Research Article

FORMULATION AND OPTIMIZATION OF SUBLINGUAL TABLETS OF RABEPRAZOLE SODIUM

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ABSTRACT

The objective of this research was to develop and optimize sublingual tablets of Rabeprazole Sodium, a class of Proton pump inhibitors which is effective in the treatment of acid peptic disorders. The tablets were prepared by wet granulation method based on a central composite design. The formulation variables included quantity of Crospovidone, (X_1), and quantity of Croscarmellose Sodium (CCS), (X_2), while the response variables determined were wetting time and *In vitro* dispersion time. A quadratic model was used to quantitatively evaluate the main effects and interaction. Surface response plots are presented, to graphically represent the effect of the independent variables on the wetting time and disintegration time. The hardness of all the formulations was in the range 3.0 – 4.0 kg/cm^2. The percentage friability of all the formulations was found to be not more than 0.6 %. In all the formulations, the drug content was found to be uniform among the different batches of tablets and ranged from 97.37 % to 100.51 % of the theoretical value. The average percentage deviation for 20 tablets from each batch was within the acceptable pharmacopoeial limits. An optimized tablet formulation was prepared which provided a short wetting time of 27 sec and *Invitro* dispersion time of 32 sec. The results indicated that, the amount of Crospovidone and Croscarmellose Sodium significantly affected the dependent variables wetting time and disintegration time. The observed responses were in close accord with the predicated values of the optimized formulation, thereby demonstrating the feasibility of the optimization procedure in developing sublingual tablets.

Keywords: Crospovidone, Croscarmellose Sodium, quadratic model, optimized formulation.

INTRODUCTION

Tablets that disintegrate or dissolve rapidly in the patient's mouth are convenient for young children, the elderly and patients with swallowing difficulties, and in situations where potable liquids are not available. Since the drug can be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa, the sublingual route bypasses the hepatic first-pass metabolic processes, thus producing rapid onset of action. The sublingual route is appropriate for drugs with short delivery period requirements, for drugs which are inactivated by first pass – intestinal or hepatic metabolism or inactivated by the proteolytic enzymes in the GI tract. Rabeprazole sodium is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the enzyme system of hydrogen/ potassium adenosine triphosphatase (H+/K+ ATPase) at the secretory surface of the gastric parietal cell. It is indicated for the treatment or symptomatic relief of various gastric disorders such as gastric and duodenal ulcers, gastroesophageal reflux disease and pathological hypersecretory conditions including Zollinger- Ellison syndrome. It is dose dependently absorbed after oral administration and undergoes excessive first pass metabolism, thereby making it a suitable candidate for sublingual dosage form[1].

The objective of the present investigation is to analyze the effect of formulation variables on the properties such as dispersion time and hardness in the preparation of Rabeprazole Sodium sublingual tablets.

MATERIALS AND METHODS

Experiments were carried out systematically to analyze the effect of different concentrations of disintegrants on the wetting time and *Invitro* dispersion time of the tablets, using a response surface methodology and to develop an optimized formulation. A central Composite design was employed to prepare experimental trials using different quantities of disintegrants [2, 3, 4].

The two independent formulation variables evaluated were X_1: Amount of Crospovidone and X_2: Amount of Croscarmellose Sodium (CCS).

The dependent variables investigated were Y_1: Wetting time and Y_2: *In vitro* dispersion time.

Formulations were prepared according to the rotatable central composite design by wet granulation method. Since Rabeprazole Sodium is a light sensitive drug, the entire process was carried out under low intensity illuminated light. The sublingual tablets of Rabeprazole Sodium were prepared using different combinations Crospovidone and croscarmellose sodium (CCS) as superdisintegrants, mannitol as a diluent, sodium saccharin as sweetening agent, alcoholic solution of PVP (10 % w/v) as binder and aerosil with talc as a flow promoters (Table 1). The drug and other ingredients were mixed together, and a sufficient quantity of alcoholic solution of PVP (10 %w/v) was added and mixed to form a coherent mass. The wet mass was granulated using sieve no. 12 and dried at 60° C for 30 min. The dried granules were regranulated by passing through sieve no. 16. The dried granules were then blended with talc, aerosil and

compressed into tablets using a 8mm punch rotary tablet machine (Rimek, RSB-4minipress Cadmach, Ahmedabad, India). During compression the hopper containing granules was covered with black paper to prevent degradation of the drug.

