Gastroretentive Drug Delivery System of Carbamazepine: Formulation Optimization Using Simplex Lattice Design: A Technical Note

Submitted: December 15, 2005; Accepted: July 29, 2006; Published: February 9, 2007

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KEYWORDS: Gastroretentive, carbamazepine, simplex lattice design, melt-granulation, floating.

INTRODUCTION

The high cost involved in the development of a new drug molecule has diverted the pharmaceutical companies to investigate various strategies in the development of new drug delivery systems.[1] Drug release from the delivery devices can be sustained up to 24 hours for many drugs using current release technologies. However, the real issue in the development of oral controlled release dosage forms is to prolong the residence time of the dosage form in the stomach or upper gastrointestinal (GI) tract until the drug is completely released.[2] Rapid GI transit could result in incomplete drug release from the drug delivery device in the absorption zone leading to diminished efficacy of the administered dose.[3]

Several approaches are currently used to retain the dosage form in the stomach. These include bioadhesive systems,[4] swelling and expanding systems,[5,6] floating systems,[7,8] and other delayed gastric emptying devices.[9,10] 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.

Carbamazepine (CBZ) is used for anticonvulsant and antineuralgic effects. The popularity of this drug is related to several beneficial properties, including proven efficacy in controlling different types of seizures. CBZ is poorly soluble in water with erratic oral absorption and bioavailability less than 70%. Preparing the drug in a floating dosage form can control the extent of bioavailability for such a poorly water-soluble drug.

The major objective of the present investigation was to develop a gastroretentive drug delivery system containing CBZ using simplex lattice design as an optimization technique.

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MATERIALS AND METHODS

Materials

Carbamazepine United States Pharmacopeia (USP) was a kind gift from Hindustan Chemicals Ltd, Chennai, India. Beeswax was purchased from Ases Chemical Works, Jodhpur, India. Hydroxypropyl methylcellulose (HPMC K4 M), ethyl cellulose (EC), and sodium bicarbonate were purchased from Laser Chemicals, Ahmedabad, India. Magnesium stearate and talc were purchased from Apex Chemicals, Ahmedabad, India. All other ingredients used were of analytical grade and were used as received.

Methods

Preparation of Carbamazepine Floating Tablets

Beeswax was melted in a large Petri dish, and the required quantity of CBZ was added to the molten mass. Previously prepared geometric mixture of HPMC K4 M and/or EC and sodium bicarbonate was added to the molten CBZ-beeswax mixture and stirred well to mix. The mass was removed from the hot plate and subjected to scraping until it attained room temperature. The coherent mass was passed through a 60-mesh sieve, and the resulting granules were resifted on a 100-mesh sieve to remove the fines. The granules (50 g) from both the 60- and 100-mesh sieves were collected and mixed with 2% wt/wt talc and 1% wt/wt magnesium stearate. This lubricated blend was compressed into tablets using 12-mm flat-face round tooling on a Rimek-I rotary tablet machine (Karnavati Engineering Pvt Ltd, Ahmedabad, India). Compression force was adjusted to obtain tablets with hardness in range of 5 to 6 kg/cm^2. Tablets weighed 515 ± 4 mg, and were round flat-face with an average diameter of 12 ± 0.1 mm and thickness of 4.6 ± 0.2 mm. Formulations of the preliminary trial batches (P1 to P7) and the simplex lattice design batches (S1 to S7) are shown in Tables 1 and 2, respectively.

In Vitro Buoyancy Studies

The in vitro buoyancy was determined by floating lag time as per the method described by Rosa et al.[11] The tablets were placed in a 100-mL glass beaker containing simulated gastric fluid (SGF), pH 1.2, as per USP. The time required for the tablet to rise to the surface and float was determined as floating lag time.

Table 1. Tablet Formulation and Evaluation Results of Preliminary Trials*

Formulation Ingredients	P1	P2	P3	P4	P5	P6	P7
Beeswax (%)	10	10	10	10	10	15	20
HPMC K4 M (%)	45	40	35	30	20	30	25
Sodium bicarbonate (%)	5	5	5	5	5	5	5
Ethyl cellulose (%)	0	5	10	15	25	10	10
Floating lag time (seconds)	300	280	265	261	257	250	325
Floating time without rupture of tablets (minutes)	<180	<180	<180	<180	<180	>720	>720

*HPMC indicates hydroxypropyl methylcellulose. All batches contained 40% wt/wt carbamazepine, 2% wt/wt talc, and 1% wt/wt magnesium stearate; the average weight of each tablet was 515 mg.

