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Design of Pulsatile Tablets of Pantoprazole Sodium: Factorial Design Approach

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Original Research Article

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Abstract: The objective of the present study was to develop and optimize an oral pulsatile drug delivery system containing pantoprazole sodium to mimic the circadian rhythm of the peptic ulcer by releasing the drug with a distinct predetermined lag time. Six fast disintegration core tablets were prepared for preliminary trials using direct compression method. The tablets were evaluated for hardness, friability assay and dissolution study. The best formulation were selected for optimization to study the influence of Micro crystalline cellulose (MCC) and Sodium starch glycolate (SSG) using 3^2 full factorial design. The optimized formulations were selected for coating for pulsatile delivery. The results of the study indicate f3 formulation was suitable for scale up.
Keywords: Pantoprazole Sodium, Factorial Design.

INTRODUCTION

Pantoprazole sodium is an anti-ulcer drug belonging to the class of proton pump inhibitor. The is effective in the treatment of duodenal or gastric ulcer, gastro oesophageal reflux disease and in the treatment Pulsatile systems constitute a relatively new class of device the important of which is especially connected with the recent advances in chronopharmacology [1]. In the last decade numerous studies in animal as well as clinical studies have provided convincing evidence, that the pharmacokinetics and / or the drug's effects – side effects can be modified by the circadian time and or/ the timing of drug application with in 24 h of the day [2-3].

The pulsatile delivery system improve the patient compliance when the drug is release at early morning. The designed core tablets coated by using pH sensitive methocrylic acid copolymers (Eudragit L00 and S100) as coat and pantoprazole as core material. The use of pH dependent and time dependent polymers as coating materials have been reported previously [4-6] the enteric coating prevents disintegration of core in the gastric fluid. On reaching the Illium (pH 7.2) the tablets losses its enteric coating and drug release occur. The lag phase created to achieve the pulsatile delivery Thus formulation taken at night, will be effective on morning.

Factorial design and response surface methodology is an important statistical tool to study the effect of several factors influencing response by varying them simultaneously by carryout limited number of experiments. Literature survey revealed no study carried out to formulate a pulsatile delivery system to demonstrate the influence of formulation variables using factorial design approach.

The objectives of the present investigation was to carry out a systematic statistical study on preparation of pulsatile delivery formulation using factorial design approach and explore the application for the formulation development.

MATERIALS AND METHODS

Pantoprazole sodium, Sodium starch glycolate, Aerosil, Eudragit S100 (Yarrow chem products, Mumbai), Magnesium stearate (lobe chemie Pvt Ltd, Mumbai).Polyethylene glycol (Sd fine chem Ltd. Mumbai.) All the materials and reagents were of analytical grade.

Methods

Preparation of core tablets

The direct compression technique was used for the preparation tablets. All the raw materials were weighed and passed through #40 mesh sieves and mixed well as per the formula given in Table 1 to meet the tablet weight to 245mg. The powder blend was lubricated using Magnesium stearate and aerosil at 1% concentration of tablet weight. The powder blend was compressed using an 8mm convex punch machine (Rimek Mini press-1).

Evaluation of Core Tablets

Hardness and Friability

The crushing strength of the tablets was measured using Monsanto hardness tester. The limit for crushing strength of the tablets was kept in the range of 3-4 kg/cm^2. The friability of the tablets was measured

using a Roche friabilator (Electrolab, India). Twenty tablets were weighed and rotated for 4 min at 25 rpm. The tablets were then reweighed and the percentage friability was calculated.

Disintegration study for Core Tablets

Disintegration procedures for the Pantoprazole sodium Pulsatile core tablets using 900 ml of 6.8 pH phosphate buffer at 37°C. Six tablets were dropped into individual tubes of the basket-rack assembly. Disks were not mounted on the tubes and the time at which all six tablets had disintegrated was recorded.

Dissolution study for Core Tablets

The dissolution studies for the pantoprazole sodium core tablets were carried out using dissolution test apparatus USP II paddle type. The dissolution medium consisted of 900 ml of phosphate buffer of pH 6.8 for 60 min. The temperature of the medium was maintained at 37±0.5°C. The speed of rotation of the paddle was kept at 50 rpm. Aliquots of 5ml were withdrawn after every 15 minutes. These samples were diluted to make up the volume of 50ml with pH 6.8 buffer. The samples so withdrawn were replaced with the fresh dissolution medium equilibrated at the same temperature. The drug released at the different time intervals from the dosage form is measured by UV visible spectrophotometer, by measuring the absorbance for the sample solutions at 289nm [7 -9]

Effect of Variables

To study the effects of variables on core tablets performance and characteristics, different batches were prepared using 3^2 factorial design. Amount of microcrystalline cellulose and SSG were selected as two independent variables. Hardness, friability, disintegration and dissolution were selected as dependent variables. Values of all variables and batch codes are as shown in Table 2.

