International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 2(3): May-June 2012

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences **Research Article……!!!**

Received: 31-05-2012; Revised; Accepted: 03-06-2012

DESIGN AND DEVELOPMENT OF CYCLODEXTRIN INCLUSION COMPLEX MATRIX TABLETS OF ORNIDAZOLE FOR COLONIC DELIVERY

Tapana Kumar Panigrahy*[1], Prasanta Kumar Choudhury[1], Padala Narasimha Murthy[1], Niraj Kanti Tripathy[2]

1. Department of Pharmaceutics, Royal College of Pharmacy and Health Sciences, Berhampur-760002, Odisha, India
2. Department of Zoology, Brahmapur University, Bhanja Bihar, Berhampur-760007, Odisha, India

Keywords:

ornidazole, ß-cyclodextrin, inclusion complex, ethyl cellulose, matrix tablets

For Correspondence:

Tapana Kumar Panigrahy

Department of Pharmaceutics, Royal College of Pharmacy and Health Sciences, Berhampur-760002, Odisha, India

E-mail:

tapanakumarpanigrahy@gmail.com

ABSTRACT

The aim of the present investigation was to prepare inclusion complex of Ornidazole and ß-cyclodextrin to impart better solubility to Ornidazole, an antiprotozoal and antibacterial drug. Inclusion complex of Ornidazole with ß-cyclodextrin was prepared by physical mixing and the matrix tablets were prepared using Ornidazole alone and Ornidazole- β-CD (1: 0.5 and 1:1) inclusion complexes by wet granulation method. Here ethyl cellulose was added as matrix forming polymer to facilitate control release of Ornidazole. Then outer coat was applied on the matrix tablets with Kolicoat MAE 100P (5% w/v) solution to deliver maximum drug to the colonic region. All the tablet formulations under study were assessed for their tabletting property, drug content uniformity and *in vitro* drug release. Matrix tablet formulations of Ornidazole- β-CD (1: 0.5 and 1:1) inclusion complexes shows better drug release profile as compared to matrix tablets using ornidazole alone The optimized and selected matrix tablet formulations were further enteric coated with Kolicoat MAE 100P (5%w/v). The enteric coated formulations are able to withstand the drug release in the upper GIT. Hence these formulations can be selected for drug delivery specifically in the colonic region.

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 were 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, 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].

The objective of the present investigation is to design enteric coated matrix tablets of Ornidazole. Ornidazole, a 5-nitroimidazole derivative with anti-protozoal and anti bacterial properties against anaerobic bacteria was selected as a drug of choice to develop enteric coated matrix tablet formulation employing ethyl cellulose (EC) as a rate retarding and matrix forming polymer 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, β-CD, Ethyl cellulose(EC), Kolicoat MAE 100P were procured from Ozon international, Mumbai, Lobachemie, Mumbai, India, and BASF, Mumbai respectively. All other solvents and reagents were of analytical grade purchased from local suppliers.

EXPERIMENTAL METHOD

Characterization of drug and analytical studies

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

Formulation of Ornidazole– ß-Cyclodextrin Inclusion Complex Matrix Tablets

Among the various approaches, preparation of drug-embedded matrix tablets is one of the least complicated approaches for obtaining controlled release and is widely used in industry. In the present study Matrix tablets of Ornidazole alone and Ornidazole- β-CD (1: 0.5) and (1:1) inclusion complexes were formulated employing Ethyl Cellulose (EC) as matrix forming polymer in different proportions of drug and polymers and tablets were evaluated for drug release kinetics and mechanism.

Preparation of Cyclodextrin Inclusion Complexes by Physical mixing[3]

Ornidazole with ß -CD in different ratios (i.e. 1:0.5, 1:1) were mixed in a mortar for about one hour with constant trituration, passed through sieve No. 80 and stored in desiccators over fused calcium chloride.

