Asian J. Pharm. Res. Vol 1, Issue 2, 53-61, 2011.

ISSN 2231 – 363X
2231 – 3621

Asian Journal
of
PHARMACEUTICAL RESEARCH
Journal homepage: - www.ajprjournal.com

DEVELOPMENT OF FAST RELEASE COMPRESSED COATED TABLETS OF RABEPRAZOLE SODIUM USING ACID BUFFER TECHNOLOGY

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ABSTRACT

The study presented in this article was to development of rabeprazole sodium fast release compressed coated tablets using acid-buffer technology gives immediate as well as sustains therapeutic effect**.** Modified Fuchs Model was used for buffer combination Selection. The fast release compressed coated tablets containing buffer, hydroxypropyl cellulose (HPC) and sodium starch glycolate (SSG) using acid buffer technique. The type of buffer combination ($NaHCO_3$: Mg $(OH)_2$) and the percentage of the disintegrant (2, 4, and 6%) were selected as independent variables in 3^2 full factorial design. Tablets were manufactured on a single and rotary (12- station) tablet machine and tablets were evaluated for friability, tensile strength, disintegration time and pH study. Regression analysis was carried to evolve full and refined models. The optimized batch was characterized for Disintegration time, pH at 60sec, pH at 30 minute and % drug release at 5 minute were selected as dependent variable. The results indicated that the batch A6 contains 6% HPC , 4% SSG and buffer ratio $NaHCO_3$:$CaCO_3$ 550:300 was selected as a optimize batch on the based on low disintegration time 50 sec, maintain pH 5 for 30 minutes and 85 % drug release within 5 minute. In the present research, Rabeprazole sodium fast release compressed coated tablets were successfully prepared and evaluated by using acid-buffer technology.

KEYWORDS: Compressed Coated, Acid Buffer Technology, and Modified Fuchs Model.

INTRODUCTION

Hyperchlorhydria is widely spread gastrointestinal disorder that prevalent by gastro esophageal reflux disease (GERD). PPI therapy in patients with Helicobacter pylori infection may potentially cause atrophy of the stomach but this atrophy could then predispose patients to dysplasia and, ultimately, gastric cancer. Another potential association of PPI therapy with hypergastrinemic side effects is fundic gland polyps, which are begin polyps in the stomach, these polyps are of concern if they are associated with a hereditary colorectal cancer condition called familial adenomatous polyposis. Proton-pump inhibitors (PPIs) represent a major therapeutic advance in the management of acid-related disorders, including gastro-esophageal reflux disease (GERD) and non-variceal upper gastrointestinal (GI) bleeding, but there still remain unmet needs, which if addressed could improve treatment [1].

All proton pump inhibitors are weak bases that are acid labile and hence rapidly degraded within minutes, in the acidic environment of the stomach. For achieve desired pharmacological property of PPIs is required delayed release of drug from formulation suggest to enteric coating. Enteric coating protects the active ingredient from degradation by gastric acid and enhances its absorption to achieve minimum therapeutic level after oral administration. The rational for the development of the fast release tablet of PPIs using acid-buffer technology gives immediate as well as sustains therapeutic effect [2].

The present investigation was to formulate that orally administrated fast release tablet comprising following; (a) Proton pump inhibitor and (b) Buffer matrix; provides higher pH environment that prevents degradation in gastric fluid [3].

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ISSN 2231 – 363X
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Present formulation is designed to achieve minimum therapeutic concentration of PPI with improved chemical and physical stability, disintegration times, and drug release profiles with desired pharmacokinetic and pharmacodynamic profile [4].

Accelerated antisecretory action of immediate-release proton-pump inhibitors is due to the activation of proton pumps by the rapid neutralization of intragastric acid by buffering agent.

The present invention is aimed to formulate the "non-enteric" formulation of immediate release rabeprazole sodium tablet using acid-buffer technology. The formulation comprising the core tablet containing rabeprazole sodium compression coated with buffer containing super disintegrant. The coat formulation disintegrates fast which provide the higher pH environment then the core formulation gives drug release so degradation of rabeprazole sodium can prevent [5].

MATERIALS AND METHODS

Hydroxypropyl Cellulose was obtained from Corel Pharma Ltd., Ahmedabad. Calcium carbonate, Sodium Bicarbonate, Magnesium Hydroxide were obtained from Finar chemicals Limited, Ahmedabad, India. Rabeprazole sodium and Sodium Starch Glycolate (SSG) were obtained as gift sample from Cadila Healthcare Ltd., Ahmedabad. Magnesium stearate was used as S.D. Fine Chem. Ltd, Mumbai, India.