Optimization of Core Tablets

The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and choice of responses. Optimization has been done by using 3^2 full factorial designs, where the amount of MCC (X1) and the amount of SSG (X2) were taken as independent variables.

Formulation of pulsatile tablets

The coating solution was developed by dissolving Eudragit S 100 (20%) in acetone and isopropyl alcohol mix solvents and then Polyethylene glycol (2%), Titanium dioxide (5%) was added and stirring. The resulting solution was adjusted with acetone and isopropyl alcohol mixed solvents. The core tablets were coated using dipping and drying method and increase in weight percent after coating was determined as the coating level.

Evaluation of pulsatile tablets

The thickness of the Eudragit S coating was measured using screw gauge and was expressed in mm. The core tablets were selected randomly and weighed individually for weight variation. The test requirement is meeting if none of the individual weights are less than 90 % or more than the 110% of the average.

Disintegration test for coated tablet

The disintegration time of the coated tablets was determined using the USP model disintegration apparatus. Six tablets were placed in the basket rack assembly, and were run for 2 hours in 0.1 N HCl media with the discs. The tablets were removed from the solution, gently dried by bloating. The test was then continued by placing the tablets in phosphate buffer pH 6.8, for 3 h, maintaining the temperature at 37±2°C

Dissolution study for coated tablet

The dissolution studies of the pulsatile tablets containing pantoprazole sodium was carried out using 900 ml of 0.1N HCl for 2h followed by pH 6.8 phosphate buffer solutions. The set condition was 37±0.5°C, 50 rpm, and paddle type USP XX111 apparatus. Aliquots withdrawn for every one hour intervals and were replenished immediately with the same volume of fresh buffer medium. Aliquots, following suitable diluents were assessed spectrophotometrically at 289nm.

Statistical analysis of data

Response of different batches obtained using factorial design is shown in Table 2. The Obtained data were subjected to multiple regression analysis using design software (USA) data were fitted in second order polynomial equation.

$$Y= b_0 + b_1 X_1 + b_2 X_2 + b11\ X_1X_2 + b22X2X2 + b_{12}\ X_1X_2$$

Where y is the dependent variables, b0 is the arithmetic mean response of the nine runs, and b_1 is the estimated coefficient for the factors X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. On the basis of the preliminary trial a 3^2 full factorial design was employed to study the effects of independent variables on dependent variables. Response surface plots were generated using mini tab software. Results of the multiple regression analysis are all parameters study is summarized in table 3.

Coating for optimized formulation

On the basis of factorial design approach core tablet batch (f3) was selected for further development of pulsatile tablets. The coating solution was prepared using Eudragit S. Dissolving Eudragit S (20%) in acetone and isopropyl alcohol mix solvents and then

Polyethylene glycol (2%), Titanium dioxide (5%) was added and stirring. The resulting solution was adjusted with acetone and isopropyl alcohol mixed solvents. The core tablets were coated using dipping and drying method and increase in weight percent after coating was determined as the coating level. Prepared pulsatile tablets were characterized for following parameter.

In vitro release study for optimized pulsatile tablets

The dissolution studies of the optimized pulsatile tablets containing pantoprazole sodium was carried out using 900 ml of 0.1N HCl for 2h followed by pH 6.8 phosphate buffer solutions. The set condition was 37±0.5°C, 50 rpm, and paddle type USP XX111 apparatus. Aliquots withdrawn for every one hour intervals and were replenished immediately with the same volume of fresh buffer medium. Aliquots, following suitable diluents were assessed spectrophotometrically at 289nm.

RESULTS AND DISCUSSION

Amount of MCC and SSG were found to be critical in preparation hence selected variables in the 3^2 factorial designs.

