CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1238402

Available online at: http://www.iajps.com *Research Article*

FORMULATION, OPTIMIZATION AND EVALUATION COLON TARGATED DRUG DELIVERY SYSTEM FOR ORNIADAZOLE

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Abstract:
The colon is a site where both local and systemic delivery of drugs can take place. The present investigation concerns with formulation and evaluation of Colon Targeted dip coated tablets of Ornidazole by using HPMCK4 M, Xanthan gum polymers .Initially core tablets were prepared and then coated by using Eudragit S100 as a enteric coating polymer with the help of Isopropyl alcohol, acetone (1:1) by deep coating. Optimization of colon targeted tablet of Ornidazole was carried out by using design expert software considering combination of HPMC K 4 M & Xanthan gum as independent variable & Time for 25% Drug release (hrs), Drug Release at 12 hrs as a dependent variable. All the formulations FB1 to FB9 were evaluated for the physicochemical parameters and were subjected to in vitro drug release studies. The tablets were passed all the tests. Among all the formulations FB5 formulation was found to be optimized as it was retarded the drug release up to 12 hours and showed maximum of 91.57% drug release. The results of the present study have demonstrated that developed colon targeted coated tablet were promising vehicle for preventing rapid hydrolysis in gastric environment and improving oral bioavailability of ornidazole for the treatment of disease of colon region.

Key Words: *Colon targeted, Ornidazole, Optimization, Eudragit S 100, Coating.*

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Please cite this article in press Shaikh Siraj N et al., ***Formulation, Optimization and Evaluation Colon Targated Drug Delivery System for Orniadazole,*** *Indo Am. J. P. Sci, 2018; 05(04).*

INTRODUCTION:

Now a day, various routes of administration have been explored for the effective delivery of the drug. The oral route is considered to be most convenient for the administration of drugs to patients. On oral administration of conventional dosage forms drug normally dissolves in the gastro-intestinal fluids and is absorbed from these regions of the gastro-intestinal tract, which depends upon the physicochemical properties of the drug [1-3]. It has a serious drawback in conditions where localized delivery of the drug in the colon is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT. Dosage forms that deliver drugs in the colon rather than upper GIT has number of advantages. Oral delivery of drugs in the colon is valuable in the treatment of various diseases of colon like colon cancer, ulcerative colitis, Crohn's disease and inflammatory bowel disease [4-6], IBS where by high local concentration can be achieved while minimizing side effects. Colon targeted drug delivery is used to deliver the substances that are degraded by the digestive enzymes in the stomach such as proteins and peptides. During the past decades research is going on in developing the methods to target the drug to the specific region [7,8].

Ornidazole is insoluble in acidic media and it is poorly absorbed from upper GIT tract. But it is soluble in alkaline media and it is almost completely absorbed from colon. More ever Ornidazole causes gastric Irritation in stomach when administered orally. Drug which is poorly absorbed from upper GIT tract and drug which could be used for colonic diseases is the best candidate for colon targeting. Ornidazole fulfills these criteria [9,10].

MATERIALS AND METHOD:

Ornidazole , HPMC K4 M,Eudragit S100, Xanthan gum, PVP K-30,Mg.stearate,Talc and MCC were purchased from Research Lab Fine Chem. Ltd. Mumbai .

DRUG POLYMER COMPATIBILITY STUDIES

1. Drug polymer compatibility studies were carried out using FTIR.
2. The study was carried out on individual pure drug and its physical mixture with the selected polymers under study.

PREPARATION OF COLON TARGETED ORNIDAZOLE TABLETS

Ornidazole, Hpmc K4 M, Xanthan gum, PVP K-30 and microcrystalline cellulose, were taken in required quantities mixed and passed through #60 sieves, lubricated with magnesium stearate and talc then was compressed into tablets by compressed on tableting machine (Rimek Mini Press-II, Karnavati Engineering Ltd.) by using 9 mm punch. The tablets were further coated with Eudragit S 100 solution of coating solution. A coating solution of Eudragit S 100 was prepared in a mixture of Isopropyl alcohol, acetone (1:1). The coating of matrix tablet was prepared by immersion in the coating solution followed by deep coating technique.