Drug - Excipients compatibility study

Differential Scanning Calorimetry (DSC) Analysis

DSC scans of powdered sample of rabeprazole sodium and mixture of excipients with drug. DSC analyses of powders were recorded using DSC- Shimadzu 60 with TDA trend line software. The pans were positioned on sample pan holder of a DSC 60. The thermal traces were obtained by heating from 50ºC to 300ºC at heating rate of 10ºC. Thermogram was obtained by the DSC 60 thermal analyzer program and recorded chart speed of 1 inch/min. The thermogram, transition temperature range, the onset of peak transition and the maximum peak of transition were recorded [6].

pH Stability Profile

The pH Stability Profile of Rabeprazole Sodium was studied at 25 ºC and the percentage of original drug left after 24 hours of elapsed time was determined. Prepare stock solution (1 mg/ml) of Rabeprazole sodium was prepare in different standard pH (1 to 8) the solution. The solutions were stored for 24 hrs and after 24 hrs. % conc. of Rabeprazole sodium was determined by UV spectroscopy method [7]. The graph of pH Vs % Drug after 24 hours was plotted.

Modified Fuchs Model for Selection of buffer combination

The selection of buffer ratio on the based on increases the gastric pH for stable the drug more than 30 minutes. It was measured by a simulated stomach model such as Fuchs kinetic *in- vitro* pH model. The procedure described simulates a gastric environment with continuous acid influx. A description of experimental set-up procedure given below.

1. The procedure described for buffer selection in simulates a gastric environment with continuous acid influx. A description of experimental set-up and sample analysis was followed.
2. A glass sample vessel (~150 ml capacity) containing 50 ml of a standardized solution of 0.1 N HCl was placed into a water bath set at 37°C (± 2 ºC).
3. A second glass vessel containing > 70 ml of a standardized solution of 0.1 N HCl was placed into the same water bath.
4. The stir paddle was then placed into the sample vessel and set at an appropriate speed. The speed of the stir paddle was recorded and used for all samples analyzed. The speed of the paddle should be adequate to dissolve the sample and added acid without causing interference with the pH measurement or splashing of the solution.
5. Prior to the start of each sample analysis, the tubing was primed and it was verified that the flow rate with 0.1 N HCl was 5 ml/min (Electrolab peristaltic pump) and the temperature was 37°C (± 2 °C). The pump and tubing was then set-up to allow the transfer of 0.1 N HCl acids into the sample vessel.
6. The pH meter was calibrated to accurately measure pH between 1 and 10 and it was verified that the electronic storage device was ready to collect pH and/or temperature data at a pre-defined rate.
7. When necessary, the sample was crushed into a fine powder using a mortar and pestle and then transferred to a suitable container and weighed.
8. The pH probe was placed into the glass sample vessel containing 50 ml of 0.1 N HCl at 37°C (± 2°C).
9. The timer and pH data collection was then started. The sample was then transferred into the vessel and the exact time that the sample was introduced into the acid was recorded. The sample container was then re-weighed to determine the exact weight added.
10. The sample was then stirred for approximately 6 minutes and the flow of the 0.1 N HCl at a rate of 5 ml/min was started. The exact start time of the acid flow was recorded. Selected buffer combination given below Table 1.

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Fast release rabeprazole sodium compression coated tablets in Preliminary study

The core tablets of Rabeprazole sodium were compression coated with different buffer formulations. The compression coated formulations were prepared using varying ratio of $NaHCO_3$: $Mg(OH)_2$. In the coat formulation contain superdisintrigating agent (conc. 4%) and binder (conc. 4%). Rabeprazole sodium core tablets were compression coated with a different buffer mixture. The composition of compression coated tablets is given in Table 2 and tablet was shown in figure 1. Initially, 40% of coat weight was placed in a die cavity of a rotary tablet machine followed by carefully centering the core tablet and addition of reminder of coat weight. The coating material was compressed around the core tablet with high compression force [8].

Optimization of formulation using 3^2 full factorial designs

A 3^2 randomized full factorial design was utilized in the present study. In this design two factors were evaluated, each at three levels, and experimental trials were carried out at all nine possible combinations. The factors were selected based on preliminary study. The Buffer combination ration (X_1) and amount of Superdisintrigating agent (X_2) were selected as independent variables. The time required for Disintrigating Time, pH At 60 sec, pH At 30 min. and % Drug release at 5 minute were selected as dependent variables. The formulations of the factorial batches (A1 to A9) are shown in Table 3.

A statistical model incorporating interactive and polynomial terms was utilized to evaluate the response.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where, Y is the dependent variables, b_0 is the arithmetic mean response of the nine runs, and b_1 is the estimated coefficient for the factor 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. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity.

