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Formulation and Evaluation of Colon Targeted Oral Drug Delivery System Using Methacrylic Acid Co-Polymers

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ABSTRACT: The objective of this research was to formulate an Ornidazole tablet capable of delivering the drug intact to the colon for the treatment of IBD, ulcerative colitis, and Crohn's disease. In the current investigation, pH-independent and pH-dependent polymers were used to target the Ornidazole tablet to the colon. This study evaluated two time-dependent (sustained release) polymers (Eudragit RS and Eudragit RL) and one pH-dependent polymer (Eudragit S100). Utilizing a statistical 32-complete factorial design, the influence of the two formulation variables of the colon drug delivery system on the two response variables were examined simultaneously. In a factorial design, X1 Ratio of Eudragit RS 100 to Eudragit RL 100 and X2% weight gain with Eudragit S 100 were taken as independent factors, while Y5 and Y12 were taken as dependent variables. By performing this process, a total of nine F9 batches were obtained. In-vitro percentage release of Y5 should not exceed 10%, whereas Y12 should exceed 85%. On the basis of these findings, batch B8 is regarded to be the best of all batches. The results indicate that the improved formulation provides optimum intact drug delivery to the targeted region.

KEYWORDS: Ornidazole, Eudragit RS 100, Eudragit RL 100, Eudragit S 100, Colon targeted drug delivery system, pH-dependent Polymer, pH independent Polymers.

I. INTRODUCTION

Colon-targeted drug delivery systems are advantageous for delivering intact drugs to the colon. Inflammatory bowel diseases (IBD) such as ulcerative colitis and crohn's disease (CD) need the administration of the drug locally and selectively to the colon.[1, 2, 3] In Crohn's disease, the small or large intestine wall becomes painful, inflamed, and swollen. The region most often affected by Crohn's disease is the terminal portion of the small intestine and the beginning of the large intestine. In this case, the numerous pharmacological techniques for delivering drugs to the colon are mostly based on a pH-dependent, time-dependent, bacteria-dependent, and pressure-dependent delivery mechanism as well as patented technologies such as Phloral® Technology, Codes ® Technology, and so on.[4, 5] In typical dosage forms, drugs used to treat IBD are not successfully delivered to the colon since the majority of the pharmaceuticals are absorbed systemically or destroyed in the upper GIT.[6, 7]

In an earlier research, a pH-dependent system was employed to restrict drug release at stomach pH while allowing for the bulk of drug release in the small intestine.[8, 9]

Thus, in the current work, a combination of techniques were used in which an inner Time-dependent (sustained release) matrix was utilized to limit drug release in the small intestine by providing appropriate lag time, which was then covered with a pH-dependent polymer. Two time-dependent (sustained release) polymers (Eudragit RS and Eudragit RL) and one pH-dependent polymer (Eudragit S100) were evaluated in study[10, 15]. Eudragit RL was more hydrophilic than Eudragit RS 100, and the release of drug was significantly faster from a single Eudragit RL 100 matrix tablet compared to a single Eudragit RS100 matrix tablet; consequently, different combinations of Eudragit RL and RS to provide varying degrees of sustained-release of the drug were used as the time-dependent system in the present study.[8, 9, 10, 11, 12]

The objective of this study was to determine the optimal ratio of polymers for delivering the greatest amount of drug to the colon. Ornidazole, utilized as a model drug, is effective in mild to moderate condition for the treatment of perianal fistulae in Crohn's Disease and is also used as an anti-amoebic agent.[13, 14, 20]

In this research, two formulation variables examined were the Ratio of Eudragit RS 100 to Eudragit RL100 and the Eudragit S100 coating level.[16, 17, 18]

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The two response variable experiments examined the quantity of drug release in five hours and twelve hours. The projected in vitro release pattern for colon targeting was less than 10% drug release up to the end of the small intestine (5 hours) for targeting and delivering the maximum quantity to the colon, and more than 85% drug release up to 12 hours due to the low water content in the colonic region. Therefore, the release across the colon would be incomplete if less than 85% was released.

