



INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND DEVELOPMENT (IJPRD)

Platform for Pharmaceutical Researches & Innovative Ideas
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DEVELOPMENT OF ENTERIC COATED PECTIN MATRIX TABLETS OF METRONIDAZOLE FOR COLON TARGETING

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ABSTRACT

A new oral drug delivery system has been developed for colon targeting which takes advantage of the combined approaches of a specific colon-biodegradable pectin matrix with a pH-sensitive Eudragit S 100 polymeric coating. Matrix tablets were prepared by mixtures of pectin, a hydrophilic swellable polymer, in which metronidazole, selected as model drug, was dispersed. Eudragit S 100, a methacrylic acid polymer soluble at colonic pH, was used as pH-sensitive polymer. The results of drug release studies, performed according to the USP basket method by using artificial gastric juice (0.1 M HCL) for 2 h, small intestinal fluid (6.8 phosphate buffer) for 2 h, large intestinal fluid (7.4 Phosphate buffer) fluid for 6 h, and effect of the presence and absence of pectinolytic enzymes was evaluated. This indicates that the Eudragit S100 coated matrix tablets were successful in achieving gastric resistance. Comparison of results obtained in the presence and absence of pectinolytic enzymes showed pectin was the most interesting candidate for colonic delivery and most susceptible to enzymatic degradation, thus assuring a greater site-specificity of drug release.

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Key Words

colon drug delivery,
metronidazole, pectin,
pectinolytic enzymes, eudragit
S100

INTRODUCTION

Amoebiasis¹ is an infection of the large intestine caused by *Entamoeba histolytica*, a single celled protozoan parasite. According to World Health Organization, 1997² amoebiasis is the second only to malaria as a cause of death resulting from protozoan parasite.

The most preferred choice of drug for effective action on *E. histolytica* is metronidazole. where trophozoites reside in the caecum and large intestine and adhere to the colonic mucus and epithelial layers¹⁴. The pharmacokinetic profile of metronidazole¹² indicates that the drug is completely and promptly absorbed after oral administration.

The oral route is the most preferred route for drug administration, especially for chronic therapies where repeated administration is required. The orally administered drugs, however, can be ineffective due to the digestive enzymes and acidic pH in the gastrointestinal tract. To overcome this disadvantage the use of polysaccharides coated with pH-sensitive polymers³ are used.

Among these polysaccharides, pectin,¹⁰ chiefly consisting of partially methoxylated poly α -(1-4)-D-galacturonic acids, are completely digested by colonic bacteria. However, their solubility and swelling properties in aqueous media make them unable to efficiently avoid the release of drugs during the transit through the upper gastrointestinal tract, and imply the combined use of insoluble polymer to assess their integrity until they reach the colon region⁴.

The aim of the present study was to formulate pectin matrix tablets coated with EudragitS100 for site-specific delivery of metronidazole (MTZ) using natural polysaccharide and pH-sensitive polymer (EudragitS100) for the treatment of Amoebiasis in colon. This system is anticipated to protect the drug loss in the upper GI tract, which results from the inherent property of Eudragit S100, and deliver MTZ in the colon only. The use of enteric polymer EudragitS100 coated pectin matrix tablets makes them able to release the drug at the particular pH of colonic fluid. A combined mechanism of release is seen, which combines specific biodegradability of polymer and pH-dependent drug release from the coated matrix tablets.

MATERIALS AND METHODS

Metronidazole was a gift sample from Comprehensive Medical Services, Chennai. Other materials purchased from commercial sources were: Pectinolytic enzyme (Novozyme), Pectin (Loba Chemie), Eudragit S100 (Yarrow Chem Products), micro crystalline cellulose (Rohm Laboratory Reagents), magnesium stearate (SD.fine Chem) and starch (Chems Pure).

Preparation of metronidazole matrix tablets .

Matrix tablets^{4,7} of Metronidazole were prepared by wet granulation method. Micro crystalline cellulose and pectin were used in different ratios, starch was used as both diluent and granulating agent. Mixture of talc and magnesium stearate 2:1 was used as lubricant. The composition of different formulations used in the study containing 200 mg of metronidazole in each case is shown in Table 1.