The counter plot was drawn using Sigma plot software (Jandel Scientific, San Rafael, CA). The plot of disintegration time, pH at 60 sec, pH at 30 minute and % drug release at 5 minute versus the amount of buffer ratio ($NaHCO_3$:$CaCO_3$) (X_1) and the amount of Superdisintegrant (SSG) (X_2) respectively.

The response surface plot was drawn using Sigma plot software (Jandel Scientific, San Rafael, CA). The plot of disintegration time, pH at 60 sec, pH at 30 minute and % drug release at 5 minute versus the amount of buffer ratio ($NaHCO_3$:$CaCO_3$) (X_1) and the amount of superdisintegrant (SSG) (X_2) respectively [9].

Evaluation parameters

Uniformity of weight

The weights were determined to within ±1mg by using Sartorious balance (Model CP- 224 S Electrolab, India). Weight control is based on a sample of 10 tablets. Determinations were made in triplicate.

Tablet hardness

The hardness of the tablets was determined by diametral compression using a dial type hardness tester (Model no 1101, Shivani Scientific India). A tablet hardness of about 4-5 kg is considered adequate for mechanical stability. Determinations were made in triplicate.

Tablet friability

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai, India). Tablets of a known weight (W_0) or samples of 10 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

$$\%Friability = \frac{W_0 - W}{W_0} \times 100 \quad \text{-------- (2)}$$

In-vitro disintegration test

The test was carried out on 6 tablets using Tablet disintegration tester ED-20 (Electrolab, Mumbai, India) distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds [10].

pH study

The test was carried out using Systonics µ pH system 361. A description of experimental procedure as per fuchs model. The duration of the test was recorded and the total volume of 0.1 N HCl added was calculated based on the flow rate and measurement pH up to 60 min.

In-vitro dissolution profile of prepared rabeprazole sodium fast release tablet

The release rate of rabeprazole sodium from fast dissolving tablets was determined using USP XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 200 ml of 0.1 N HCl (pH=1.2), maintained temperature at 37±0.5ºC and stirring rate at 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 1, 2, 5, 10, 15,

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20, 25 and 30min. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a 0.45 µm membrane filter. Absorbance was measured at 285 nm using a Shimadzu UV-1700 UV/Visible double beam spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve [11].

RESULT AND DISCUSSION

Differential Scanning Calorimetry (DSC) Analysis

Differential scanning calorimetry enables the quantitative detection of all processes in which energy is required or produced (i.e., endothermic or exothermic phase transformations). The thermo grams of rabeprazole sodium and mixture of excipients with drug in Figure 2. The melting peak of rabeprazole sodium is 140 ºC in figure peak is shown at 142.63 ºC and in physical mixture was present at position i.e. near 150 ºC. This confirmed the physicochemical stability of drug with the formulation excipients used in the study [12].

pH stability profile

The stability of Rabeprazole sodium was strongly dependent on the pH of the solution. The stability of drug was determined in the range of pH 1-8. The results of pH stability profile were depicted in Figure 3. It was found that the drug was least stable at low pH and highest stability of drug at higher pH than 5.

Selection of buffer

Selection of buffer ratio ($NaHCO_3$: $Mg(OH)_2$) base on the amount of buffer had increased the gastric pH to at least 5 for more than 30 minutes. In the method, minimum amount of sodium bicarbonate and Magnesium Hydroxide combination buffer was increased the pH above 5 for 30 minutes. Batch AD1 to AD5 decreases the amount of $Mg(OH)_2$ Where as batch ADP1 to ADP5 increases the amount of $NaHCO_3$. As per result exhibited in table 1, batch AD1, AD2 and AD3 was depicted that increase the pH above 5 for 30 minutes but AD2 and AD3 minimum amount of $NaHCO_3$ and $Mg(OH)_2$ buffer was increased the pH above 5 for 30 minutes. In the batch ADP4 and ADP5 was increased the pH above 5 for 30 minutes. ADP4 and ADP5 was minimum amount of $NaHCO_3$ and $CaCO_3$ buffer to increase the pH above 5 for 30 minutes. From the result selected batch exhibited in figure 4.

Preliminary study of fast release Rabeprazole sodium compression coated tablets

The concentrations of superdisintrigating agent (SSG) were varied from 0% to 12% in the outer core for the immediate action. While the concentration of binder HPC (klucel) was, 4% selected as per the preliminary study. The effect of superdisintrigating agent (SSG) in the outer core was base on the evaluation parameter as if disintegration time and friability were exhibited in table 4.