Table-1: Composition of core tablets of Pantoprazole Sodium for Preliminary trial

Ingredients (mg)	D1	D2	D3	D4	D5	D6
Pantoprazole	40	40	40	40	40	40
MCC	200	200	200	200	200	200
Cross Carmellose	-	-	-	1	1.5	2
SSG	1	1.5	2	-	-	-
Magnesium stearate	2	2	2	2	2	2
Aerosil	2	1.5	1	2	1.5	1
Total weight	245	245	245	245	245	245

Table-2: Lay out of 3^2 full factorial designs

	Independent variables		Dependent variables			
Code	X1	X2	Y1 (Kg Cm^2)	Y2 (%)	Y3(S)	Y4(%)
f1	-1	- 1	3.8	0.78	115	83.7
f2	-1	0	4.0	0.79	116	85.5
f3	-1	+1	4.2	0.65	117	95.8
f4	0	-1	4.4	0.62	118	85.5
f6	0	+1	4.6	0.64	120	86.8
f7	+1	-1	4.8	0.57	121	89.1
f8	+1	0	5.0	0.56	123	81.2
f9	+1	+1	5..5	0.53	127	85.5

Note: all the values are average of three such determinations

Table-3: Summary of regression analysis and results of measured responses

	Parameters			Coefficients		
β_0 β_1	β_2	β_{11}	β_{22}	β_{12}	r^2	*p*
Y1	4.122	0.50	0.10	0.166	0.166	0.001
Y2	0.656	-0.93	-0.02	-0.010	-0.030	0.016
Y3	124.0	2.66	-1.00	-1.000	-0.000	0.416
Y4	86.00	-2.55	3.33	-1.35	1.70	0.031

