and the drug and sodium bicarbonate mixture were added to this with proper mixing and cooled to room temperature. The mass was passed through a 510-μm sieve to obtain uniform-sized granules, which were then lubricated with magnesium stearate and compressed into tablet. The compositions for formulations of the factorial design batches F1 to F9 are shown in Table 2.

Factorial Design

A 3^2 randomized reduced factorial design was used in this study and 2 factors were evaluated, each at 3 levels; experimental trials were performed at all 9 possible combinations. The percentage of Methocel K100M CR (X_1) and Compritol 888 ATO (X_2) were selected as independent variables. The times required for 50% (t_{50}) and 85% (t_{85}) drug dissolution were selected as dependent variables. The resulting data were fitted into Stat Ease, Inc. (Minneapolis, MN) Design Expert 7.0.3 software and analyzed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to determine the influence of Methocel K100M CR and Compritol 888 ATO on dependent variables. Tablet weight was not constant because that would require the use of diluents for weight adjustment, which in turn may have caused variation in release profile. Thus, we did not alter the amount of diluents in the formulation to nullify any effect due to change in the proportion of diluents (Table 3).

All batches contained 240 mg DTZ, 10% wt/wt sodium bicarbonate, 2% wt/wt talc, and 2% wt/wt magnesium stearate. X_1 and X_2 are the amounts of Methocel K100M CR and Compritol 888 ATO in percentage, respectively.

In Vitro Buoyancy Studies

The in vitro buoyancy was determined by floating lag time, as per the method described by Rosa et al.[15] The tablets were placed in a 100-mL beaker containing 0.1 N HCl and the time

Table 1. Tablet Formulations for Preliminary Trials*

Ingredients (mg)	H1	H2	H3	H4	H5	H6	H7	H8	H9	C1	C2	C3	C4	C5
DTZ	240	240	240	240	240	240	240	240	240	240	240	240	240	240
Methocel K100M CR	60	120	120	120	120	180	240	300	360	—	—	—	—	—
Compritol 888 ATO	—	—	—	—	—	—	—	—	—	60	120	180	240	180
Sodium bicarbonate	—	—	20	40	86	50	55	60	65	40	40	50	55	50
Succinic acid	—	86	66	46	—	—	—	—	—	—	—	—	—	—
Magnesium stearate	6	9	9	9	9	9.5	11	12	13.5	6	8	10	11	10
Talc	6	9	9	9	9	9.5	11	12	13.5	6	8	10	11	10
Total weight	312	464	464	464	464	489	557	624	692	352	416	490	557	490

*DTZ indicates diltiazem hydrochloride.

Table 2. In Vitro Dissolution Data of Tablet Formulations for Preliminary Trials*

Formulation No.	Floating Lag Time (minutes) ± SD	Floating Time (hours)	Matrix Integrity	T_{50} (Time for 50% of drug release) ± SD	T_{85} (Time for 85% of drug release) ± SD
H1	—	6	—	—	—
H2	—	24	+	6.5 ± 2.4	12.3 ± 2.9
H3	30 ± 2.9	—	+	7.0 ± 2.6	12.7 ± 2.5
H4	4.2 ± 1.8	24	+	7.1 ± 3.1	12.9 ± 2.7
H5	4.1 ± 1.2	24	+	7.1 ± 2.9	13.2 ± 3.5
H6	4.4 ± 2.7	24	+	8.5 ± 2.7	20.4 ± 3.1
H7	4.6 ± 1.3	24	+	9.8 ± 2.0	23.5 ± 2.2
H8	4.5 ± 2.8	24	+	9.8 ± 2.6	23.9 ± 2.1
H9	4.4 ± 2.1	24	+	9.9 ± 3.2	24.1 ± 1.9
C1	—	—	—	0.9 ± 2.8	4.0 ± 3.5
C2	—	—	+	2.8 ± 2.9	7.9 ± 3.6
C3	—	—	+	3.6 ± 3.7	11.2 ± 3.9
C4	—	—	+	5.4 ± 3.9	13.1 ± 4.1
C5	—	—	+	4.2 ± 3.1	12.1 ± 5.0

*SD indicates standard deviation.

required for the tablet to rise to the surface and float was determined as floating lag time.

