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FORMULATION AND EVALUATION OF COLON DRUG DELIVERY OF METRONIDAZOLE MINI-TABLETS

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ABSTRACT

The objective of the current study was to develop and optimize a Metronidazole mini-tablets colon specific drug delivery formulation which is an effective drug in the treatment of amoebiasis. In this mini-tablets were prepared by direct compression method and coated with pH sensitive polymers Eudragit S-100, Eudragit L-100 and combination of Eudragit S-100 & L-100 in different ratios. The optimized tablet formulation i.e., F5 is coated with 12% of Eudragit S-100 & L-100. The drug release studies were performed using 0.1 N HCl for 2 h, followed by phosphate buffer pH 6.8 for 3 h and finally in phosphate buffer pH 7.4. F5 shows the best *in-vitro* drug release of about 97.32% within 24 h in 7.4 pH buffer whereas with pectinase enzyme the drug release was found to be 99.70% within 12 h, following Korsemeyer-peppas and non-fickian diffusion (n=0.67).

KEYWORDS: Amoebiasis, Eudragit S-100 Eudragit L-100, Pectin, Pectinase.

INTRODUCTION

Targeting of drugs to the colon by the oral route could be achieved by different approaches including matrix and coated system, for which the drug release is controlled by the gastro intestinal pH, transit times or intestinal flora. Conventional oral formulations dissolve in the stomach or intestine and are absorbed from these regions. The major problem 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. In conditions where localized delivery of the drug 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.[1,2,3]

Mini-tablets are very small tablets compared to normal tablets having diameter 2-4 mm. Other advantage of mini-tablets include: they are more uniform in size so very less unit-to-unit variation in drug occur and accurately weighed amount of drug can be loaded into mini-tablets.[4] It is relatively easy to coat in order to delay the drug release because of their excellent smooth surface area. They can also be filled in capsules like other multiple unit dosage forms.[4]

Metronidazole can be used in colonic diseases as it is having less dose comparative to other antibiotics. It is highly desirable to design a dosage form which can reduce side effects by prolonging action following controlled release. Several natural and synthetic polymers can be used to modify the drug release.[3]

MATERIALS AND METHODS

Materials

Metronidazole was obtained as gift sample from Euro chemicals, Hyderabad. Pectin and Sodium starch glycolate from Research-lab fine chemicals, Mumbai. Lactose from Yarrow Chem products. PVP K 30 and Magnesium stearate from Qualikems Fine Chem Pvt. Ltd. Talc was obtained from Sd fine chem limited.

METHODOLOGY

Determination of Absorption maxima (λ max): Pure drug Metronidazole was scanned in between 200-400 nm regions spectrophotometrically; absorption maxima were 270 nm, 320 nm at 0.1 N HCl, 6.8 and 7.4 pH phosphate buffers respectively.

Preparation of calibration curve: 10 mg of drug was accurately weighed and dissolved in 10 ml of 0.1 HCl, 6.8pH and 7.4 pH in 10 mL volumetric flask, to make (1000 µg/mL) 1° stock solutions. Then 1 mL stock solution (1) was taken in another 10 mL volumetric flask to get 100 µg/mL (2^{o} stock solution). Further concentrations, were prepared 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 µg/mL with 0.1N HCl, 6.8 pH and 7.4 pH. The absorbance of standard solution was determined using UV/ spectrophotometer at 270 nm and 320 nm.

Pre-compression parameters

The powder blend was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.[5]

Bulk density (ρ_b): It is the ratio of total mass of powder to the bulk volume of powder.

Tapped density (ρ_t): It is the ratio of total mass of powder to the tapped volume of powder. It is expressed in g/cc and is given by: $\rho_{tap} = M/Vt$

Carr's index (%): The percentage compressibility (Carr's index) was calculated as 100 times the ratio of difference between tapped density and bulk density to the tapped density.

Hausner's Ratio: It is the ratio of bulk density to tapped density.

Angle of repose (ɵ): It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. tan ɵ = h/r; Where, h= height of the cone, r = radius of the powder cone, ɵ = is the angle of repose.

Preparation of Metronidazole core tablets

Core tablets of Metronidazole were prepared by direct compression. The composition of core tablets was given in Table 1. All the excipients were mixed vigorously and successfully punched into tablets using 4 mm concave punches was shown in Figure 1. After compression, five coated mini tablets equivalent to 200 mg of Metronidazole were filled into capsule.[6]

"Fig. 1" Multi-tip punch (4mm) die and core tablets.