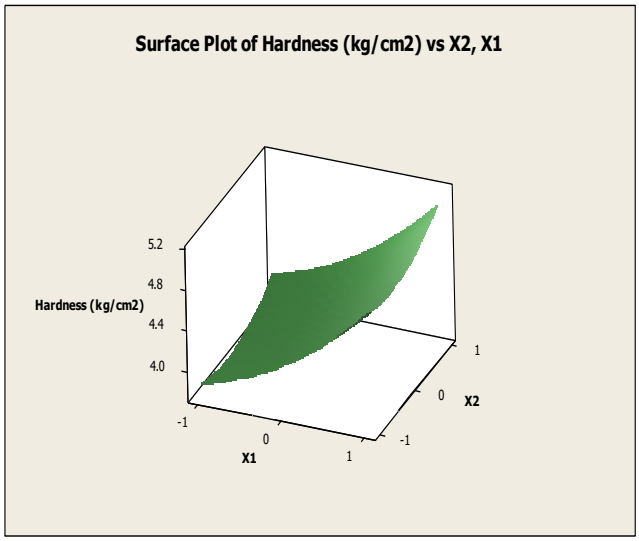

Fig-1: Surface Plot for Hardness

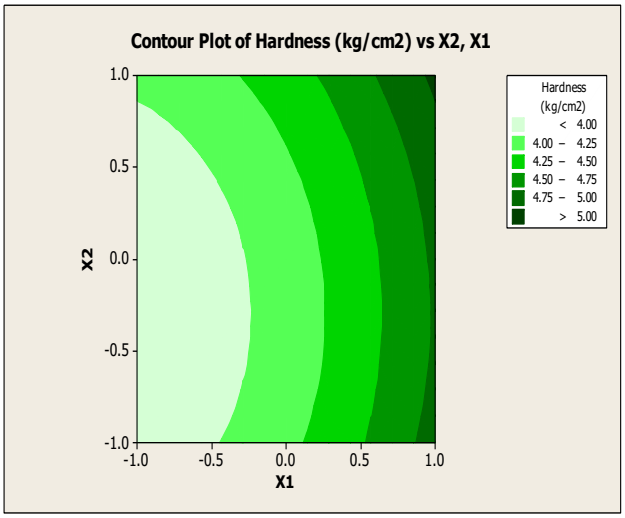

Fig-2: Contour Plot for Hardness

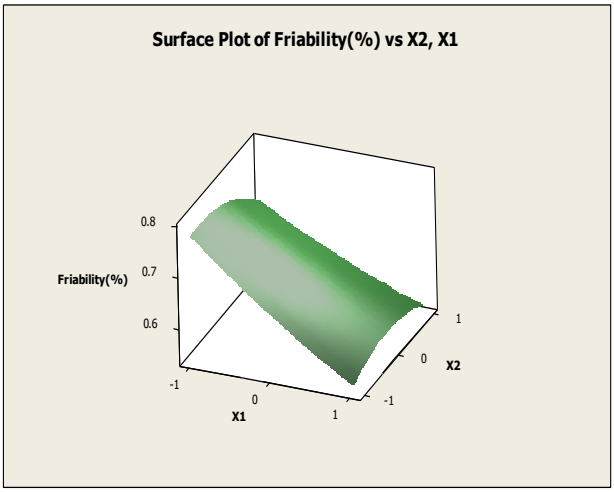

Fig-3: Surface Plot for Friability

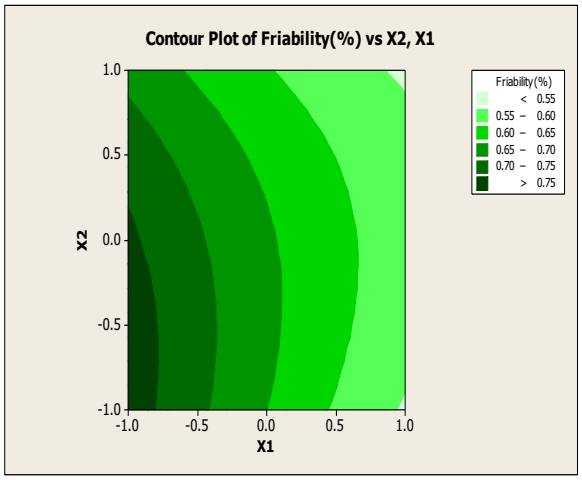

Fig-4: Contour plot for Friability

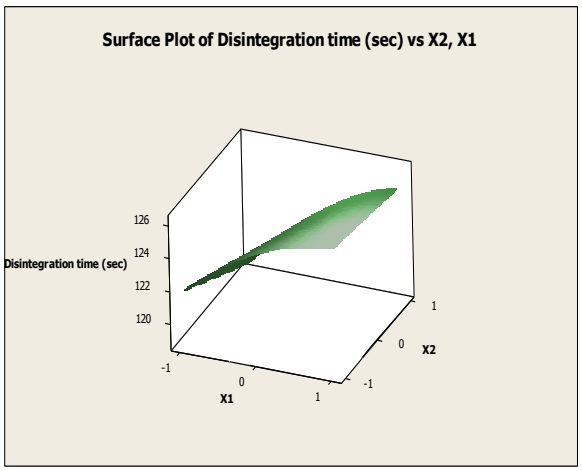

Fig-5: Surface plot for disintegration time

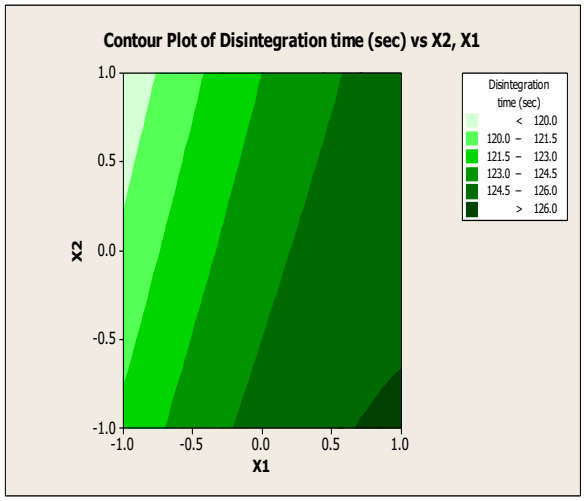

Fig-6: Contour plot for disintegration Time

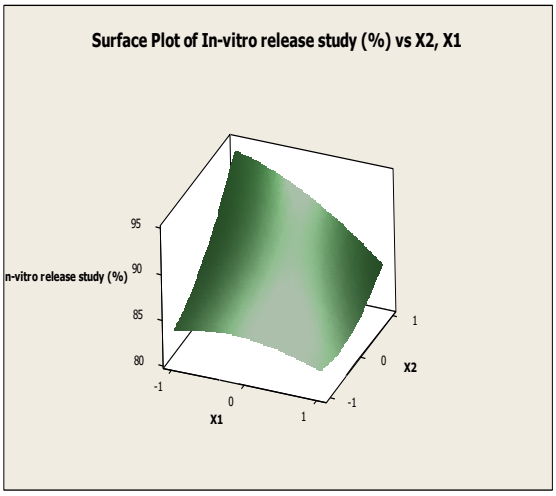

Fig-7: Surface Plot for *in vitro* Release Study

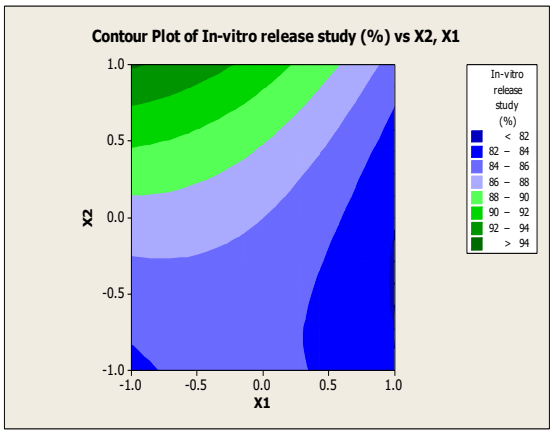

Fig-8: Contour Plot for *in vitro* Release Study

Statistical analysis of data

Response of different batches obtained using factorial design is shown in Table 3. Obtained data were subjected to multiple regression analysis using design software (USA) data were fitted in second order polynomial equation.

