Research Article

ISSN:2230-7346
Journal of Global Trends in Pharmaceutical Sciences
Vol.3, Issue 1, pp -564-575, January–March 2012

DESIGN AND EVALUATION OF TIME DEPENDENT ORAL COLON TARGETED DRUG DELIVERY SYSTEMS FOR TINIDAZOLE USING EUDRAGIT® NE 30D

K.Sravya*, S.Rajeswari, K.V.Ramana Murthy

Pharmaceutical Technology Division, A.U. College of Pharmaceutical Sciences.
Andhra University, Visakhapatnam- 530 003.

***Corresponding author E-mail: sravya.kudamala@gmail.com**

ABSTRACT:

Tinidazole is an anti-infective drug which is widely used in the treatment of colonic disorders like amoebiasis, an infection of the large intestine caused by *Entamoeba histolytica*, a single celled protozoan parasite. The main aim of the present work is to design and evaluate timed release oral colon targeted drug delivery system for tinidazole which would release negligible amount of drug in the first 6 hours lag period when the drug is in the upper GIT followed by complete release of the drug in the colon, in a controlled manner in the next 18hours. The tinidazole core tablets are prepared by wet granulation and then coated with Eudragit® NE 30D to achieve time dependent release profile for colon targeting. The prepared tablets were evaluated for various tabletting parameters and based on the pharmacopeial tests conducted and the study of release kinetics of the prepared tablets, FE4 having the Eudragit® NE30D polymer coat load of 25%w/w was selected as the optimized formula as it showed timed release profile for achieving colon targeting of tinidazole.

KEY WORDS:

Timed release delivery, colon targeting, lag period, Eudragit® NE30D, coating, HPMC.

INTRODUCTION:

Oral delivery of drugs to the colon is very valuable in the treatment of the diseases of the colon like ulcerative colitis, carcinomas, amoebiasis and Chron's disease whereby high local concentrations of the drug can be achieved while minimizing the side effects that occur due to the release of drug in the upper GIT (Gastro Intestinal Tract) or systemic absorption. Tinidazole is an anti-infective drug which is widely used in the treatment of colonic disorders like giardiasis, trichomoniasis and amoebiasis. Tinidazole is the drug of choice in the treatment of amoebiasis, an infection of the large intestine caused by *Entamoeba histolytica*, a single celled protozoan parasite. According to World Health Organization's report on Amoebiasis (1997) *Entamoeba histolytica* is responsible for up to 100,000 deaths each year. But the pharmacokinetic profile of tinidazole indicates that the drug is absorbed completely after oral administration, reaching a concentration of about 10µg/ml in plasma approximately 1hr after a single 500mg dose.

Conventional tablets of tinidazole provide minimal amount of drug for local action in the colon, still resulting in the relief of amoebiasis, but with systemic side effects like nausea and discomfort if released in the stomach. In humans, studies have shown that, after leaving the stomach, a formulation arrives at the ileocaecal junction in about 6 hr after administration. The need of the hour is to design colon targeting drug delivery system of tinidazole that can not only increase the presence of the drug locally for a prolonged period, but also reduce the risk of systemic toxicity as a result of reduced dose. Hence, the main objective is to develop colon targeted tablets of tinidazole which will not release the drug in the first 6 hours but will release it in a slow manner after 6 hours can be very useful in the treatment of amoebiasis.

Colon targeting can be achieved by different formulation strategies[1] like pH-Dependent (Or Delayed-Release) System designed to release a drug in response to change in pH, Time-Dependent (Or Timed Release) System designed to release a drug after a predetermined time, Microbially-Dependent (Or Microbially Controlled) System making use of the abundant enterobacteria in the colon, and Pressure-Dependent System making use of luminal pressure of the colon. Among these, first three are most widespread formulation technologies which are being developed for pharmaceutical market[2]. To achieve colon

targeting timed release systems are explored to a lesser extent as most of the researchers[3-9] so far have studied the use of enteric coating polymers and insoluble coating materials mostly limiting to ethyl cellulose to achieve colon targeting. Timed release with Eudragit® NE30D[10] is a novel approach to achieve colon targeting. Eudragit® NE30D polymer film is water insoluble, pH independent, water swellable, and water permeable. Eudragit® NE 30 D leads to a delay in drug release which is dependent on the thickness of the coating since these films have slow rates of swelling. Moreover, the core contains HPMC (HydroxyPropyl MethylCellulose) which would swell in the presence of the fluid that has permeated through the outer polymer coating and would also control the release of the drug.