Table 1: Composition of core mini-tablets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Metronidazole	40	40	40	40	40	40
Pectin	-	3.0	3.0	3.0	3.0	3.0
Poly vinyl pyrrolidone	1.2	0.1	0.8	1.2	1.6	2.0
Lactose	6.2	4.3	3.6	3.2	2.8	2.4
Sodium starch glycolate	1.6	1.6	1.6	1.6	1.6	1.6
Talc	0.8	0.8	0.8	0.8	0.8	0.8
Magnesium sterate	0.2	0.2	0.2	0.2	0.2	0.2
Total weight (mg)	50	50	50	50	50	50

Evaluation of core tablets

Physicochemical characteristic of tablets

The designed Metronidazole tablets were studied for their physiochemical properties like weight properties, hardness, thickness, friability and drug content.[7]

Weight variation: To study the weight variation, twenty mini-tablets were randomly taken and weighed individually to determine variation. The percent deviation was calculated using the following formula

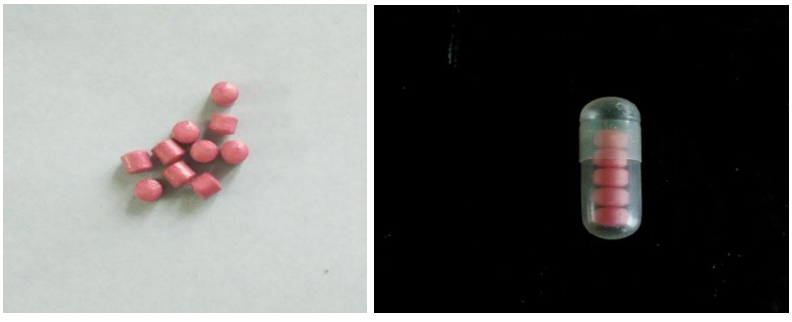
% Deviation = (Individual weight – Average weight)/Average weight *100

Friability: Friability of the tablets was checked by using Roche Friabilator. Percent friability was calculated using the formula given below: % Friability = $[(W_1-W_2)/W_1]*100$

Where W_1= Intial weight of 20 tablets, W_2 = Weight of 20 tablets after testing

Coating of Metronidazole core tablets

The core tablets of Metronidazole were coated in a coating pan (VJ instruments, India) was shown in Figure 2. The composition of coating solution used for coating of Metronidazole mini-tablets was shown in Table 2. Various components of the coating solution were added to the solvent mixture in a sequence. Initially, pan was rotated at low speed (2-5 rpm) and hot air was passed, when pan gets heated, core tablets of Metronidazole were placed in the coating pan along with 2 g of filler tablets.[8] Hot air was passed through the tablet bed and pan speed was increased to 23-27 rpm. The optimized coating measurements were given Table 3.



"Fig. 2" Coated tablets & capsule with coated mini-tablets.

Preparation of coating solution

Coating solution was prepared by simple solution method.[9] It was prepared by dissolving 2 g of Eudragit L 100 and 2 g of Eudragit S 100 as an enteric polymer, dibutyl phthalate as

plasticizer and isopropyl alcohol, acetone was used as solvent. This mixture was constantly stirred for 5 h on a magnetic stirrer and stirring coating solution was filtered through muslin cloth, a clear solution was obtained. Then the coating solution is ready for coating.

Table 2: Composition of optimized coating solution.

Ingredients	Amount/ 100 mL solution
Eudragit S 100 & Eudragit L 100	4.0 g
Dibutyl phthalate	0.48 mL
Isopropyl alcohol	50 mL
Acetone	50 mL
Colour	Q.S

Table 3: Optimized coating parameters.

Parameter	Value
Atomizing air pressure	12 psi
Inlet air temperature	55℃
Tablet bed temperature	50℃
Exhaust air temperature	50℃
Pan speed	20 rpm
Flow rate	1-4 mL/min
Pan capacity	50 g

Evaluation of coated tablets[10]

Thickness: From each formulation batch, six mini-tablets were randomly taken and measured for thickness using a micro meter screw gauge before and after coating.

***In-vitro* drug release:** Dissolution studies were carried out by using USP XXIII dissolution test apparatus using basket method. For dissolution testing of core mini-tablets, five mini-tablets were filled into each capsule as they are equivalent to 200 mg of Metronidazole and evaluated in 0.1 N HCl, 6.8 pH phosphate buffer, 7.4 pH phosphate buffer. Rotation speed was 100 rpm and temperature was maintained at 37±0.5℃. At predetermined time intervals, 5 mL of dissolution media were taken and then replaced with fresh dissolution media. The withdrawn samples were analyzed at 270 nm and 320 nm for pH 1.2, 6.8 and 7.4 buffers, respectively by UV absorption spectroscopy.

