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Original article

Floating matrix tablets of domperidone: formulation and optimization using simplex lattice design

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Abstract:

One method of achieving sustained drug release is by the use of hydrophilic polymeric excipients directly compressed with active ingredients into tablets. Hydrophilic polymers swell in the presence of water to form hydrogel structures from which drugs are released by slow diffusion. The release rate modulation is obtained by the use of different types of polymer alone or in combinations. Optimization of the release rate of domperidone from mixtures containing two hydrophilic polymers, poly (ethylene oxide) WSR 303 (PEO) and hydroxypropylmethylcellulose (HPMC) and sodium bicarbonate was made by simplex lattice design. Experimental results were examined using a simplex lattice quadratic model. Tablets were evaluated for *in vitro* floating ability and drug release study. It was observed that as the PEO increased release rate constant decreased. Mechanism of drug release was anomalous type and dependent upon proportion of HPMC and PEO. It was observed that independent factors had significant contribution on all dependent variables studied.

Keywords: Domperidone; Floating; Simplex lattice design; Release kinetics; Tablets

Introduction

Rapid gastrointestinal transit could result in incomplete drug release from the device above the absorption zone leading to diminished efficacy of the administered dose [1]. Therefore different approaches have been proposed to retain the dosage form in the stomach. These include bioadhesive systems, [2] swelling and expanding systems, [3, 4] and floating systems [5, 6]. Large single-unit dosage forms undergo significant swelling after oral administration, and the swollen matrix inhibits the gastric emptying even at an uncontractile state of the pyloric sphincter. Park and Park reported medicated polymeric sheets and swelling of balloon hydrogels [7]. But the swelling and expanding systems may show hazard of permanent retention. Bioadhesive systems may cause problems such as irritation of the mucous layer owing to high localized concentration of the drug [8].

In recent years poly (ethylene oxide) (PEO) has attracted much attention as a polymeric excipient that can be used in formulations for different purposes. For instance, formulations with PEO have been extruded to make different products such as swellable and erodible implants [9], scaffolds for tissue engineering [10], or, in the production of micelles with amphiphilic drugs, when solid dispersions incorporating these drugs are placed in aqueous environments [11], However, PEOs are mostly used to produce controlled release solid dosage forms such as matrices, reservoirs, or coated cores [12-14]. Due to their chemical structure, PEOs are among various hydrophilic polymers that, in the presence of water, control the release of the active moiety either by swelling (large molecular weight, > 2 MDa) or by eroding and swelling (small molecular weight, < 0.9 MDa), forming a hydrogel. In both cases, the water triggers the process starting the erosion and/or the swelling processes. All this attention to PEOs is due to a consequence of their physical and chemical stability, compressibility, high swelling ability, and good solubility in water. Thus, PEOs have been proposed as alternatives to cellulose or other ethylene glycol derivatives in the production of tablets or granules.

Domperidone is a synthetic benzimidazole compound that acts as a dopamine D2 receptor antagonist. Its localization outside the blood-brain barrier and antiemetic properties has made it a useful adjunct in therapy for Parkinson's disease. There has been renewed interest in antidopaminergic prokinetic agents since the withdrawal of cisapride, a 5-HT4 agonist, from the market. Domperidone is also used as a prokinetic agent for treatment of upper gastrointestinal motility disorders [15, 16]. It continues to be an attractive alternative to metoclopramide because it has fewer neurological side effects. Patients receiving domperidone or other prokinetic agents for diabetic gastropathy or gastroparesis should also manage diet, lifestyle, and other medications to optimize gastric motility [17]. It is rapidly absorbed from the stomach and the upper part of the gastrointestinal tract [18], after oral administration, and few side effects have been reported [15, 16]. It is a weak base with good solubility in acidic pH but in alkaline pH solubility is significantly reduced. Oral controlled release dosage forms containing drug, which is a weak base, when exposed to environments of increasing pH and poorly soluble freebase may be precipitated within the formulation in the intestinal fluid. Precipitated drug is no longer capable of being released from formulation [19, 20]. The short biological half-life of drug (7 h) also favors development of a sustained release formulation. The objective of the present investigation was to develop a gastroretentive drug delivery system containing domperidone using simplex lattice design as an optimization technique.

