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STATISTICAL OPTIMIZATION FOR DEVELOPMENT OF COLON TARGETED pH DEPENDANT METRONIDAZOLE GRANULES USING FULL FACTORIAL DESIGN

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Keywords:

Quality by design, Factorial design, Colon, Metronidazole, Eudragit coating

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ABSTRACT: The objective of this study was to evaluate and optimize Eudragit concentration and coating level on metronidazole release from granules for colon delivery using 3^2 full factorial design. Independent variables selected were Eudragit conc. (10, 15 and 20%) and coating level (10, 15 and 20%), the evaluated responses were percent drug release at 5 h, 24 h and time to release 50% of the drug. The dissolution was carried out at different pH media of 1.2, 7.4 and 6.8. The dissolution data revealed that polymer conc. and coating level were having significant role in achieving optimum formulation. Using surface response, contour plot and statistical equations, the optimum formulation consisting of 15% of polymer conc. and 20% coating level was predicted. Experimental data showed that the granular formulations releases no drug at pH 1.2 (simulating stomach) and only 12.85 ± 1.63% at pH 6.8 (simulating small intestine) and controlled at pH 7.4. The result of this study showed that the factorial design is a suitable tool for optimization of coating for colon delivery. The optimized formulation produced dissolution profiles that were close to predicted values.

INTRODUCTION: Colon drug delivery system (CDDS) comprises of combination of one or more controlled release mechanisms which prevent drug release in the upper part of the gastrointestinal tract (GIT), but controlled release in the colon following oral administration. Multi - particulate delivery system are having advantages of increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying compared to single unit dosage form [1].

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Metronidazole (MTZ) (1- [2 - hydroxyethyl] - 2 - methyl - nitroimidazole) is effective against protozoal and bacterial infections. It has been a preferred drug treatment of anaerobic infections and in colonic surgery [2, 3].

It has also been effectively used against Entamoeba histolytica and Clostridium difficile infections [4] and has been included in the essential drug list by World Health Organisation [5]. But pharmacokinetic profile of MTZ indicates that drug is completely absorbed in approximately 1 h after oral administration. The administration of this drug in conventional tablet dosage forms provides a minimal amount for local action in the colon with unwanted systemic side effects [6]. The various strategies used in the literature for colon targeting through oral route include prodrugs, enzymatic

activity of colonic microflora, higher pH, colonic pressure and transit time [7]. In addition to it, overall dimensions of delivery system are significantly affecting the inflamed colon targeting. The use of pH sensitive polymers is the most practical approach for colon targeting, pH of the gastrointestinal tract (GIT) steadily increases as one moves down from stomach (pH 1–3) to terminal ileum (pH 7–8) and to 5.6–7.0, the dosage forms which disintegrate at colonic pH levels have the potential for site-specific delivery [8] and Eudragit S100 is most commonly used pH sensitive polymer used for colon targeting.

The objective of this study was to optimize the effect of Eudragit S100 conc. and coating level on MTZ granules release using quality by design (QbD) approach through 3^2 full factorial design to support and accelerate the development process of novel formulations. A QbD approach was performed not only to extract the maximum amount of information from the collected data, but also to establish the influence of several factors on the formulation [9, 10].

MATERIAL: Metronidazole (MTZ) was received ex-gratia from La Pharma Pvt. Ltd. Ludhiana, Punjab, India, β-CD, guar gum and citric acid was purchased from Central Drug House Pvt. Ltd., New Delhi, polyvinilpirrolidone (PVP) K 30 from Hi Media Labs Pvt. Ltd, Mumbai, Eudragit S100 from Sigma Aldrich, USA and microcrystalline cellulose (MCC) from Loba Chemie, Mumbai, India. All solvent used were analytical grade reagent.

Method:

Experimental Design: A full factorial 3^2 design was used for optimization procedure. The independent variables selected were Eudragit S100 conc. (X1) and coating level (X2). The dependent variables were percent drug release at 5th h (Y1), percent drug release at 24th h (Y2) and time required to release at 50% of the drug (Y3). **Table 1** summarizes the independent and dependent variables Response surface. Nine formulations were prepared and evaluated for response. The obtained data were fitted into Design Expert software 10.0.6.0 (Trial version), Stat-Ease, Minneapolis, MN). Analysis of variance (ANOVA) was used to validate design. The resulted formulations are listed in **Table 2**.