Table no.1 Composition of colon targeted tablets Ornidazole

Sr no.	Batch code	Ornidazole	HPMC K-4 M	Xanthan gum	PVP K-30	Talc	Mg stearate	MCC	Total
1	FB1	100	40	60	40	5	5	100	350
2	FB2	100	40	80	40	5	5	80	350
3	FB3	100	40	100	40	5	5	60	350
4	FB4	100	50	60	40	5	5	90	350
5	FB5	100	50	80	40	5	5	70	350
6	FB6	100	50	100	40	5	5	50	350
7	FB7	100	60	60	40	5	5	80	350
8	FB8	100	60	80	40	5	5	60	350
9	FB9	100	60	100	40	5	5	40	350

*** All ingredients are in mg.**

EVALUATION OF COLON TARGETED ORNIDAZOLE TABLETS

a) Hardness test:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness of core tablets was determined using Monsanto hardness tester. It is measured in kg/cm2. Three tablets were randomly picked from each batch and analyzed for hardness.

b) Thickness: Thickness of Core tablets were measured using a vernier calipers. Three tablets of each formulation were picked randomly determined. It is measured in mm.

c) Friability: Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions, the tablets were deducted and weighed again. The percentage friability was measured using formula.

$$\% F = \{1-(Wt/W)\} \times 100$$

Where, % F = Friability in per
W = Initial weight of tablets
Wt = Weight of tablets after revolution

d) Weight variation: To study weight variation 20 tablets of each colon specific formulation were weighed separately using a electronic balance and the test was performed according to the official method.

e) Uniformity of drug content:

The prepared Ornidazole tablet was tested for their drug content. Ten tablets of each formulation were weighed and finely powdered. Powder taken equivalent to dose of drug and completely dissolved in pH 6.8 phosphate buffers and the solution was filtered. 10 ml filtrate was suitably diluted with phosphate buffer pH 6.8 and analyzed for drug content in spectrophotometry atλ_{max}319 nm.

f) *In-vitro* release studies:

Prepared colon targeted tablet were placed in vessels of dissolution USP type 1 apparatus (Basket method) at 100 rpm and 37 ±0.5 ,containing 900 ml of 0.1 N HCl for first 2 hrs then replaced by phosphate buffer (pH 6.8) solutions as dissolution medium up to 12 hrs. At pre-determined time intervals, 1ml samples were withdrawn and replaced with equal volumes of fresh buffer medium. Withdrawn test samples were filtered and analyzed by using uv-visible spectrometer.

RESULT AND DISCUSSION:

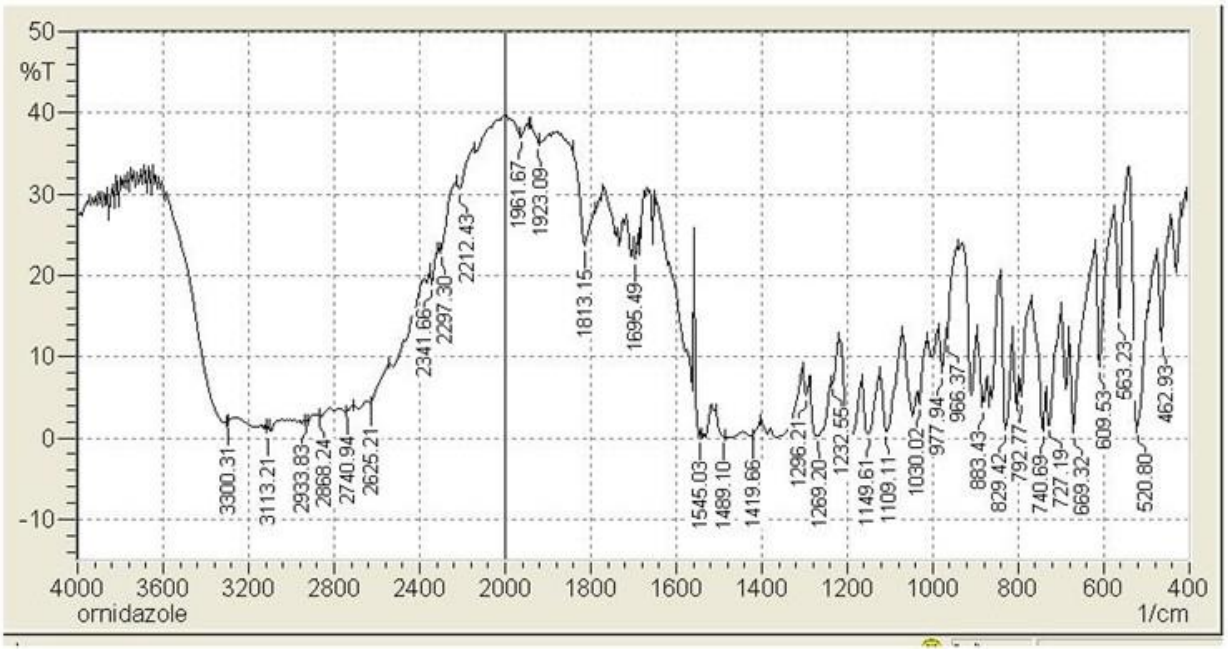

Fig.1: FTIR spectra of Ornidazole

The IR spectrum of pure drug was found to be similar to their reference standard IR spectrum of Ornidazole given in British pharmacopoeia

