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Research Article

FORMULATION DESIGN AND DEVELOPMENT OF ENTERIC COATED MATRIX TABLETS OF ORNIDAZOLE FOR COLONIC DELIVERY

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ABSTRACT

In the present study a novel colon specific drug delivery system of an Anti-amoebic drug (Ornidazole) for treatment of colonic diseases like Diverticulitis, inflammatory bowel syndrome, Chron's diseases was developed. Matrix tablets of Ornidazole were prepared by wet granulation method using matrix forming natural polymers like Guar gum and Xanthan gum in combination with different proportions. The further effect of enteric coat on the matrix tablets for colon specific drug release was investigated. The Ornidazole optimized matrix formulation OM1 shows drug release around 32.37±0.33% in 2 hrs. So it was further enteric coated with 5% Eudragit® S100 and coded as OME1 which showed 44.09±0.16% of drug release after 12 hrs. All formulations were subjected to Hardness test, Friability test, determination of uniform diameter and thickness, drug content for optimization and further evaluation. *In vitro* dissolution studies indicated that the drug release in upper part of GIT from matrix tablets of Ornidazole can be prevented by enteric coating with pH sensitive polymer (Eudragit®S100), which releases the drug specifically in colonic region to achieve target delivery.

Keywords: Ornidazole; Xanthan gum; Guar gum; Eudragit®S100, *in vitro* drug release; Colon-Specific Drug Delivery.

INTRODUCTION

The Colonic Drug Delivery Systems have recently gained importance for delivering a variety of drugs. Colonic drug delivery may be achieved by either oral or rectal administration. Rectal administrations of drugs for colon targeting always face high variability in the distribution of drug, when they are administered in form of dosage forms like enemas and suppositories, which are not always effective. Therefore, the oral route is the most preferred. Conventional oral formulations dissolve in the stomach or intestine and are absorbed from these regions. The major obstacle with the delivery of drugs by oral route to the colon is the absorption and degradation of the drug in the upper part of the gastrointestinal tract (GIT) which must be overcome for successful colonic drug delivery[1].

In conditions where localized delivery of the drugs is required in the colon or drugs which are prone to degradation in the environment of the upper GIT, colonic drug delivery may be valuable. Drug release at this site will ensure maximum therapeutic benefits. Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, Crohn's disease, Diverticulitis, Carcinomas and infections) whereby high local concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or help to avoid unnecessary systemic absorption of the drug. Ulcerative colitis is the inflammatory disease of the colonic mucosa which is usually treated with salicylates or glucocorticoids. However, during the periods of remission, Ornidazole is the drug of choice. In this case it is desirable to localize the release of Ornidazole to the afflicted site in the colon. Thus, Ornidazole was used as a model drug in the present study[2].

Ornidazole, a 5-nitroimidazole derivative with anti-protozoal and anti bacterial properties against anaerobic bacteria was selected as a drug of choice to develop multilayered tablet formulation to minimize the influence of the stomach emptying time on drug release and to guarantee that the tablet could enter the small intestine intact for treatment of some colonic diseases like ulcerative colitis, irritable bowel syndrome[2].

MATERIALS AND METHODS

Materials

Ornidazole was obtained as a gift sample from Micro Lab. Limited, Chennai, India, Eudragit®S100 from Rohm Pharma, India. Guar gum, Xanthan gum, Micro crystalline cellulose (MCC), Poly vinyl pyrolidine (PVP), Aerosil, purchased from Lobachemie, Mumbai, India. All the other chemicals and solvents used were of laboratory reagent grade.

EXPERIMENTAL METHOD

Characterization of drug and analytical studies

The drug was characterized for Physical appearance, Solubility, UV spectral analysis, IR Spectral analysis.

Drug Polymer Interaction Study by FTIR Analysis

To eliminate the possibility of polymer interfering with the analysis of drug, Infra-red spectrum was taken by using the Shimadzu, FTIR model no. affinity-1 by scanning the sample in potassium bromide (KBr) discs. Before taking the spectrum of the sample, a blank spectrum of air background was taken. The sample of pure drug, pure polymer and the formulations/physical mixtures containing both the drug and polymer were scanned which were stored at 40°C/75%RH for 1month prior the study carried out.