MATERIALS:

Tinidazole was obtained as a gift sample from Zydus Cadilla Health Care Limited, Ahmedabad. Eudragit® NE30D was obtained from Evonik Industries AG, Germany and Hydroxypropyl methylcellulose (HPMC) 5cps was obtained as a gift sample from Aurobindo Pharma Ltd, Hyderabad. All other ingredients were of laboratory grade.

METHODS:

Preparation of tablets:

Core tablets each containing 300 mg of tinidazole were prepared employing HPMC 5% as per the formulae given in Table.1. The required quantities of medicament, HPMC, lactose and microcrystalline cellulose were mixed thoroughly in a mortar by following geometric dilution technique. The binder, 1.5% w/v PVP in IPA 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 60^0C for 1 h. The dried granules were passed through mesh No. 16 to break aggregates. Magnesium stearate (1%) 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 multi-station punching machine (Cadmach Machinery Co. Pvt. Ltd., Mumbai) to a hardness of 6-7 kg/sq.cm. using 9 mm round and flat punches.

Coating with Eudragit® NE 30D.

To prepare the spray suspension, talc was suspended in water and the suspension was poured into Eudragit® NE 30 D with continuous gentle stirring. 50 tablets were coated using Conventional KALWEKA

Coating pan, Phillips hot air dryer and a spray gun to different thickness values equivalent to theoretical polymer loads of 10, 15, 20 and 25% w/w and samples were drawn for analysis simultaneously after each level of polymer load. The process parameters are shown in Table 2. Uncoated, 10%, 15%, 20% and 25 % w/w of polymer load were labeled as UNCOATED, FE1, FE2, FE3 and FE4 respectively.

Estimation of Tinidazole in tablets:

Five tablets were accurately weighed and powdered. Tablet powder equivalent to 300 mg of medicament was taken into 25ml volumetric flask and 20 ml of methanol was added. The mixture was shaken thoroughly for about 30 min. while warming in hot water bath to dissolve the Tinidazole. The solution was then made upto volume with methanol. The methanolic solution was subsequently diluted suitably with phosphate buffer of pH 7.4 and assayed for tinidazole at 310 nm. Four samples of tablet powder were analyzed in each case.

Hardness:

Hardness of the matrix tablets prepared was tested using a Monsanto Hardness Tester.

Friability:

Friability of the matrix tablets prepared was determined in a Roche Friabilator.

Disintegration Time:

Disintegration times were determined in Thermonic Tablet Disintegration Test Machine using 0.1 N HCl and phosphate buffer of pH 7.4 as fluids.

***In-Vitro* Drug Release Study:**

Tinidazole release from tablets prepared was studied using 8 station dissolution rate test apparatus (Lab India, DS 8000) employing a paddle stirrer with a dissolution fluid volume of 900ml at 75 rpm and at 37± 0.5^0C. Dissolution was carried out in 0.1N HCl in the first 2 hrs and in pH 7.4 phosphate buffer for the remaining 22h. Samples of 5 ml of each were withdrawn at different time intervals over a period of 24 h. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and assayed at 310 nm for tinidazole using an Elico BL 198 double beam UV-spectrophotometer. The drug release experiments were conducted in triplicate.

Data analysis:

Release data were analyzed as per zero order, first order, Higuchi[11] and Peppas[12] equation models to assess the drug release kinetics and mechanism from the matrix tablets prepared.