Materials and Methods

Materials

Domperidone was a kind gift from Maan Pharmaceutical Ltd, Mehsana, India. Poly(ethylene oxide) WSR 303 (Polyox® WSR 303, mw = 7 x 10^6) was received as a gift sample from Dow Chemical company, New Jersey (USA). Hydroxypropyl methylcellulose (HPMC K15 M), 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.

Preparation of domperidone floating tablets

Domperidone, the required quantity of polymers (Polyox® WSR 303 and HPMC K15M), sodium bicarbonate and starch were mixed in mortar by spatula for 15 min. The powder blend was then lubricated with talc and magnesium stearate and compressed in tablets using 8 mm flat-face round tooling on rotary tablet press (Rimek, India, Ahmedabad). Compression force was adjusted to obtain tablets with hardness in range of 4-5 kg/cm^2. The tablets weighed 145 ± 2 mg, had a round flat face with average diameter of 8 ± 0.1 mm and a thickness of 2.5 ± 0.2 mm.

In vitro buoyancy studies

The *in vitro* buoyancy was determined by floating lag time as per the method described by Rosa *et al.* [21]. The tablets were placed in a 100-mL glass beaker containing simulated 0.1N hydrochloric acid, as per USP. The time required for the tablet to rise to the surface and float was determined as floating lag time.

In vitro dissolution studies

The *in vitro* dissolution study of domperidone tablets was performed according to British Pharmacopoeia [22] using USP apparatus II (model TDT-06T, Electrolab, Mumbai, India) fitted with paddles (50 rpm) at 37 °C ± 0.5 °C and using hydrochloric acid (pH 1.2, 900 ml) as a dissolution medium [22]. At the predetermined time interval, 5-ml samples were withdrawn, filtered through a 0.45 µm membrane filter, diluted, and assayed at 284 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 experiments were conducted in triplicate.

Simplex lattice design

A simplex lattice design [23] was adopted to optimize the formulation variables. In this design three factors were evaluated by changing their concentrations simultaneously and keeping their total concentration constant. The simplex lattice design for a 3-component system (A, B and C) is represented by an equilateral triangle in 2-dimensional space (Figure 1). The amounts of matrixing agent (poly (ethylene oxide) WSR 303, X_1), gelling agent, (HPMC K15M, X_2), and gas-generating agent (sodium bicarbonate, X_3) were selected as independent variables. Floating lag time (FLT), time required for 50% and 80% drug release ($t_{50\%}$ and $t_{80\%}$ respectively), diffusion exponent (n), and release rate constant (k) were selected as dependent variables.

Statistical analysis

The statistical analysis of the simplex lattice design batches was performed by multiple regression analysis using Microsoft Excel. To evaluate contribution of each factor with different levels on response, two way analysis of variance (ANOVA) ($P < 0.05$) was performed using Design Expert 6.0.11 (State Ease, Inc., Minneapolis) demo version software. To graphically demonstrate the influence

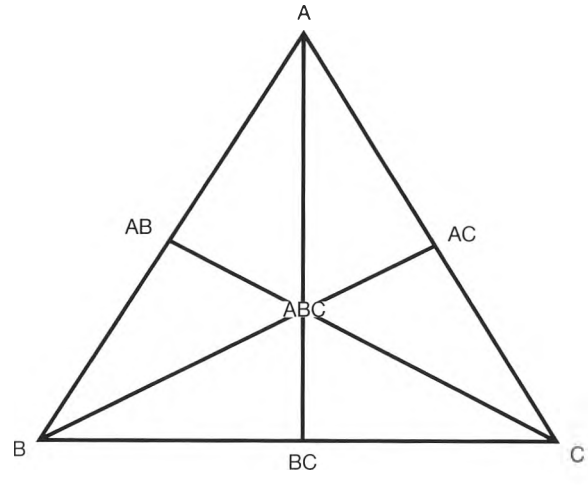

Figure 1 Equilateral triangle representing simplex lattice design for 3 components (A, B, and C).

of each factor on response, the response surface plots were generated using Design Expert 6.0.11 (State Ease, Inc., Minneapolis) demo version software.