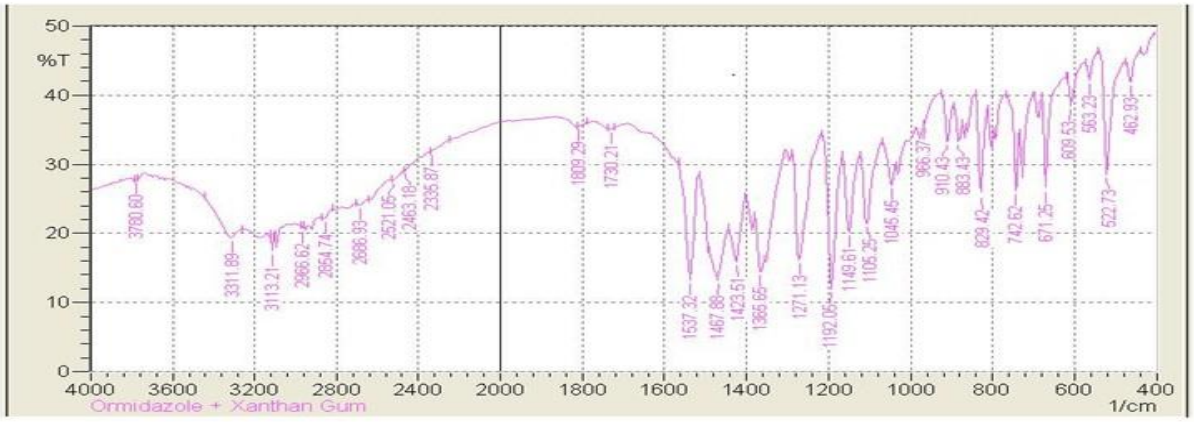

Fig.2: FTIR spectra of Ornidazole+Xanthan gum

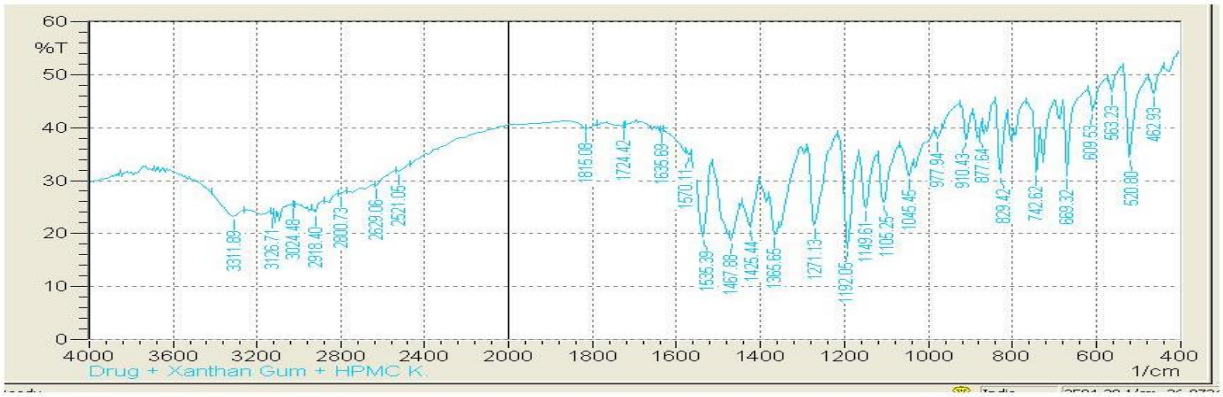

Fig.3: FTIR spectrum of Ornidazole +HPMC K4 + Xanthan Gum in formulation blend

From FTIR study it can concluded that the drug Ornidazole have maintained its identity without losing its characteristic properties in formulation blend.

