International Journal of Pharmaceutical Research and Development (IJPRD)
Platform for Pharmaceutical Researches & Ideas
www.ijprd.com

DEVELOPMENT AND EVALUATION OF COMPRESSION COATED TABLETS OF METRONIDAZOLE FOR COLON TARGETED DRUG DELIVERY

Praveen Singh M*[1], Manjula BP[1]

[1]Department of Pharmaceutics, Government College of Pharmacy, P.Kaling Rao road, Bangalore-560027, Karnataka, India

ABSTRACT

Colon targeting is of value in the treatment of Crohn's disease, ulcerative colitis and amoebiasis. The present work is a time dependent and pH dependent compression coated tablets of Metronidazole targeting drug release in the colon.200mg of Metronidazole core tablets were prepared by wet granulation method. Ethyl cellulose was used as a time dependent polymer and polymethacrylates Eudragit L and Eudragit S were used as pH dependent polymers. The compression coatings were used in the polymer concentrations of 200mg and 225mg. The ability of formulations to provide colon specific drug delivery were assessed by in-vitro drug release studies in buffer pH 1.2 for the first two hours, simulated intestinal fluid [pH 7.4 buffer] for three hours and simulated colonic fluid [pH 6.8 buffer] for the subsequent hours. The results indicated that all the formulations release considerable amount of drug in simulated intestinal fluid and major portion of the drug was released in the colonic fluid. But the formulations containing 200mg and 225mg of Eudragit polymers, 100mg each of Ethyl cellulose and Eudragit polymers and 112.5mg each of Ethyl cellulose and Eudragit polymers had better release profile. It was therefore concluded that Metronidazole could be successfully colon targeted by the use of time dependent and pH dependent polymers.

Correspondence Author

PRAVEEN SINGH M

Department of Pharmaceutics, Government College of Pharmacy, P.Kaling Rao road, Bangalore-560027, Karnataka, India

Email: mpsingh1981@gmail.com

Keywords:- *Colon targeting; Compression coating; Metronidazole; Time dependent and pH dependent polymers; Ethyl cellulose; Eudragit polymers.*

INTRODUCTION

Oral administration of drugs by conventional pharmaceutical formulations is the most convenient and effective delivery system and preferred over parenteral medication, due to its ease of administration, high patient compliance, least sterility constraints and flexibility in the design of the dosage form.

Drug targeting to colon is highly desirable in a variety of colonic disorders such as inflammatory bowel diseases, amoebiasis and colon cancer. Colon is also found to be a promising site for systemic absorption of peptide and protein drugs because of less hostile environment prevailing in the colon compared with stomach and small intestine. [1] The different approaches for targeting orally administered drugs to the colon include coating with pH dependent polymers, design of timed release dosage forms and the utilization of carriers that are degraded exclusively by colonic bacteria. [2] The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. The colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. [3]

Pharmaceutical coatings are an essential tool to achieve superior aesthetic property of a dosage form [Eg: colour, texture, mouth feel and taste masking], physical and chemical protection for the drugs in cores, and modified drug release characteristics.Compression coating is the absolute dry coating without solvent and heat use. A compression-coated tablet is a system in which the entire surface of an inner core is completely surrounded by the coat. These coats prevent drug release from the core until the polymeric coat is entirely eroded, dissolved or removed [breaking down]. Different drug release fashions could be obtained depending on the coating layer and core composition. [4]

Metronidazole is commonly used antibioticwhich can be used in colonic diseases as it is having less dose when compared to other antibiotics.[5] It is having 98-100% bioavailability with 7-8 hrs of half-life and hepatic metabolism. [6] The adverse effects involve the gastrointestinal tract and nervous system especially with high doses. Reduction of side effects while prolonging its action by using controlled release of oral dosage forms is highly desirable.