II. MATERIALS AND METHODS

2.1 MATERIALS

Ornidazole (Endoc pharma, Rajkot),Tablettose 100, Flowlac 100, Plasdone K 90 (Anshul agencies, Mumbai), Eudragit S 100, Eudragit RS 100, Eudragit RL 100 (Degussa Rohm Pharma, Mumbai), Polyvinyl pyrrolidone (PVP-K30), Sodium starch glycolate (SSG), Titanium dioxide, Tartrazine (LobaChemie, Pvt. Ltd., Mumbai), Tri Ethyl citrate (Himedia lab. Mumbai).

2.2 Preparation of Ornidazole tablets:

Matrix tablets of Ornidazolewere prepared by direct compression technique using various proportions of Eudragit RS/RL 100; Flowlac 100 as diluents, PVP K30 as Binder, SSG as super Disintegrants. All the ingredients were passed through 100 # sieve. All the ingredients except Talc and Magnesium Stearate were blended in glass mortar uniformly. After sufficient mixing of drug as well as other components, Talc and Magnesium Stearate was added and further mixed for additional 2-3 minutes. The tablets were compressed using 12mm concave faced punch in single stroke punching machine.

Composition of formulations of Ornidazole Matrix Tablet were summarized in **Table 1**

Table 1 Composition of formulations of Ornidazole Matrix Tablet A1- A5 batches

Ingredients	**A1**	**A2**	**A3**	**A4**	**A5**
Ornidazole	500	500	500	500	500
Eudragit RS 100	110	-	27.5	55	82.5
Eudragit RL 100	-	110	82.5	55	27.5
Flowlac	69	69	69	69	69
Talc	14	14	14	14	14
Magnesium Stearate	7	7	7	7	7
Total	700	700	700	700	700

2.3 Drug content.

The Ornidazole tablets were tested for their drug content. Ten tablets were finely powdered; quantities of the powder equivalent to 50 mg of Ornidazole were accurately weighed and transferred to a 100-ml of volumetric flask. The flask was filled with pH 6.8 phosphate buffer solution and mixed thoroughly. The solution was made up to volume and filtered. From this 10 ml of solution was withdrawn and diluted up to 250 ml with pH 6.8 phosphate buffer. The absorbance of the resulting solution was measured against pH 6.8 phosphate buffer as a blank at 319.6 nm using a UV/Visible double beam spectrophotometer.[22, 23]

2.4 Swelling Studies and Erosion Studies

2.4.1 Swelling index: The extent of swelling can be measured in terms of % gain by the tablet.

The swelling index was calculated using formula

% swelling = S/R * 100

Where, S = Weight of matrix after swelling

R = Weight of eroded matrix.

2.4.2 Erosion Studies.

In this method tablets were weighed initially and kept in dissolution apparatus with rotational speed of paddle 50 rpm and after each hour the tablet was removed and dried in oven at 50^0C. After cooling in the desicator these were weighed accurately and % weight loss (% erosion) was calculated using formula

% Erosion = (T- R)/ T * 100

Where, T = Initial weight of the matrix

R = Weight of eroded matrix

2.5 Dissolution test.

Drug release studies were carried out using a XXIII dissolution test apparatus (Type 2: paddle apparatus, 100 rpm, 37±0.5 ^{0}C) for 2 hrs in 0.1 N HCl (900ml) as the average gastric emptying time. Then the dissolution medium was replaced with pH 7.4 phosphate buffer solution (900ml) and tested for 3 hr, as the average intestinal transit time. Then the dissolution medium was replaced with pH 6.8 phosphate buffer solutions (900ml). At regular time interval period, 1 ml of the samples were withdrawn

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and filtered with Whatmanns filter paper (0.45 microns pore size). Each 1 ml was further diluted with appropriate dissolution medium up to 10 ml and analyzed for Ornidazole content. Dissolution study for each formulation was done in triplicate.