Table 2: showing physicochemical properties of colon targeted tablets batches FB1to FB9

Batch	Hardness (kg/cm^2	Thickness (mm)	Weight variation (mg)	% Friability	Drug Content (%)
FB1	4.6	3.46 ±0.05	353.2 ±2.19	0.46 ±0.15	98.15
FB2	4.5	3.5 ±0.1	355.5 ±2.64	0.35 ±0.18	98.75
FB3	4.6	3.4 ±0.15	354.3 ±2.45	0.43 ±0.05	97.56
FB4	4.5	3.5 ±0.1	352.5 ±2.25	0.6 ±0.1	96.45
FB5	4.3	3.5 ±0.2	353.9 ±2.58	0.5 ±0.1	98.50
FB6	4.4	3.4 ±0.4	352.7 ±1.65	0.6 ±0.1	98.73
FB7	4.5	3.5 ±0.2	354.8 ±2.04	0.36 ±0.11	97.30
FB8	4.7	3.4 ±0.05	354.15 ±1.78	0.48 ±0.10	96.94
FB9	4.5	3.5 ±0.36	353.2 ±1.75	0.59 ±0.07	98.49

All the tablet formulations were subjected for evaluation according to various official specifications and other parameters. Shape, thickness, hardness, friability, weight variation, thickness and, in vitro drug release study. All tablets have shown smooth appearance.

Formulated colon targeted tablet has showed smooth flat surface and was white in colour colon targeted

tablet was found to be 3.4-3.5 mm. weight variation was found within the pharmacopoeia limits of ±10%. Hardness colon targeted tablet was found to be 4.3 to 4.7 kg/cm2 . Friability value of colon targeted tablet was found to be 0.35 to 0.60% indicates that core tablet possess good mechanical strength. Result for % Drug Content for all batches was found to be from 96.56 to 98.75 % which was within the approved limit (95 to 105 %) indicates that all batches passed the % Drug Content test. Results for all above tests were tabulated in table no.2.

