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DESIGN AND EVALUATION OF COMPRESSION COATED TABLET OF METRONIDAZOLE FOR COLON-SPECIFIC DRUG DELIVERY SYSTEM

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Abstract:

The present study aims to formulate colon-targeted drug delivery of metronidazole compression-coated tablets using different ratios of chitosan and pectin. The core tablets of metronidazole (400 mg) were prepared using swellable and pH-dependent polymers like chitosan and pectin, and PVP-K30 was used as a binder. The compression-coated tablets containing chitosan as a polymer released 95-99% of metronidazole in simulated colonic fluid, whereas tablets containing pectin released 94-99% of metronidazole. The stability study for prepared tablets at 40°C/75% relative humidity for 6 weeks showed no significant change in physical appearance, drug content uniformity and in vitro drug release pattern. The result indicates that formulations F4 and F8 were suitable for colonic drug delivery as drug release is maximum compared to other formulations.

Keywords: *Colon drug delivery system, Chitosan, Pectin, Compression Coating, and Metronidazole*

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1. INTRODUCTION:

Oral colon-targeted drug delivery has many important implications in the field of pharmacotherapy. To achieve successful colon-targeted drug delivery, a drug must be protected from degradation, release and absorption in the upper portion of the GI tract and then be ensured abrupt or controlled release in the proximal colon [(1)]. Metronidazole is classified in the WHO essential medicines list as anti-amoebic, anti-giardiasis, and anti-bacterial. Chemically, 1-(β- Hydroxy Ethyl)-2-Methyl-5-nitroimidazole inhibits nucleic acid synthesis [(2)]. Drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amoebiasis, colonic cancer, local therapy of colonic pathologies, and systemic delivery of protein and peptide drugs [(3)].

As a site for drug delivery, the colon offers distinct advantages due to a near-neutral pH, a much longer transit time, relatively low proteolytic enzyme activity, and much more excellent responsiveness to absorption enhancers [(4)]. To achieve successful colon-targeted drug delivery, a drug needs to be protected from degradation, release or absorption in the upper portion of the GI tract and then to be ensured abrupt or controlled release in the proximal colon [(5)]. The present study aims to formulate colon-targeted drug delivery of metronidazole compression-coated tablets using different ratios of chitosan and pectin. Carbopol 934P coating is given for compression-coated tablets, which allows them to release the drug at the pH of the colonic fluid.

2. MATERIALS AND METHODS:

2.1. Materials

Metronidazole was acquired as a gift sample from Abbott, India. Chitosan and Carbopol 934P were procured from Ozone International, Mumbai. Pectin was procured from Sisco Research Laboratories, Mumbai. PVP K-30 was a gift sample from Qualikems Fine Chemicals, Gujarat, and Microcrystalline Cellulose was obtained from Loba Chemicals, Mumbai.

2.2. Methods

2.2.1. Preparation of metronidazole core tablets

The compression-coated tablet formulations containing 200mg of metronidazole and weighing 400mg tablets were prepared using a direct compression technique using Chitosan and pectin matrices. Metronidazole, Polymers (Chitosan and Pectin), PVP-K30 (as a binder), and microcrystalline cellulose were triturated well and sieved through sieve no.60 and mixed thoroughly by using mortar and pestle. The powder mass lubricants (Talc and Magnesium stearate) were added and mixed thoroughly. The powder is evaluated for precompression parameters. The powder was then compressed using a 10 mm flat-faced punch using a Rimek tablet punching machine. The total weight of the tablet was maintained at 400 mg [(6)]. The composition of formulations are listed in Table 1.

Table 1: Composition of colon-targeted core tablets of metronidazole

Ingredients (mg/tablet)	Formulations									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Metronidazole	200	200	200	200	200	200	200	200	200	200
Chitosan	25	50	75	100	125	--	--	--	--	--
Pectin	--	--	--	--	--	50	75	100	125	150
PVP- K30	10	10	10	10	10	10	10	10	10	10
MCC	156	131	106	81	56	131	106	81	56	31
Magnesium Stearate	4	4	4	4	4	4	4	4	4	4
Talc	5	5	5	5	5	5	5	5	5	5
Total weight (mg)	400	400	400	400	400	400	400	400	400	400

2.2.2. Preparation of metronidazole compression-coated tablets

The different ratios of chitosan and pectin core metronidazole tablets were compression coated using a coat formulation. The compression coat formulations were prepared using carbopol 934 P and chitosan (Table 2). Initially, 40% of the coat weight was placed in a 12.4 mm die cavity of a tablet punching machine, followed by carefully centring the core tablet and adding a reminder of coat weight. The coating material was compressed around the core tablet with high compression force [7].