Table 1 :Composition of F1-F6 formulations per tablet in (mg)

Ingredients	F1	F2	F3	F4	F5	F6
Metronidazole	200	200	200	200	200	200
Pectin	200	100	200	200	100	100
MCC	50	100	100	200	25	50
Starch	36.5	86.5	36.5	36.5	161.5	136.5
Talc	9	9	9	9	9	9
Magnesium stearate	4.5	4.5	4.5	4.5	4.5	4.5

In all the formulations, pectin was sieved and mixed with metronidazole and MCC. The powders were blended and granulated by using starch paste. The wet mass was passed through a mesh size of 16 and were dried at 50 °C for 2 hrs. The dried granules were passed through mesh and lubricated with a mixture of talc and magnesium stearate. The lubricated granules were

compressed with maximum force of compression by using 9 mm round, flat and plain punches on rotary tableting machine (Cadmach Machinery, Ahmedabad, India). Granules^{5,6} for all formulations were tested for their packing characteristics and flowability given in (Table 2).

Table 2: Evaluation of granules

Formulation Code	Angle of Repose(θ)	Bulk Density (g/cm^3)	Tapped Density(g/cm^3)	Carr's Index(%)	Hausner's Ratio(%)
F1	22.29 \pm 2.25	0.350 \pm 0.018	0.392 \pm 0.008	10.7 \pm 1.88	1.114 \pm 0.031
F2	20.80 \pm 1.85	0.361 \pm 0.005	0.412 \pm 0.011	12.3 \pm 1.90	1.141 \pm 0.014
F3	23.12 \pm 1.59	0.370 \pm 0.011	0.420 \pm 0.013	11.9 \pm 1.67	1.135 \pm 0.033
F4	24.84 \pm 0.76	0.356 \pm 0.005	0.404 \pm 0.016	11.8 \pm 1.85	1.134 \pm 0.024
F5	23.98 \pm 0.87	0.380 \pm 0.007	0.436 \pm 0.009	12.8 \pm 1.78	1.147 \pm 0.029
F6	23.17 \pm 0.67	0.376 \pm 0.015	0.431 \pm 0.026	12.7 \pm 1.72	1.146 \pm 0.018

All values are expressed as mean \pm SD, n=3

Matrix tablets for all formulations were tested for their hardness, friability, drug content and weight variation

with a suitable number of matrix tablets for each test given in (Table 3).

Table 3: Tablet evaluation

Formulation Code	Weight variation(%)	Hardness(kg/cm^2)	Friability(%)	Drug content(%)
F1	Within the limits	4.6	0.20	95.905
F2	Within the limits	4.8	0.18	98.116
F3	Within the limits	4.6	0.16	95.211
F4	Within the limits	4.7	0.19	96.300
F5	Within the limits	4.65	0.21	95.812
F6	Within the limits	4.9	0.21	96.125

Tablet coating:

Enteric coating of tablets was performed by pan coating (Cipweka, India). Coating solution was prepared using 12% w/v Eudragit S100 using acetone and PEG 400¹¹ (1.25 %w/w) as plasticizer. Tablets were placed in the pan and coating solution was sprayed and dried with the help of inlet air (temperature 45-50 °C). The coating process was repeated till the desired level of coating was achieved. The percentage mass increases of tablets upon coating to 10 % was taken to be indicative of coat thickness⁴.

***In vitro* drug release study in the presence and absence of pectinolytic enzyme**

The ability of prepared tablets to retard drug release in the physiological environment of the stomach, the small intestine and the large intestine were evaluated for the *in vitro* drug release. The dissolution test of different formulations (F1-F6) was

performed by using USP basket apparatus at stirring speed of 100 rpm at 37⁰ C in 900 ml of dissolution medium. The simulation of GI transit conditions was achieved by altering the pH of dissolution medium at different time intervals. The pH of dissolution medium was kept 1.2 for 2 hrs using 0.1 M hydrochloric acid. After 2 hours, 1.7 g of KH₂PO₄ and 2.225g of Na₂PO₄.2H₂O were added, the pH of the dissolution medium was adjusted to 6.8 by 1.0 M sodium hydroxide and dissolution was carried out for 2 hours. After 4 hrs, in presence or absence of pectinolytic enzyme¹³ the pH of the dissolution medium was adjusted to 7.4 with 1.0 M sodium hydroxide, and maintained up to 10 hours⁹. At predetermined intervals, samples were withdrawn from the dissolution medium at various time intervals and analyzed by using UV -visible spectrophotometry at λ_{\max} of 274 nm⁴. The results were given in Fig 1,2.