2.6 Preparation of coating solutions and coating of tablets.

Weighed quantity of Eudragit S100 was dissolved in Acetone in which good solubility by keeping it on magnetic stirrer at 50 rpm. After the complete solubilization of Eudragit S100, Tri- ethyl citrate was used as the plasticizer (10% of dry weight of polymers) which is the most suitable plasticizer for Eudragit S 100. Talc, Tartrazine and Titanium dioxide were used as antiadherent, coloring agent and opacifier respectively. The solution was filtered before use.

Coating process was done at a spray rate of 0.4ml/min with a nozzle to bed distance of 7 inches and a drying temp of 50^0 C.

2.7 Experimental design.

A 3^2 full factorial design was used for preparation of the formulations. The Independent variables were the ratio of Eudragit RS100 to Eudragit RL100 (X1), and coating level of Eudragit S100 (X2). The Dependent variables (responses) were amount of drug release up to 5 hr. (Y5) and amount of drug release up to 12 hrs (Y12)**.** The Independent variables and the Dependent variables and their levels for factorial design were summarized in **Table 2** and batches prepared according to **table 3**

Table 2 The Independent variables and the Dependent variables and their levels for factorial design

VARIABLES (Independent)	**LEVELS**			**VARIABLES (dependent)**
	LOWER (-1)	MIDDLE (0)	UPPER (+1)	**Y5= amount of drug release up to 5 hrs. Y12= Amount of drug release up to 12 hrs.**
X1- Ratio of Eudragit RS 100 to the Eudragit RL 100	25%	50%	75%	
X2- Coating level of Eudragit S 100	**0%**	**5%**	**10%**	

Table No. 3: Batches of Coded value and actual value of variables in factorial design

Batch No.	**Coded values**		**Actual values**	
	X_1	**X_2**	**X_1**	**X_2**
B1	-1	-1	25%	0%
B2	0	-1	50%	0%
B3	1	-1	75%	0%
B4	-1	0	25%	5%
B5	0	0	50%	5%
B6	1	0	75%	5%
B7	-1	1	25%	10%
B8	0	1	50%	10%
B9	1	1	75%	10%

2.8 Statistical analysis of data

The effects of independent variables upon the dependent variables were based on following Regression equation.

$$Y = b0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{22}X_2^2 + b_{12}X_1X_2 \quad (1)$$

The coefficients were derived using Microsoft Excel

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III. RESULTS

The calculated drug content of batches A1 – A5 were 99.68±0.20, 99.73±0.24, 100.68±0.28, 98.77±0.28 and 99.31±0.14 respectively. **Figure 1** shows the dissolution profile of formulation A1 – A5 of Ornidazole matrix tablets without coating.The results of % swelling index and% Erosion for A1 to A5 batches were shown in **Figure 2 (a and b).**

The expected in vitro release pattern selected for the colon targeting was not more than 10% of drug release up to the end of small intestine (5 hrs) and more than 85% of drug should be release up to 12 hrs. The formulation batches from B1-B9 were prepared by using 3^2 Factorial design in which X1 was the ratio of Eudragit RS 100 to the RL 100 (25%, 50%, 75%) and X2 was the coating level of Eudragit S100 (0%, 5%, 10%). Dissolution profiles of Ornidazole coated tablets from B1-B9 in 0.1 N HCl, 7.4 pH phosphate buffer & 6.8 pH phosphate buffer is summarized in **Figure 3**. From results obtained in the present study, it was observed that optimum formulation was the matrix tablet containing of Eudragit RS: Eudragit RL (1:1) which super coated with 10% coating level of Eudragit S100.