Table 2: Composition of coat formulation

Ingredients	Weight (mg)
Chitosan	20
Carbopol 934P	160
PVP-K30	10
Magnesium Stearate	6
Talc	4
Total weight	200
* Quantity in mg for one tablet	

2.2.3. EVALUATION OF TABLETS

2.2.3.1. Precompression parameters

Angle of repose (□)

The angle of repose can measure the frictional forces in a loose powder or granules. This is the maximum angle between the surface of a pile of powder or granules and the horizontal plane.

$$tan\theta = \frac{h}{r}$$

Where □is the angle of repose, h is the height, and r is the radius.

$$\theta = \tan^{-1}\frac{h}{r}$$

The granules were allowed to flow through the funnel fixed to a stand at a definite height. It was then calculated by measuring the height and radius of the heap of granules formed [8].

Bulk density and tapped density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. The accurately weighed sample taken in a 25ml measuring cylinder of Borosil measured/recorded the packing volume and tapped 100 times on a plane hard wooden surface. The tapped packing volume was recorded, and LBD and TBD were calculated [9].

$$Tapped\ buk\ density = \frac{Mass\ of\ the\ powder}{Tapped\ volume\ of\ packing}$$

$$Loose\ bulk\ density = \frac{Massof\ the\ powder}{Bulk\ volume\ of\ packing}$$

Compressibility index:

The percent compressibility of the powder mix was determined by Carr's Compressibility index**,** which was calculated by following the formula.

$$Carr's\ Index\ \% = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100$$

Hausner's ratio:

It is a number that is correlated to the flow ability of apowder or granular material [10].

$$Hauser's\ Ratio = \frac{Tapped\ density}{Bulk\ density}$$

2.2.3.2. Post-compression parameters

Uniformity of thickness

Three tablets were picked from each formulation randomly, and thickness was measured individually. It is expressed in mm, and the standard deviation was also calculated. The tablet thickness was measured using a dial-caliper (Mitutoyo, Japan) [11].

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while packaging, handling and transportation. The hardness of the tablets was determined using a Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and analyzed for hardness. The mean values were calculated [12].

Friability test

It is where tablet surfaces are damaged and show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined using the Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and transferred into a friabilator. It was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}) [13].

Weight variation test

Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation. U.S. Pharmacopoeia allows a slight variation in the weight of a tablet [14].

Drug content uniformity

Twenty tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 50mg of metronidazole was transferred into a 100 ml volumetric flask and extracted with 0.1N Hydrochloric acid solution, filtered and kept aside for 2 hours. Dilute 10 ml of the resulting solution to 250 ml with 0.1N HCL and the absorbance of the resulting solution at the maximum at 277nm using a Shimadzu UV-visible spectrophotometer [15].

Swelling studies

The swelling behaviour of the polymer can be characterized by measuring its water uptake ability at appropriate time intervals; each tablet was removed from its water with forceps, briefly patted with clean tissue paper to remove the solution, wetted its surface and weighed. The swelling study was done in a distilled water medium at 37°C. The results were expressed as %of water uptake (%of swelling) in the function of time (hours). The method was used to record water uptake in triplicate [16].

Disintegration time

Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated intestinal fluid) maintained at $37^0 \square 2^0$C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute at a pH of 6.8 maintained at $37^0 \square 2^0$C. The time in seconds or minutes taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded. Enteric-coated tablets pass the test if each of the six tablets disintegrates in the simulated intestinal fluid in not more than 60 minutes [17].