Results and Discussion

Poly (ethylene oxide) WSR 303 was selected as a matrixing agent to impart sufficient integrity to the tablets. HPMC K15M was selected as a gelling 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), thus decreasing the density of the tablet. As the density of the tablet falls below 1 (density of water), the tablet becomes buoyant. It was observed that as the amount of poly (ethylene oxide) WSR 303 was increased, cumulative % drug release was decreased (Table 1, Figure 2). Hence, it was decided to optimize the amount of poly (ethylene oxide) WSR 303, drug and poly(ethylene oxide) WSR 303 ratio. As the amount of HPMC K15M was increased from 1:1 to 1:3 drug to polymer ratio, the floating lag time increased, indicating that a high amount of HPMC is undesirable to achieve low floating lag time. Below 1:1 drug to polymer ratio, HPMC K15M might not give sufficient strength to the matrix to prolong drug release up to 24 h. Hence, it was decided to optimize HPMC K15M at 1:1 drug to HPMC K15M ratio. Twenty mg of sodium bicarbonate was optimized as CO_2 producing agent from preliminary studies.

Simplex Lattice Design

The amounts of matrixing agent (Polyox WSR 303), gelling agent (HPMC K15M), and gas generating agent (sodium bicarbonate) were selected as independent variables in a simplex lattice design. A statistical model incorporating 7 interactive terms was used to evaluate the responses.

Table 1 Formulation and evaluation of domperidone tablets (batches 1-7) in simplex lattice design

Batch code	Transformed fraction of variables			Dependent variables				
	X_1	X_2	X_3	FLT ± SD (sec)	$t_{50\%}$ ± SD (hr)	$t_{80\%}$ ± SD (hr)	n ± SD	k ± SD
S_1	1	0	0	20 ± 2	9.583 ± 1.900	12.344 ± 2.200	0.733 ± 0.045	6.445 ± 0.300
S_2	0	1	0	55 ± 3	12.684 ± 2.300	17.435 ± 2.600	0.591 ± 0.007	9.853 ± 1.200
S_3	0	0	1	10 ± 4	11.702 ± 0.800	21.527 ± 0.800	0.620 ± 0.004	9.929 ± 0.400
S_4	0.50	0.50	0	35 ± 5	17.077 ± 1.700	26.350 ± 1.700	0.513 ± 0.032	14.435 ± 2.100
S_5	0	0.50	0.50	98 ± 3	18.110 ± 1.400	28.490 ± 1.100	0.489 ± 0.002	15.402 ± 0.300
S_6	0.50	0	0.50	25 ± 2	11.194 ± 0.500	23.811 ± 0.700	0.635 ± 0.002	10.386 ± 0.700
S_7	0.33	0.33	0.33	39 ± 3	15.277 ± 1.200	23.071 ± 2.000	0.575 ± 0.002	12.319 ± 1.800

	Actual value		
Coded Value	X_1	X_2	X_3
1	60	30	20
0	50	20	10

*Mean ± SD, n=3

FLT indicates floating lag time; SD, standard deviation; $t_{50\%}$ and $t_{80\%}$, time required for 50% and 80% drug dissolution, respectively; n, diffusion coefficient; k, release rate constant; HPMC, hydroxypropyl methylcellulose.

All batches contained 30 mg domperidone, 20 mg maize starch, 2% wt/wt talc, and 1% wt/wt magnesium stearate. Average weight of each tablet was 145 mg. X_1 is the amount of poly (ethylene oxide) WSR 303 (mg), X_2 is the amount of HPMC K15 (mg), and X_3 is the amount of sodium bicarbonate (mg).