In the current research Ethyl cellulose is used as a time dependent polymer and Eudragit S-100 and Eudragit L-100 as pH dependent polymers.Ethyl cellulose is used as a hydrophobic coating agent for tablets and granules. Ethyl cellulose coatings are used to modify the release of a drug, to mask an unpleasant taste and to improve the stability of formulation. Modified release tablet formulations may also be produced using ethyl cellulose as a matrix former.PolymethacrylatesEudragit S-100 and Eudragit L-100 are used as enteric coating agents since they are resistant to gastric fluid.Eudragit L-100 soluble in intestinal fluid from pH 6 and Eudragit S-100 soluble in intestinal fluid from pH 7. [7]

MATERIALS AND METHOD:

Materials:

Metronidazole, Sodium starch glycollate and Lactose were kindly supplied by Ceechem pharmaceuticals, Bangalore. Polymers Eudragit S-100 and L-100 were generously supplied by Strides Arco labs, Bangalore. Ethyl cellulose was procured from Central Drug House Pvt. Ltd. New Delhi. Magnesium stearate was procured from Lobachemie, Mumbai and Talc was procured from Reidel [India] chemicals, Hapur.

Preparation of Metronidazole core and compression coated tablets:

The core tablets of Metronidazole were prepared by wet granulation technique using the composition given in table no 1.The mixture was compressed into tablets on a multi station tablet punching machine using 8 mm round, flat faced, plain punches.

Table 1: Composition of Metronidazole core tablets

Sl no	Ingredients	Quantity [mg]
1	Metronidazole	200
2	Lactose	35
3	Sodium starch glycolate	10
4	Talc	2.5
5	Magnesium stearate	2.5
6	PVP [Q.S]	-
	Average	**250 mg**

The composition of compression coating material is shown in table no 2. 50% of coating mixture was placed in the die cavity of multi station tablet punching machine, the core tablet was placed on it at centre, remaining 50% of coating mixture was carefully transferred to the die cavity and tablets were compressed using 12 mm flat punches. The total weight of the compression coated tablet was about 500 mg [250 + 250].

Table 2: Formulation table

Formulation	Ethyl cellulose [mg]	Eudragit S 100 [mg]	Eudragit L 100 [mg]	Lactose [mg]	Talc [mg]	Magnesium stearate [mg]	Average [mg]
F1	200	_	_	45	2.5	2.5	**250**
F2	225	_	_	20	2.5	2.5	**250**
F3	_	100	100	45	2.5	2.5	**250**
F4		112.5	112.5	20	2.5	2.5	**250**
F5	100	50	50	45	2.5	2.5	**250**
F6	112.5	56.25	56.25	20	2.5	2.5	**250**

Physical characterization of Metronidazole core and compression coated tablets:

The developed core and compression-coated tablet formulations were studied for their physical properties like thickness, weight variation, hardness, friability and drug content uniformity using reported procedure.[8-11] For estimating weight variation, 20 tablets of each formulation were weighed using a single pan electronic balance. The thickness of the tablet was measured by using a micrometer screw gauge. The hardness of five tablets was measured using Pfizer tablet hardness tester. Friability was determined on 10 tablets using Roche friability testing apparatus for 4 min at 25 rpm. The drug content studies were carried out to evaluate the amount of drug present in the core and compressioncoated tablets.

Estimation of drug content:

The core and compression-coated tablets of Metronidazole were tested for their drug content. 10 tablets were finely powdered, and quantity of the powder equivalent to 200 mg of Metronidazole was accurately weighed and transferred to 100 ml volumetric flasks containing 100 ml of 0.1N HCl. The solution was filtered; 2 ml of the filtrate was taken and diluted to 100 ml with 0.1N HCl.The absorbance of the resulting solution was measured using UV-spectrophotometer at 277 nm using 0.1 N HCl as blank.