Formulation of Ornidazole Matrix tablets[3]

Matrix tablets of Ornidazole were prepared by wet granulation method using Guar gum, Xanthan gum in combination as matrix forming agent in different proportions (Table 1). Microcrystalline cellulose was used as diluent.Tablet formulations (OM1 to OM5) were blended and granulated with 5% of polyvinyl pyrrolidone K-30 in isopropyl alcohol. The wet mass passed through mesh sieve no. 18# and the granules were dried in Hot air oven for 15-20 minutes at 60^{0}C. The dried granules were sieved through mesh sieve no. 22#, lubricated with Aerosil and Talc mixture and the granules compressed on a multi-punch tablet machine (Rimek, karnavati Engineering Pvt., Ahmedabad, India) using 13 mm round slightly concave punches with constant compression force around 20 KN. All the tablet formulations under study were assessed for their drug content uniformity, hardness, weight variation, friability and *in vitro* drug release study.

Table 1: Composition formula for Ornidazole matrix tablet (single tablet)

Sl. no.	Ingredients	Formulation codes				
		OM1	OM2	OM3	OM4	OM5
1	Ornidazole	100	100	100	100	100
2	Guar gum	125	150	175	200	225
3	Xanthan gum	125	100	75	50	25

4	P.V.P K-30	20	20	20	20	20
5	Microcrystalline cellulose	25	25	25	25	25
6	Aerosil	2	2	2	2	2
7	Talc	3	3	3	3	3
	Total weight	**400**	**400**	**400**	**400**	**400**

Preparation of enteric coated Ornidazole Matrix tablets[4,5]

The outer coating layer was applied on the matrix tablets using dip coating method. An organic polymer solution consisting of 5% w/v Eudragit® S100 in acetone was used for the coating. Castor oil was incorporated in the coating solution as a plasticizer (20% w/w based on the polymer). An Opacifier, titanium dioxide (0.05% w/w) and an antiadherant, talc (5% w/w) to prevent adhering of tablets during the coating process were also added to the coating solution.

The enteric coated Ornidazole matrix tablets (OM1 to OM5) with 5% Eudragit®S100 solution, were coded as OME1 to OME5.

EVALUATION OF COLONIC TABLETS OF ORNIDAZOLE

Physical characterization of tablet

All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and reported for further optimization and evaluation.

Drug content uniformity[6,7]

Ten tablets from each formulation were powdered and a quantity equivalent to 100 mg of drug content was dissolved in 100 ml of phosphate buffer pH 6.8. 10ml of filtrate was suitably diluted and analyzed for drug content by spectrophotometry at 319nm.

In vitro drug release study from tablets[8,9,10]

In vitro drug release studies were carried out using USP apparatus (Paddle type, Lab India Tablet Dissolution apparatus, Mumbai, India) at 100 rpm, 37 ± 0.5°C and 900 ml dissolution medium by buffer change technique. Tablet bearing Ornidazole were suspended in simulated gastric fluid pH 1.2 (900 ml), for 2hr. The dissolution media was then replaced with mixture of simulated gastric fluid and simulated intestinal fluid pH 4.5 (900 ml) for next 2hrs, then for next 2 hrs simulated intestinal fluid pH 6.8 (900ml) and the release study was carried out further in simulated intestinal fluid (900ml) pH 7.4.

Samples were withdrawn periodically and compensated with an equal amount of fresh dissolution media. The samples were analyzed for drug content by measuring absorbance at corresponding λmax of the dissolution medium, using UV- spectrophotometer (UV-18OO, Shimadzu, Japan). The percentage cumulative release for Ornidazole was calculated over the sampling times using Beer Lambert's curve generated in the respective medium. Studies were performed in triplicate and the mean cumulative percentage of drug calculated (± SD) and plotted against time.

Drug release data model fitting

The suitability of several equation that are reported in the literature to identify the mechanisms for the release of drug was tested with respect to the release data up to the first 50% drug release. The data were evaluated according to the following equations:

Zero order model[11]

$$Mt = M_0 + K_0 t$$

Higuchi model[12]

$$Mt = M_0 + K_H \sqrt{t}$$

Korsmeyer-Peppas model[13]

$$Mt = M_0 + K_0 t^n$$

Where 'Mt' is the amount of drug dissolved in time 't'. 'M' is the initial amount of the drug. K_0 is the Zero order release constant, K_H is the Higuchi rate constant, K_k is a release constant and n is the release exponent that characterizes the mechanism of drug release.