TABLE 1: EXPERIMENTAL DESIGN: FACTORS AND RESPONSES

Factor (Independent variables)	Level			Response (dependent variables)
XI = Eudragit S100 (%)	-1 (10)	0 (15)	1 (20)	Y1= Percent release at 5 h
X2 = Coating level (%)	-1 (10)	0 (15)	1 (20)	Y2= Percent release at 24 h Y3= Time to release 50% of drug

TABLE 2: COMPOSITION OF EXPERIMENTAL FORMULATIONS

Run	X1 Eudragit S100 (%)	X2 Coating level (%)
CG 1	10	10
CG 2	10	15
CG 3	10	20
CG 4	15	10
CG 5	15	15
CG 6	15	20
CG 7	20	10
CG 8	20	15
CG 9	20	20

Preparation of MTZIC Granules: MTZIC core granules were prepared by wet granulation technique using MTZIC (40%), MCC (10%), guar gum (20%), PVP K 30 (20%) [11] and Citric acid (10%) [12]. PVP K 30 was solublize in water ethanol mixture (1:2) and this was added to homogenous mixture to make wet mass. The wet mass was then passed through sieve no. 16. The resulting granules were dried in hot air oven at 40 °C for 24 h. The dried granules were then passed through sieve no. 20 and were kept in desicater till used further.

Preparation of Coating Solution: Eudragit S100 (10 - 20%) was dissolved in mixture of isopropyl alcohol (IPA) and acetone in 7:3 ratio by vigorous shaking. Castor oil (1%) as plasticizer and talc (0.5%) as dispersing was also added.

Coating of Granules: MTZIC granules (100g) were coated in a fluidized bed coating apparatus (Cronimach). The granules were preheated for 10 minutes at air flow rate of 40m^3/h and outlet temp of 400 °C ± 50 °C and spray rate was kept 1g/min. The coating solution was 10, 15 and 20% w/w solution of Eudragit S100. Samples of coated pellets were removed from the apparatus when the coating loads had reached 10, 15 and 20% (w/w). At each stage the pellets were fluidized for about 5 min and samples were kept in an oven for 2 h at

50°C. The coating process was evaluated by weighing coated granules at different time interval and the process was continued till the weight gain of 10 -20% was achieved using equation 1.

Weight gain = (W2-W1) / W1×100…… (1)

Where W1: Weight (g) of uncoated granules, W2: Weight (g) of coated granules.

Drug Content Estimation: The Eudragit S100 coated MTZIC granules were tested for drug content. Granules equivalent to 100mg of MTZ were finely powdered and transferred to 100 ml volumetric flasks containing 50ml of PBS pH 7.4 and allowed to stand for 8 hour with occasional shaking to ensure complete solubility of the drug. The solution then made up to 100ml volume with PBS pH 6.8 and mixed thoroughly. The solution was filtered, diluted and drug content was estimated spectrophotometrically using UV-Spectrophotometer at 277nm. The procedure was repeated three times and data were expressed in mean ± SD.

***In vitro* Release Studies:** The dissolution studies were performed on Eudragit S100 coated MTZIC granules according to USP XXIII guidelines (1995) using USP II dissolution apparatus in 750ml of 0.1 N HCl (pH 1.2) at 100 rpm, 37 °C ± 0.5 °C for first 2 h, then pH of the solution was raised to 7.4 by adding 200ml of 0.2 M trisodium orthophosphate dodecahydrate. After 5 h pH of the solution was adjusted to 6.8 by adding 2 M HCl [11, 13]. The dissolution media were replaced in order to simulate the pH change along the GIT. Samples (2ml) were withdrawn from the dissolution media at regular time intervals and filtered with Whatman filter paper (0.22µm), suitably diluted with PBS and analyzed spectrophotometrically using UV-Spectrophotometer (UV-1700 Pharmaspec Shimadzu, Japan) at 277nm. The procedure was repeated three times and data were expressed in mean ± SD [14].