Optimization of formulation using 3^2 full factorial designs

The statistical analysis of 3^2 full factorial design batches were performed by multiple linear regression analysis carried out by using Microsoft Excel 2003. The time required for Disintrigating Time, pH at 60 sec, pH at 30 minute and percentage drug release at 5 minute. The values of dependent variable for the nine batches (P1 to P9) are shown in Table 5.

The data clearly indicated that the values of dependent variable like disintrigating Time, pH At 60 sec, pH At 30 minute and percentage drug release at 5 minute are strongly dependent on the independent variables. The fitted equations relating the response time required for disintrigating Time, pH at 60 sec, pH at 30 minute and percentage drug release at 5 minute to the transformed factor are shown in following equations. The polynomial equation can be used to drawn the conclusions after considering the magnitude of coefficient and the mathematical sign it carries,i.e.positive or negative. The high values of correlation coefficient for the dependent variables indicate a good fit [13].

Full model Y (**Disintrigating Time**) = $70.55–63.33\ X_1–29.16\ X_2+15\ X_1X_2+51.66\ X_1^2+4.16\ X_2^2$ ($R^2 = 0.994$)

Reduced model Y (**Disintrigating Time**) = $70.55–63.33\ X_1–29.16\ X_2+15\ X_1X_2+51.66\ X_1^2$

Full model Y (**pH at 60 sec**) = $5.83+ 0.3X_1+ 0.58\ X_2 – 0.075\ X_1X_2 - 1.3\ X_1^2 – 0.15\ X_2^2$($R^2 = 0.9949$)

Reduced model Y (**pH at 60 sec**) = $5.83+ 0.3X_1+ 0.58\ X_2 - 1.3\ X_1^2$

Full model Y (**pH at 30 min.**)= $5.47 – 1.25\ X_1 – 0.06\ X_2 - 0.075\ X_1X_2 - 1.11\ X_1^2 - 0.066X_2^2$ ($R^2 = 0.9964$)

Reduced model Y (**pH at 30 min.**)= $5.47 – 1.25\ X_1 – 0.06\ X_2 - 1.11\ X_1^2$.

Full model Y (% Drug release at 5 min.) = $79.66 + 15.33\ X_1+ 8.83\ X_2 – 2\ X_1X_2 - 12\ X_1^2 – 3.5\ X_2^2$ ($R^2 = 0.9987$)

Reduced model Y (% Drug release at 5 min.) = $79.66 + 15.33\ X_1+ 8.83\ X_2 – 2\ X_1X_2 - 12\ X_1^2$

Figure 5 and 6 show Counter plot and Response surface plot disintegration time, pH at 60 sec, pH at 30 minute and % drug release at 5 minute versus the amount of buffer ratio ($NaHCO_3$:$CaCO_3$) (X_1) and the amount of Superdisintegrant (SSG) (X_2) respectively. In the figures the darken area was optimize region of the formulation.

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Table 1: Sodium bicarbonate and Magnesium hydroxide combination buffer: Magnesium hydroxide effect

Batch	$NaHCO_3$	$Mg(OH)_2$	Batch	$NaHCO_3$	$Mg(OH)_2$
AD-1	350	600	**ADP-1**	250	300
AD-2	350	500	**ADP-2**	350	300
AD-3	350	400	**ADP-3**	450	300
AD-4	350	300	**ADP-4**	550	300
AD-5	350	200	**ADP-5**	650	300

Table 2: Fast release rabeprazole sodium compression coated tablets in Preliminary study

Core tablet						
Ingredient	**FORMULATION**					
	AF1	**AF2**	**AF3**	**AF4**	**AF5**	**AF6**
Rabeprazole sodium	20	20	20	20	20	20
$NaHCO_3$	150	150	150	150	150	150
Mg $(OH)_2$	150	150	150	150	150	150
HPC(klucel)	17	17	17	17	17	17
Lactose	33	33	33	33	33	33
Mg.stearate	5	5	5	5	5	5
TOTAL	425	425	425	425	425	425
Coat composition						
Ingredient	**FORMULATION**					
	AF1	**AF2**	**AF3**	**AF4**	**AF5**	**AF6**
$NaHCO_3$	200	200	200	200	200	200
Mg $(OH)_2$	350	350	350	350	350	350
HPC(klucel)	32	32	32	32	32	32
Lactose	113	97	81	65	52	33
SSG	0	16	32	48	64	80
Mg.stearate	5	5	5	5	5	5
TOTAL	700	700	700	700	700	700

Table 3: Full factorial design layout

Batch code	**X_1**	**X_2**
A1	-1	-1
A2	-1	0
A3	-1	1
A4	0	-1
A5	0	0
A6	0	1
A7	1	-1
A8	1	0
A9	1	1
Coded value	**Buffer combination ration($NaHCO_3$:$Mg(OH)_2$) X_1**	**Superdisintrigrating agent (%) X_2**
-1	350:500	2%
0	550:300	4%
1	750:100	6%

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Table 4 : Evaluation parameter of fast release Rabeprazole sodium tablet in Superdisintrigating agent effect.