IR studies:

FT-IR studies were carried out for pure drug Metronidazole and compression coated tablets of Metronidazole to confirm absence of chemical interaction during tablet processing and storage. The IR spectrum was obtained in the range of 400-4000 cm^{-1}. [12]

In-vitro drug release studies:

The ability of the prepared compression coated tablet formulations of Metronidazole to prevent or to remain intact with respect to time in the physiological environment of stomach and small intestine in pH conditions prevailing in stomach and small intestine was assessed by in vitro drug release dissolution rate test apparatus (apparatus type 2, 100rpm, 37±0.5ºC) for 2 hrs in pH 1.2 (900ml), as the average gastric emptying time is 2 hrs, then the dissolution media was replaced with pH 7.4 phosphate buffer (900ml) and dissolution was continued for another 3 hrs as the usual small intestine transit time is 3-5 hrs and finally dissolution was continued in phosphate buffer pH 6.8 until completion of 24 hrs as the usual colon transit time is 20-30hrs. At the end of the time periods 5 ml sample were taken and analyzed for percentage of drug release by UV spectrophotometer at 277 nm.

RESULTS AND DISCUSSION:

Physical characterization of Metronidazolecore tablets:

The rapidly disintegrating Metronidazole core tablets were prepared by wet granulation technique using sodium starch glycolate as a super disintegrant to aid fast disintegration of the core tablets and PVP K-30 as binding agent. The compressional force was adjusted to give core tablets with approximately 4 kg/cm2 hardness. The physical parameters for the core tablet formulations were found to be within the limits. Average weight of the core tablet was fixed at 250 mg to accommodate maximum amount of coat material over the core tablet and the average percentage deviation of core tablet was within the official limit. The core tablet formulations passed the test for friability (<0.4%) and core tablets showed 97.43% of labeled amount of drug indicating uniformity of drug content in the core tablet formulation. (Table 3)

Physical characterization of Metronidazole compression coated tablets:

The compression-coated tablet formulations were prepared according to the coat formula given in table 2.The compression-coated tablets of different formulations were subjected to various evaluation tests, such as thickness, uniformity of weight, drug content, hardness, friability and in vitro dissolution. All the formulations showed uniform thickness in the range of 5.65 to 5.89 mm. In a weight variation test, the pharmacopoeia limit for the percentage deviation for tablets of more than 250mg is ± 5%.The average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformity of weight as per official requirements. Good uniformity in drugcontent was found among different batches of the tablets, and the percent of drug content was in the range of 93.62 % to 97.06 %. All the formulation showed a hardness value in the range of 6.03 to 6.16 kg/cm^2.The compressed tablets that lose less than 1% of their weights are generally considered acceptable. In the present study, the percentage friability of all the batches formulation was below 1% indicating that the friability is within the limits. All the tablet formulations showed acceptable properties and complied with the specification for weight variation, drug content, hardness and friability. (Table 3)

Fourier Transform Infrared studies:

The FT-IR spectra of the formulations were compared with the FT-IR spectra of the pure drug. The results indicated that the characteristic absorption peaks due to pure Metronidazole have appeared in the formulated tablets, without any significant change in their position after successful formulation, indicating no chemical interaction between Metronidazole and polymers.

of Metronidazole using Ethyl cellulose as a time dependent polymer and Eudragit L-100 and Eudragit S-100 as pH dependent polymers for better treatment of amoebiasis and other protozoal infections.Drug release were conducted in 0.1N HCl for the initial 2 hours, followed by

***In vitro* drug release studies:**

The present investigation was aimed to develop and evaluate compression coated tablets for colon specific delivery phosphate buffer pH 7.4 for next 3 hours and phosphate buffer pH 6.8 for 19 hours. The data obtained indicate that all the formulations showed sustained release beyond 24 h. All the formulations remained intact in the gastric pH of 1.2.

In formulations FM-1 and FM-2, the increase in polymer concentration retards the drug release and also the lag time was also increased with increase in polymer concentration. In formulations FM-3 and FM-4, the increase in polymer concentration there is decrease in the drug release and there is also slight difference in the amount of drug released in the simulated intestinal fluid [pH 7.4 buffer] when polymer concentration is increased, this showed a further increase in the polymer concentration might retard the rate of drug release in simulated intestinal fluid [pH 7.4 buffer] and the drug can be more effectively targeted to colon. In formulations FM-5 and FM-6, the increase in polymer concentrations there is decrease in the drug release but in formulation FM-6 the amount of drug released is less in simulated

intestinal fluid [pH 7.4 buffer], this showed that the major portion of the drug will be released in the colon thereby effectively targeting the colonic area.