RESULTS AND DISCUSSION

Characterization of drug and analytical studies

After selection of model drug (Ornidazole), through analytical study and characterization of the drug was done. The UV spectral analysis showed the maxima at 277nm in Hydrochloric acid buffer pH 1.2, at 320nm in phosphate buffer solution pH 4.5, at 319nm in phosphate buffer solution pH 6.8,and at 319nm in phosphate buffer solution pH 7.4, which is relevant to literatures and the monograph for Ornidazole.

Drug Polymer Interaction Study by FTIR Analysis

FTIR was performed on Ornidazole, PVP K 30 and solid dispersion of Ornidazole with all carriers. The IR spectra of solid dispersion (Figure 2) showed all the principal IR absorption peak of Ornidazole at 3174.00 cm-1, 1536.37 cm-1, 1361.80 cm-1, 1268.25 cm-1, 1150.59 cm-1, 828cm-1. FTIR of formulations of drug and polymers used in studies shows that all the peaks of drug and polymer as it is and drug is present in free form. This indicates that there is no Chemical interaction in between Ornidazole and the polymers employed in formulations.

Formulation and In vitro Characterization of Ornidazole Colon specific tablets

The Ornidazole matrix tablet formulations were prepared successfully by wet granulation method, using the combination of Guar gum and Xanthan gum in different proportions (OM1 to OM5) as rate retarding and matrix forming polymers (The composition of the Ornidazole matrix tablet formulations were shown in Table 1). The matrix tablets were further enteric coated with Eudragit® S100 (5% found to be optimized,coated tablets were coded as OME1 to OME5).

All the tablet formulations under study were assessed and characterized for weight variation, hardness and friability, disintegration time, drug content uniformity. data were found to be satisfactory as revealed in Table 3.

In vitro drug release Studies[14,15,16]

In vitro drug release study was done by buffer change method to mimic the GI environment and the drug release study was continued for 12 hours for all formulations in order to check the variability of the drug release pattern. The drug release kinetics and mechanism of drug release was studied by fitting the *in vitro* dissolution data into different kinetic models like zero order, first order, Higuchi's model and Korsemeyer-peppas model.

The tablet formulations were subjected to *in vitro* drug release rate studies in SGF (pH 1.2) for 2 hrs and in mixture of SGF and SIF (pH 4.5) for next 2 hrs in order to investigate the capability of the formulation to withstand the physiological environment of the stomach and small intestine. The Ornidazole matrix tablets optimized formulation OM1 shows desired drug release 58.11±0.26% after 12 hrs as it is composed of equal amount of Xanthan gum and guar gum (125:125), but it releases around 32.37±0.33% of drug in 2 hrs. So it was further enteric coated with 5% Eudragit® S100 coded as OME1. It prevents the drug release in upper part of GIT and shows 44.09±0.16% of drug release after 12 hrs as compared than other formulations.

Table 2: UV Spectral analysis of Ornidazole in different buffer solutions of varying pH conditions and determination of λmax

Sl. no.	Solvents	Max. Wavelength (λmax)	Absorbance* at corresponding λmax
1.	HCl Acid Buffer pH 1.2	277 nm	0.272 ± 0.003
2.	PBS pH 4.5	320 nm	0.405 ± 0.004
3.	PBS pH 6.8	319 nm	0.404 ± 0.005
4.	PBS pH 7.4	319 nm	0.433 ± 0.008