In Vitro Dissolution Studies

The in vitro dissolution study of CBZ tablets was performed using USP apparatus (model TDT-06T, Electrolab, Mumbai, India) fitted with paddles (75 rpm) at 37°C ± 0.5°C using SGF (pH 1.2; 900 mL) as a dissolution medium. At the predetermined time interval, 10-mL samples were withdrawn, filtered through a 0.45-μm membrane filter, diluted, and assayed at 285 nm using a Shimadzu UV/vis double-beam spectrophotometer (Shimadzu, Kyoto, Japan). Cumulative percentage drug release was calculated using an equation obtained from a calibration curve. The drug release profile is shown in Figure 1. The time required for 50% and 80% drug release was calculated.

Simplex Lattice Design

A simplex lattice design[12] was adopted to optimize the formulation variables. In this design, 3 factors were evaluated by changing their concentrations simultaneously and keeping their total concentration constant. The simplex lattice design for a 3-component system is represented by an equilateral triangle in 2-dimensional space (Figure 2). Seven batches (S1-S7) were prepared: one at each vertex (A, B, C), one at the halfway point between vertices (AB, BC, AC), and one at the center point (ABC). Each vertex represents a formulation containing the maximum amount of 1 component, with the other 2 components at a minimum level. The halfway point between the 2 vertices represents a formulation containing the average of the minimum and maximum amounts of the 2 ingredients represented by 2 vertices. The center point represents a formulation containing one third of each ingredient. The amounts of matrixing agent (HPMC K4 M, X_1), gas-generating agent (sodium bicarbonate, X_2), and floating enhancer (EC, X_3) were selected as independent variables. The floating lag time (F_{lag}) and the time required for 50% (t_{50}) and 80% drug dissolution (t_{80}) were taken as responses.

Kinetic Modeling of Drug Release

The dissolution profile of all the batches was fitted to various models such as zero-order, first-order,[13] Higuchi,[14] Hixon-Crowell,[15] Korsmeyer and Peppas,[16-18] and Weibull models[19-21] to ascertain the kinetic modeling of drug release. The method of Bamba and Puisieux[22] was adopted for deciding the most appropriate model.

Table 2. Formulation and Evaluation of Batches in Simplex Lattice Design*

	Transformed Fractions of Variables†					
Batch Code	X_1	X_2	X_3	F_{lag} ± SD (seconds)	t_{50} ± SD (minutes)	t_{80} ± SD (minutes)
S1	1	0	0	255 ± 3.1	479 ± 2.3	767 ± 4.4
S2	0	1	0	175 ± 1.2	388 ± 1.9	620 ± 1.2
S3	0	0	1	158 ± 0.9	366 ± 3.2	586 ± 2.9
S4	0.5	0.5	0	186 ± 1.4	549 ± 2.7	878 ± 5.4
S5	0	0.5	0.5	167 ± 0.8	411 ± 3.1	657 ± 3.6
S6	0.5	0	0.5	185 ± 1.7	398 ± 1.8	633 ± 2.9
S7	0.33	0.33	0.33	153 ± 0.6	479 ± 2.5	767 ± 5.6
	Actual Values†					
Coded Values†	X_1	X_2	X_3			
0	125	50	0			
1	175	100	50			

*F_{lag} indicates floating lag time; SD, standard deviation; t_{50} and t_{80}, time required for 50% and 80% drug dissolution, respectively; and HPMC, hydroxypropyl methylcellulose. All batches contained 200 mg carbamazepine, 75 mg beeswax, 2% wt/wt talc, and 1% wt/wt magnesium stearate. Average weight of each tablet was 515 mg.

†X_1 is the amount of HPMC K4 M (mg); X_2 is the amount of sodium bicarbonate (mg); X_3 is the amount of ethyl cellulose (mg).

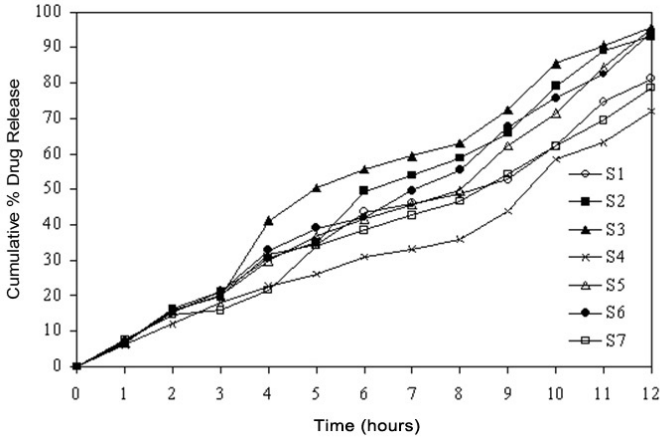

Figure 1. Release rate profile of formulated batches.