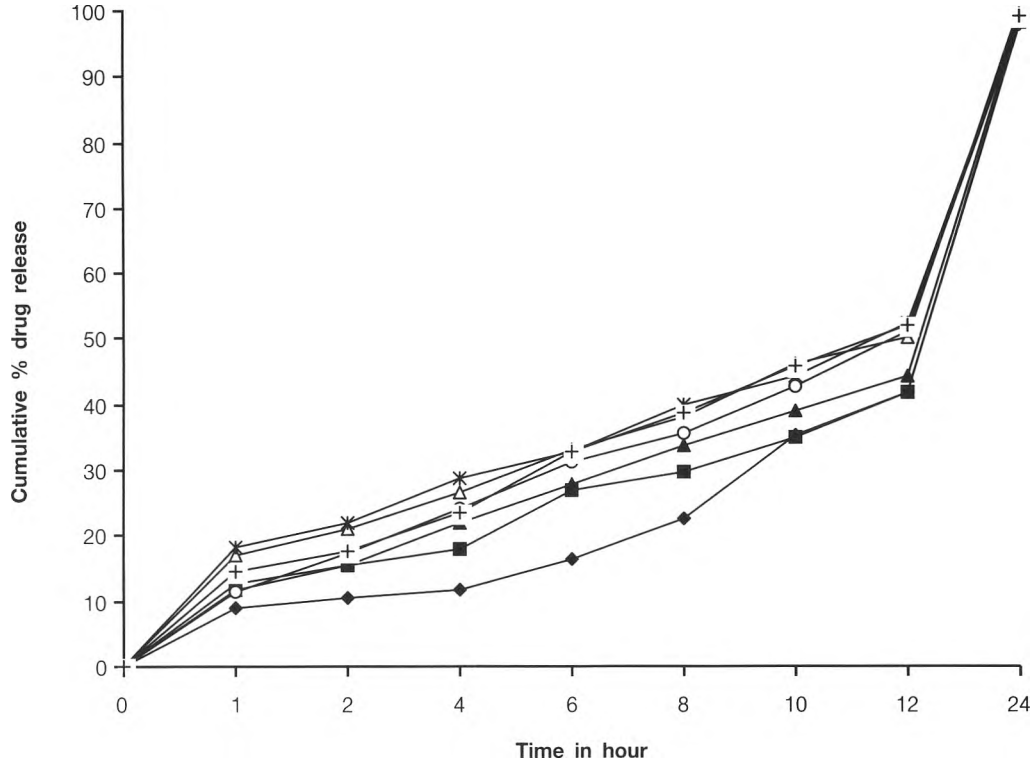

Figure 2 Release profiles of simplex lattice design batches.

Batch S1 Batch S2 Batch S3 Batch S4
Batch S5 Batch S6 Batch S7

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{23}X_2X_3 + b_{13}X_1X_3 + b_{123}X_1X_2X_3$$

where, Y is the dependent variable, b_0 is the arithmetic mean response of the 7 runs, and bi 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 Floating lag time (FLT), time required for 50% and 80% drug release ($t_{50\%}$ and $t_{80\%}$ respectively), release rate constant (k) and diffusion component (n) for all 7 batches (S1-S7) showed a wide variation (Table 2). The data clearly indicate that the values of FLT, $T_{50\%}$, $T_{80\%}$, k and n are strongly dependent on the selected independent variables.

Calculation of immediate release part

The pharmacokinetic parameters domperidone were used to calculate a theoretical drug release profile for a 24-h dosage form. The immediate release part for sustained release domperidone was calculated using equation (1) and was found to be 4.211 mg.

Immediate release part = (Css x Vd)/F (1)

where, *Css* is steady-state plasma concentration (average Cmax), *Vd* is volume of distribution, and *F* is fraction bioavailable. Hence, the formulation should release 4.211 mg (14.04%) of drug in 1 h like conventional tablets and 1.121 mg (3.74%) per h up to 24 h.

The similarity factor, f2, given by Scale Up and Pose Approval Changes (SUPAC) guidelines for modified release dosage form was used as a basis to compare dissolution profiles [24]. Dissolution profiles of all batches of factorial design were compared with theoretical dissolution profile. The results of similarity factor indicated that batches S_2 to S_7 fulfilled the above criteria.

But batch S_7 showed highest f2 among all the batches. Hence the dissolution of batch S_7 was similar to theoretical compared to other batches of simplex lattice design. Similarity between theoretical dissolution profile and dissolution profile of S_7 is shown in Figure 3.

Table 2 Analysis of variance for dependent variables from simplex lattice design

Source	SS	df	MS	F value	Prob
Floating lag time (FLT)					
Model	4	5179.885	1294.971	28.292	0.0344300
Residual	2	91.544	45.772		
Total	6	5271.429			
Time required for 50% drug release ($T_{50\%}$)					
Model	3	6.4598999	2.1532999	9.5385260	0.0481850
Residual	3	0.6772429	0.2257477		
Total	6	7.1371429			
Time required for 80% drug release ($T_{80\%}$)					
Model	1	16.8147360	16.8147360	6.8883130	0.0468390
Residual	5	12.2052640	2.4410528		
Total	6	29.0200000			
Diffusion exponent (n)					
Model	3	0.0335908	0.0111969	35.0759000	0.0077690
Residual	3	0.0009577	0.0003192		
Total	6	0.0345485			
Release rate constant (k)					
Model	2	57.0932443	28.5466222	10.7279800	0.0246910
Residual	4	10.6437974	2.6609494		
Total	6	67.7370417			