b) *In Vitro* Dissolution Study

In vitro Drug Release Study of colon targeted batches FB1to FB9

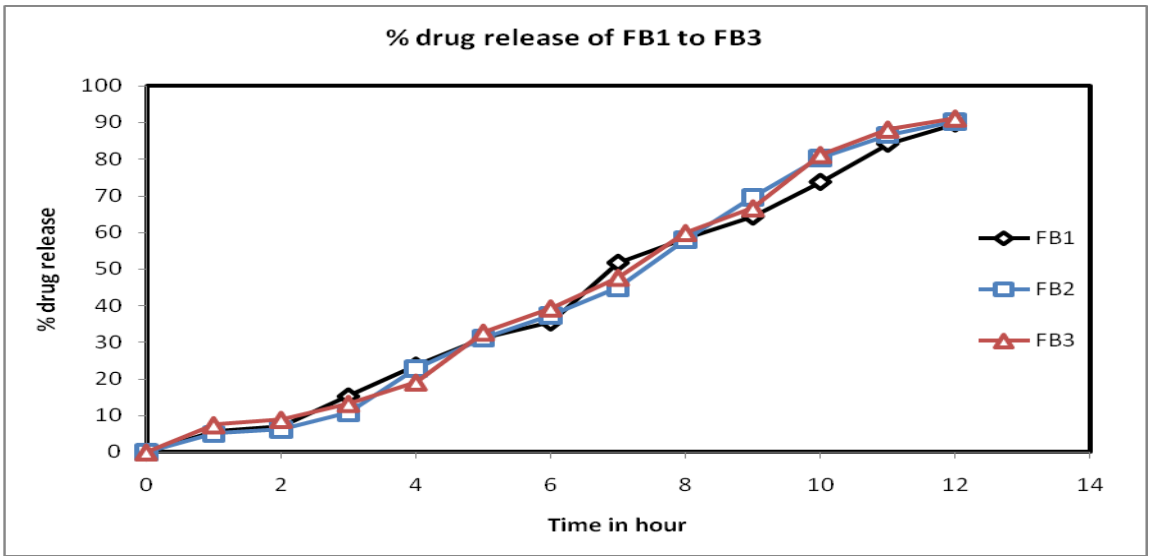

Fig.4: Time v/s %CDR of FB1 to FB3 Batches

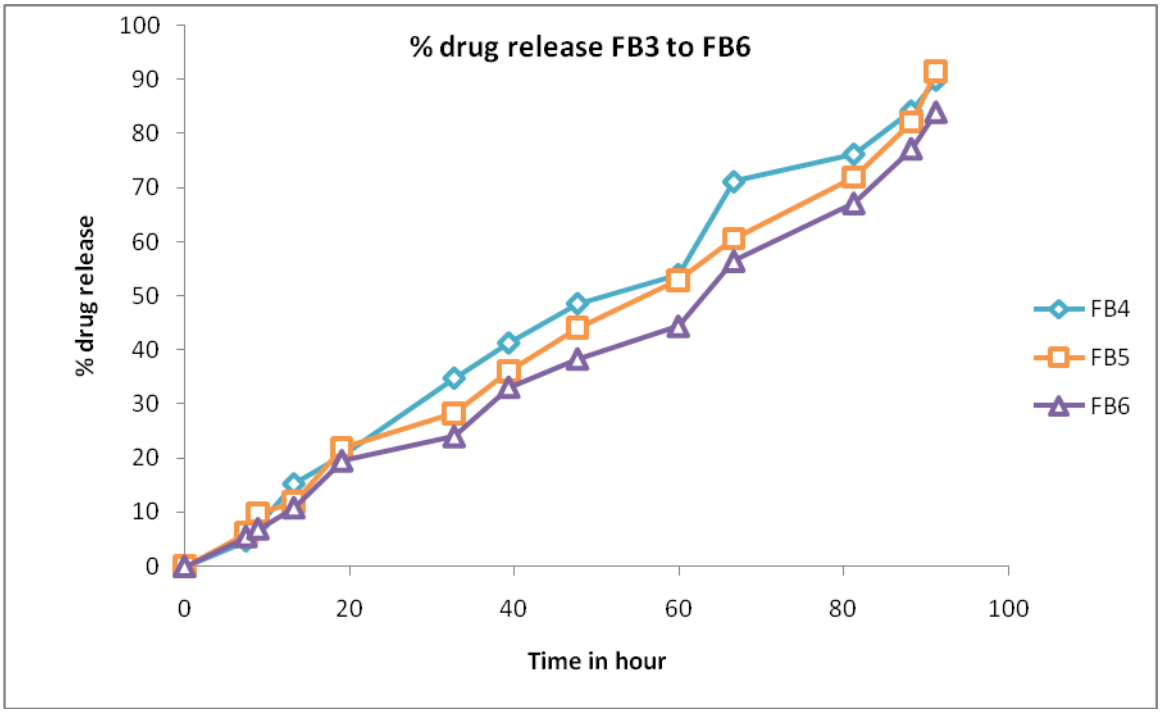

Fig.5: Time v/s %CDR of FB3 to FB6 Batches

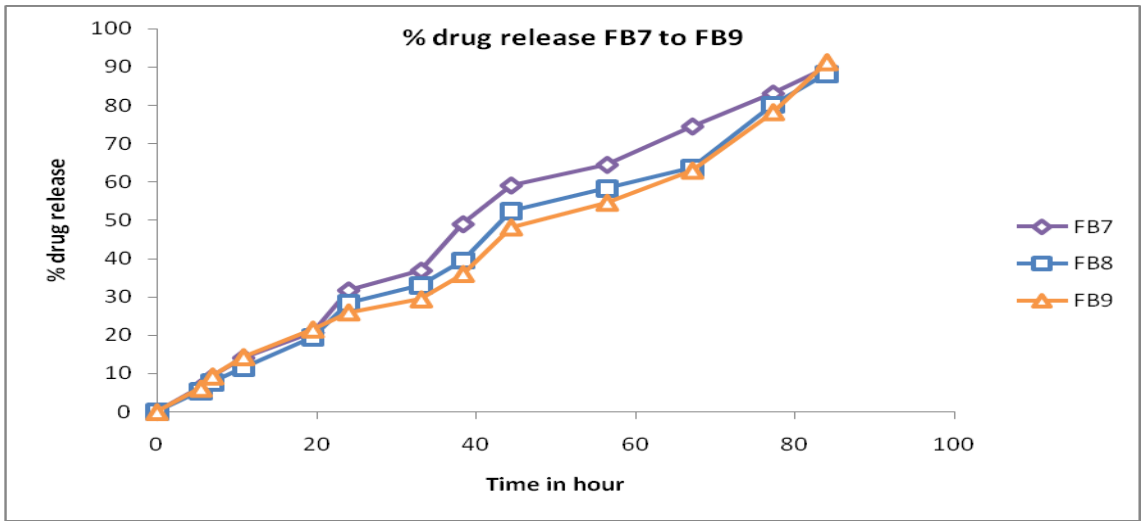

Fig.6: Time v/s %CDR of FB7 to FB9 Batches

The Time v/s Cumulative % Drug release graph of batches FB1-FB9 was shown in Figure 4,5 &6. FB5 batch of colon targeted tablets containing Ornidazole has shown 91.57% drug release in 12 hrs so it was selected as an optimized batch.