$Y= b_0 +b_1X_1 + b_2 X_2 + b11 X_1X_2 + b22 X_2X_2 + b_{12} X_1X_2$

Where y is the dependent variables, b0 is the arithmetic mean response of the nine runs, and b_1 is the estimated coefficient for the factors X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. On the basis of the preliminary trial a 3^2 full factorial design was employed to study the effects of independent variables on dependent variables. Response surface plots were generated using mini tab software. Results of the multiple regression analysis are all parameters study is summarized in Table 3 and Fig 1-8.

Effect on hardness

To study the effect of MCC and SSG on hardness of the tablets Eq.(1) was generated after fitting the observed coefficient in Eq . (2).

$Y= b_0 +b_1X_1 + b_2 X_2 + b11 X_1X_2 + b22 X_2X_2 + b_{12} X_1X_2$

$Y_1 = 4.122+ 0.50 X_1 +0.10 X_2 +0.166 X_1X_1 + 0.166X_2X_2 - 0.00X1X2$

The values for hardness of the tablets Y_1 ranges between 3.8-5.1Kg/cm^2 and were significantly influenced (P = <0.05) by one study factor (X_1).

Hardness was found to an inverse function of X_1 and X_2. Hardness of the tablets slightly increased with increasing amount of MCC and SSG. Both MCC and SSG showed inhibitory effect of on hardness. MCC alone were more predominant than SSG on hardness of the tablet. It has indicated by the observed respective coefficient. (Table 3)

Effect on friability

To understand the effect of concentration of MCC and SSG on friability of tablets was fitted in Eqs (1) to generate Eq. (3) respectively.

$Y_2 = 0.656 – 0.93X_1 – 0.023X2 + 0.010X_1X_1 – 0.030 X_2X_2 – 0.02X_1 X_2$

The value for friability of tablets Y_2 ranges between 0.53- 0.78% indicated all the formulation were successfully passed the friability test. Optimum concentration of MCC significantly influences the friability values. i.e increased value of friability. But SSG and combination of SSG and MCC favorable for the reduction of friability.

Effect of disintegration and dissolution

The drug dissolution and disintegration are important variables for bioavailability of drug. These parameters are dependent on the process of preparation, physiochemical properties of drug and formulation variables. The drug disintegration varied from 117 to 127 sec. The value for disintegration time of tablets ranges between 117-127 sec. The response was insignificant by the one study factor. Combination of SSG and MCC significantly influence the disintegration time.

$Y_3 = 124.00 + 2.667\ X_1 - 1.00\ X_2 - 1.00X_1X_1 - 0.00\ X_2X_2 + 0.500\ X_1X_2$

Dissolution studies for core tablets

In vitro release studies were carried out using USP XX111 dissolution assembly. The release profile obtained for all the formulations were shown in Fig 2. It was observed that the drug release from the formulations increase amount of MCC and SSG. 80 – 90 % of incorporated drug within 30 min after lag time of 5 h. The negative results of MCC and SSG indicate both the excipients insignificant value so that the values are not considered for the study.

$Y_4 = 86.0 - 2.55\ X_1 + 3.33\ X_2 - 1.35\ X_1X_1 + 1.70\ X_2X_2 - 1.95\ X_1X_2$

Evaluation of pulsatile tablets

On the basis of hardness, friability, disintegration and dissolution f5 was selected as better formulation for designing pulsatile tablets. The release of the drug from the tablets is strongly affected by the PH of the medium. During the dissolution study the cumulative percentage of pantoprazole from the tablets was plotted as a function of time.

CONCLUSION

As indicated in introduction, the main aim of the work described here was to design new pulsatile delivery tablets of pantoprazole using factorial design approach for better treatment out come for peptic ulcer. The present study demonstrates that the pantoprazole pulsatile tablets could be successfully designed for chronopharmcological effects to reduce the symptoms of peptic ulcer at early morning. Preparation of Pulsatile tablets using factorial design was found to be well suited and sound approach to obtain the successful formulations. Inclusion of MCC and sodium starch glycolate greatly influence the quality of formulation.

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