***Value expressed as mean ± SD (n=3), PBS- Phosphate buffer solution**

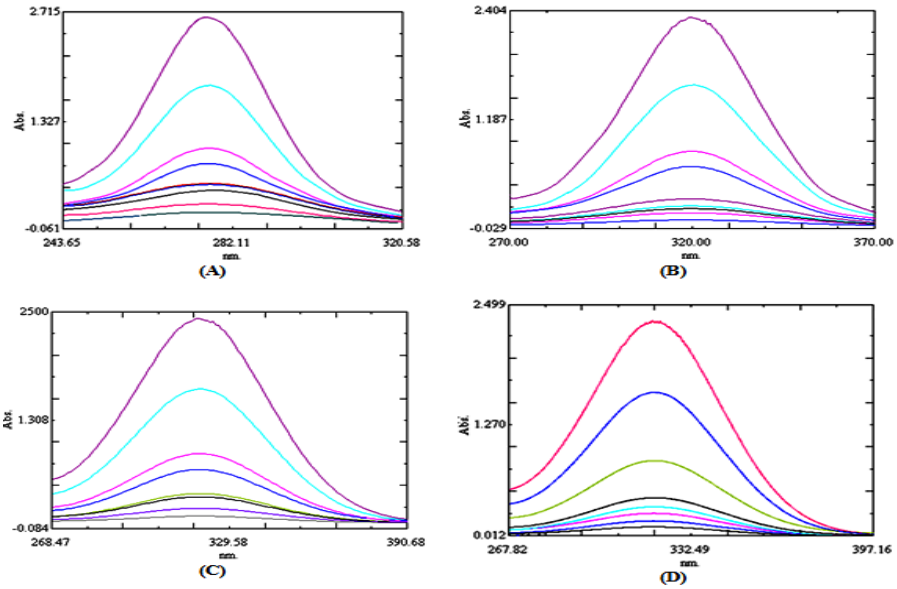

Figure 1: Overlay Spectra Of Ornidazole (A) In Hydrochloric Acid Buffer pH 1.2, (B) In Acetate Buffer pH 4.5, (C) In Phosphate Buffer pH 6.8, (D) In Phosphate Buffer pH 7.4

Table 3: FTIR Peak Interpretation Of Ornidazole

Sl. No.	Assignment	Reported Peak (cm^{-1})	Observed Peak (cm^{-1})
1.	O-H stretching mode asymmetric	3174.1	3174.00
2.	NO_2 stretching mode	1536.9	1536.37
3.	NO_2 stretching mode symmetric	1361, 1269.5	1361.80, 1268.25
4.	C-O stretching mode	1149	1150.59
5.	C-N, N_2 stretching mode	828	828.46

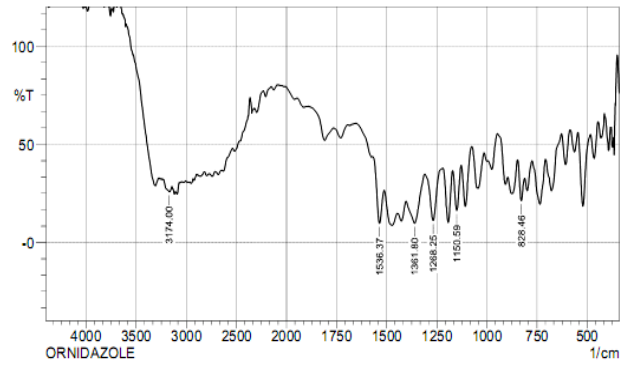

Figure 2: FTIR spectra of pure Ornidazole

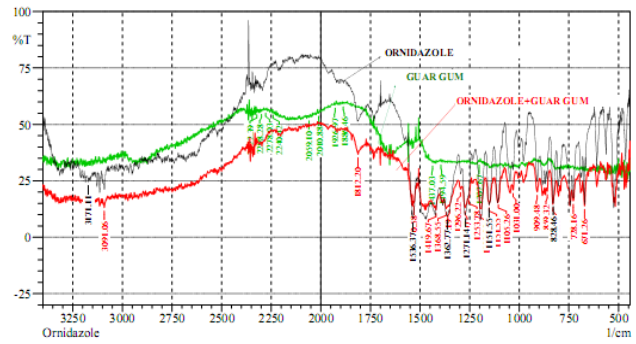

Figure 3: FTIR overlay spectra of Ornidazole, guar gum, Ornidazole and guar gum physical mixtures

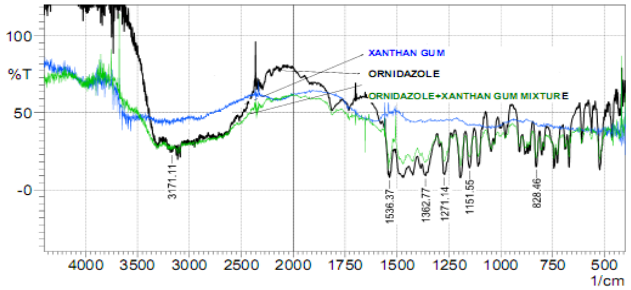

Figure 4: FTIR overlay Spectra of Ornidazole, Xanthan Gum, Ornidazole and Xanthan Gum Physical Mixtures