The dissolution studies showed that the combination of Ethyl cellulose and Eudragit polymers can be effectively used for targeting the drug to the colon than when used individually. The studies also showed that Eudragit polymers have better drug release profile when compared to Ethyl cellulose.

CONCLUSION:

The present investigation was carried out to develop a time dependent and pH dependent colon specific drug delivery system for targeting Metronidazole to the colon.The release of Metronidazole from the compression coated tablets is directly proportional to the concentration of polymer used. As the concentration of polymer is increased, the drug release rate decreased.Ethyl cellulose as time dependent polymer and Eudragit L and Eudragit S as pH dependent polymer can be effectively used to target Metronidazole to the colon.Eudragit polymers have better drug release profile when compared to Ethyl cellulose. Ethyl cellulose when used individually as a compression coating agent will not be suitable for targeting the drug to colon but will be more acceptable when used in combination for drug targeting. Whereas Eudragit polymers will provide good choice for drug targeting to colon both when used individually or in combination with other polymers. Therefore, the study proves that Metronidazole can be successfully colon targeted by the use of a time dependent polymer and pH dependent polymer.

Table 3: Physical characteristics of core and compression-coated tablets

Formulation code	Hardness [kg/cm^2]	Friability [%]	Thickness [mm]	Drug content [%]
Core tablets	4.23±0.124	0.41±0.015	4.42±0.021	97.43±0.44
FM 1	6.03±0.057	0.26±0.052	5.65±0.01	94.17±0.17
FM 2	6.13±0.152	0.22±0.031	5.49±0.007	93.62±0.4
FM 3	6.03±0.057	0.18±0.01	5.74±0.017	97.06±0.07
FM 4	6.33±0.152	0.74±0.026	5.78±0.007	95.29±0.14
FM 5	6.3±0.1	0.55±0.015	5.86±0.01	95.54±0.09
FM 6	6.16±0.208	0.80±0.012	5.89±0.015	96.63±0.37

Table 4: Comparative *in-vitro*release data of Metronidazole compression coated tablets

Time [hours]	%CDR					
	FM 1	**FM 2**	**FM 3**	**FM 4**	**FM 5**	**FM 6**
1	0	0	0	0	0	0
2	0	0	0	0	0	0
3	8.87	0.50	10.24	9.61	9.25	0.72
4	12.07	3.75	15.13	13.68	12.65	3.79
5	15.71	11.44	17.23	16.64	16.41	9.79
6	16.18	15.98	18.93	18.40	17.55	13.85
7	19.44	18.86	22.51	21.34	19.68	15.71
8	23.29	21.84	24.72	23.97	23.01	19.35
9	25.48	25.15	28.72	27.65	25.80	23.48
10	29.83	28.25	33.28	33.15	31.12	26.79
11	33.73	32.55	38.64	37.66	35.68	30.65

12	40.67	38.16	43.17	41.56	40.19	35.30
13	43.67	41.8	47.81	47.61	44.10	39.75
14	49.08	46.34	50.78	50.70	47.63	42.67
18	58.32	55.78	63.80	64.75	60.91	59.00
22	62.77	58.64	70.25	68.80	69.08	66.13
24	67.72	61.19	75.65	70.90	73.62	70.82