Preparation of Rat Caecal Content for Dissolution Study: The Wistar rats aged 2-3 months old, weighing 100 -150g maintained on normal diet were used for the study. The study protocol was approved (Protocol number: IAEC/ M17/311/2016) as per the regulation of Institutional Animal Ethical Committee of ISF College of Pharmacy, Moga, Punjab, India. The enzyme induction was done by administering orally 2ml of a 1% w/v dispersion of Eudragit S100 in water was to the rats daily for 7 days. Half an hour before the starting of the study, rats were killed humanly, abdomen was opened, cecum was located, dissected and contents was removed, measured, homogenized and suspended in 6.8 pH PBS to make 4% concentration of rat caecal content. Carbon dioxide (CO_2) was continuously passed to pooled content to maintain anaerobic environment [15].

***Ex-vivo* Release Studies in Presence of Rat Caecal Content:** The *Ex-vivo* release studies were done out in same way as *in-vitro* with slight modification [16]. A 250ml beaker was taken which contain dissolution medium 100ml and then immersed water bath. The drug release for first two hours was carried out in 0.1 N HCl, next three hours in 6.8 pH PBS and then 4% of rat caecal content was added in the dissolution medium. A regular supply of carbon dioxide was given to the beaker to stimulate caecum anaerobic atmosphere. At predetermined time interval, 2ml of the samples were withdrawn and replaced with fresh media. Then the samples were analyzed using UV spectrophotometer at the λ_{max} of 277 nm.

Kinetic Analysis of Dissolution Data: To study the mechanism of drug release, the release data were fitted to different equations such as zero order ($M = kt$), first order equation ($M = \ln M_0 + kt$), Higuchi model ($M = k\sqrt{t}$) and Korsemeyer Peppas equation ($M = kt^n$). A value of $n = 0.5$ indicates case I (Fickian) diffusion, $0.5 < n < 1$ is for anomalous (non-Fickian) diffusion, $n = 1$ is for case II transport and $n > 1$ indicates supercase II transport. M is the amount of drug (%) released after time t; M_0 is the amount of drug released at zero time; k is the release rate constant and n is the exponent. Drug release following particular mechanism is adjudged by the linearity (R^2) of plot [17].

Stability Study: The stability study was conducted according to International Conference on Harmonisation (ICH) guidelines. The optimized formulation was stored in aluminium packaging laminated with polyethylene (cellophane packets) and kept in stability chamber at 30 °C ± 2 °C / 65% ± 5% RH (room temperature studies) and 40 °C ± 2 °C / 75% ± 5 % RH (accelerated temperature

studies) for 3 months. The granules were analyzed after 0 day, 1 month, 2 months and 3 months. At the end of the study period, granules were observed for the change in physical appearance, flow characteristics and drug content.

RESULT AND DISCUSSIONS: Release profile of uncoated granules showed 86.33 ± 4.33% of drug release within half an hour (**Fig. 1**). This demonstrated that MTZIC have more solubility than MTZ.

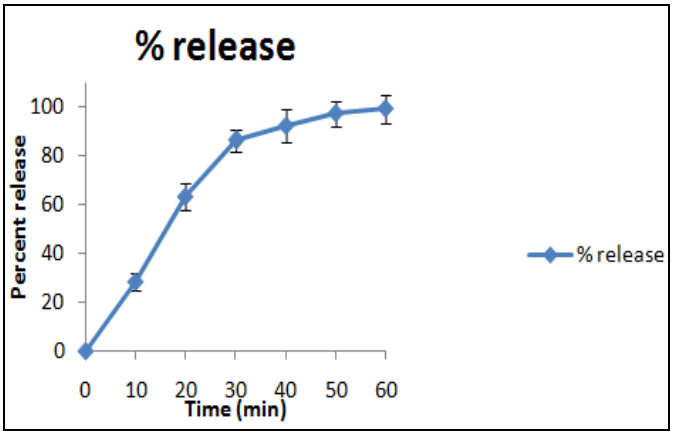

FIG. 1: RELEASE PROFILE OF UNCOATED GRANULES

Thus increases the dissolution of drug, secondly, multi-particulate delivery systems have more solubility than single unit dosage forms due to more surface area. The dissolution studies of Eudragit S100 coated granules were carried out as per the transient time of stomach and small intestine, *i.e.* 2 h stomach, 3-5 h small intestine and also with different pH media of 1.2, 6.8 and 7.4. Drug content was found to be in the range of 96.68 ± 1.55 to 99.45 ± 0.37. The release profile of Eudragit S100 coated granules at different pH media are shown in **Fig. 2**.