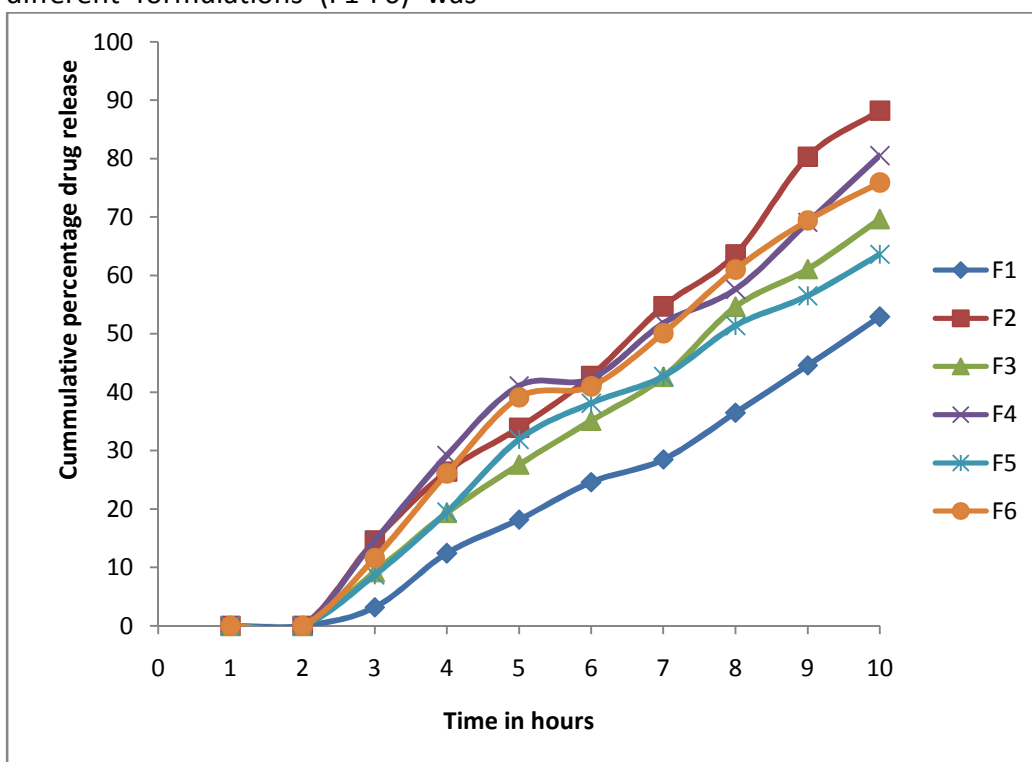


Fig.1: Cummulative percentage of metronidazole released in absence of pectinase enzyme for formulations F1-F6

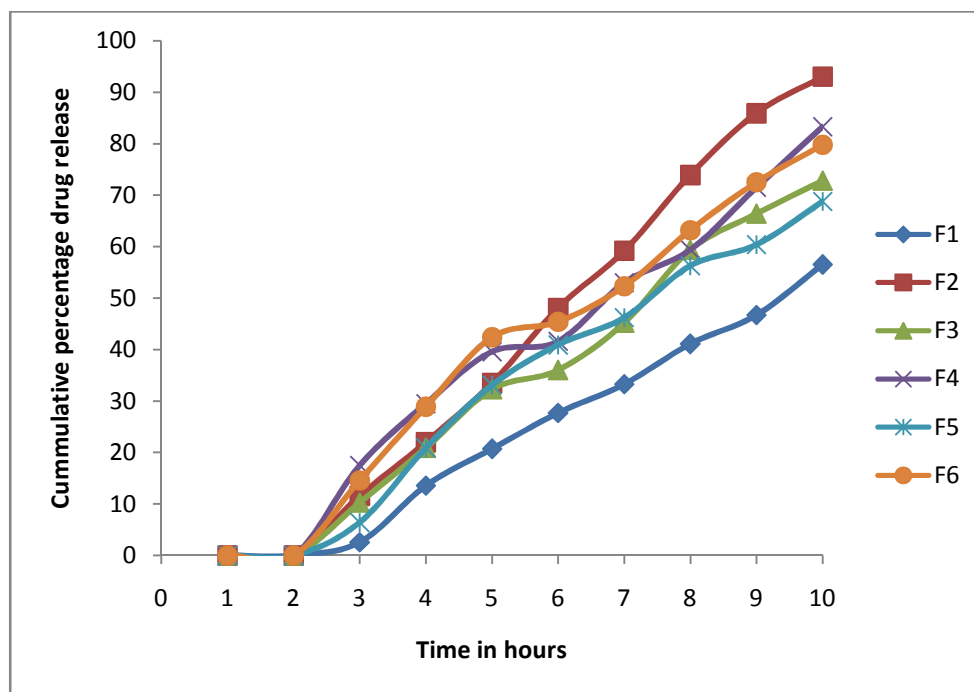


Fig.2: Cumulative percentage of metronidazole released in presence of pectinase enzyme for formulations F1-F6