Fig 1: FT-IR of pure drug Metronidazole

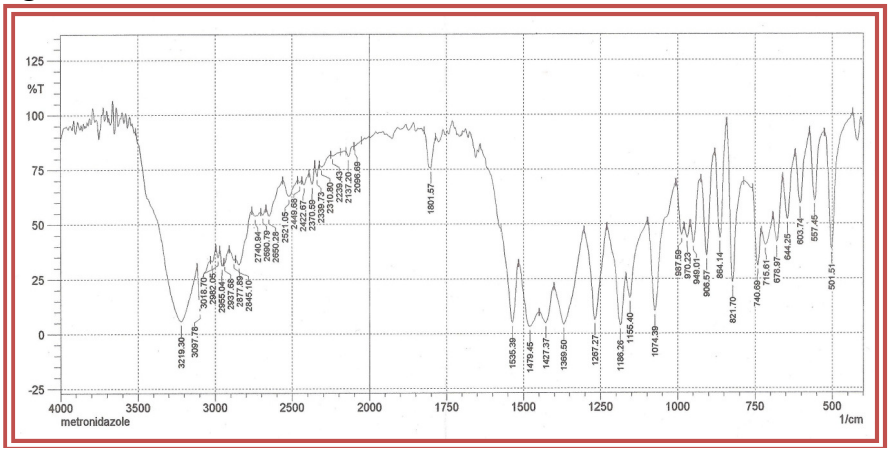


Fig 2: FT-IR of formulation FM-1

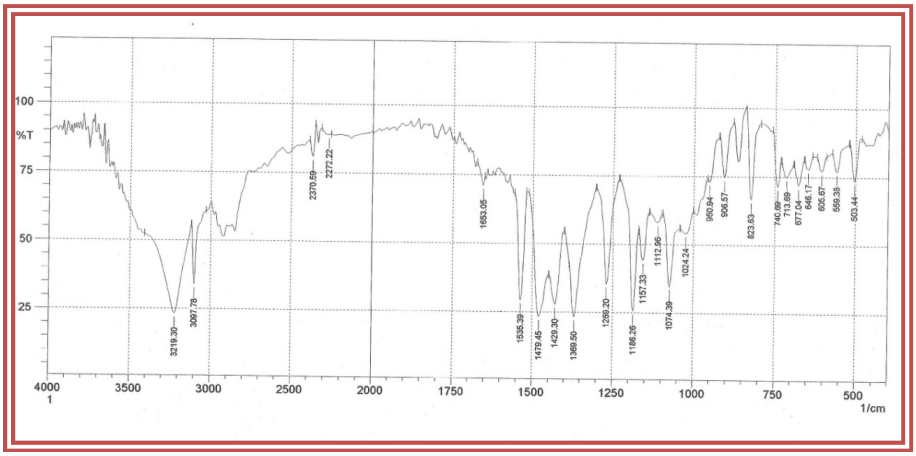


Fig 3: FT-IR of formulation FM-3

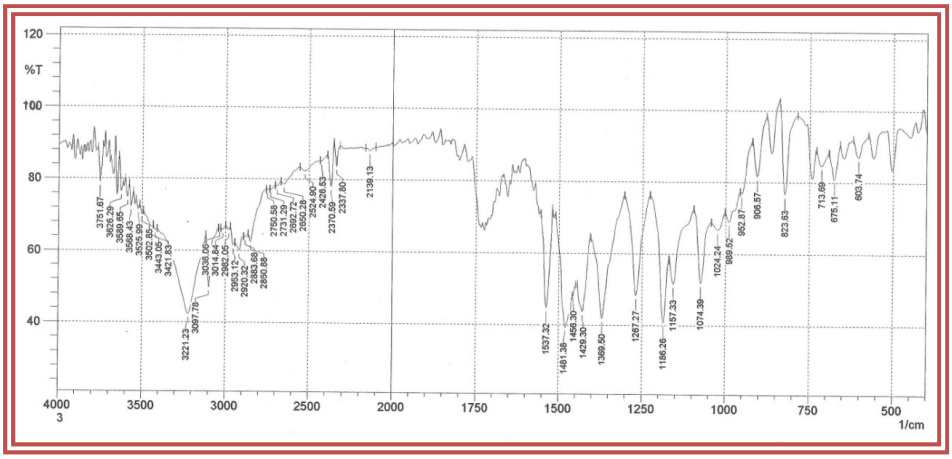


Fig 4: FT-IR of formulation FM-5

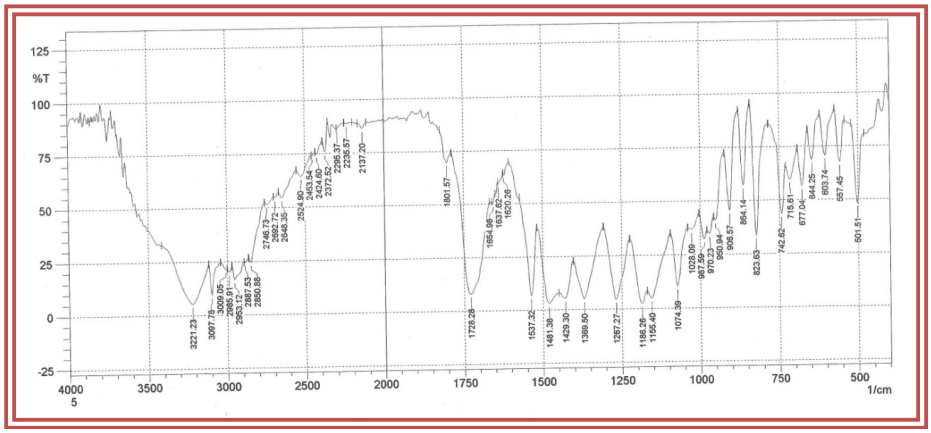