Dissolution studies

Drug release studies were conducted using a USP Type II test apparatus (Paddle Type). (Apparatus Type II, 100 rpm, 37±1°C) for 2 hrs in 0.1 N HCl (900 ml), as the average gastric emptying time is about 2 hr. Then, the dissolution medium was replaced with pH-7.4 phosphate buffer (900 ml) and tested for drug release for 3 hours, with the average small intestinal transit time being about 3 hours. After 5 hrs, the dissolution medium was replaced with pH 6.8 Phosphate buffer (900 ml) and tested for drug release up to 24 hr. At the end of each period, 10 ml of the samples were taken. From this, 1 ml was diluted to 10 ml with the respective dissolution medium and analyzed for metronidazole content. After each sample withdrawal, a 10 ml volume of fresh and filtered respective dissolution medium was added to make the volume. In vitro dissolution studies are done without rat caecal content [18].

Curve fitting analysis

The release kinetics data obtained from in vitro drug release studies were plotted in various kinetic models: zero order as the cumulative amount of drug released vs. time, first order as the log cumulative percentage of drug remaining vs. time, and Higuchi's model as cumulative percentage of drug released vs. square root of time. Korsmeyer equation as log cumulative percentage of drug released vs. log time and the exponent n was calculated through the slope of the straight line [19].

Stability Studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or product varies with time under the influence of various factors and conditions. In the present study, stability studies were carried out at 40^0C /75% RH for a specific period of up to 6 weeks for selected formulations [20].

3. RESULTS AND DISCUSSION:

Compressed coated tablets of metronidazole were prepared by using the direct compression method. Before compression, the powder blends were subjected to pre-pre-compression evaluation parameters to determine the flow properties and the compressibility.

3.1. Precompression evaluation parameters of metronidazole

The values were found to be in the range of 25^0.8' to 29^0.9'. All formulations showed an angle of repose within 30^0, indicating the powder's suitable flow property. The loose bulk density and tapped bulk density for all the formulations varied from 0.46 gm/cm^3 to 0.52gm/cm^3 and 0.50gm/cm^3 to 0.60gm/cm^{3,} respectively. The values obtained lie within the acceptable range, and no significant differences were found between loose and tapped bulk densities. This result helps calculate the % compressibility of the powder, and the results are presented in Table 3.

Table 3: Evaluation of precompression parameters

Formulations	Angle of repose(□)	Bulk density (gm./cm^3)	Tapped density (gm/cm^3)	Hausner's ratio	Carr's index (%)
F1	29°.9'	0.51	0.60	1.17	15.0
F2	28°.9'	0.48	0.56	1.16	14.2
F3	28°.1'	0.46	0.52	1.13	11.5
F4	29°.6'	0.48	0.57	1.18	15.78
F5	26°.7'	0.50	0.58	1.16	13.79
F6	25°.8'	0.52	0.60	1.15	13.33
F7	29°.9'	0.48	0.57	1.18	15.78
F8	28°.9'	0.50	0.58	1.16	13.79
F9	28°.1'	0.51	0.60	1.17	15.00
F10	29°.5'	0.48	0.56	1.16	14.28

3.2. Post-compression evaluation parameters of metronidazole

The developed formulations were evaluated according to official specifications and other parameters. Thickness was found in the range of 3.0 mm to 4.1 mm respectively. A Monsanto hardness tester performed the hardness test. Hardness was found to be within 5.2 kg/cm^2 to 6.2 kg/cm^2,as these tablets are delayed disintegrating. %. Its weight variation varied between 396.0 to 404.0 mg. The weight of all the tablets was found to be uniform. The drug content values were between 98.10% and 98.77%. All formulations showed a disintegration time of less than 45 minutes. The results are presented in Table 4.

Table 4: Evaluation of post-compression Parameters

Formulations	Thickness (µm)	Hardness (kg/cm^2)	Weight Variation (mg)	Friability (%)	DT (min)	Assay (%)
F1	3.0	5.5	396	0.39	28	98.36
F2	3.2	6.2	398	0.36	35	98.67
F3	3.1	5.6	402	0.39	40	99.26
F4	4.1	5.2	397	0.56	26	98.10
F5	4.1	5.3	404	0.53	32	98.39
F6	4.1	5.4	403	0.49	45	98.77
F7	3.8	5.5	403	0.34	28	98.67
F8	3.6	6.2	415	0.42	35	99.26
F9	4.1	5.7	408	0.45	40	98.10
F10	3.8	5.6	397	0.51	37	97.38

Swelling index

The percentage of a swelling index of chitosan increased as time increased. The results are shown in Fig 1.