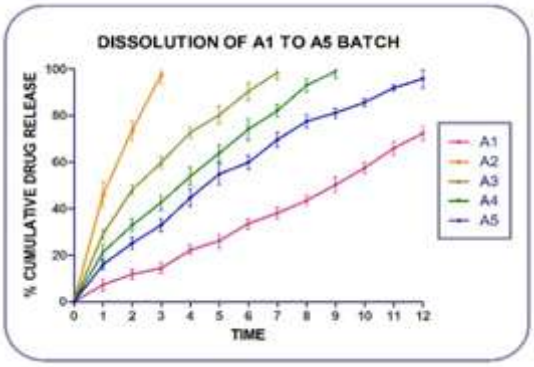

Figure 1dissolution profile of formulation A1 – A5 of Ornidazole matrix tablets

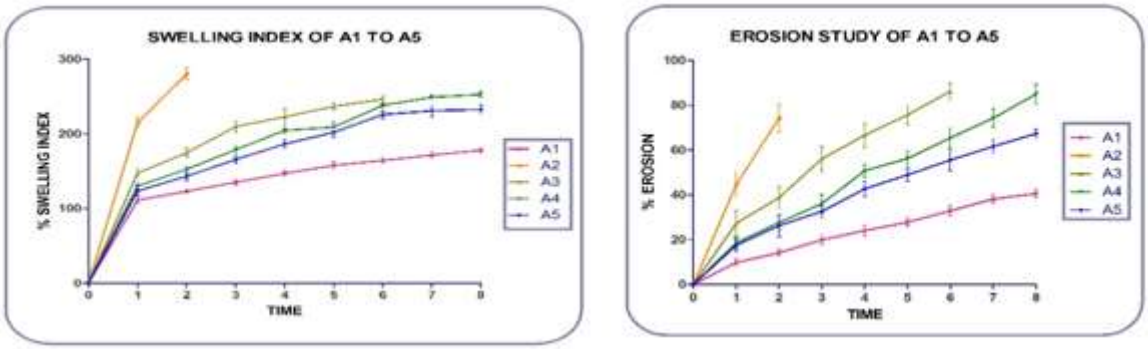

Figure 2 The results of (a) % swelling index and (b) % Erosion for A1- A5 batches

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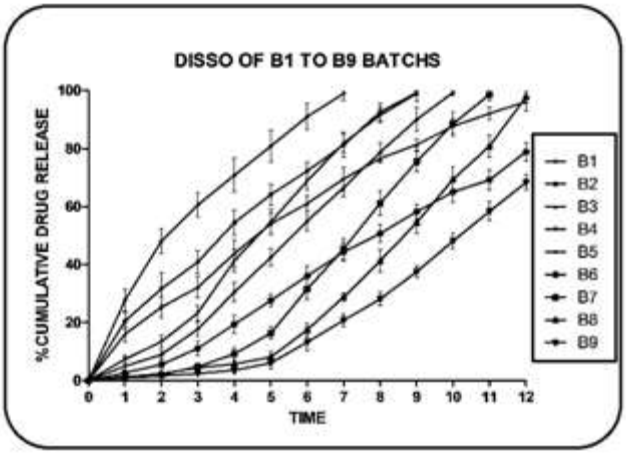

Figure 3 Dissolution profiles of Ornidazole coated tablets from B1-B9 in 0.1 N HCl, 7.4 pH phosphate buffer & 6.8 pH phosphate buffer

IV. DISCUSSION

In vitro dissolution of batch A2 indicates that the complete release of drug within 3 hrs because contain only the Eudragit RL 100 which was hydrophilic in nature. In vitro dissolution of batch A1 indicates that the only 72% of drug release within 12 hrs. Because contain only the Eudragit RS 100 which was hydrophobic in nature. In batches A3, A4 and A5 various proportion of hydrophilic and hydrophobic polymer ware taken and provide drug release within 7, 9 and 12 hrs respectively.

From the results of swelling studies it was observed that the swelling of matrix was dependent on hydrophilic and hydrophobic nature of polymers. In case of the tablets A2 containing only Eudragit RL 100, it was observed that there was an increase in swelling index; this may be due to high hydrophilicity of Eudragit RL 100. But due to presence of only the hydrophilic polymer, erosion rate of polymer was very high so ruptured within 3 hrs.

In case of swelling index of batch A3 the swelling index increased but increase was less as compared to A2, this may be due to presence of the hydrophobic Eudragit RS100 and also reduced erosion rate of formulation so ruptured within 7 hrs.