RESULTS:

Table- 1: Formula of Core tablets for Time dependent oral delivery system for colon targeting of Tinidazole

Ingredients	Quantity (mg/tablet)
Tinidazole	300.0
HPMC	20.0
Lactose	30.0
Microcrystalline cellulose	46.0
Magnesium Stearate	4.0
Granulating fluid (1.5% w/v PVP in IPA)	q.s
Total weight	400.0

Table -2: Coating Parameters

Coating Parameters	
Pan rotation speed	36 rpm
Angle of coating pan	45º
Nozzle port size	0.8mm
Inlet air temperature	45ºC
Tablet bed temperatures	35 ºC

Table 3. Hardness, Friability, Disintegration Time and Drug Content of Time dependent oral delivery system for colon targeting of Tinidazole

Formulation	Hardness (Kg/sq.cm)	Friability (%)	Disintegration Time (min)	Tinidazole Content (mg/tablet)
FE1	6.5	0.2	Non-disintegrating	300.2
FE2	6.0	0.1	Non-disintegrating	300.15
FE3	7.0	0.3	Non-disintegrating	300.2
FE4	6.5	0.1	Non-disintegrating	300.11

Table- 4: Drug Release Profiles of Time dependent oral delivery system for colon targeting of Tinidazole

Time (h)	Mean Percent of Tinidazole Released ($\bar{x}$ ± s.d) (n = 3)				
	UNCOATED	FE1	FE2	FE3	FE4
0	0	0	0	0	0
1	68.4±0.2	15.31±0.3	11.12±0.21	8.605±0.2	3.51±0.17
2	86.8±0.4	20.9±0.1	15.7±0.13	10.61±0.21	4.97±0.23
4	99.8±0.3	22.5±0.42	18.9±0.31	12.85±0.3	10.34±0.13
5		42.71±0.23	40.4±0.14	36.4±0.11	34.2±0.25
6		64.94±0.2	58.7±0.15	50.1±0.19	41.59±0.11
8		76.8±0.1	71.3±0.12	62.2±0.21	53.3±0.16
10		78.7±0.12	76.1±0.1	66.4±0.18	58.64±0.24
12		79.1±0.22	78.4±0.3	70.29±0.15	60.2±0.31
16		86.7±0.12	85.7±0.14	75.97±0.16	65.1±0.12
24		92.04±0.23	88.4±0.14	83.64±0.16	71.5±0.12

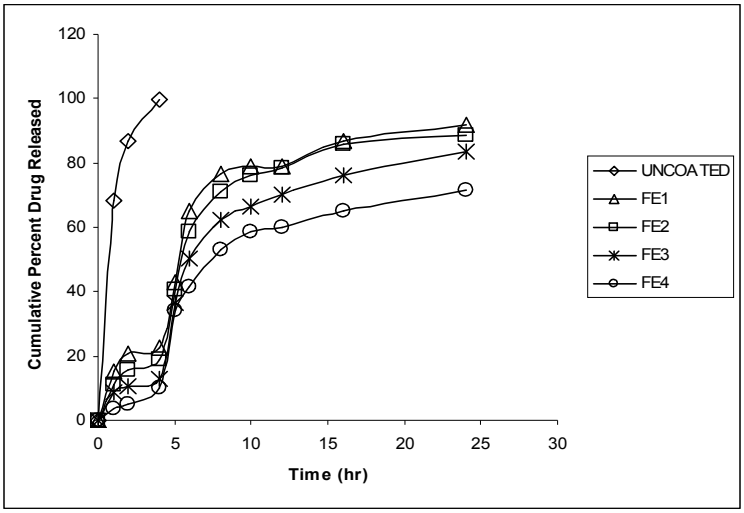

Fig. 1: Drug Release Profiles of Time dependent oral delivery system for colon targeting of Tinidazole