In Vitro Dissolution Studies

The release rate of DTZ from floating tablets (n = 3) was determined. The dissolution test was performed using United States Pharmacopeia (USP) type II (paddle) apparatus, 900 mL of 0.1 N HCl, at 37°C ± 0.5°C and 100 rpm. A sample (5 mL) of the solution was withdrawn from the dissolution apparatus at the appropriate time for 24 hours, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45-μm membrane filter and diluted to a suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 238 nm using a Shimadzu UV-1601 UV/Visible double-beam spectrophotometer (Shimadzu Corp, Kyoto, Japan). Cumulative percentage drug release was calculated using a PCP Disso Version 2.08 software (Poona College of Pharmacy, Pune, India),[16] the time required for 50% and 85% drug release was calculated based on the Korsmeyer and Peppas model.[17]

Kinetic Modeling of Drug Release

The dissolution profile of all the batches was fitted to zero-order, first-order,[18,19] Higuchi,[20-22] Hixon-Crowell,[23] Korsmeyer and Peppas,[17,24,25] and Weibull models[26-29] to ascertain the kinetic modeling of drug release by using a PCP Disso Version 2.08 software, and the model with the highest correlation coefficient was considered to be the best model.

Table 3. Amount of Variables in a 3^2 Factorial Design

	Actual Values	
Coded Values	X_1	X_2
–1	25	15
0	30	20
1	35	25

Comparison of Optimized Formulation With Dilacor XR 240 mg Marketed Tablet

Dilacor XR[30,31] (Watson Pharma, Inc., Corona, CA) capsules contain 4 units of 60 mg tablets in a capsule shell, resulting in 240 mg dosage strength, designed to release diltiazem over a 24-hour period. This commercial product, a Dilacor XR unit, is a triple-layered tablet that contains 2 outer polymeric layers and 1 middle drug layer, therefore the polymeric outer layers control the drug release in the middle layer to give zero-order release kinetics. The similarity factor f 2 was used as a basis to compare the dissolution profiles.[32]

Effect of Tablet Hardness on the Drug Release

In addition to the tablets of 4 to 4.5 kg/cm^2 hardness, another 2 sets of tablets, each of formulation H7, with different hardness (2 and 8 kg/cm^2) were subjected to the in vitro release test as described in the section "In Vitro Dissolution Studies," to study the effect of tablet hardness on the drug release profile.[33] Times for 50% (t_{50}) and 85% (t_{85}) of drug release were calculated.

Scanning Electron Microscopy

Scanning Electron Microscopy (SEM) of intact tablet containing formulation F9 was done before and after dissolution of 24 hours. The morphological characters of these 2 scans

were compared to hypothesize the mechanism of drug release and floating.

The surface of the tablets was studied by SEM. The preparation of the samples was accomplished by placing the intact tablets before and after 24 hours dissolution, by drying them to remove water content and placing these tablets on a specimen holder. The samples were coated with a gold-palladium target using a Novatec (Palazzuolo Sul Senio, Italy) vacuum evaporator for 15 minutes. SEM images were obtained at an acceleration voltage of 8 to 10 kV. Study of the morphology of the particles using SEM was done, which provided information about the 3-D structure of the particles with the resolution power up to 5°A. Imaging was done at a magnification of 200 μm and pressure of 0.98 torr.

Results and Discussion

In Vitro Buoyancy Studies

The initial batches of H1 and H2 prepared without sodium bicarbonate did not show any sign of floating. Therefore, sodium bicarbonate was used as a gas-generating agent in order to float the tablet. The sodium bicarbonate induces CO_2 generation in the presence of dissolution medium (0.1 N HCl). The gas generated is trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of the tablet below 1 gm/mL, and the tablet becomes buoyant. To study the effect of sodium bicarbonate concentration on floating lag time, batches H3 to H5 were selected. It was found that as the amount of sodium bicarbonate increases, the floating lag time decreases. Thus, sodium bicarbonate 10% was essential to achieve optimum in vitro buoyancy (ie, floating lag time of 4 to 5 minutes and floating duration of 24 hours). Further increase in concentration of sodium bicarbonate does not show any significant effect on floating behavior. Moreover, the increased amount of sodium bicarbonate caused a large amount of effervescence, which in turn resulted in pore formation, which led to rapid hydration of the polymer matrix and thereby to rapid drug release. Thus 10% concentration of sodium bicarbonate was kept constant for batches H6 to H9, which showed floating lag time between 4 and 6 minutes and remained floating for 24 hours. Succinic acid[34] was incorporated in the formulation batches H3 to H5 to keep the tablet weight constant and to nullify the effect of the acidic dissolution media on the drug release. No formulation from batches C1 to C5 containing Compritol 888 ATO showed floating because the formulation did not swell and hence failed to form a gel.