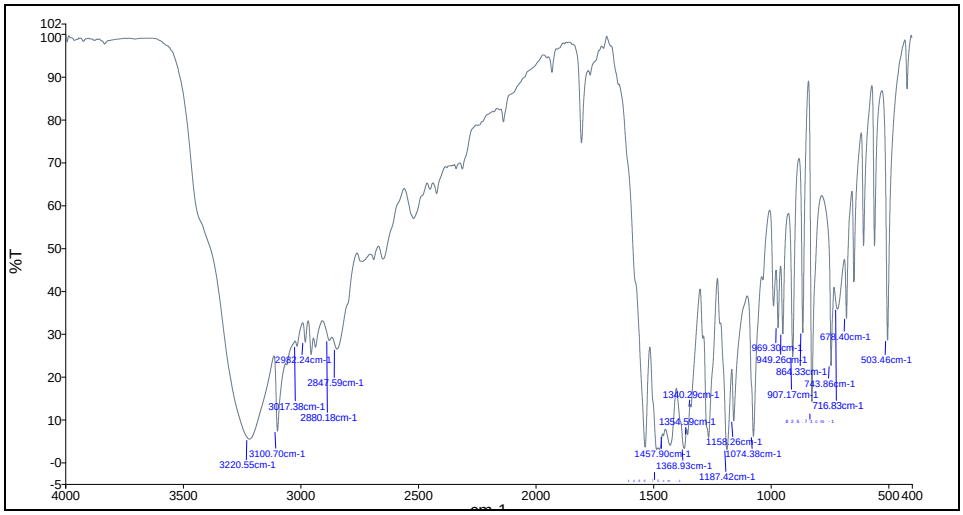
Drug release kinetics: Dissolution data was fitted to zero order, first order, Higuchi equations and korsemeyer- peppas to determine the kinetics of drug release.

RESULTS AND DISCUSSION

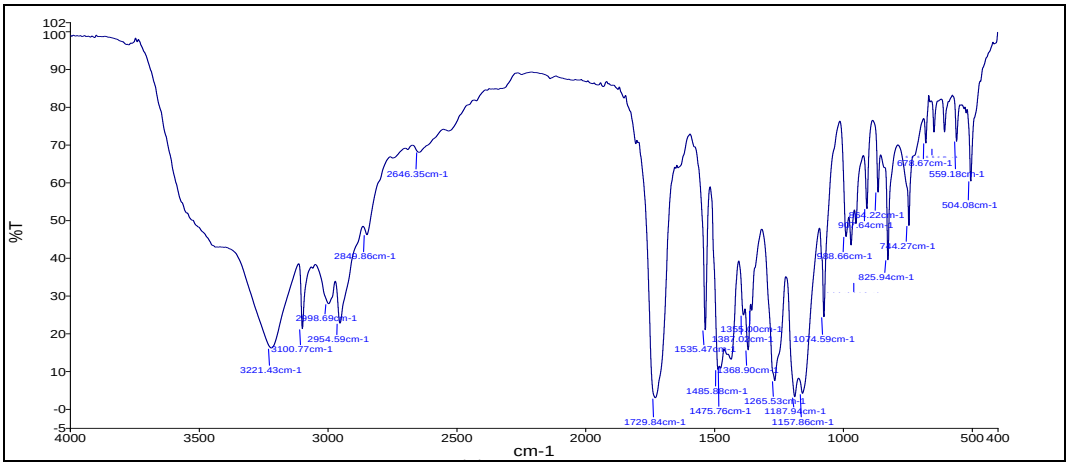
Results

FTIR spectra

FTIR spectral analysis showed no chemical interaction between pure drug and Eudragit polymers as all the peaks remained intact at their positions as shown in Figure.3 and 4.Values of FTIR spectra was recorded in Table 4.



"Fig. 3" FTIR plot of Metronidazole drug.



"Fig. 4" FTIR plot of optimized formulation.

Table 4: Values of FTIR spectra.

IR Spectra	Peak of functional group wave length (cm^{-1})			
	O-H Stretching	C=C Stretching	C-N Stretching	C-O Stretching
Drug	3200	1630	1158	1074
Optimized Formulation	3221	-	1157	1074

Table 5: Physical properties of powder blends of tablet formulations.

Formulation code	Angle of Repose (^{0})	Bulk Density (g/cc)	Tapped Density (g/cc)	Hausner's ratio	Compressibility Index (%)
F1	28.52 ±1.20	0.55±0.02	0.62±0.04	1.14±0.41	11.29±0.13
F2	22.45±2.42	0.46±0.05	0.51±0.02	1.11 ±0.36	9.80±0.41
F3	27.19±1.61	0.49±0.01	0.55±0.06	1.12±0.23	10.90±0.30
F4	24.62±1.40	0.51±0.07	0.55±0.04	1.06±0.61	7.27±0.55
F5	26.23±2.20	0.48±0.05	0.51±0.02	1.05±0.49	5.88±0.22
F6	27.33±0.91	0.51±0.09	0.58±0.01	1.13±0.45	12.0±0.53

Table 6: Characterization of core tablets.