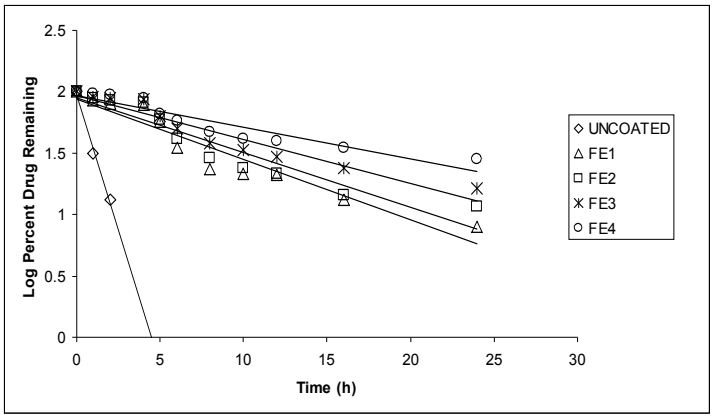

Fig. 2: First Order Plots of Drug Release from Tinidazole Matrix Tablets

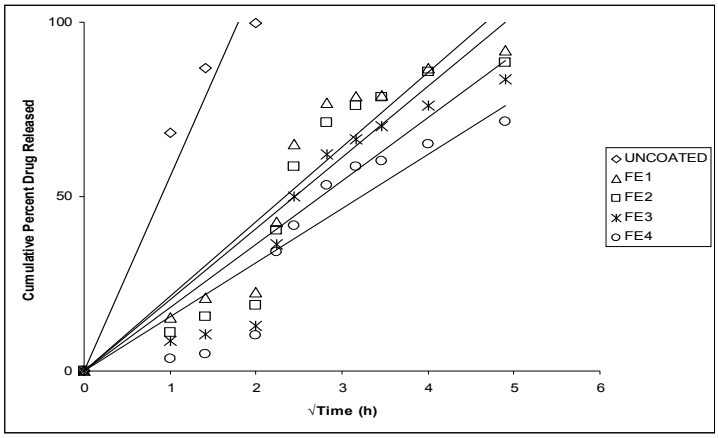

Fig. 3: Percent Released Vs Square Root Time Plots of Time dependent oral delivery system for colon targeting of Tinidazole

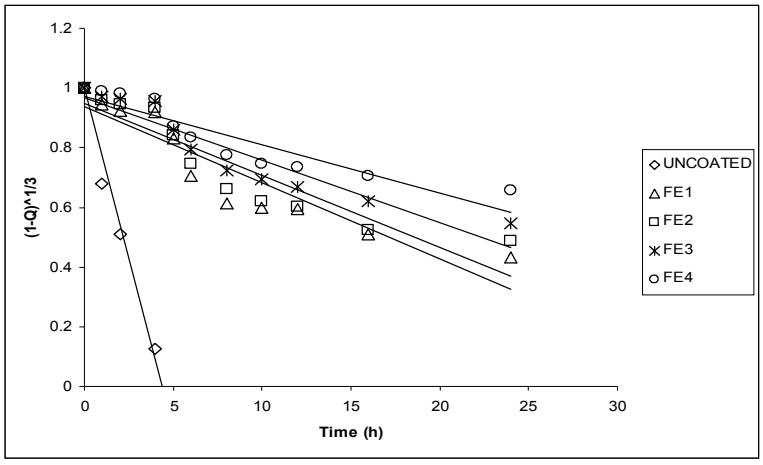

Fig. 4: (1-Q) ^1/3 vs Time (h) Plots of Time dependent oral delivery system for colon targeting of Tinidazole

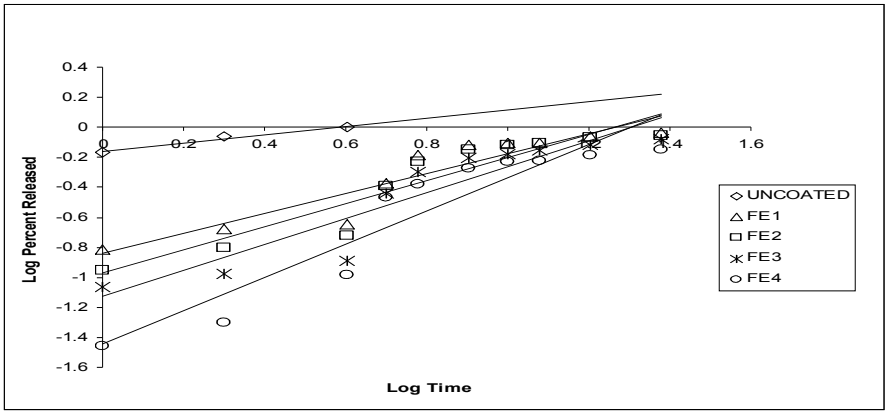

Fig. 5: Log Percent Released Vs Log Time Plots of Time dependent oral delivery system for colon targeting of Tinidazole