Method of Preparation of Matrix Tablets[4]

Matrix tablets of Ornidazole were prepared as per the formulae given in Table 9 & 10. The required quantities of medicament, lactose and matrix forming polymer were mixed thoroughly in a mortar by following geometric dilution technique. The granulating fluid (solvent blend of water and alcohol in 1:1 ratio) was added and mixed thoroughly to form dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 40ºC for 6hrs. The dried granules were passed through mesh No. 16 to break the aggregates. Lubricants talc and magnesium stearate were passed through mesh No. 100 on to dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a rotary tablet punching machine (Rimek Mini Press-1, karnavati Engineering Pvt., Ahmedabad, India**)** Using 13 mm concave punches.

Table 1: List of Ornidazole matrix tablets prepared employing Ornidazole alone and Ornidazole Inclusion complexes

S.NO.	Drug form	Matrix Polymer	Code
1	Ornidazole	Ethyl Cellulose	OZEC1
2	Ornidazole-βCD(1:0.5)	Ethyl Cellulose	OZEC2
3	Ornidazole- βCD(1:1)	Ethyl Cellulose	OZEC3

Table 2: Formulae of Ornidazole matrix tablets

Ingredient (mg/tablet)	Matrix Tablet Formulation		
	OZEC1	OZEC2	OZEC3
Ornidazole	100	-	-
Ornidazole- βCD(1:0.5)	-	150	-
Ornidazole- βCD(1:1)	-	-	200
Ethyl Cellulose	40	40	40
Lactose	244	194	144
Talc	8	8	8
Magnesium stearate	8	8	8
Total weight of Tablet (mg)	400	400	400

Preparation of enteric coated Ornidazole Matrix tablets[5]

The outer coating layer was applied on the matrix tablets using dip coating method to prevent the drug release in the upper part of GIT. An organic polymer solution consisting of 5%w/v KOLICOAT MAE 100P 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.

Evaluation of matrix tablet formulations

Physical characterization of tablet[6]

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[7, 8]

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 spectrophotometer at its corresponding wavelength.

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 1hr. 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 drug content by measuring absorbance at corresponding λmax of the dissolution medium, using UV- spectrometer (UV-18OO, Shimadzu, Japan). The cumulative percentage release for Ornidazole 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.

RESULTS AND DISCUSSION

1. 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, at 319nm in phosphate buffer solution pH 7.4, which is relevant to literatures and the monograph for Ornidazole.