Table 4: Evaluation parameters of Ornidazole Matrix tablets

Test parameters	Formulation code				
	OM1	OM2	OM3	OM4	OM5
Hardness* (kg/cm^2)	5.3 ± 1.1	5.4 ± 1.5	5.3 ± 1.6	5.4 ± 1.4	5.4 ± 1.1
Diameter (in mm)	9.566	9.567	9.571	9.569	9.567
Thickness (in mm)	5.414	5.416	5.420	5.416	5.418
% Friability	0.567	0.532	0.565	0.565	0.423
Weight variation test	Passes	Passes	Passes	Passes	Passes
Drug content* (mg)	95.62 ± 0.38	94.85 ± 0.38	95.25 ± 0.53	95.53 ± 0.42	95.01 ± 0.20

***All values are expressed as mean ± SD, n=3**

Table 5: Evaluation parameters of Ornidazole Matrix tablets coated with 5% Eudragit® S100

Test parameters	Formulation code				
	OME1	OME2	OME3	OME4	OME5
Diameter (in mm)	9.598	9.599	9.589	9.588	9.593
Thickness (in mm)	5.473	5.478	5.478	5.481	5.479
Coating Thickness (in mm)	0.059	0.062	0.058	0.065	0.061

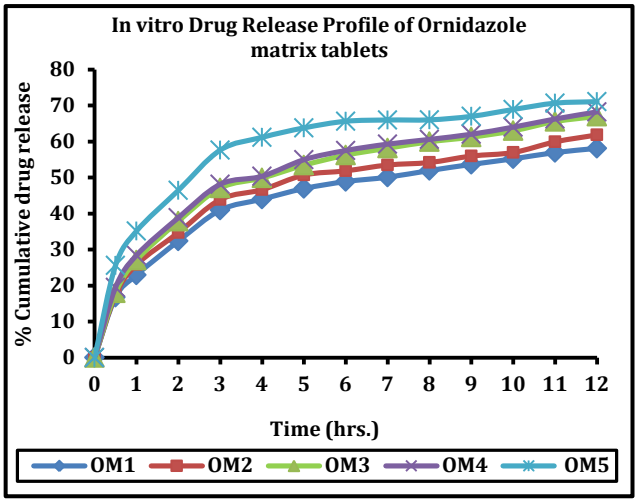

Figure 5:*In vitro* drug release profile of Ornidazole Matrix tablets

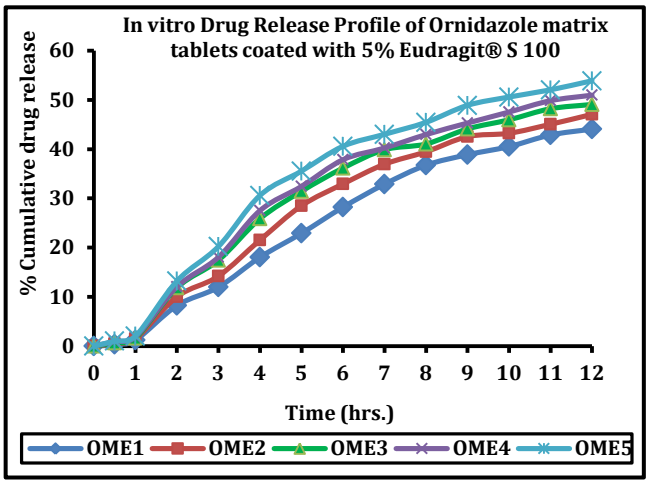

Figure 6: *In vitro* drug release profile of Ornidazole matrix tablets coated with 5% Eudragit® S 100

Table 6: Dissolution kinetics of optimized Matrix and enteric coated tablet formulations

Optimized Formulation Code	Zero Order (R^2)	First Order (R^2)	Higuchi (R^2)	Korsmeyer's Plot (R^2)	Korsmeyer's Exponent "n"
OM1	0.67	0.33	0.880	0.375	0.674
OME1	0.925	0.694	0.958	0.911	1.397

CONCLUSION

From the above research outcomes it can be concluded that guar gum, xanthan gum has the potentiality for colon specific drug delivery of Ornidazole. Eudragit S100 can be used to protect the drug release in the hostile environment of upper GIT when Ornidazole administered as tablet dosage form. The bioavailability of Ornidazole at the colonic site found to be improved through colonic delivery.

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