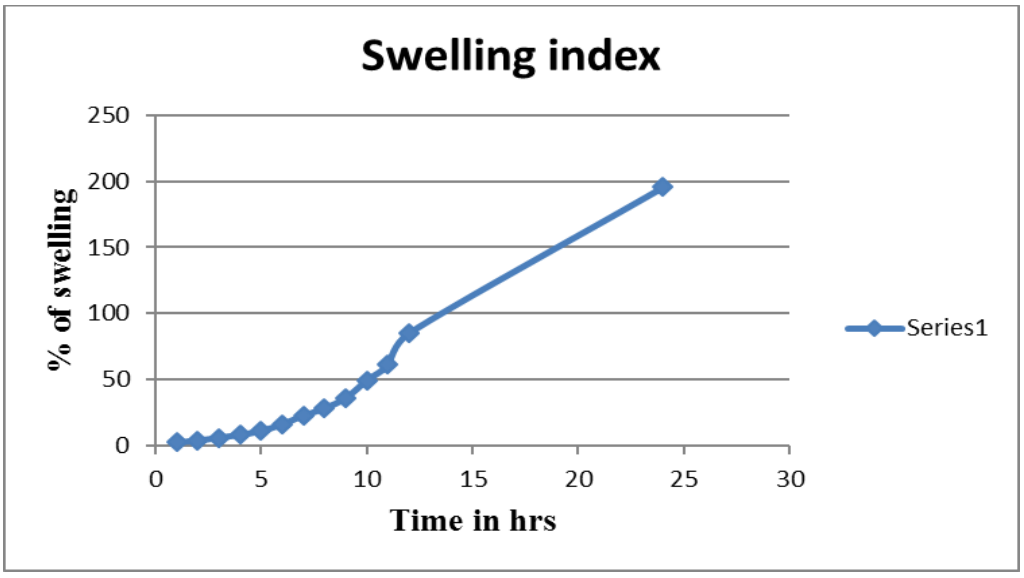

Fig 1: Percentage of swelling index

3.3. *In Vitro* dissolution studies

The dissolution rate was found to decrease linearly with increasingconcentration of polymer. Formulations F1 to F5 containing drug plus chitosan polymer with carbopol934P coating have recorded drug release 95.26% to 98.77%, respectively, at the end of 24 hours. Formulations F6 to F10 containing drug plus pectin polymer with carbopol 934P coating have recorded drug release 94.97% to 99.72%, respectively, at the end of 24 hours, and the results are presented in Fig 2 & 3. The relative efficiency of different ratios of polymers to improve the dissolution rate of tablets.

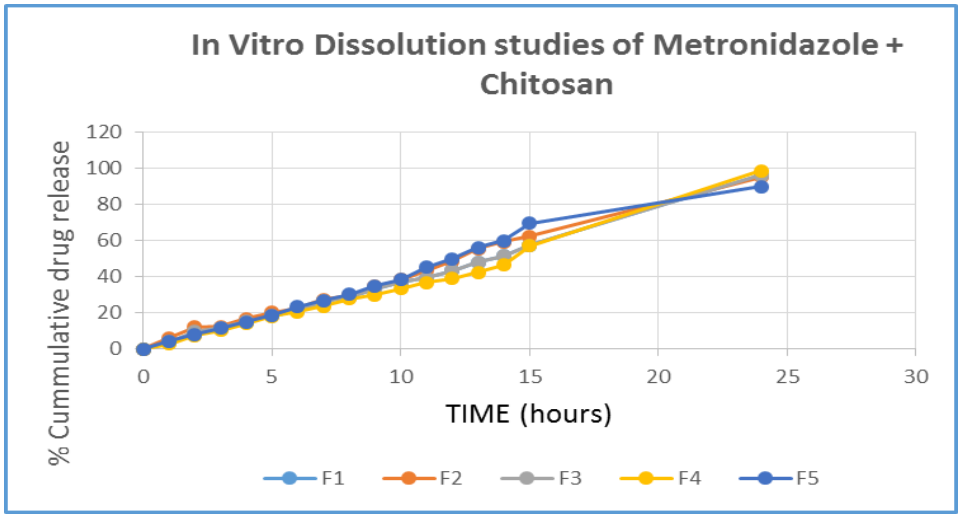

Fig 2: Release profile of the formulations (F1 to F5)