Table 3: 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

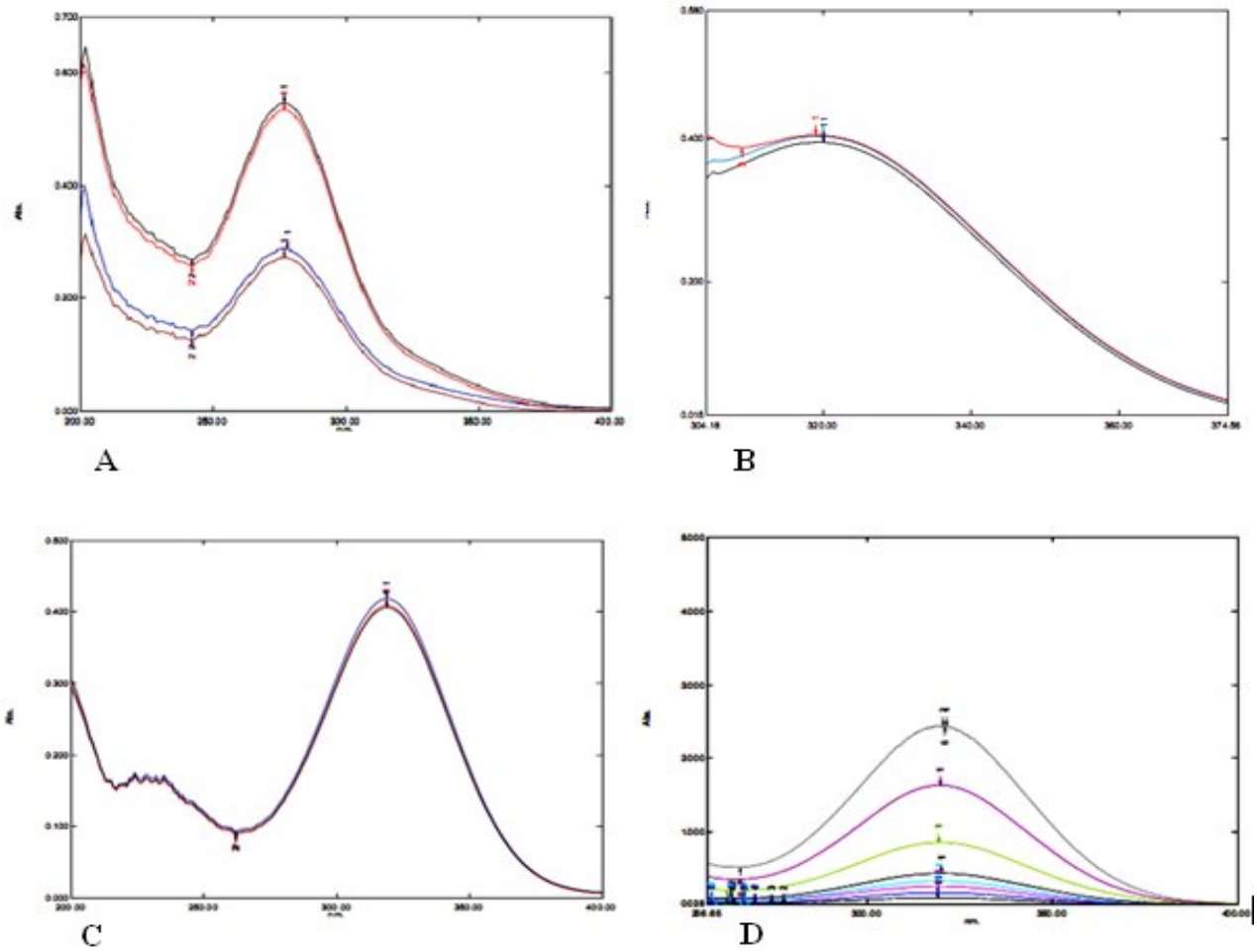

Figure 1: Overlay Spectra of Ornidazole (A) In Hydrochloric Acid Buffer pH 1.2, (B) In Acetate Buffer pH 4.5, (C) In Phosphate Buffer pH 6.8, (D) In Phosphate Buffer pH 7.4

2. Formulation of Ornidazole– ß-Cyclodextrin Inclusion Complex Matrix Tablets and in vitro characterization

As discussed earlier Matrix tablets were formulated employing ornidazole alone and their β-CD (1:0.5 and 1:1) inclusion complexes were formulated employing Ethyl Cellulose (EC) as matrix forming polymer by wet granulation technique, with an objective of evaluating the feasibility of employing drug-β-CD complexes in the design of controlled release tablet formulations for obtaining slow, controlled and complete drug release in 12 hrs. All the matrix tablets formulated found to contain 98.85 ± 0.59, 97.12 ± 0.45, 96.02 ± 0.86 of the labeled claim. As such, the formulated matrix tablets were of good quality with regard to drug content, hardness and friability. The matrix tablets formulated employing, ethyl cellulose (EC) as matrix forming polymer was subjected to in vitro drug

release study for 12hrs. Drug release from formulations found to be 35.335, 97.472, and 99.891 for OZEC1, OZEC2, and OZEC3 respectively. Hence it was observed drug release from OZEC1 (composed of ornidazole alone with ethyl cellulose) was very slow and not up to the desired requirements, where as when Ornidazole- β-CD (1: 0.5) and (1:1) inclusion complexes were used in the matrix tablet (OZEC2 and OZEC3) drug release was improved. Hence when ornidazole- βCD complexes were used, ornidazole release rates were much higher in the case of matrix tablets containing Ornidazple– β-CD complexes when compared to those containing ornidazole alone. But it was found that in first 6hrs of drug release study for the formulation OZEC2 and OZEC3 amount of drug release was 42.515% and 45.590% respectively.