Results and Discussion

Preliminary Trials

Beeswax was selected as a hydrophobic meltable material to impart sufficient integrity to the tablets. HPMC K4 M was selected as a matrixing agent, considering its widespread applicability and excellent gelling activity in sustained release formulations. Sodium bicarbonate generates CO_2 gas in the presence of hydrochloric acid present in dissolution medium. The gas generated is trapped and protected within the gel (formed by hydration of HPMC K4 M), thus decreasing the density of the tablet. As the density of the tablet falls below 1 (density of water), the tablet becomes buoyant. EC was used as floating enhancer. It also works as a dissolution retardant, being insoluble in gastric pH. Five batches (P1-P5) were prepared using the same amounts of sodium bicarbonate and beeswax but different amounts of HPMC K4 M and EC. The amount of HPMC K4 M was decreased, while the amount of EC was increased from batch P1 to P5. From the evaluation results (Table 1), it was observed that as the amount of EC was increased from 0% to 25%, the F_{lag} decreased, and this effect was significant on reducing F_{lag} up to 10% of EC. Hence, it was decided to optimize the amount of EC between 0% and 10%. As the amount of HPMC K4 M was increased from 20% to 45%, the F_{lag} increased, indicating that a high amount of HPMC K4 M is undesirable to achieve low F_{lag}. Below 25%, HPMC K4 M might not give sufficient strength to the matrix to prolong drug release up to 12 hours. Hence, it was decided to optimize HPMC K4 M between 25% and 35%. Formulations P1 to P5 were subjected to in vitro dissolution study. All the tablets ruptured within 3 hours with more than 80% drug release. This result might be due to poor strength of tablets or to insufficient binding provided by beeswax, which failed to keep the matrix intact. Formulations P6 and P7 were prepared using 15% and 20% of beeswax, respectively, and were found to remain intact for more than 12 hours under stirring at 75 rpm in the dissolution studies. Formulation P7 exhibited floating lag time of 325 seconds. This result might be due to poor penetration of SGF in a tablet core owing to a high amount of beeswax. Hence, it was decided to keep the beeswax at 15%. It is quite well known that a higher percentage of sodium bicarbonate decreases the F_{lag}, so it was decided to optimize sodium bicarbonate between 10% and 20% to decrease the F_{lag} to less than 3 minutes. In order to optimize the formulation for acceptance criteria (ie, F_{lag}, less than 3 minutes; t_{50}, between 300 and 420 minutes; and t_{80}, between 540 and 600 minutes), a simplex lattice design was used in the present investigation.

Simplex Lattice Design

The amounts of matrixing agent (HPMC K4 M, X_1), gas-generating agent (sodium bicarbonate, X_2), and floating enhancer (EC, X_3) were selected as independent variables in a simplex lattice design. The floating lag time (F_{lag}) and times required for 50% (t_{50}) and 80% drug dissolution (t_{80}) were taken as responses. A statistical model incorporating 7 interactive terms was used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{23}X_2X_3 + b_{13}X_1X_3 + b_{123}X_1X_2X_3 \quad (1)$$

where Y is the dependent variable, b_0 is the arithmetic mean response of the 7 runs, and b_i is the estimated coefficient for the factor X_i. The main effects (X_1, X_2, and X_3) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms (X_1X_2, X_2X_3, X_1X_3, and $X_1X_2X_3$) show how the response changes when 2 or more factors are simultaneously changed. The statistical analysis of the simplex lattice design batches was performed by multiple linear regression analysis using Microsoft Excel. The values for F_{lag}, t_{50}, and t_{80} for all 7 batches (S1-S7) showed a wide variation (ie, 153 to 255 seconds, 366 to 549 minutes, and 586 to 878 minutes, respectively) (Table 2). The data clearly indicate that the values of F_{lag}, t_{50}, and t_{80} are strongly dependent on the selected independent variables.

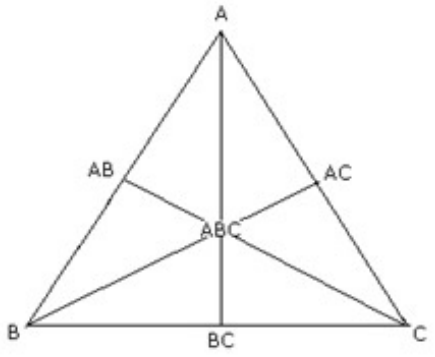

Figure 2. Equilateral triangle representing simplex lattice design for 3 components (A, B, and C).