Fig 5: Comparative *in-vitro* release profile of formulation FM-1 and FM-2

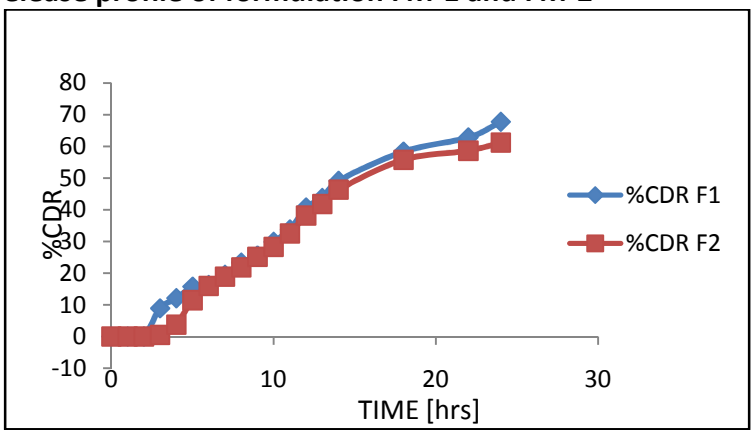


Fig 6: Comparative *in-vitro* release profile of formulation FM-3 and FM-4

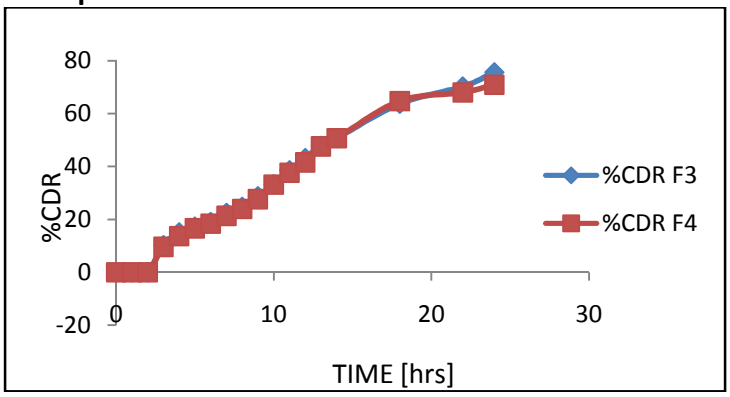


Fig 7: Comparative *in-vitro* release profile of formulation FM-5 and FM-6

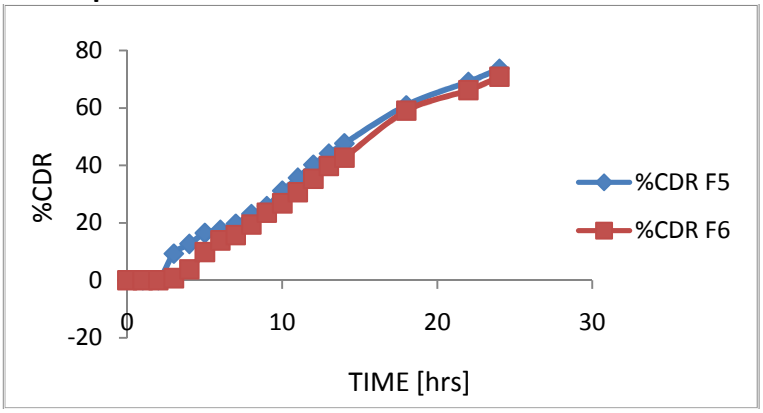