*df indicates degree of freedom; SS, sum of square; MS, mean of square; F, Fischer's ratio

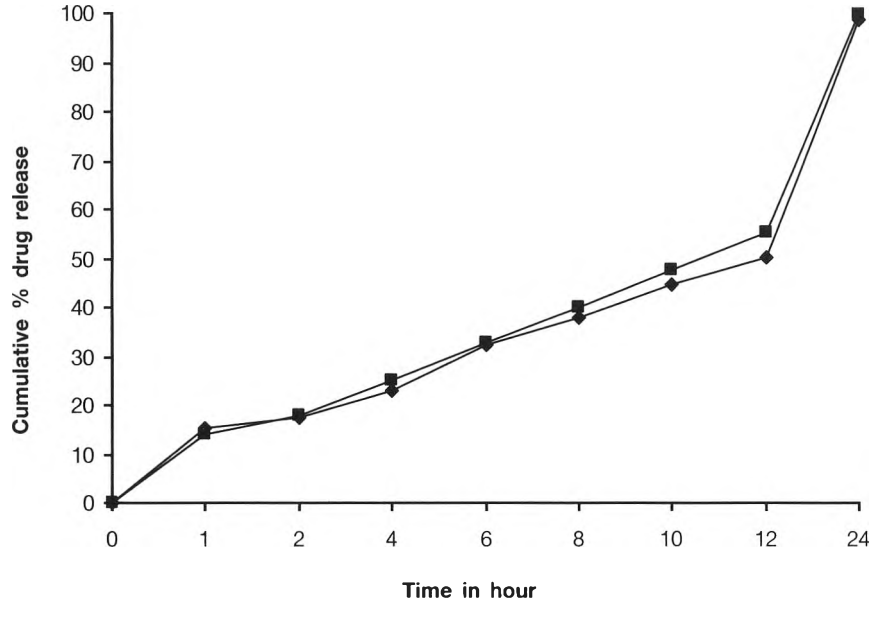

Figure 3 Comparison of *in vitro* dissolution profile of batch S_7 and theoretical dissolution profile (–◆– Batch S_7 –■– Theoretical profile).

The fitted equation relating to the responses floating lag time (FLT), time required for 50% and 80% drug release ($t_{50\%}$ and $t_{80\%}$ respectively), diffusion component (n) and release rate constant (k) to the transformed factors are shown in equations 2 to 6 respectively.

$$FLT = 98.7859-62.4770 *X_2-87.4770 *X_3-62.7759 *X_1X_2-132.7759 *X_2X_3 \quad (2)$$

R-square = 0.98263

$$t_{50\%} = 12.4872-1.2714 *X_3-9.6857 *X_1X_2-5.9428 *X_2X_3 \quad (3)$$

R-square = 0.90511

$$t_{80\%} = 19.1078+17.2948 *X_1X_2 \quad (4)$$

R-square = 0.94189

$$n = 0.6422+0.0676 *X_1-0.6017 *X_1X_2-0.4456 *X_2X_3 \quad (5)$$

R-square = 0.97228

$$k = 9.0676+22.9004 *X_1X_2+24.8700 *X_2X_3 \quad (6)$$

R-square = 0.91808

The high value of correlation coefficient for FLT, $t_{50\%}$, $t_{80\%}$, n and k indicate good fit (i.e., good agreement between the dependent and independent variables). The polynomial equations can be used to draw conclusion after considering the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative).

Tablets of all batches (S_1 to S_7) had floating lag time varied from 10 sec to 98 sec. Polynomial equation (eq.2) for floating lag time suggests that amount of sodium bicarbonate and HPMC K15M has more significant effect on floating lag time. It may be due to interaction between gas generating agent ($NaHCO_3$) and dissolution medium (0.1N HCl, pH 1.2) which reduces FLT. and hydrophilic nature of HPMC produces easy swelling of tablets. Figure 4 shows the 3D surface plot of the amount of PEO WSR 303 (X_1), amount of HPMC K15M (X_2) and amount of sodium bicarbonate (X_3) versus FLT. The plot was drawn using Design Expert 6.0.11 (State Ease, Inc.). The data demonstrated that X_1, X_2 and X_3 affect the floating lag time. It may also be concluded that the low level of X_1 (amount of PEO WSR 303) and the higher level of X_3 (amount of sodium bicarbonate) favor low floating lag time. The high value of X_2X_3 coefficient also suggests that the interaction