Optimization study

Optimization of colon targeted tablet of Ornidazole was carried out by using design expert software considering combination of HPMC K 4 M & Xanthan gum as independent variable & Time for 25% Drug release (hrs.), Drug Release at 12 hrs. As a dependent variable. Optimized formulation shows release of drug profile and response was close to the predictable value.

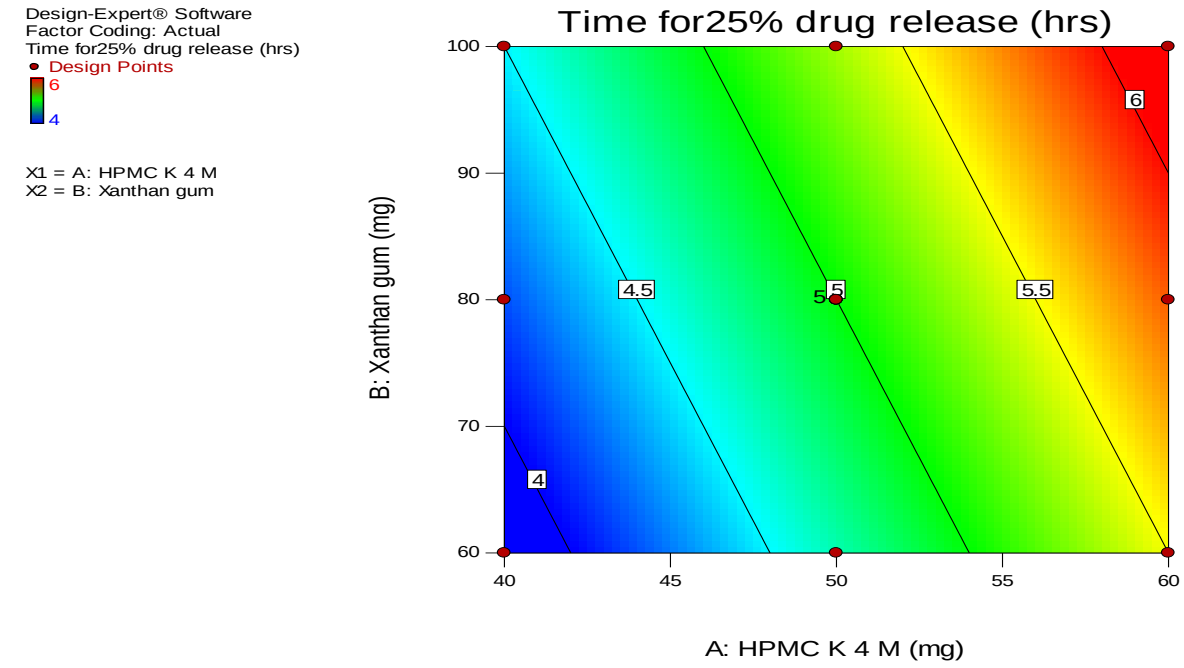

Fig.7: A counter plot showing relationship between various levels of independent variables to gain fixed value of 25% drug release.