Table 1: Composition of sublingual tablets of Rabeprazole Sodium

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Rabeprazole Sodium	20	20	20	20	20	20	20	20	20	20
Crospovidone	12.50	3.45	8.75	8.75	5.00	12.50	8.75	8.75	14.05	5.00
Croscarmellose Sodium	12.50	7.50	7.50	14.57	12.50	2.50	0.43	7.50	7.50	2.50
Aspartame	5	5	5	5	5	5	5	5	5	5
Mango flavor	2	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3	3
Aerosil	1	1	1	1	1	1	1	1	1	1
Mannitol	194	208.05	202.75	195.68	201.50	204	209.82	202.75	197.45	211.50
TOTAL	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Table 2: Central Composite Design with the corresponding responses for wetting time and *In-vitro* dispersion time.

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Wetting Time (sec) (Y_1)	15	129	30	23	125	55	42	30	22	118
In vitro dispersion time (sec) (Y_2)	20	135	35	25	130	60	45	35	25	120

Table 3: Summary of ANOVA results in the analysis of lack of fit and pure error.

Source	Sum of Squares	DF	Mean Square	F Value	Prob >F
Wetting time (sec)					
Model	20012.74	5	4002.55	22.60	0.0003
X_1	13148.00	1	13148.00	*74.25*	< 0.0001
X_2	448.05	1	448.05	*2.53*	0.1557
X_1^2	5775.03	1	5775.03	*32.61*	0.0007
X_2^2	371.98	1	371.98	*2.10*	0.1905
$X_1 X_2$	552.25	1	552.25	*3.12*	0.1207
Residual	1239.57	7	177.08	-	-
Lack of fit	1239.57	3	413.19	-	-
Pure error	0.000	4	0.000	-	-
Total	21252.31	12	-	-	-
***In-vitro* dispersion time (sec)**					
Model	20092.81	5	4018.56	22.04	0.0004
X_1	132248.95	1	13248.95	72.66	< 0.0001
X_2	424.63	1	424.63	2.33	0.1708
X_1^2	5750.00	1	5750.00	31.53	0.0008
X_1^2	271.74	1	271.74	1.49	0.2617
$X_1 X_2$	625.00	1	625.00	3.43	0.1066
Residual	1276.42	7	182.35	-	-
Lack of fit	1276.42	3	425.47	-	-
Pure error	0.000	4	0.000	-	-
Total	21369.23	12	-	-	-

EVALUATION OF TABLETS

Hardness: The crushing strength of the tablets was measured using a Monsanto hardness tester. Three tablets from each formulation batch were tested randomly and the average reading was noted [5, 6].

Friability: The friability of a sample of 20 tablets was measured using a Roche friabilator (Electrolab). 20 previously weighed tablets were rotated at 25 rpm for 4 min. The weight loss of the tablets before and after measurement was calculated using the following formula

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Weight variation: Twenty tablets were selected randomly from each formulation after compression, weighed individually using a digital balance and average weight was determined. The individual weights are compared with the average weight for the weight variation.

Drug content: Ten tablets were randomly sampled from each formulation batch, finely powdered and individually estimated for the drug content after suitable dilution, using UV-VIS spectrophotometer (UV-1601, Shimadzu) at 284 nm after suitable dilution with distilled water [7]. The mean percent drug content was calculated as an average of three determinations.

Wetting time: A piece of tissue paper (12cmx10.75cm) folded twice was placed in a Petri dish (Internal Diameter=9cm) containing 9ml of buffer solution simulating saliva pH 6.8, which had the following composition, NaCl (0.126g), KCl (0.964g), KSCN (0.189g), KH_2PO4 (0.655g) and urea (0.200g) in 1Litre of distilled water. A tablet was placed on the paper and the time taken for complete wetting was noted [8]. Three tablets from each formulation were randomly selected and the average wetting time was noted.

***In vitro* dispersion time:** *In vitro* dispersion time was measured by dropping a tablet in a 10ml measuring cylinder containing 6ml of buffer solution simulating saliva fluid (pH 6.8) [9,10].

Drug Dissolution: Dissolution test was performed according to USP paddle method. The dissolution media used was phosphate buffer, pH 6.8 maintained at 37°C and the media was rotated at 50 rpm. Aliquots were withdrawn at different time intervals, filtered and analyzed spectrophotometrically at 284 nm for cumulative drug release.