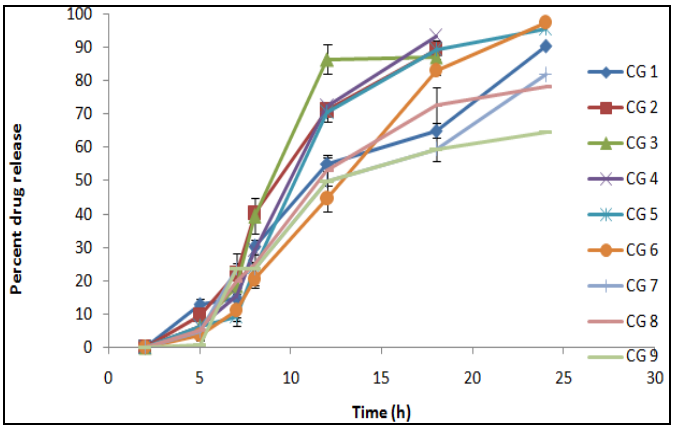

FIG. 2: RELEASE PROFILE OF EUDRAGIT S100 COATED GRANULES

At simulating stomach pH of 1.2, none of the formulation released drug and only maximum of 12.85 ± 3.32% of drug released at pH 6.8, but when pH of media was raised to 7.4, there was burst release. This was due to the fact that pH sensitive Eudragits are ionize and solublize at pH range. The release rate was slower at higher coating level because of the increased diffusion path length [8]. Colon targeting polymers should withstand at acidic conditions of stomach and should disintegrate at the neutral or slightly alkaline media [16].

The constraints used for responses were less than 20% of drug release up to 5 h *i.e.* Y1, maximum drug release till 24 h *i.e.* Y2 and time to release 50% of the drug should be between 11-12 h (Y3). The observed responses are shown in **Table 3**.

TABLE 3: OBSERVED RESULTS FOR EXPERIMENTAL RUNS

Formulation Code	X1	X2	Y1	Y2	Y3
CG 1	-1	-1	12.85	90.4	16.9
CG 2	-1	0	9.52	89.55	11.55
CG 3	-1	1	6.31	87.23	11
CG 4	0	-1	6.38	93.4	9.25
CG 5	0	0	6.21	95.54	10.66
CG 6	0	1	3.61	97.48	9.9
CG 7	1	-1	4.69	81.8	23.1
CG 8	1	0	5.28	78.39	23.35
CG 9	1	1	0.67	64.51	23.05

At these constraints, formulation close to the values was having 15% of polymer conc. and 20% of coating level. The mathematical relationship generated between independent and dependent variables using design expert software were:

$Y1 = 6.17-3.01\times A-2.22\times B$ (linear model)

$Y2 = 96.82-7.08\times A- 2.73\times B- 3.53\times AB -13.49\times A^2- 2.02\times B^2$ (quadratic model)

$Y3= 9.71+5.01\times A- 0.88\times B+ 1.46\times AB+8.22\times A^2 +0.35\times B^2$ (quadratic model)

The equations represents the quantitative effects of independent variables (X1 and X2) on dependent variables *i.e.* responses (Y1, Y2 and Y3). Co-efficient with more than one factor represents interactions between the factors and follows quadratic model. Statistical estimation was established on the basis of ANOVA. Further analysis using ANOVA indicated significant

effects of the independent factors (p > F) on response Y1, Y2, and Y3. F-value for Y1 = 21.24, Y2 = 5.85 and Y3 = 20.36, while resulted R^2 for Y1 = 0.8487, Y2 = 0.8657 and Y3 = 0.9819. Statistical models were generated for each response parameter and tested for significance (**Table 4**). Values of ''p'' less than 0.05 indicated that model terms were significant.