Batch	EVALUTION PARAMETER						
	Weight (mg)	Hardness (kg/cm^2)	D.T. (sec)	Friability (%)	pH study		
					0sec	90sec	1800sec
AF1	1235 ± 27	3.5 ± 0.3	150 ± 10	0.74 ± 0.11	1.2	3.8	5.1
AF2	1272 ± 19	3.4 ± 0.4	110 ± 12	0.71 ± 0.14	1.2	4.2	5.2
AF3	1238 ±16	3.5 ± 0.3	68 ± 8	0.61± 0.17	1.2	5.8	5.3
AF4	1242 ± 20	3.5 ± 0.4	85 ±10	0.64 ± 0.12	1.2	4.8	5.1
AF5	1229 ± 21	3.4 ± 0.5	89 ± 8	0.59 ± 0.19	1.2	3.9	5.2
AF6	1246 ± 15	3.5 ± 0.4	98 ± 11	0.67 ± 0.16	1.2	3.8	5.2

Table 5: Result of 3^2full Factorial Design

Batch Code	Variable level in coded form		Disintrigating Time	pH At 60 sec	pH At 30 min.	% Drug release at 5 min.
	X_1	X_2				
A1	-1	-1	240	3.4	5.6	38
A2	-1	0	180	4.2	5.5	52
A3	-1	1	145	4.8	5.6	60
A4	0	-1	95	5.2	5.4	68
A5	0	0	75	5.8	5.6	79
A6	0	1	50	6.2	5.3	85
A7	1	-1	80	4.1	3.2	72
A8	1	0	60	4.9	3.1	84
A9	1	1	45	5.2	2.9	86

Translation of Coded Levels in Actual Units

Variables Level	Low (−1)	Medium (0)	High (+1)
Buffer combination ration (X_1) ($NaHCO_3$:$Mg(OH)_2$)	350:500	550:300	750:100
Superdisintrigrating agent (X_2)	2%	4%	6%

Figure 1: Rabeprazole sodium compression coated tablets

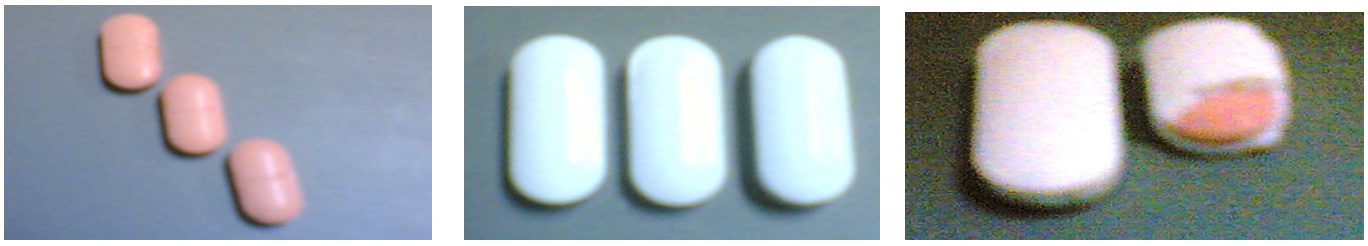

Figure 2: ***(a) DSC study of Drug + excipients (b) DSC study of Rabeprazole sodium***

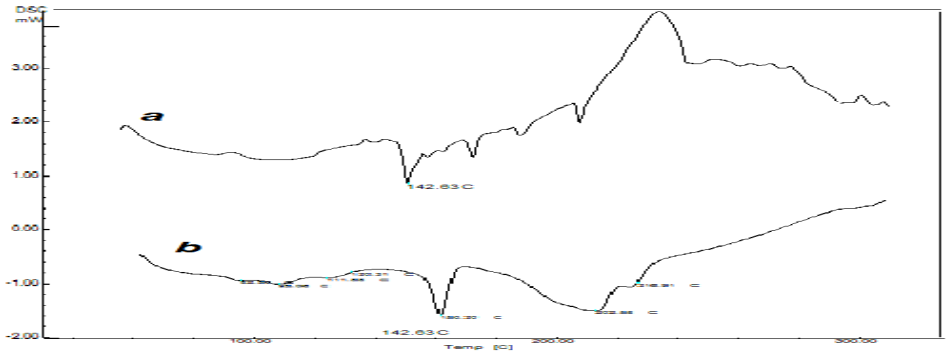

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Figure 3: ***pH Stability Profile of Rabeprazole Sodium***