In Vitro Dissolution Studies

In batch H1, DTZ tablets were prepared using Methocel K100M CR in the absence of sodium bicarbonate. The tablet failed to float and did not remain intact; moreover, 45% of the drug was released within 1 hour at this low concentration of Methocel K100M CR. Hence the concentration of Methocel K100M CR was increased by using the drug: polymer ratio of 1:0.5 for batch H2, which showed matrix integrity, but the release of drug was too rapid. In batches H3 to H5, the concentration of sodium bicarbonate was increased in order to get the desired floating behavior. Furthermore, the polymer concentration was increased in order to achieve the desired release profile from batches H6 to H9. Formulation H7 gave the best results in terms of floating behavior (lag time 4.6 minutes, duration 24 hours), and drug release was in accordance with the USP specification. According to USP test-4, the amount dissolved at 4, 8, 12, and 24 hours should be 10% to 25%, 35% to 60%, 55% to 80%, and more than 80%, respectively. Batches H8 and H9 showed greater retardation of drug release because of the high concentration of polymer.

The hydrophobic polymer Compritol 888 ATO, having low density, was tried for floating controlled release. But the tablet formulation did not swell because the CO_2 generated by the interaction between 0.1 N HCL and sodium bicarbonate did not get entrapped, thus this formulation failed to float the tablet. The formula C1 showed a burst release pattern, and more than 50% of the drug was released in 1 hour. The matrix did not remain intact in low concentration because in low concentration it acts as a disintegrant. The concentration of Compritol 888 ATO was further increased in order to get the desired release profile. But the formulations C2, C3, and C4 showed no satisfactory drug release or floating behavior. Formula C5 had the same composition as that of C3, but it was prepared by the melt granulation method in order to see the effect of melt granulation on the release of the drug. But the experiment did not show any significant difference in the release profile or floating behavior. The effect of the polymer concentration from preliminary trials

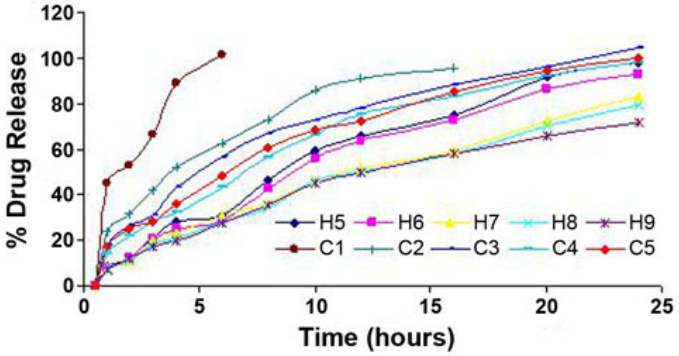

Figure 1. Effect of polymer concentration on release profile of diltiazem hydrochloride from tablet formulations for preliminary trials.

Table 4. Formulation and Dissolution Characteristics of Batches in a 3^2 Reduced Factorial Design*

Formulation No.	Variable Level in Coded Form X_1	X_2	Total Weight of Tablet (mg)	Floating Lag Time (minutes)	Floating Time (hours)	Matrix Integrity	Response in Time t_{50} (hours) ± SD	Response in Time t_{85} (hours) ± SD
F1	–1	–1	510	4.5	24	+	5.8 ± 1.2	13.8 ± 2.9
F2	–1	0	565	4.5	24	+	6.3 ± 1.6	14.9 ± 14.9
F3	–1	+1	631	4.3	24	+	6.1 ± 2.1	14.3 ± 2.4
F4	0	–1	565	4.1	24	+	6.5 ± 0.8	14.9 ± 4.8
F4	0	–1	565	4.1	24	+	6.5 ± 0.8	14.9 ± 4.8
F5	0	0	630	4.6	24	+	7.2 ± 2.2	16.2 ± 4.3
F6	0	+1	723	4.5	24	+	8.2 ± 0.6	19.7 ± 1.6
F7	+1	–1	630	4.2	24	+	7.7 ± 0.9	17.1 ± 3.9
F8	+1	0	723	4.7	24	+	8.7 ± 1.8	20.8 ± 6.3
F9	+1	+1	837	4.4	24	+	10.2 ± 2.5	24.9 ± 5.4

*All batches contained 240 mg diltiazem hydrochloride, 10% sodium bicarbonate, 2% talc, and 2% magnesium stearate; X_1 is the percentage of Methocel K100M CR; and X_2 is the percentage of Compritol 888.

on release profile of diltiazem hydrochloride is shown in Figure 1.