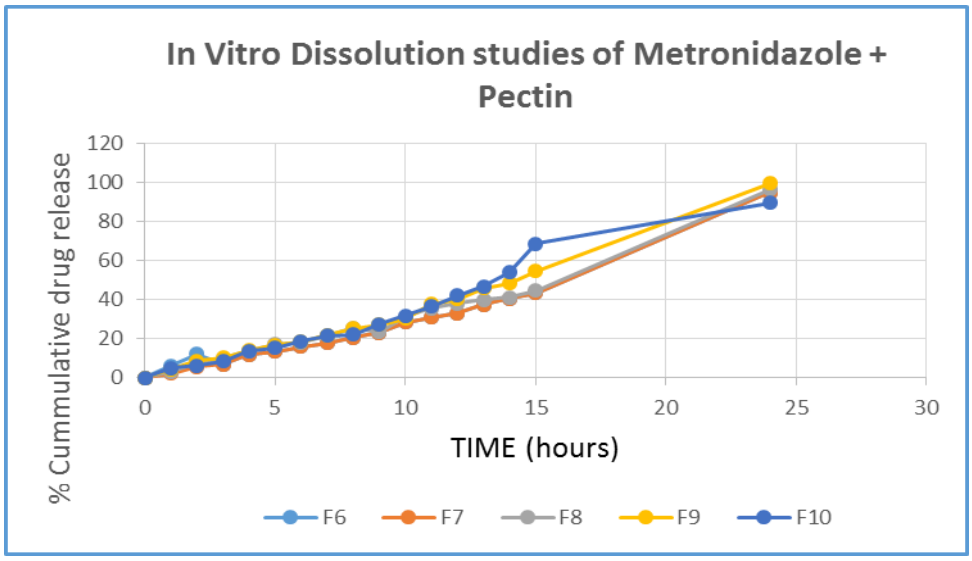

Fig 4: Release profile of the formulations (F6 to F10)

3.4. Drug release kinetics

The dissolution data was fitted to zero order, first order, Higuchi model and Korsmeyer-peppas model to analyze the drug mechanism. The correlation coefficient for (r^2) for zero order ranges from 0.9513 to 0.9946; first order ranges from 0.7102 to 0.8015, the Higuchi model ranges from 0.7787 to 0.888, and that of the Korsmeyer-peppas model ranges from 0.8849 to 0.9715. The results are shown in Fig 5.

3.5. Stability studies

The formulations F4 and F9 were selected for stability studies based on their high cumulative % drug release. The stability studies were carried out at 40^0C/75% RH for all the formulations chosen up to 6 weeks of analysis for drug content, physical appearance, and drug release. These formulations showed not much variation in any parameter. The results obtained are tabulated in Table 5. These results concluded that formulations F4 and F9 are stable and retained their original properties.

Table 5: Stability data of F3 formulation

Time in Week	Formulation F4 stored at 40^0C / 75% RH		
	Physical appearance	**% Drug content**	**Dissolution studies**
2	+++	98.36	98.72
4	+++	97.79	98.82
6	++	97.98	98.77
	Formulation F9 stored at 40^0C / 75% RH		
2	+++	98.10	99.72
4	+++	98.24	98.38
6	++	99.02	98.48