RESULTS AND DISCUSSION

10 batches of tablets were prepared using Central composite design. In this study, amount of Crospovidone and CCS were chosen as the independent formulation variables. The dependent variables included wetting time and *in vitro* dispersion time. The effect of formulation variables on the response variables were statically evaluated by applying one-way ANOVA at 0.05 level using Design-Expert® 6.05 (Stat Ease, USA). The design was evaluated using a quadratic model, which bears the form of the equation:

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_1 X_2 + b_4 X_1^2 + b_5 X_2^2$$

Where Y is the response variable, b_0 the constant and b_1, b_2, $b_3 \ldots b_5$ is the regression coefficient. X_1 and X_2 stand for the main effect; X_1X_2 are the interaction terms that shows how the response changes when two factors are simultaneously changed. X_1^2 and X_2^2 are quadratic terms of the independent variables to evaluate the nonlinearity. The dependent variables were tested for all the 10batches and the results are shown in Table 2. A numerical optimization procedure using desirability approach was used to identify the optimal settings of the formulation variables to obtain the target response. The data of pure error and lack of fit are summarized in ANOVA table (Table 3), which can provide a mean response and an estimate of pure experimental uncertainty. The optimized formula of the batch *RS1* is given in Table 4.

Table 4: Composition of optimized formulation (RS1)

Ingredients	Quantities (mg)
Rabeprazole Sodium	20.0
Crospovidone	9.40
Croscarmellose Sodium	6.91
Aspartame	5.0
Mango flavor	2.0
Talc	3.0
Aerosil	1.0
Mannitol	202.69
TOTAL	250

The results in Table 5 demonstrated a good relationship between the predicted and experimental values, confirming the validity of the model. The hardness of formulation batch *RS1* was found to be 4.0 kg/cm^2. The percentage friability of *RS1 was* 0.6 %. The drug content was found to be 98.3 % of the theoretical value. The percentage deviation for 20 tablets was within the acceptable pharmacoepial limits (± 7.5%). The formulation *RS1* showed rapid dissolution rate and the cumulative drug release was found to be 95.4 % and complete dissolution was achieved in 30 minutes. The response surface plots showing the effect of amount of Crospovidone (X_1) and amount of CCS (X_2) on the response Wetting Time (Y_1) and *Invitro* dispersion time (Y_2) are shown in Figure 1 and 2 respectively**.**

Table 5: Comparison chart of predicted and experimental values for optimized formulation (RS1)

Dependent variables	Optimized formulation	
	Predicted value	Experimental value
Wetting time (sec)	25	27 ± 2.45
In vitro dispersion time (sec)	30	32 ± 1.27

Figure 1: Response surface plot showing the effect of amount of Crospovidone ($X_{1)}$ and amount of CCS (X_2) on the response Wetting Time (Y_1).