Factorial Design

A 3^2 full-factorial design was constructed to study the effect of the amount of Methocel K100M CR and Compritol 888 ATO on the drug release from floating DTZ tablets. The dependent variables chosen were time required for 50% and 85% drug dissolution. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (1)$$

where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_i (b_1, b_2, b_{12}, b_{11} and b_{22}) is the estimated coefficient for the corresponding factor X_i (X_1, X_2, X_1X_2, X_{12} and X_{22}), which represents the average result of changing 1 factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The t_{50} and t_{85} for the 9 batches (F1-F9) showed a wide variation (ie, 5.8-10.2 hours and 13.8-24.9 hours, respectively). The responses of formulation prepared by 3^2 factorial designs are indicated in Table 4. The data clearly indicate that the t_{50} and t_{85} values are strongly dependent on the selected independent variables. The fitted equations relating the response t_{50} and t_{85} to the transformed factor are shown in Equation 2 and Equation 4, respectively.

Final Equation in Terms of Coded Factors:

$$t_{50} = +7.41 + 1.40X_1 + 0.75X_2 + 0.55X_1X_2 \quad (2)$$

Final Equation in Terms of Actual Factors:

$$t_{50} = +9.21 - 0.16 \text{ Methocel K100M CR} - 0.51 \text{ Compritol 888 ATO} + 0.02 \text{ Methocel K100M CR Compritol} \quad (3)$$

Final Equation in Terms of Coded Factors:

$$t_{85} = +17.40 + 3.30X_1 + 2.18X_2 + 1.82X_1X_2 \quad (4)$$

Final Equation in Terms of Actual Factors:

$$t_{85} = +32.666 - 0.800 \text{ Methocel K100M CR} - 1.753 \text{ Compritol 888 ATO} + 0.073 \text{ Methocel K100M CR Compritol} \quad (5)$$

Table 5 shows ANOVA for dependent variables t_{50} and t_{85}. Only significant terms of the model are retained in the tables. The coefficients of X_1, X_2, and X_1X_2 were found to be significant at $P < .05$, hence they were retained in the reduced model. Increasing the concentration of either Methocel K100M CR (X_1) or Compritol 888 ATO (X_2) resulted in reduction of drug release. However, its interaction terms had a retardation influence on the release of DTZ. ANOVA and multiple regression analysis were done using Stat-Ease Design Expert 7.0.3 trial software.

Figures 2 and 3 show the plot of the percentage of Methocel K100M CR (X_1) and the percentage of Compritol 888 ATO (X_2) vs t_{50} and t_{85} (hours), respectively. The plot was drawn using Stat-Ease Design Expert 7.0.3 trial. The data demonstrate that both X_1 and X_2 affect the drug release (t_{50} and t_{85}). It is concluded that a high level of both Methocel

Table 5. Analysis of Variance

For t_{50}						
Source	Sum of Squares	Degrees of Freedom	Mean Square	F Value	*P* Value	Model Significant/ Nonsignificant Relative to Noise
Model	16.34	3	5.45	121.67	<.0001	Significant
X_1	11.76	1	11.76	262.63	<.0001	Significant
X_2	3.37	1	3.37	75.37	.0003	Significant
X_1X_2	1.21	1	1.21	27.02	.0035	Significant
$(X_1)^2$	—	—	—	—	>.05	Nonsignificant
$(X_2)^2$	—	—	—	—	>.05	Nonsignificant
Residual	0.22	5	0.045	—	—	—
Core Total	16.57	8	—	—	—	—

For t_{85}						
Source	Sum of Squares	Degrees of Freedom	Mean Square	F Value	*P* Value	Model Significant/ Nonsignificant Relative to Noise
Model	107.26	3	35.75	73.39	.0001	Significant
X_1	65.34	1	65.34	134.12	<.0001	Significant
X_2	28.60	1	28.60	58.71	.0006	Significant
X_1X_2	13.32	1	13.32	27.35	.0034	Significant
$(X_1)^2$	—	—	—	—	>.05	Nonsignificant
$(X_2)^2$	—	—	—	—	>.05	Nonsignificant
Residual	2.44	5	0.04	—	—	—
Core total	109.70	8	—	—	—	—