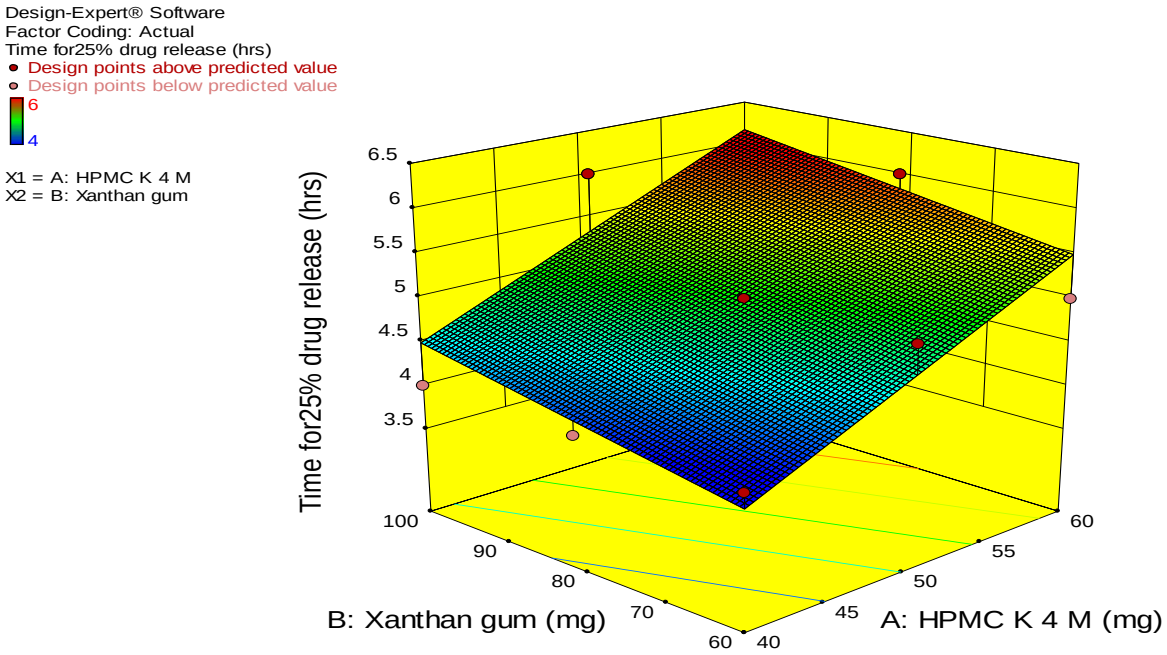

Fig.8: A response surface plot showing effect of concentration of independent variables on the 25% drug release.

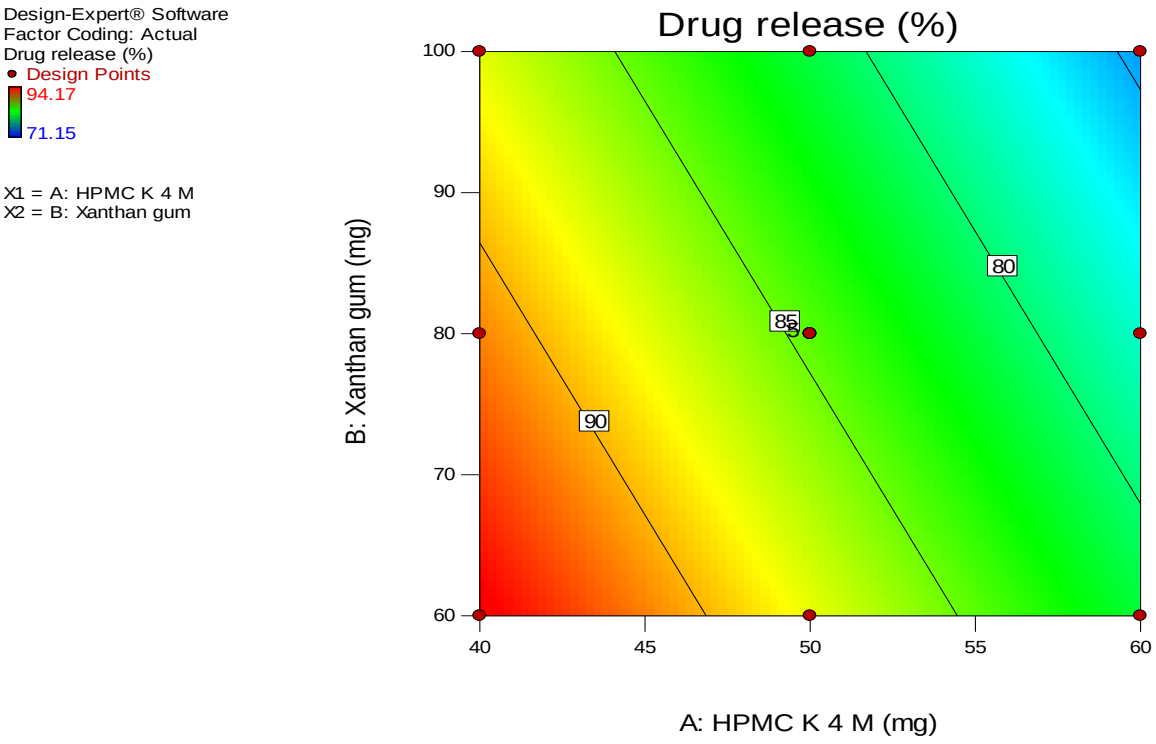

Fig.9: A counter plot of showing relationship between various levels of independent variables to gain fixed value of Drug Release (%).