TABLE 4: ANOVA OF FACTORIAL MODELS FOR THE RESPONSE

Response	Source	Sum of squares	df	Mean squares	F value	p-value Prob > F	
Y1	Model	83.86	2	41.93	21.24	0.0019	Significant
	A-Polymer conc.	54.24	1	54.24	27.48	0.0019	
	B-Coating level	29.61	1	29.61	15.01	0.0082	
	Residual	11.84	6	1.97			
	Cor Total	95.7	8				
Y2	Model	767.65	5	153.53	5.85	0.0484	Significant
	A-Polymer conc.	300.76	1	300.76	11.46	0.0429	
	B-Coating level	44.72	1	44.72	1.7	0.2828	
	AB	49.84	1	49.84	1.9	0.2619	
	A^2	364.14	1	364.14	13.88	0.0337	
	B^2	8.19	1	8.19	0.31	0.6154	
	Residual	78.71	3	26.24			
	Cor Total	846.36	8				
Y3	Model	299.17	5	59.83	20.36	0.016	Significant
	A-Polymer conc.	150.5	1	150.5	51.22	0.0056	
	B-Coating level	4.68	1	4.68	1.59	0.2961	
	AB	8.56	1	8.56	2.91	0.1865	
	A^2	135.19	1	135.19	46.01	0.0065	
	B^2	0.24	1	0.24	0.082	0.7935	
	Residual	8.82	3	2.94			
	Cor Total	307.98	8				

Response Surface 3-D and Contour Plot Analysis: The obtained results can be observed visually in 3-D response surface and contour plots (**Fig. 3, 4** and **5**), the response surface graph showed that with increasing polymer conc. and coating level, the release decreases, this may be due to increased path length in coated granules, resulted in less release. Both the independent variables X1 and X2 having negative effects on Y1 *i.e.* release at 5^{th} h.

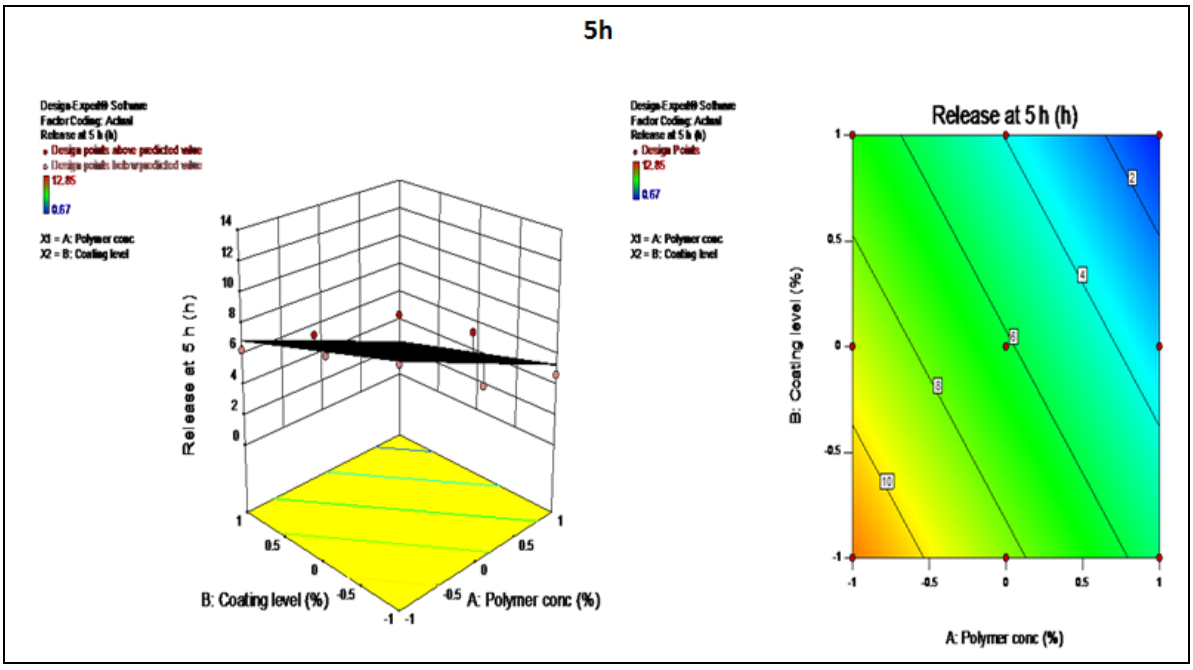

FIG. 3: RESPONSE SURFACE AND CONTOUR PLOTS FOR RESPONSE Y1

As the level of A and B increased, there was linear decrease in the release, effects on Y2 and Y3 followed quadratic model where polymer conc. played major role compared to coating level because when polymer conc. increased beyond 15%, the release was further decreased and which was not in our constraints. Thus a formulation coated with 15% of polymer at 20% coating level showed results significantly close to the predicted values (**Table 5**).