Table 4: Evaluation parameters of Matrix tablets

Formulation code	Weight variation test	Friability (%)	Hardness (Kg/cm^2)	Ornidazole content (%)
OZEC1	Passed	0.31 ± 0.12	5.51 ± 0.41	98.85 ± 0.59
OZEC2	Passed	0.34 ± 0.14	5.01 ± 0.31	97.12 ± 0.45
OZEC3	Passed	0.52 ± 0.16	6.10 ± 0.51	96.02 ± 0.86

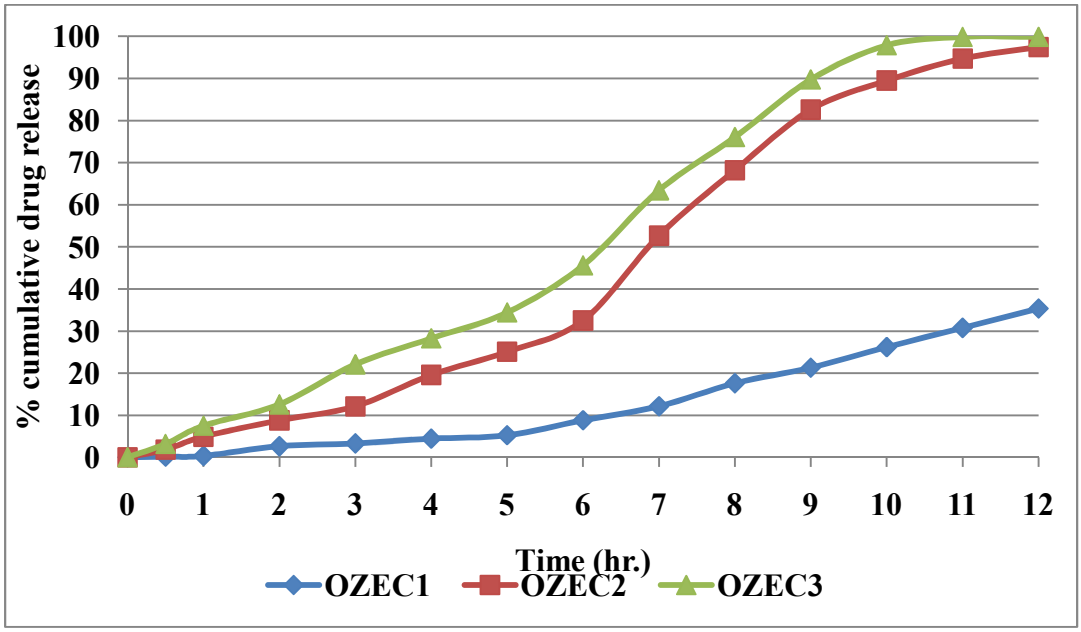

Figure 2: In vitro drug release profile of Matrix tablets Ornidazole (OZEC1, OZEC2, OZEC3)

As the ornidazole matrix tablets were designed with an aim to delivery maximum amount of drug at the site of colon, the drug release need to be restricted in the upper part of GIT, hence the formulations containing ornidazole- β-CD complexes were further enteric coated with 5 %w/v KOLICOAT MAE 100P to prevent the drug release in the upper part of GIT. Drug release from enteric coated Matrix tablets (OZECT1 and OZECT2) with in 4(hr) was restricted. Hence these formulations may be suitable for drug delivery to the colonic region.