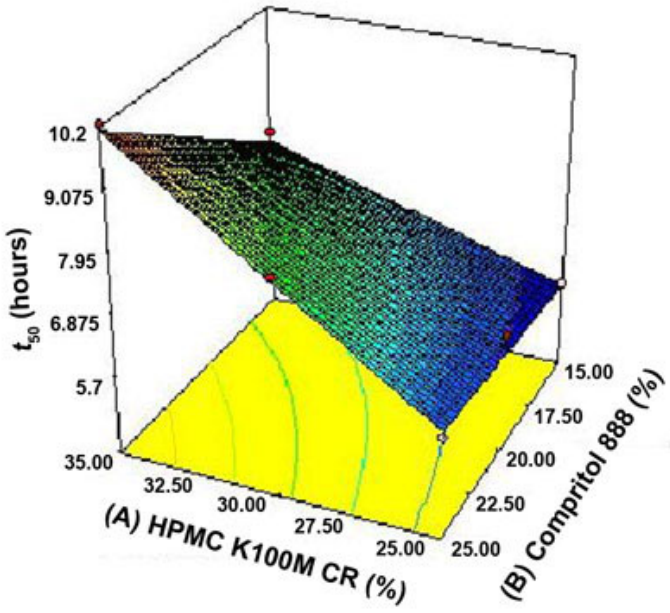

Figure 2. Response surface plot for t_{50}. HPMC indicates hydroxypropylmethylcellulose.

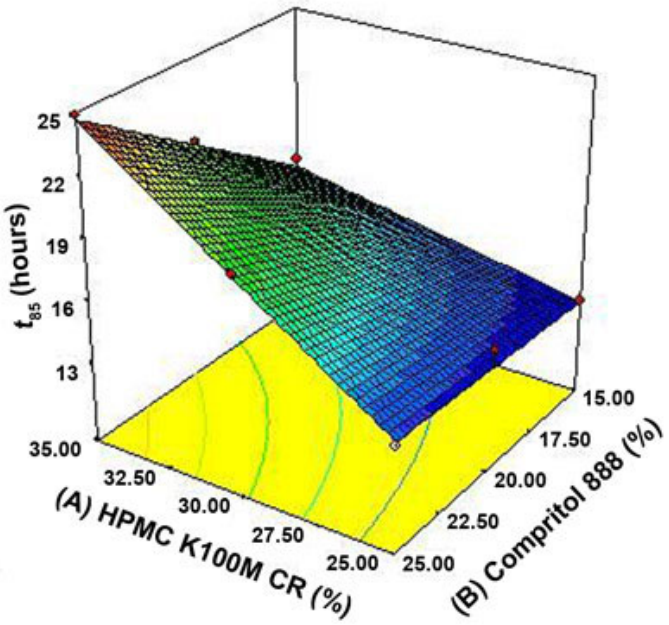

Figure 3. Response surface plot for t_{85}. HPMC indicates hydroxypropylmethylcellulose.

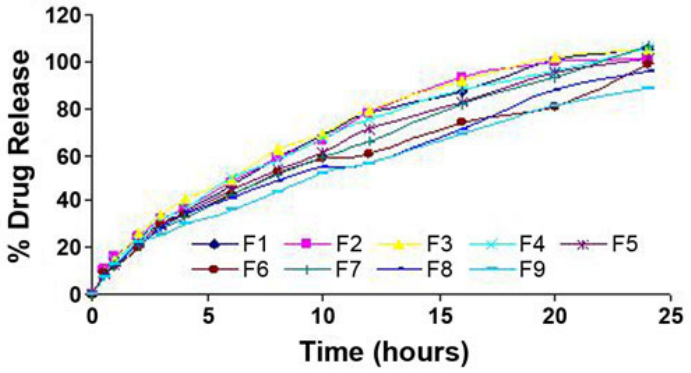

Figure 4. Release profile of diltiazem hydrochloride from 3^2 factorial designs.