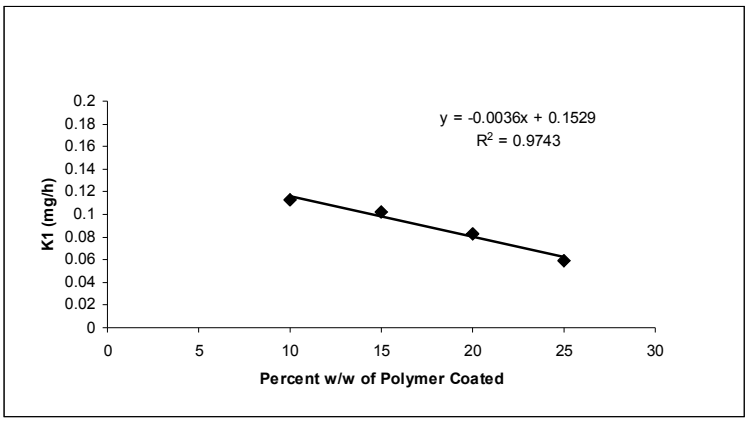

Fig 6 Relationship between Percent w/w of Polymer Load and Release Rate of Tinidazole from of Tinidazole Time dependent oral delivery system for colon targeting

Table 5.Correlation Coefficient (r) Values in the Analysis of Release Data as per Zero, First Order, Higuchi and Peppas Equation Models

Formulation	Correlation coefficient (r-value)			
	Zero order model	First order model	Higuchi model	Erosion Plot
UNCOATED	0.853505	0.86575	0.986788	0.98128
FE1	0.743983	0.917696	0.884334	0.861104
FE2	0.758192	0.89867	0.891416	0.853538
FE3	0.794351	0.924201	0.877799	0.883264
FE4	0.779784	0.87465	0.986788	0.84347

Table 6.Drug Release Characteristics of Time dependent oral delivery system for colon targeting of Tinidazole

Formulation	Polymer Load (%w/w)	T_{50} (h)	T_{90} (h)	K_1 (h^{-1})	'n' in Peppas equation
UNCOATED	0	0.5	2.5	1.62669	0.289176
FE1	10	5.2	20	0.113192	0.661942
FE2	15	5.5	-	0.102345	0.770039
FE3	20	6	-	0.083069	0.861079
FE4	25	7.5	-	0.059141	1.109531

DISCUSSION:

Time dependent oral delivery systems for colon targeting of tinidazole were formulated by first preparing core tablets containing 300 mg of tinidazole and 20 mg HPMC and then by coating the core tablets with Eudragit® NE 30 D to different thickness values equivalent to theoretical polymer loads of 10, 15, 20, 25 %w/w. As expected, as the percentage of Eudragit® NE 30D in tablet increased, the release of drug from the tablet also extended over time. This may be due to thick coat of polymer around the drug. Eudragit® NE 30D, being a binding agent, produces strong binding among granules in higher quantity and prolongs disintegration time of tablets. The increase in disintegration time further favours prolonged release of the drug from the tablets.

Hardness of the tablets was in the range of 6-7kg/sq.cm. Weight loss in the friability test was less than 0.3 % in all the cases. All the matrix tablets prepared contained 100±2.5% of the labeled claim. All the tablets were found to be non-disint-egrating in acidic (pH 1.2) and alkaline (pH 7.4) fluids. As such, the prepared tablets were of good quality with regard to drug content, hardness and friability. As the tablets formulated were non-disintegrating in acidic and alkaline fluids, they are considered suitable for colon targeting.

Tinidazole release from the tablets prepared was studied in 0.1N HCl for the first two hours followed by phosphate buffer

of pH 7.4 for the next 22h. The release profile of the formulations are given in Table 4 and shown in Figs. 1-6 . The drug release parameters are summarized in Table 6 .Tinidazole release from the prepared tablets was relatively slow in the first 4h followed by release spread over 24 h and depended on the theoretical polymer load on the tablet core.