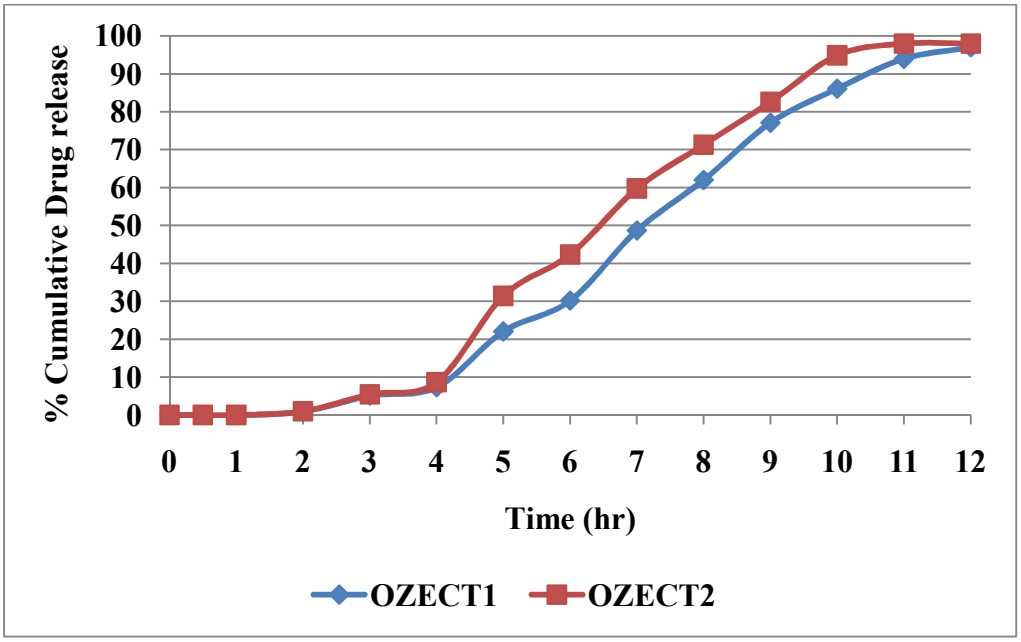

Figure 3: In vitro drug release profile of enteric coated Matrix tablets Ornidazole(OZECT1, OZECT2)

CONCLUSION

From the above study outcomes it can be concluded that β-CD inclusion complexes of poorly soluble drugs improves drug release rate as compared to the drug alone and Ethyl cellulose can be exploited as matrix forming polymer to design control release formulations, further an out coat of enteric coating polymer, Kolicoat MAE 100P may be suitable for preventing drug release in upper part of GIT and drug delivery specifically to colonic region for better bioavailability of drugs.

REFERENCES

1. Kumar Ravi, Patil B M, Patil S R and Paschapur M S, "Polysaccharides Based Colon Specific Drug delivery: A Review", International Journal of PharmTech Research, 2009; 1(2): 334-346.

2. Patel J M, Patel V V, Muley S V and Yeole G P, "Colon targeted oral delivery of ornidazole using combination of pH and time dependent drug Delivery system", International Journal of Pharmaceutical Research, 2010; 2(1): 78-84.
3. Shirse P, Rao K S and Iqbal M M, "Formulation and evaluation of cyclodextrin inclusion complex tablets of water insoluble Drug-glimipiride", International Journal of Research in Pharmacy and Chemistry**,** 2012; 2(1): 222-230.
4. Reddy P D, Chowdary KP R, "Formulation Development Studies On ß-cyclodextrin complexation of pioglitazone matrix tablets", International Journal of Advances in Pharmaceutical Research, 2011; 2(12): 607 - 612
5. Pozzi F., Furlani P., Gazzaniga A., Davis S. S. and Wilding I. R., "The Time-Clock® system: a new oral dosage form for fast and complete release of drug after a predetermined lag time". J. Control. Release, 1994; 31: 99–108.
6. Lieon Lachman, Lieberman, Joseph L. Kanig, "The theory and practice of industrial pharmacy", 3rd Edition, Varghese publishing house, Bombay, 1990, pp 298-303.
7. Nasra M. A., Naggar V. F., "Development of Metronidazole colon-specific delivery systems", Asian Journal of Pharmaceutical Sciences, 2007; 2 (1): 18-28.
8. Abhishek K J, "Effect of superdisintegrating agent and osmogens on ciprofloxacin loaded naturally occurring biodegradable coated tablets for colon targeting", International Journal of Pharmacy and Pharmaceutical Sciences, 2010; 2(4): 161-164.
9. Mei-Juan Zou, Gang Cheng, Hirokazu Okamoto, Xiu-Hua Hao, Feng An, Fu-De Cui, Kazumi Danjo, "Colon-specific drug delivery systems based on cyclodextrin-prodrugs: In vivo evaluation of 5-aminosalicylic acid from its cyclodextrin conjugates", World JoranalGastroenterol, 2005, 11(47):7457-7460
10. Khan M.Z., Prebeg Z., "pH-dependent colon targeted oral drug delivery system using methacrylic acid copolymer I. Manipulation drug release using Eudragit® L100-55 and Eudragit® S100 combination", J. Control Release, 1999; 58: 215-222.