The fitted equations relating the responses F_{lag}, t_{50}, and t_{80} to the transformed factor are shown in Equation 2, Equation 3, and Equation 4, respectively.

$$F_{lag} = -1928.7 + 2183.7X_1 + 2103.78X_2 + 2086.28X_3 - 118.17X_1X_2 - 85.67X_1X_3 \quad (2)$$

$$t_{50} = 2093.17 - 1624.93X_1 - 1691.9X_2 - 1724.67X_3 + 455.81X_1X_2 \quad (3)$$

$$t_{80} = 3380.34 - 2631.38X_1 - 2738.65X_2 - 2791.4X_3 + 729.58X_1X_2 \quad (4)$$

The high values of correlation coefficients for F_{lag} (R^2 = 0.999), t_{50} (R^2 = 0.945), and t_{80} (R^2 = 0.940) indicate a good fit (ie, good agreement between the dependent and independent variables). The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (ie, positive or negative). The equation for F_{lag} suggests that the factor X_1 has more significant effect on floating lag time, followed by factors X_2 and X_3. Therefore, a high level of factor X_1 should not be selected for lower floating lag time. From Equations 3 and 4, it can be concluded that factor X_1 has a more important role in prolonging both the t_{50} and t_{80}. The magnitude of coefficients indicates that the factor X_2 has a more favorable effect on both the dependent variables than factor X_3. The high value of X_1X_2 coefficient also suggests that the interaction between X_1 and X_2 has a significant effect on t_{50} and t_{80}. From the results of multiple linear regression analysis, it can be concluded that the drug release pattern may be changed by appropriate selection of the X_1, X_2, and X_3 levels.

The promising formulation was selected on the basis of the acceptance criteria for F_{lag}, t_{50}, and t_{80} as mentioned earlier. Formulations S2, S3, S5, and S7 passed the criteria for F_{lag}. Formulations S2, S3, S5, and S6 passed the criteria for t_{50}. The criterion for t_{80} was passed only by Formulation S3. Hence, Formulation S3 was selected as a promising formulation from the simplex lattice design batches.

In Vitro Buoyancy of Simplex Lattice Design Batches

All the simplex lattice design batches showed good in vitro buoyancy with maximum floating lag time of 255 seconds. All the tablet formulations remained buoyant for more than 12 hours in SGF, pH 1.2. The in vitro buoyancy study was also conducted at an elevated pH condition (~ 4.5). The floating tendency of all the formulations remained unaltered at higher pH.

Kinetics of Drug Release

The dissolution data of batches S1 to S7 were fitted to zero-order, first-order, Higuchi, Hixon-Crowell, Korsmeyer and Peppas, and Weibull models. The method of Bamba and Puisieux[22] was adopted for deciding the most appropriate model. The results of F statistics were used to select the most appropriate model. The release profile of promising batch, S3, fitted best to zero-order model (F = 23.64). This superiority is statistically insignificant with the Korsmeyer and Peppas model (F = 41.81) as well as the Weibull model (F = 26.54) as shown by the goodness-of-fit test (F-ratio test). But priority should be given to the model with the lowest F value. Thus, it may be concluded that drug release from gastroretentive CBZ tablets is best explained by the zero-order model. The other simplex lattice design batches also followed the zero-order model with either significant or insignificant differences with the other models.

The factorial batches were subjected to short-term stability studies at 40°C and 75% relative humidity (RH) for 3 months. Samples withdrawn after 3 months showed no significant change in appearance of the tablets, floating lag time, and in vitro drug release.

Summary and Conclusion

An attempt was made to develop a gastroretentive drug delivery system of carbamazepine using HPMC, sodium bicarbonate, and EC as matrixing agent, gas-generating agent, and floating enhancer, respectively. A simplex lattice design was applied to investigate the combined effect of 3 formulation variables (ie, amount of HPMC (X_1), EC (X_2), and sodium bicarbonate (X_3). Results of multiple regression analysis indicated that low levels of X_1 and X_2 and a high level of X_3 should be used to manufacture the tablet formulation with desired in vitro floating time and dissolution. Formulation S3 was selected as a promising formulation and was found stable at 40°C temperature and 75% RH for 3 months.

Acknowledgments

The authors thank Hindustan Chemicals Ltd (Chennai, India) for providing the gift sample of carbamazepine USP. Authors also thank the Shri M. L. Gandhi Higher Education Society (Modasa, India) for extending required laboratory facilities for the present work.

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