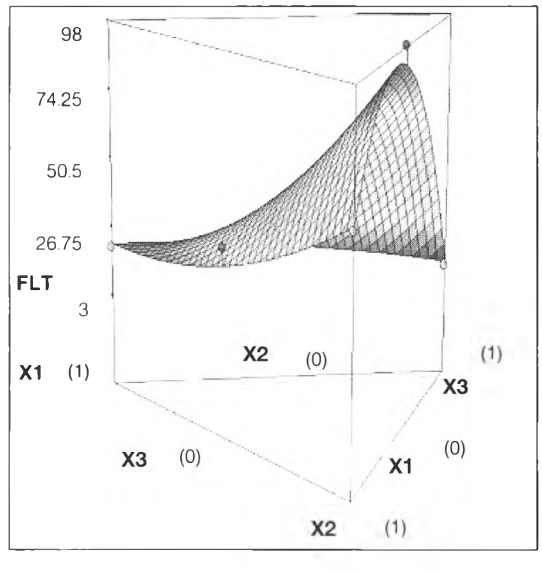

Figure 4 Response surface plot (3D) showing the effect of the amount of amount of PEO, amount of HPMC and amount of sodium bicarbonate on floating lag time (FLT).

between X_2 and X_3 has a significant effect on FLT. It can be concluded that the FLT changed by appropriate selection of the X_2 and X_3 levels.

Time required release to 50% of drug ($t_{50\%}$) and time required release to 80% of drug ($t_{80\%}$) showed wide variation (Table 1). Figures 5 and 6 show the 3D surface plot of the amount of PEO WSR 303 (X_1), amount of HPMC K15M (X_2) and amount of sodium bicarbonate (X_3) versus $t_{50\%}$ and $t_{80\%}$, respectively. The data clearly indicated that the dependent variables ($t_{50\%}$, $t_{80\%}$) are strongly dependent on the independent variables. The fitted equation relating the response $t_{50\%}$ and $t_{80\%}$ to the transformed factors are shown in equations 3 and 4. Data of $t_{50\%}$ and $t_{80\%}$ clearly indicated that as the amount of sodium bicarbonate increased time required to 50% drug release decreased. It may be due to pores formation in tablets by sodium bicarbonate which produces CO_2 from interaction with dissolution medium. The high value of X_1X_2 coefficient also suggests that the interaction between X_1 and X_2 has a significant effect on $t_{80\%}$. It can be concluded that the $t_{80\%}$ changed by appropriate selection of the X_1 and X_2 levels.

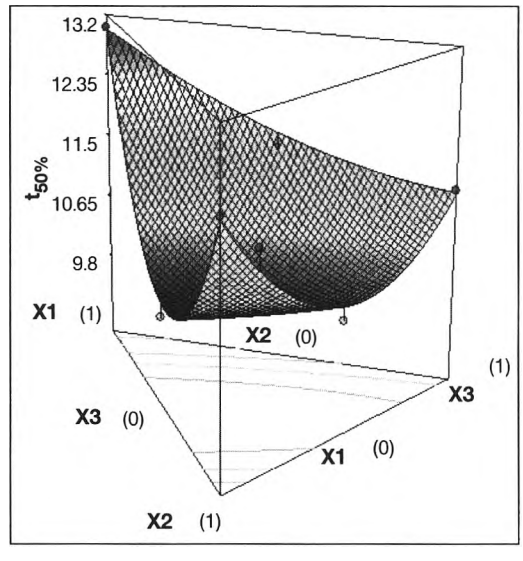

Figure 5 Response surface plot (3D) the effect of the amount of amount of PEO, amount of HPMC and amount of sodium bicarbonate on time required for 50% drug release ($t_{50\%}$).

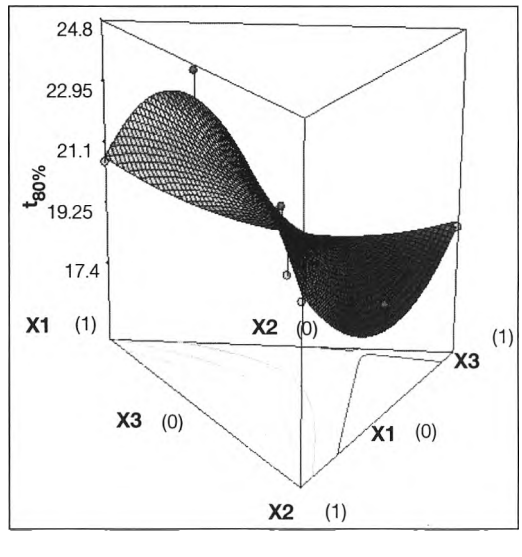

Figure 6 Response surface plot (3D) showing the effect of the amount of amount of PEO, amount of HPMC and amount of sodium bicarbonate on time required for 80% drug release ($t_{80\%}$).