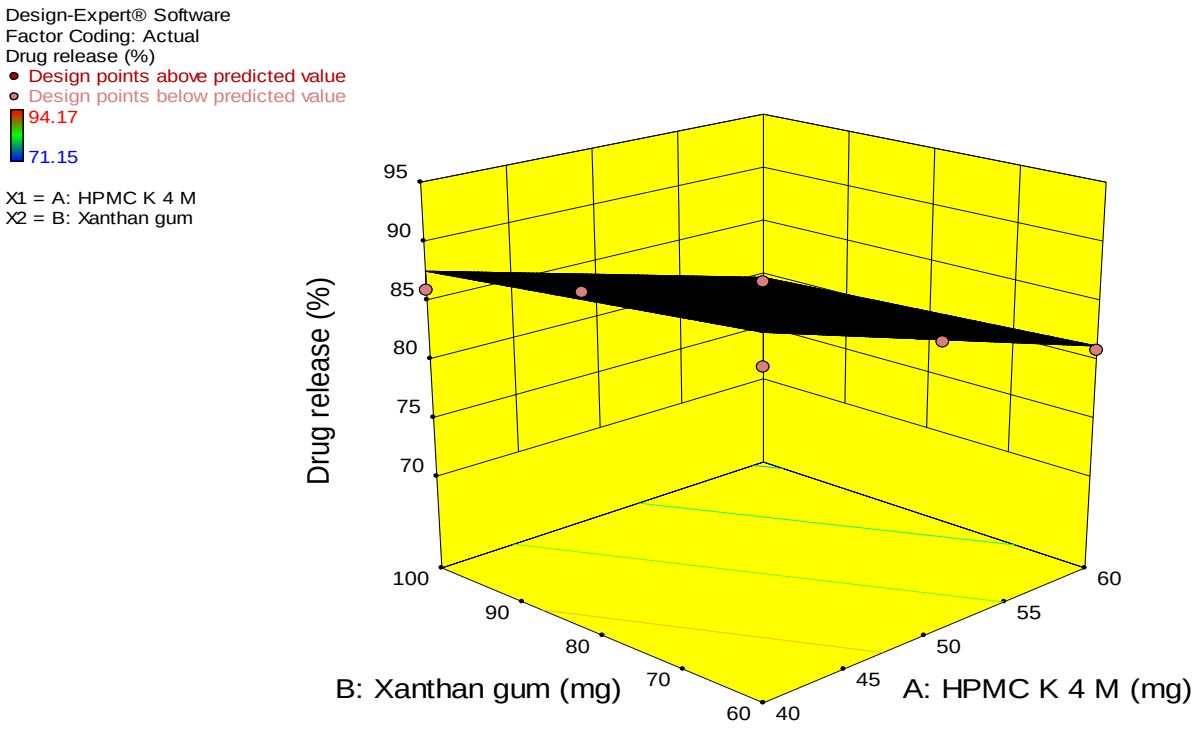

Fig.10: A response surface plot showing effect of concentration of independent variables on Drug Release (%).

Table 3: showing results of Anova

Response model	Sum of square	Degree of freedom	Mean square	F value	P value	R square	Model significant/non-significant
Drug Release (%)	**363.99**	12	168.03	47.14	< 0.0001	0.9041	Significant
Time for 25% Drug release (hrs)	6.00	12	2.54	20.71	0.0003	0.8056	Significant

CONCLUSION:

From the IR study and physical observation it could be concluded that there was no significant Drug-Excipients interaction. So Formulations were subjected to Evaluation of all physicochemical parameters. Developed film coated colon targeted tablets possessed the required physicochemical parameters such as hardness, friability, weight variation, drug content. Optimization study indicates feasibility of model for colon targeted drug delivery. Optimized formulation FB5 of colon targeted tablets containing Ornidazole has shown 91.57% drug release in 12 hrs. This developed dosage form will be beneficial for treating various diseases of colon.

ACKNOWLEDGEMENT:

The authors are thankful to Hazrat MaulanaG.M.Vastanvi Sahab, President, Akbar Patel Sir Coordinator of JamiaIslamia Ishaatul Uloom's Ali Allana College of Pharmacy Akkalkuwa,Dist-Nandurbar for providing the work facilities.

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