The batch A4 the swelling index was increased but increase was less as compared to A2 and A3; this may be due to reduced hydrophilic Eudragit RL 100 and increase the hydrophobic Eudragit RS100. Due to increase of hydrophobicity of the Eudragit RS100, erosion rate of polymer was decrease so do not ruptured up to 8 hrs.

The batch A5 the swelling index was increased but increase was less as compared to A4, this may be due to reduce of hydrophilic of Eudragit RL 100 and increase the hydrophobic of the Eudragit RS100 compare to batch A4. Due to increase of hydrophobicity of the Eudragit RS100, erosion rate of polymer was decrease so do not ruptured up to 8 hrs.

The tablets of batch A3, A4, A5 and A1 showed lowering the swelling index as compared to A2. But erosion rate of batch A2 was very high. In case of A3 erosion rate less compared to A2 but erode within 7 hrs. So, could not be taken as the approved batch for further study. In case of A4 the swelling were less compared to A2 and A3 and higher than A5 and A1, but the erosion were less compared to A2 and A3. So, Batch A4 was not ruptured up to target release time.

A statistical full factorial design was used in order to design various formulations. The Independent variables were the ratio of Eudragit RS100 to RL100 (X1) and Coating level of Eudragit S100 (X2). The levels of independent variable were 25%, 50%, 75% for X1 and 0%, 5%, 10% for X2.

Formulation containing RS100 in higher proportion with super coating (Eudragit S100) release very less amount of drug due to synergistic effect where possible ionic interaction between cationic ammonia groups of Eudragit RS with carboxylic group of Eudragit S100 which protect anionic group from rapid ionization and as results retard dissolution of pH dependent polymers.

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Optimization of formulation

For the optimization, the expected in vitro release pattern selected for the colon targeting was not more than 10% of drug release up to the end of small intestine (5 hrs) and more than 85% of drug should be release up to 12 hrs. Actually GI tract Transit time is 15-30 hrs yet also second dependent variable decided that more than 85% drug should be release within 12hrs because the main function of colon is absorption of water so, water amount in colon is reduced which may impede the drug release from dosage form as time progresses. Hence, a time value of 12 h was considered suitable for 85-100% release of drug from the delivery system in the colon.

The second order polynomial equations resulted from Microsoft excel for all of the responses are given below

$Y5 = 40.10667 - 10.5183X_1 - 28.2617X_2 + 1.627\ X_1^2 - 2.795\ X_2^2 + 3.795\ X_1X_2$ --------- (2)

$Y12 = 98.946 - 9.315X_1 - 4.77X_2 - 7.696X_1^2 + 0.85X_2^2 - 5.95X_1X_2$ -------- (3)

Analysis of variance (ANOVA) (**Table 5**) indicated that the selected regression models were significant and valid for each considered response.

	Source of variation	Sum of squares	Degree of freedom	Mean square	F-ratio	Significance F
Y5	Regression	5534.656	5	1106.931	98.81736	**0.001583**
	Residual	33.60537	3	11.20179	-	-
Y12	Regression	918.1382	5	183.6276	29.10413	**0.009571**
	Residual	**18.928**	**3**	**6.309333**	-	-

From the equation of regression analysis, it can be concluded that X_1 and X_2 had negative effect on response of Y_5, which indicate that as X1 and X2 increase the release of Ornidazole decrease. Result of regression analysis indicates that X2 is more significant than X1 since X2 having more negative effect as compare to X1. So, release within 5 hr is significantly affected by Eudragit S 100 coating level. Similarly X1 and X2 also had negative effect on response of Y12 but here X1 is more significant than X2 which indicate that dependent variable Y12 is significantly affected by ratio of Eudragit RS100/RL100. As a matter of fact, Eudragit RS and Eudragit RL 100 as a sustained release polymer can modify drug release after dissolution of pH-dependent polymers in different media. Finally by optimizing two factors X1 and X2, we could be delivered the drug in intact form to the colon.

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International Journal of Pharmaceutical Research and Applications
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