Dissolution profiles were fitted with the power law equation given by Korsemeyer, Gurny and Peppas [25]. Diffusion exponents (n) ranged from 0.489 to 0.733 (Table 1) indicating anomalous drug release involving combination of swelling diffusion and/or erosion of matrices. This might be due to poor water solubility of domperidone as well as difference in characteristics of polymers. Nonlinear relationship was obtained between diffusion exponent and two independent variables. Figure 7 shows the 3D surface plot of the amount of PEO WSR 303 (X_1), amount of HPMC K15M (X_2) and amount of sodium bicarbonate (X_3) versus diffusion exponent.

Release rate constant showed that independent factors had significant influence ($p < 0.05$). The high value of X_1X_2 and X_2X_3 coefficient also suggests that the interaction between X_1X_2 and X_2X_3 has a significant effect on release rate constant. It can be concluded that the release rate constant changed by appropriate selection of the X_1, X_2 and X_3 levels. Figures 8 show the 3D surface plot of the amount of PEO WSR 303 (X_1), amount of HPMC K15M (X_2) and amount of sodium bicarbonate (X_3) versus release rate constant.

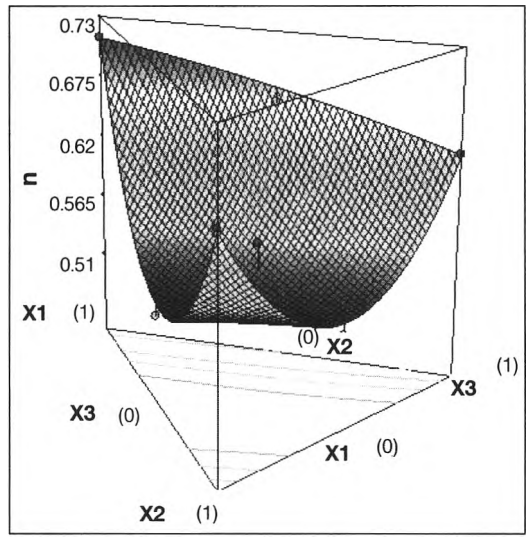

Figure 7 Response surface plot (3D) showing the effect of the amount of amount of PEO, amount of HPMC and amount of sodium bicarbonate on diffusion exponent (n).

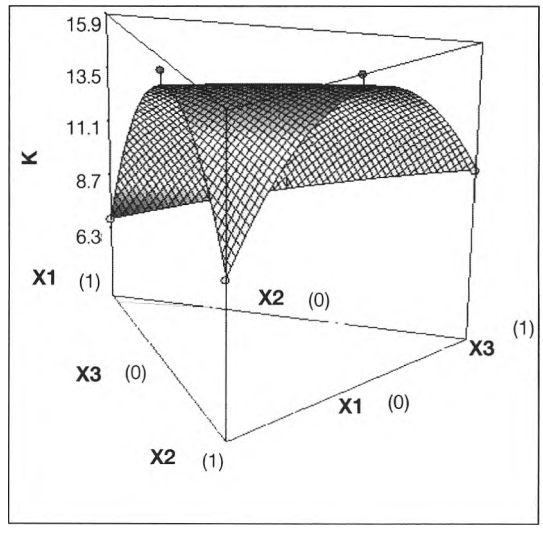

Figure 8 Response surface plot (3D) showing the effect of the amount of amount of PEO, amount of HPMC and amount of sodium bicarbonate on release rate constant (k).

Conclusion

An attempt was made to develop a floating drug delivery system of domperidone using poly (ethylene oxide) WSR 303, HPMC K15M, and sodium bicarbonate as matrixing agent, gelling agent, and gas generating agent, respectively. A simplex lattice design was applied to investigate the combined effect of three formulation variables. Results of multiple regression analysis indicated that moderate level of all three independent variables is useful for development of floating drug delivery.

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