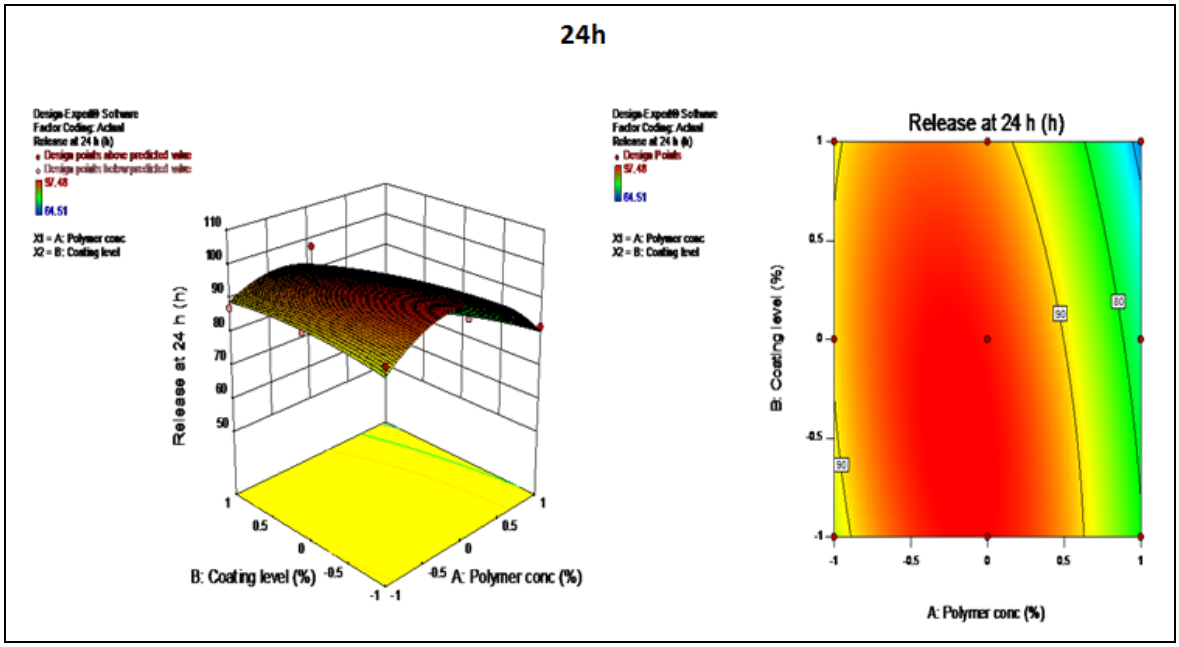

FIG. 4: RESPONSE SURFACE AND CONTOUR PLOTS FOR RESPONSE Y2

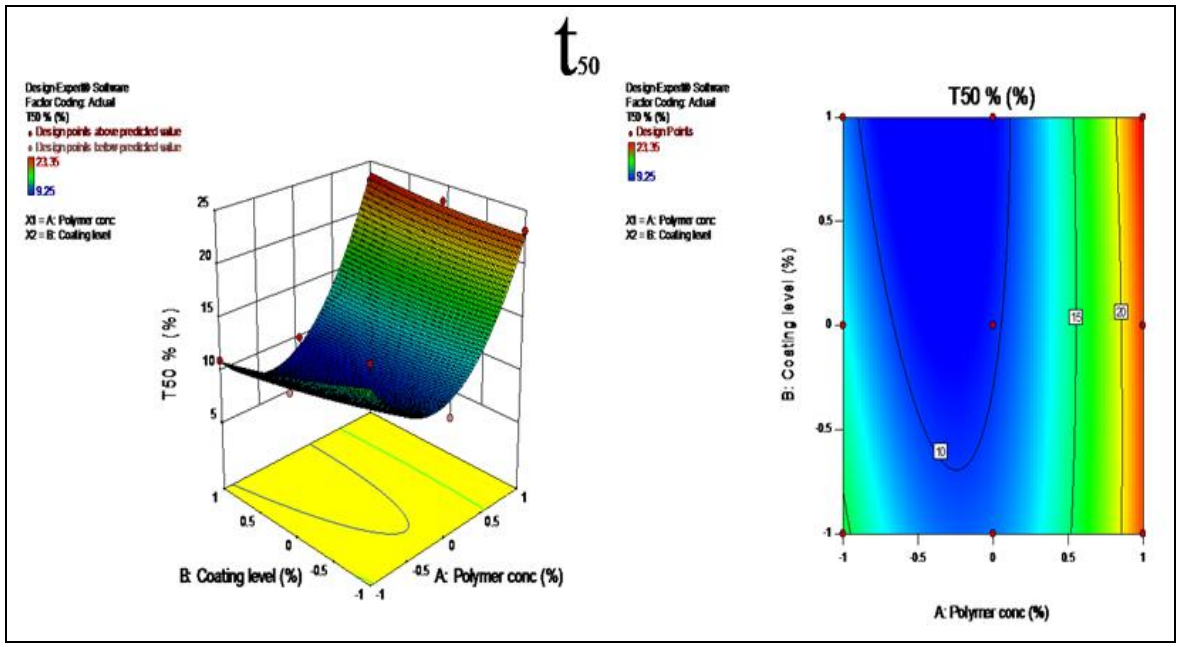

FIG. 5: RESPONSE SURFACE AND CONTOUR PLOTS FOR RESPONSE Y3

Optimization of Formulation on Desirability Approach: The search for the optimized formulation composition was carried out using the desirability function approach with Design expert software, criterion being one having the maximum desirability value. The optimization process was performed by setting the Y1 at minimum, Y2 at maximum, Y3 between 11-12 h while X1 and X2 within