+++ = Same as on zero day, ++ = Slight change in color

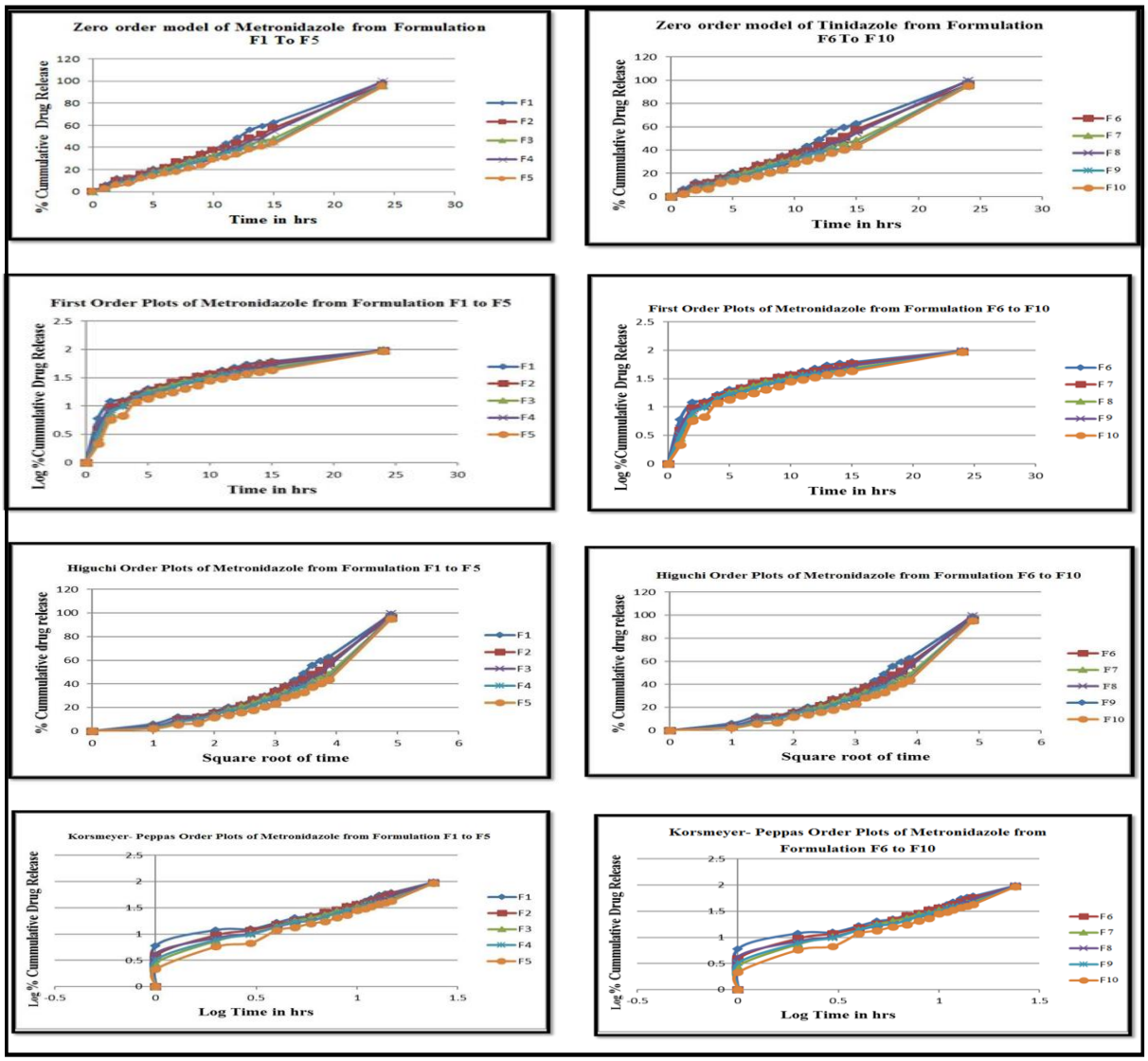

Fig 5: Release kinetics of formulations

4. CONCLUSION:

In this study, an attempt was made to design colon-targeted compression-coated tablets of metronidazole to treat amoebiasis. From the results, it can be concluded that the prepared metronidazole-targeted compression-coated tablets can control drug release over prolonged periods. It has been observed that Formulation F4 (chitosan compression coated tablets) and Formulation F9 (pectin compression coated tablets) were suitable for colonic drug delivery as drug release is maximum while compared to other formulations. The in vitro drug release studies revealed that the level of the polymer in the compression-coated tablets played an essential role in the modulation of drug release.

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