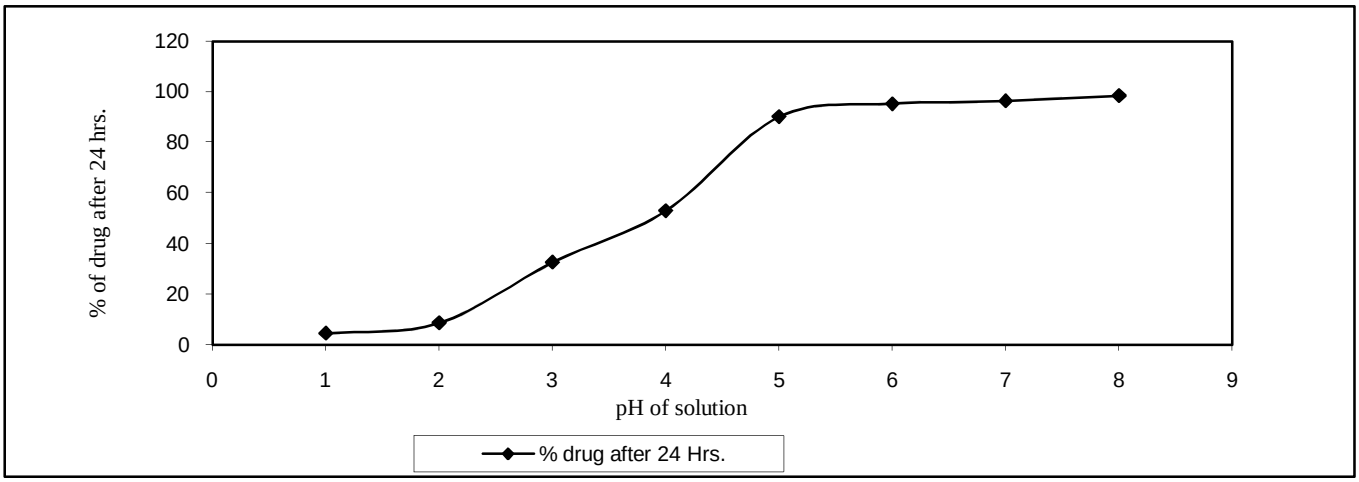


Figure 4: Buffer study on AD-1 to ADP-5

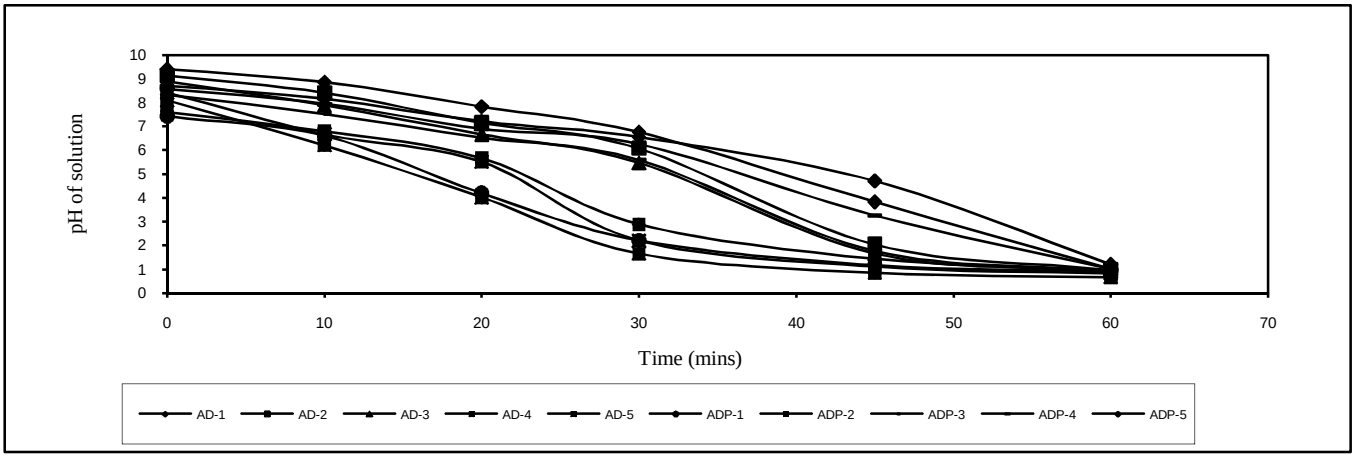
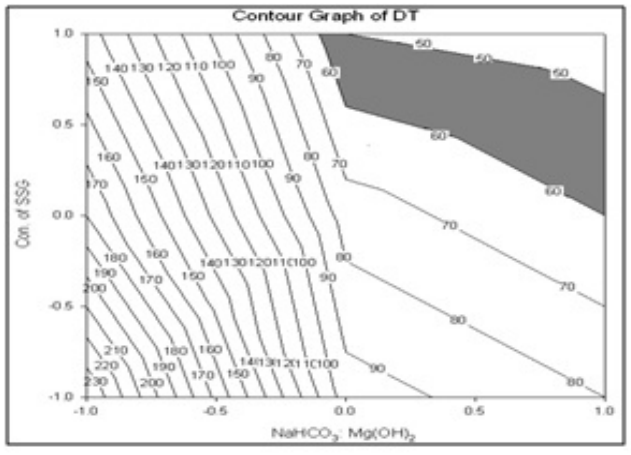
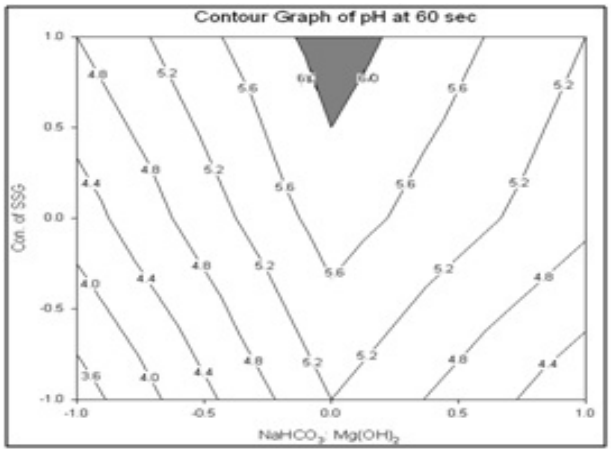