the range obtained. The optimized formulation was achieved at X1=0, X2=1 with the corresponding desirability (D) value of 0.768 (**Fig. 6**). This factor level combination predicted the responses Y1=3.61%, Y2= 97.48% and Y3= 9.9 h.

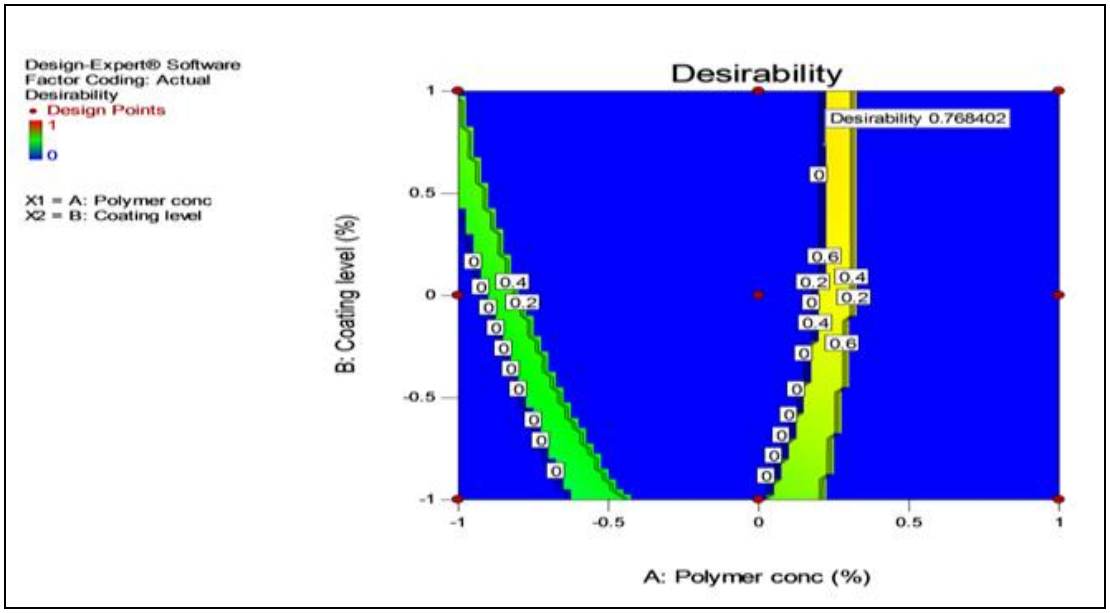

FIG. 6: OPTIMIZATION ON DESIRABILITY APPROACH

Checkpoint Analysis: The comparisons of predicted and experimental results shows very close agreement, indicating the success of the design combined with a desirability function for the evaluation and optimization of granules formulations (**Table 5**).