Study of drug release profiles

Uncoated tablets released the entire drug within 4.5h. Tinidazole release was relatively rapid in the case of tablets with 10% w/w polymer coat load (FE1) and by the end of the lag time of 6h, 65% of release was observed (Fig.1). When 15% of polymer load was obtained on the tablets in the formula, FE2, the release at the end of the lag time was about 59% . FE3 tablets which are coated with 20% polymer load released 50% drug at the end of the lag period while the FE4 tablets which are coated with 25% polymer load released 42% at the end of the lag period. Of all the different formulae prepared FE4 is the most suitable formula in this approach of Time dependent oral delivery system for colon targeting for achieving minimum release during the lag period.

Effect of Percent w/w of Polymer Load on drug release

As the percent w/w of the Eudragit® NE 30 D Polymer load was increased, the release rate was decreased. A good linear relationship was observed between percent w/w of polymer (Eudragit® NE 30 D) and release rate (K_1) of the timed release tablets prepared (Fig.6). The relationship could be expressed by the following linear equation.

$$Y = -0.0036X + 0.1529$$

Where X is the percent w/w of polymer load and Y is release rate, K_1 (mg/h).

Drug release kinetics and mechanism

The drug release data were analyzed as per Zero order, First order, Higuchi, Erosion and Peppas equation models. The correlation coefficient (r) values in the analysis of the release data as per different kinetic models are given in Table.6.5. Analysis of release data as per zero order and first order kinetic models indicated that the tinidazole release from the timed release tablets followed first order kinetics. The correlation coefficient (r)-values were higher in the first order model than in the zero order model. Plots of percent release versus square root of time were found to be linear with r values greater than the r values obtained from the Erosion Plot, (1-Q)^1/3 vs

time. Hence, with all the tablets prepared drug release from these matrix tablets was diffusion controlled.

When the release data were analyzed as per Peppas equation, the release exponent 'n' was in the range 0.68 - 0.81 in the case FE1 to FE3 of timed release tablets indicating non - Fickian (anomalous) diffusion as the release mechanism from them. The drug release of the optimized formula, FE4 (n > 0.89) followed Super Case II Transport type of release.

CONCLUSION:

Eudragit® NE 30 D was proved to be a good polymer to achieve time dependent release of the drug. Tinidazole release from the tablets 25% w/w of polymer load was slows during the lag period and spread over 24 h and the release was diffusion controlled and followed first order kinetics. Though a burst release was observed after 4h, complete release of the drug was not observed at the end of the 24h study period. Super Case II Transport type of release was observed in the optimized FE4 formulation. The change in the mechanism of drug release (from the non-Fickian release) was attributed to the swelling process of high rank in FE4 formulation having relatively high percent polymer load of 25% w/w. Timed release tablets, FE4 are best suited to be used for colon targeting of tinidazole employing the timed release approach.

ACKNOWLEDGEMENTS:

We sincerely thank Zydus Cadilla Health Care Ltd. and Aurobindo Pharma Ltd. for their gift samples and A.U.College of Pharmaceutical Sciences for providing required facilities.

REFERENCES:

1. Singh BN, Kim, KH. In: Swarbrick J, Boylan JC (Eds.), Encyclopedia of Pharmaceutical Technology, New York, Marcel Dekker, Inc., 2002; 886-909.
2. Valducci, R.: US20067022345 (2006).
3. Ueda, Y., Hata, T., Yamaguchi, H., Ueda, S., Kodani, M.:US4871549 (1989)
4. Takada, K.: US5637319 (1997).
5. Shah, N.H., Railkar, A.M., Phuapradit, W.: US20006039975 (2000).

6. Lerner, E.I., Flashner, M., Penhasi, A.: US5840332 (1998).
7. Kiyoshi Niwa, Tomohiro Takaya, Tsuyoshi Morimoto and Kanji Takada. Preparation and Evaluation of a Time-Controlled Release Capsule Made of Ethylcellulose for Colon Delivery of Drugs. Journal of Drug Targeting ;1995 (3, 2,) : 83-89
8. Wright, J.C., Guittard, G.V.: US5650170 (1997).
9. Savastano, L., Carr, J., Quadros, E., Shah, S., Khanna, S.C.: US5681584 (1997).
10. Grietje Molema, D. K. F. Meijer, Drug targeting, Chapter 6;166-167.
11. T. J. Higuchi, Pharm. Sci., 52, 1145 (1963).
12. P. L. Ritger and N. A. Peppas, J. Control. Release, 5, 37 (1987).