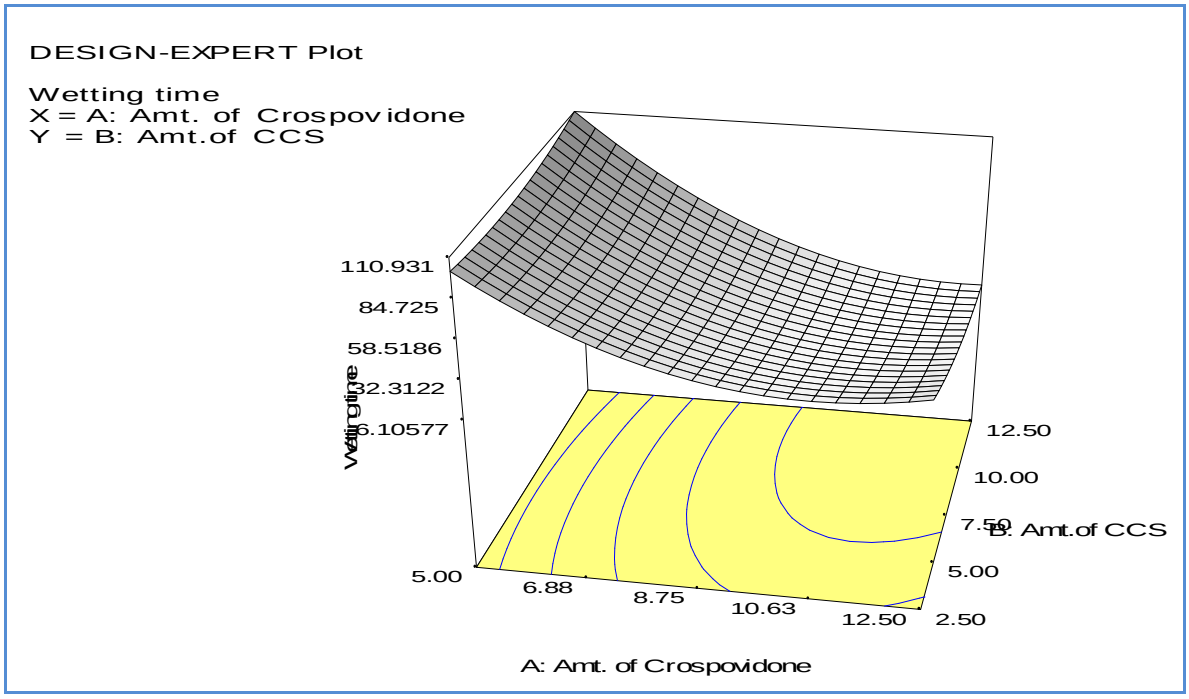
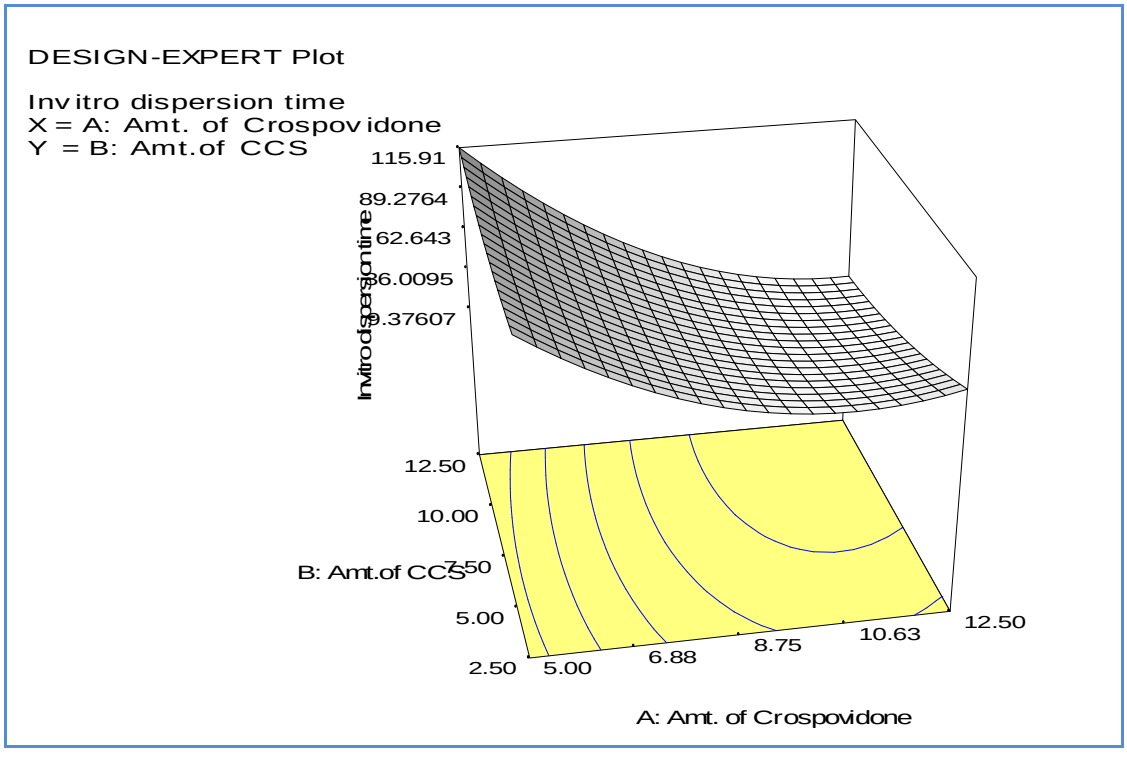


Figure 2: surface plot showing the effect of amount of Crospovidone ($X_{1)}$ and amount of CCS (X_2) on the response *Invitro* dispersion time (Y_2)



CONCLUSION

The effect of formulation variables on wetting time and *Invitro* dispersion time of sublingual tablets of Rabeprazole sodium was studied by applying optimization technique. The results indicated that the amount of Crospovidone and Croscarmellose Sodium significantly affected the dependent variables wetting time and disintegration time. The observed responses were in close accord with the predicated values of the optimized formulation, thereby demonstrating the feasibility of the optimization procedure in developing sublingual tablets.

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