TABLE 5: PREDICTED AND OBSERVED RESPONSES OF OPTIMUM FORMULATION

Independent variable		Dependent variable					
X1	X2	Y1		Y2		Y3	
		Observed	Predicted	Observed	Predicted	Observed	Predicted
1	-1	3.61	4.66	97.48	95.65	9.9	10.2
Prediction error (%)		-1.05		1.83		-0.4	

Characterization of Optimized Formulation:

Release Profile Optimized Batch with and without Rat Caecal Content: There was comparatively fast release of drug when studies were conducted in the presence of rat caecal content. Time taken to release 50% of the drug was reduced to 7.45 h compared to 9.9 h in rat caecal content (**Fig. 7**). This could be explained on the basis of higher enzymatic activity, causing rapid release of the coated granules.

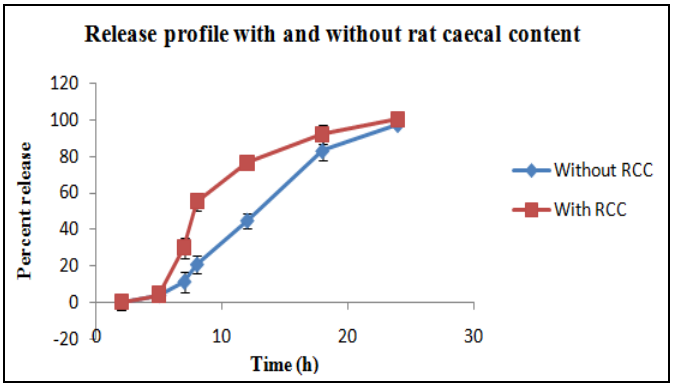

FIG. 7: RELEASE PROFILE WITH AND WITHOUT RAT CAECAL CONTENT

Kinetic Analysis of Optimized Batch: Model fitting was applied to the optimized batch (CG 6) using design expert software, zero order, first order, Higuchi, Koresmeyer Peppas and Hixon crowell models were tested. The best fitted kinetic model for drug release was selected by considering sum of squares, R^2 values and F values. A model with higher R^2 values and lower sum of squares and F values gives the best fitted model for drug release and according to the kinetic release data, best fitted model was first order.

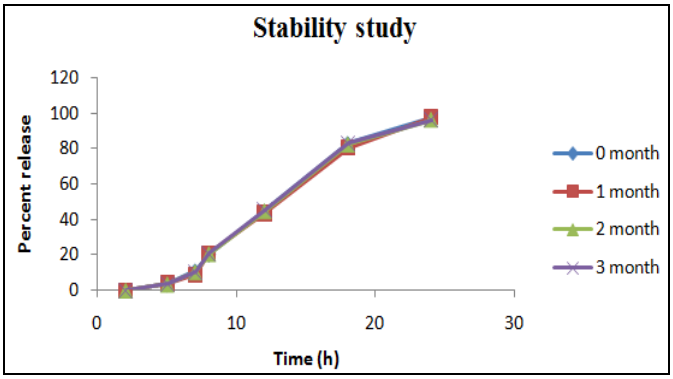

FIG. 8: STABILITY STUDY OF OPTIMIZED BATCH

Stability Study of Optimized Batch: Stability study was carried out for the optimized batch as per ICH guidelines showed no change in physical appearance and the dissolution profile for 0 month, 1st month, 2nd month and 3rd month (**Fig. 8**) were significantly same and statistical analysis also proved sameness in dissolution profile.

CONCLUSION: Factorial design used in the present study for optimization of Eudragit S100 coating can be successfully used for colon delivery. Response surface and contour plots enabled for designing formulation of desired release profile of metronidazole granules coated with pH sensitive polymer Eudragit S100 in 15% conc. at 20% coating level has potential for colonic delivery. The optimized formulation showed release profiles and responses which were close to the predicted responses.

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CONFLICT OF INTEREST: The authors declare that no conflict of interest exists with regard to this work.

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