Release Kinetics

The order and mechanism of metronidazole release from the matrix tablets were determined by fitting the release rate data in various kinetic equations⁹ like zero order (%release vs t), first order (log% release vs t) and Higuchi model (M_t/M_∞ vs $t^{1/2}$). In order to define a model which will represent a better fit for the

formulation, drug release data was further analyzed by Peppas equation, $M_t/M_\infty = kt^n$, where M_t is the amount of drug released at time t and M_∞ is the amount released at time ∞ , thus the M_t/M_∞ is the fraction of drug released at time t, k is the kinetic constant and n is the diffusional exponent. The results were given in Table 4.

Table 4: Kinetic evaluation of drug release data for formulations F1-F6

S.No	Formulation	Regression coefficient for selected release kinetic models			
		Zero order	First order	Higuchi Kinetics	Korsmeyer-Peppas
1	F1	0.9736	0.8551	0.9187	0.9926
2	F2	0.9916	0.9246	0.8833	0.9944
3	F3	0.9980	0.9761	0.9220	0.9981
4	F4	0.9833	0.9083	0.9530	0.9935
5	F5	0.9826	0.9749	0.9518	0.9830
6	F6	0.9810	0.9743	0.9515	0.9829

The zero order, first order and Higuchi equations failed to explain the drug release mechanism from polymeric system that undergo swelling and erosion during dissolution. In such cases based on the value of n , obtained by fitting in Peppas Korsmeyer equation, the mechanism of drug release could be described. In case of the Fickian release mechanism, the rate of drug release was much less than of polymer relaxation (erosion). So the drug release was chiefly dependent on the diffusion through the matrix. In the non Fickian (anomalous) case the rate of drug release was due to the combined effect of drug diffusion and polymer relaxation. Case-II release generally to polymer relaxation.

DISCUSSION

The values of angle of repose ($20.4-24.8^{\circ}$), tapped density (0.392 to 0.436 g/cm^3), bulk density (0.350 - 0.380 g/cm^3), Carr's (10.70 - 12.7 %), Hausner ratio (1.114 - 1.147 %) of formulations (F1-F6), indicate good flow properties for the granules.

The values of weight variations are within the limits (*i.e* 5% tablet weighing more than 324 mg). The matrix tablets were prepared by applying maximum force of compression and hardness of tablets was found to be in the range of $4.6-4.9$ kg/cm^2 . The friability test was conducted and the values are in the range of $0.16-0.21\%$ which shows all formulations are within the limits (1%). Metronidazole tablets of different concentrations of pectin and MCC were prepared, and were subjected to drug content. The matrix tablets were found to contain $95.90-98.11\%$ of labelled amount of metronidazole.

The percentage Metronidazole released in 0.1M HCL is null due to pH sensitive Eudragit coat on matrix tablets. In the pH of 6.8 drug started to release from matrix tablets. In pH 7.4 the drug releases from formulations. Depending on the concentrations of pectin and MCC F2 formulation shows good release of drug at 10 h considered as best formulation.

With the aim of evaluating the influence of the pectin biodegradation process on the drug release profile, a series of experiments was performed by

adding a commercially available pectinase enzyme (Pectinex Ultra SP-L), whose pectinolytic activity is closely related with that of the *Bacteroides ovatus*⁴, the main colon producer of pectinolytic enzymes. The drug release curves and the relevant kinetic data obtained from experiments in the presence of pectinolytic enzymes were clearly different from those previously obtained from the same tablets in the absence of pectinolytic enzymes.

Comparison of pectin matrix tablets collected at the end of test performed in the presence or absence of pectinolytic enzymes made it possible to visibly appreciate the effect of enzymatic activity on the aspect of the residual matrix. The matrix tablets in presence of pectinolytic enzymes, undergoes a faster erosion process which, in agreement with the results of release studies, resulted in a more marked increase in drug release rate.

From curve fitting the drug release shows good correlation coefficients (R values) for Korsmeyer-Peppas equation. The n values was found to be in between $0.85-1.26$. The values are closer to 1 and hence it is concluded that the drug release was more dependent on the effect of polymer relaxation (case II transport).

CONCLUSION

In vitro studies on eudragit coated pectin matrix tablets of metronidazole shows drug release in colonic pH. And in presence of pectinolytic enzymes in colonic pH enhances drug release. Hence the formulations represent a promising novel tool for targeting drug to the colon.

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