K100M CR and Compritol 888 ATO (X_2) favors the preparation of controlled release tablets of DTZ in terms of desired release profile. An increase in the concentration of Methocel K100M CR (X_1) or Compritol 888 ATO (X_2) decreases the rate of release of DTZ from matrix. Release profile of diltiazem hydrochloride from 3^2 factorial designs are shown in Figure 4.

All the tablets of factorial design batches showed good in vitro buoyancy, having the lag point between 4 and 5 minutes and remaining buoyant for 24 hours. Thus, formulation F9 was selected for further studies as an optimized formulation because it gave the best results in terms of the required floating behavior (lag time 4.4 minutes, duration 24 hours), and drug release was in accordance with the USP specification and matched with marketed formulation.

Kinetic Modeling of Drug Release

Linear regression analysis and model fitting showed that all these formulations followed Korsmeyer and Peppas model, which had higher value of correlation coefficient, r (Table 6). Thus, the release of DTZ was controlled by Korsmeyer and Peppas dissolution model.

$$\log \%R = \log K + n\log t \qquad (6)$$

where $\%R$ is the percentage drug release; K is a release rate constant; n is the diffusional release exponent that could be used to characterize the different release mechanism as, n = 0.5 (Fickian diffusion), $0.5 < n < 1$ (anomalous transport), $n = 1$ (case II transport; ie, zero-order release), and $n > 1$ (super case II transport).

In this formulation, Methocel K100M CR (X_1) retards the release by diffusion mechanism, and Compritol 888 ATO (X_2) decreases the hydration of matrix and retards the release by erosion mechanism owing to its hydrophobic property. Together, these polymers retard the release of drug using different mechanisms.

This model is widely used when the release mechanism is not well known or when more than one type of release phenomenon could be involved.

Comparison of Optimized Formulation With Dilacor XR 240 mg Marketed Tablet

The dissolution profile of the formulation F9 and commercial product Dilacor XR 240 mg shows the similarity factor $f2 = 64.1 \pm 2$. It is obvious that the designed matrix

Table 6. Diffusion Kinetics and Model Fitting Data of Floating Controlled Release Tablets of 3^2 Factorial Design

Formulation	Models	*r*	*n*	*K*
F4	Zero order	0.936	—	—
	First order	—	—	—
	Matrix	0.989	—	—
	Korsmeyer and Peppas	0.999	0.646	14.835
	Hixon-Crowell	0.900	—	—
F5	Zero order	0.949	—	—
	First order	—	—	—
	Matrix	0.986	—	—
	Korsmeyer and Peppas	0.999	0.656	13.678
	Hixon-Crowell	0.896	—	—
F6	Zero order	0.915	—	—
	First order	0.872	—	—
	Matrix	0.987	—	—
	Korsmeyer and Peppas	0.993	0.620	13.580
	Hixon-Crowell	0.954	—	—
F7	Zero order	0.955	—	—
	First order	—	—	—
	Matrix	0.984	—	—
	Korsmeyer and Peppas	0.999	0.670	12.691
	Hixon-Crowell	0.887	—	—
F8	Zero order	0.908	—	—
	First order	0.919	—	—
	Matrix	0.987	—	—
	Korsmeyer and Peppas	0.994	0.612	13.273
	Hixon-Crowell	0.961	—	—
F9	Zero order	0.916	—	—
	First order	0.966	—	—
	Matrix	0.984	—	—
	Korsmeyer and Peppas	0.998	0.591	12.681
	Hixon-Crowell	0.950	—	—

system is capable of releasing its content by diffusion mechanism in a similar manner to that of commercially available formulation.

Effect of Tablet Hardness on the Release Profile

Results of the in vitro dissolution studies of formulation H7 with hardness 2, 4, and 8 kg/cm^2 were found to be 9.1, 9.7, and 9.8 hours at t_{50}, respectively, and 21.1, 23.3, and 23.8 hours at t_{85}, respectively.

These findings can be attributed to the fact that variations in the release pattern as a result of differences in tablet hardness occurred during the initial period of dissolution; later on release time could possibly have been diminished by the high affinity of the polymer (Methocel K100M CR) to the solution. Statistical analysis revealed no significant difference in the release rate constants ($P > .5$). Therefore, such an effect is expected to be prominent during the initial phase of dissolution curve. However, results showed that tablet hardness had no (or little) effect on the release profile but was found to be a determining factor with regards to buoyancy of the tablets. A difference in tablet hardness resulted in differences in density and porosity, which are supposed to result in different release pattern of the drug by affecting the rate of penetration of the dissolution fluid at the surface of the tablet and formation of the gel barrier. Thus, tablets with low hardness and less floating lag time showed faster drug release compared with those having higher hardness.