Fig 8: Comparative *in-vitro* release profile of formulation FM-1 and FM-3

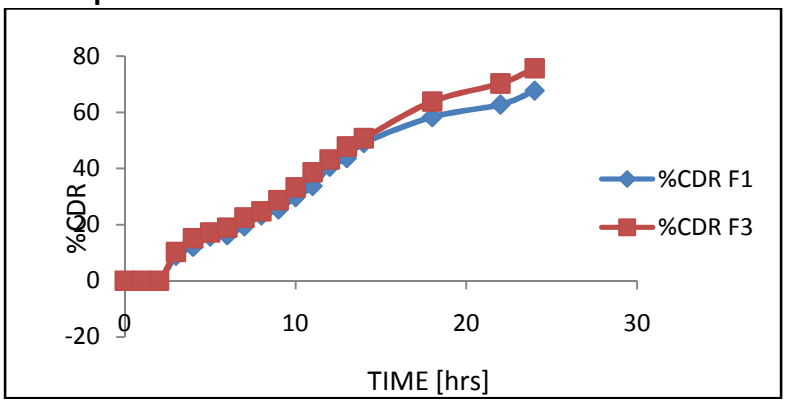


Fig 9: Comparative *in-vitro* release profile of formulation FM-2 and FM-4

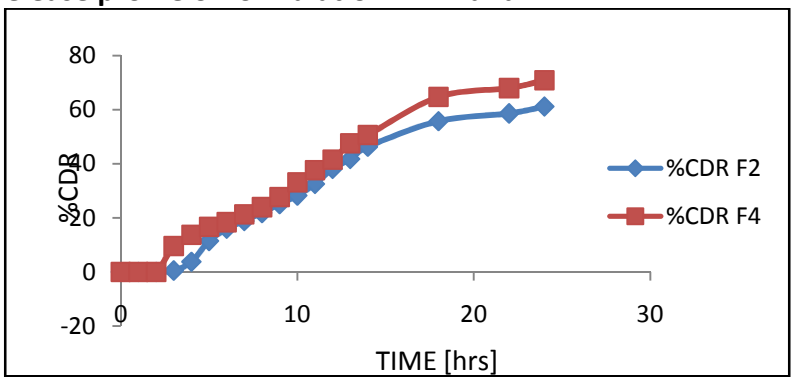


Fig 10: Comparative *in-vitro* release profile of formulation FM-1, FM-3 and FM-5