Figure 5: Counter plot for (a) Disintrigrating Time, (b) pH at 60 sec, (c) pH at 30 minute,(d) % drug release at 5 minute

(A) **(B)**





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(C) **(D)**

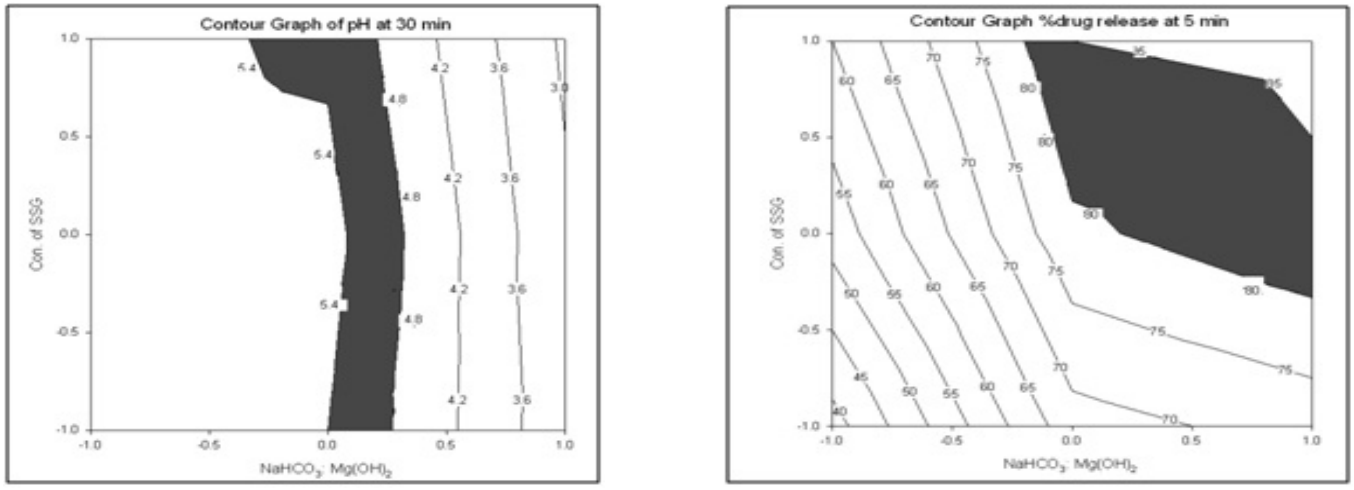
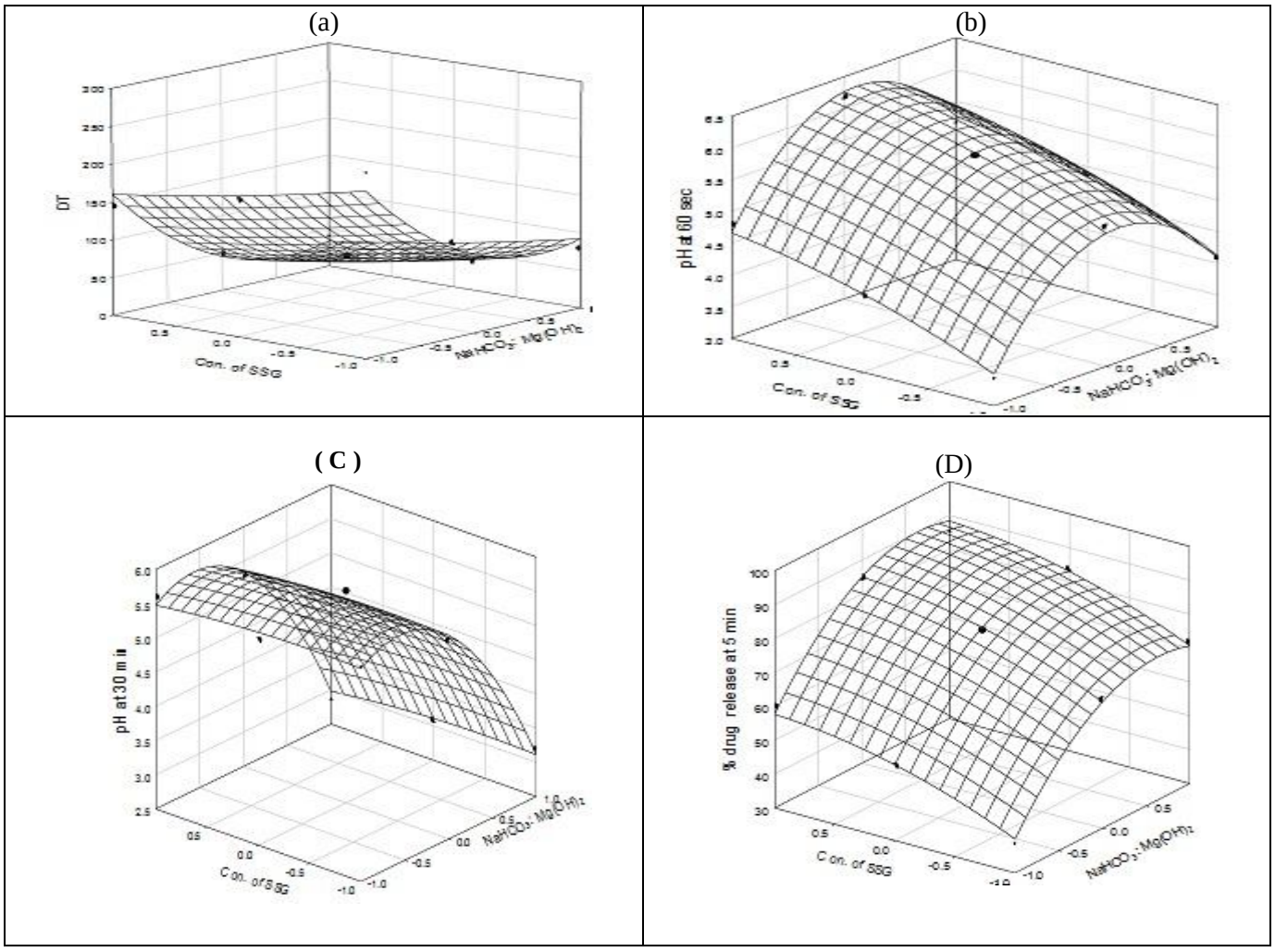


Figure 6: Response surface plot for (a) Disintrigrating Time, (b) pH at 60 sec, (c) pH at 30 minute,(d) % drug release at 5 minute



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CONCLUSION

The fast release tablet of Rabeprazole sodium was optimize using 3^2 full factorial designs (batches A1 to A9). The amount of buffer ratio (X_1) and super disintegrant (X_2) were selected as independent variables. Disintegration time, pH at 60sec, pH at 30 minute and % drug release at 5 minute were selected as dependent variable (response; Y). Full and reduced models were derived for the prediction of the response variable, Y. Based on result of multiple linear regression analysis, it was concluded that lower disintegration time and maintain the pH 5 for 30 minute of tablets could be obtained when X_1 is kept at optimum level and X_2 is kept at higher level. It was concluded that by adopting a systematic formulation approach, an optimum point could be reached in the shortest time with minimum efforts.

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