Scanning Electron Microscopy

The SEM images of the tablet were taken before and after dissolution. Figure 5 showed intact surface without any perforations, channels, or troughs. After dissolution, the solvent front enters the matrix and moves slowly toward the center of the tablet. The drug diffuses out of the matrix after it comes in contact with dissolution medium. The images of the tablet showed a network in the swollen polymer through which the drug diffused to the surrounding medium. Thus, it was concluded that the drug was released from matrix by diffusion mechanism.

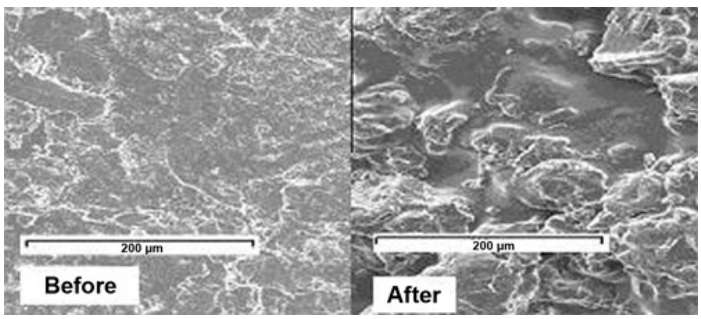

Figure 5. Scanning electron microscopy images of tablet surfaces before and after dissolution. Original magnification ×199.

CONCLUSION

The effervescent-based floating drug delivery is a promising approach to achieve in vitro buoyancy by using gel-forming polymer Methocel K100M CR and gas-generating agent sodium bicarbonate. Combination of Methocel K100M CR and Compritol 888 ATO has resulted in minimal variation in drug release. A systematic study using a 3^2 full-factorial design revealed that by selecting a suitable composition of Methocel K100M CR and Compritol 888 ATO, the desired dissolution profile could be achieved. The optimized formulation gives the best result in terms of the required lag time (4.4 minutes) and floating duration of 24 hours, and drug release was in accordance with the USP dissolution criteria for extended release capsule for DTZ and matched with marketed formulation.

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REFERENCES

1. Santus G, Lazzarini G, Bottoni G, et al. An in vitro-in vivo investigation of oral bioadhesive controlled release furosemide formulations. *Eur J Pharm Biopharm.* 1997;44:39–52.

2. Deshpande AA, Rhodes CT, Shah NH, Malick AW. Controlled-release drug delivery systems for prolonged gastric residence: an overview. *Drug Dev Ind Pharm.* 1996;22:531–539.

3. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled-release system for gastric retention. *Pharm Res.* 1997;14:815–819.

4. Menon A, Ritschel WA, Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. *J Pharm Sci.* 1994;83:239–245.

5. Whitehead L, Fell JT, Collett JH, Sharma HL, Smith AM. Floating dosage forms: an in vivo study demonstrating prolonged gastric retention. *J Control Release.* 1998;55:3–12.

6. Chawla G, Bansal A. A means to address regional variability in intestinal drug absorption. *Pharm Technol.* 2003;27:50–68.

7. Buckley MT, Grant SM, Goa KL, McTavish D, Sorkin EM. Diltiazem. A reappraisal of its pharmacological properties and therapeutic use. *Drugs.* 1990;39:757–806.

8. Pichard L, Gillet G, Fabre I, et al. Identification of the rabbit and human cytochromes P-450IIIA as the major enzymes involved in the N-demethylation of diltiazem. *Drug Metab Dispos.* 1990;18:711–719.

9. Hermann P, Rodger SD, Remones G, Thenot JP, London DR, Morselli PL. Pharmacokinetics of diltiazem after intravenous and oral administration. *Eur J Clin Pharmacol.* 1983;24:349–352.

10. Smith MS, Verghese CP, Shand DG, Pritchett ELC. Pharmacokinetic and pharmacodynamic effects of diltiazem. *Am J Cardiol.* 1983;51: 1369–1374.

11. Iannuccelli V, Coppi G, Bernabei MT, Cameroni R. Air compartment multiple-unit system for prolonged gastric residence. Part I. Formulation study. *Int J Pharm.* 1998;174:47–54.