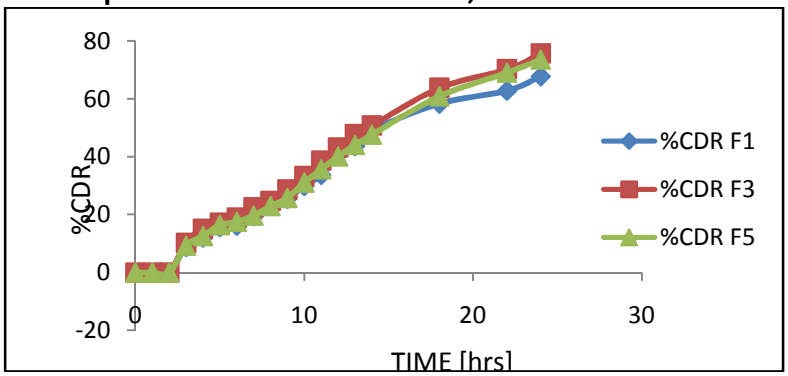
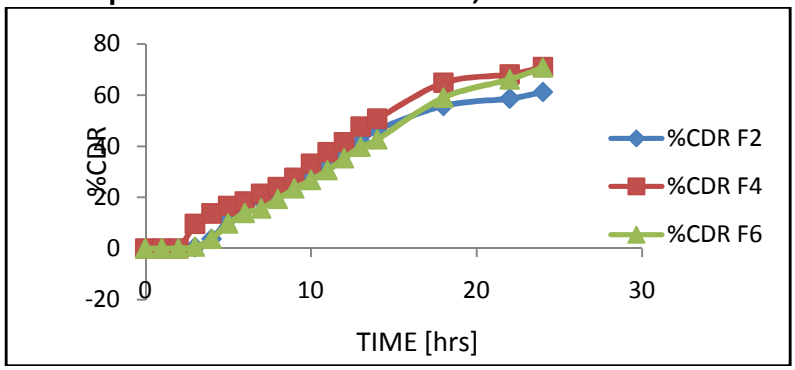


Fig 11: Comparative *in-vitro* release profile of formulation FM-2, FM-4 and FM-6



ACKNOWLEDGEMENT:

The authors acknowledge the kind help received from Ceechem pharmaceuticals, Bengaluru, Karnataka for gift samples of Metronidazole. The authors gratefully acknowledge the Principal, Government College of pharmacy, Bengaluru,

Karnataka for providing necessary facilities to carry out this research work.

REFERENCES

1. Antonin K H, Rak R, Beick P R, Schenker U,Hastewell J, Fox R, Mackay M. The absorption of human calcitonin from the transverse colon of man. Int. J. Pharm, 1996: 130: 33-39.
2. Rama Prasad Y V, Krishnaiah Y S R, Satyanarayana S. Trends in colonic drug delivery: A review. Indian drugs, 1996: 33: 1-10.
3. M.K.Chourasia, S.K.Jain. Pharmaceutical approaches to colon targeted drug delivery systems. J. Pharm. Sci, 2003: 6 (1): 33-66.
4. Kiran B. Aher, Girija B. Bhavar, Hemant P. Joshi, Sanjay R. Chaudhari. Recent advances in compression-coated tablets as a controlled drug delivery system. Saudi pharmaceutical journal, 2011: 1-14.
5. Rivera E, Almodovav Y. Local application of metronidazole in vaginal ovules for treatment of trichomoniasis. Pubmed, 1984: 149 (7): 807.
6. Martindale. The complete drug reference, 33rd edition. London: The pharmaceutical press: 2001.
7. Handbook of pharmaceutical excipients, 5th edition. London: The pharmaceutical press: 2006.
8. The Japanese pharmacopoeia, 16th edition.
9. Swamy N.G.N, Dharmarajan T.S, Paranjothi K.L.K. Study of the binding properties of hydroxypropyl guar and its utilization in the formulation and evaluation of Metoprololtartarate tablets. RGUHS J Pharm Sci, 2012 : Vol 2: 45-54
10. Nitesh J. Patel, C.S.R. Lakshmi, Hitesh P. Patel and SagarAkul. Formulation and evaluation of oral dispersible tablets of Cinnarizine using direct compression technique. IJPSR, 2011: Vol. 2(4): 961-967.
11. Chickpetty S.M and Raga Baswaraj. Studies on design and in vitro evaluation of compression-coated delivery systems for colon targeting of Diclofenac sodium. IJPRIF, 2010: Vol. 2(3): 1714-1722.
12. Lucia Maria Rus, IoanTomuta, Cristina Iuga, Codruta Maier, Irina Kacso, Gheorghe Borodi, IoanBratu, Marius Bojita. Compatibility studies of Indapamide/pharmaceutical excipients used in tablet formulation. Farmacia, 2012: Vol. 60(1): 92-101.

*****