12. Brijesh SD, Avani FA, Madhabhai MP. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and in vitro evaluation. *AAPS PharmSciTech.* 2004;5:Article 34.

13. Hariharan M, Wowchuk C, Nkansah P, Gupta VK. Effect of formulation composition on the properties of controlled release tablets prepared by roller compaction. *Drug Dev Ind Pharm.* 2004;30:565–572.

14. Shimpi S, Chauhan B, Mahadik KR, Paradkar A. Preparation and evaluation of diltiazem hydrochloride-gelucire 43/01 floating granules prepared by melt granulation. *AAPS PharmSciTech.* 2004;5:Article 43.

15. Rosa M, Zia H, Rhodes T. Dosing and testing in-vitro of a bioadhesive and floating drug delivery system for oral application. *Int J Pharm.* 1994;105:65–70.

16. Ketkar AR, Patil VB, Paradkar AR. Computer Aided Exploratory Data Analysis Model Fitting for Dissolution Kinetics. 4th International Symposium on Advances in Technology and Business Potential of New Drug Delivery System; February 22-23, 2002; Mumbai, India.

17. Korsmeyer R, Gurny R, Peppas N. Mechanisms of solute release from porous hydrophilic polymers. *Int J Pharm.* 1983;15:25–35.

18. Wagner JG. Interpretation of percent dissolved-time plots derived from in vitro testing of conventional tablets and capsules. *J Pharm Sci.* 1969;58:1253–1257.

19. Gibaldi M, Feldman S. Establishment of sink conditions in dissolution rate determinations: theoretical considerations and application to nondisintegrating dosage forms. *J Pharm Sci.* 1967; 56:1238–1242.

20. Higuchi T. Rate of release of medicaments from ointment bases containing drugs in suspension. *J Pharm Sci.* 1961;50:874–875.

21. Higuchi T. Mechanism of sustained-action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J Pharm Sci.* 1963;52:1145–1149.

22. Cobby J, Mayersohn M, Walker GC. Influence of shape factors on kinetics of drug release from matrix tablets. II. Experimental. *J Pharm Sci.* 1974;63:732–737.

23. Hixson AW, Crowell JH. Dependence of reaction velocity upon surface and agitation. *Ind Eng Chem.* 1931;23:923–931.

24. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. *Pharm Acta Helv.* 1985;60:110–111.

25. Harland RS, Gazzaniga A, Sangalli ME, Colombo P, Peppas NA. Drug/polymer matrix swelling and dissolution. *Pharm Res.* 1988; 5:488–494.

26. Langenbucher F. Linearization of dissolution rate curves by the Weibull distribution. *J Pharm Pharmacol.* 1972;24:979–981.

27. Goldsmith JA, Randall N, Ross SD. On methods of expressing dissolution rate data. *J Pharm Pharmacol.* 1978;30:347–349.

28. Romero P, Costa JB, Chulia D. Statistical optimization of a controlled release formulation obtained by a double compression process: application of a Hadamard matrix and a factorial design. In: Wells JI, Rubinstein MH, Horwood E, eds. *Pharmaceutical Technology: Controlled Drug Release.* vol. 2. New York, NY: Ellis Harwood; 1991:44–58.

29. Vudathala GK, Rogers JA. Dissolution of fludrocortisone from phospholipid coprecipitates. *J Pharm Sci.* 1992;81:282–286.

30. Hyunjo K, Reza F. A ternary polymeric matrix system for controlled drug delivery of highly soluble drug with high drug loading: diltiazem hydrochloride. *J Kor Pharm Sci.* 2001;31:19–25.

31. Katz B, Rosenberg A, William H. Controlled release drug delivery systems in cardiovascular medicine. *Am Heart J.* 1995;129:359–368.

32. FDA/CDER. Guidance for Industry SUPAC-MR. Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation. Food and Drug Administration Web site. Available at: http://www.fda.gov/cder/guidance/index.htm. Accessed: August 2, 2007.

33. Nur AO, Zhang JS. Captopril floating and/or bioadhesive tablets: design and release kinetics. *Drug Dev Ind Pharm.* 2000; 26:965–969.

34. Basak SC, Nageswara RK, Manavalan RR, Rama RP. Development and in vitro evaluation of an oral floating matrix tablet formulation of ciprofloxacin. *Indian J Pharm Sci.* 2004;66:313–316.