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)
F1	48±0.18	3.57±0.3	3.97±0.06	0.54±0.02	99.8±0.21
F2	50±0.24	3.51±0.55	3.97±0.58	0.580±0.05	98.6±0.46
F3	49±0.45	3.46±0.56	3.98±0.20	0.59±0.38	99.5±0.32
F4	52±0.37	3.03±0.056	3.99±0.53	0.55±0.06	97.7±0.56
F5	50±0.05	3.60±0.36	3.98±0.76	0.48±0.63	99.9±0.12
F6	48±0.03	3.25±0.57	3.97±0.37	0.57±0.02	97.6±0.45

Table 7: Characterization of coated tablets.

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Drug content (%)
F1	53±0.04	4.03±0.43	4.02± 0.12	98.22±0.23
F2	54±0.03	4.08±0.57	4.05±0.03	99.45±0.36
F3	52±0.06	4.02±0.41	4.01±0.34	97.83±0.18
F4	55±0.03	4.05±0.32	4.03±0.54	98.49±0.44
F5	54±0.46	4.09±0.79	4.05±0.45	99.98±0.83
F6	53±0.52	4.08±0.32	4.03±0.06	97.86±0.51

***In-vitro* drug release studies**

Table 8: Percentage drug release from F1-F6.

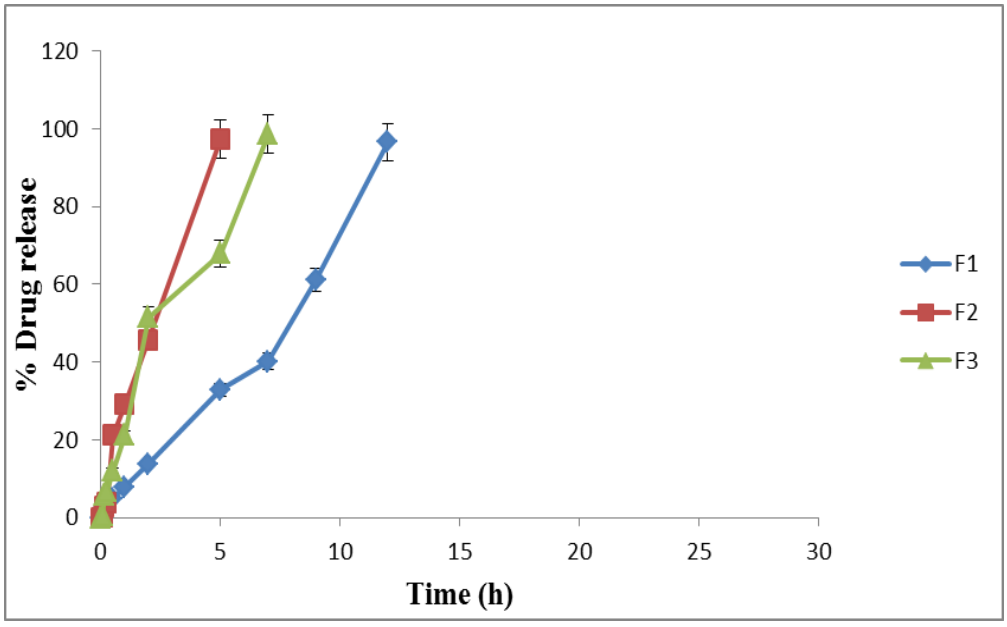
Time (h)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	**0**	0
0.062	0.16±0.5	0.32±0.1	0.41±0.1	2.0±0.7	**0.2±0.3**	2.0±0.7
0.125	0.36±0.1	2.8±0.5	5.9±0.6	2.1±0.7	**0.4±0.4**	2.1±0.7
0.25	0.57±0.2	3.6±0.3	6.8±0.3	4.6±0.5	**0.5±0.5**	3.4±0.9
0.5	0.69±0.2	21.1±0.4	12.0±0.8	7.3±0.2	**0.7±0.7**	3.6±0.6
1	1.68±0.6	29.0±0.8	21.1±0.3	9.1±0.5	**1.0±0.6**	4.8±0.1
2	2.28±0.8	45.7±0.4	51.5±0.2	13.8±0.3	**1.5±0.2**	12.5±0.3
5	14.5±0.4	97.4±0.2	67.9±0.1	32.4±0.5	**29.7±0.7**	30.2±0.8
7	40.5±0.6	-	98.6±0.6	40.2±0.4	**32.2±0.3**	38.3±0.3
9	78.3±0.8	-	-	61.1±0.7	**45.2±0.5**	59.2±0.7
12	99.7±0.3	-	-	96.6±0.3	**55.5±0.6**	96.6±0.5
24	-	-	-	-	**97.3±0.3**	-

Table 9: Percentage of drug release from optimized formulation (F5) with pectinase.

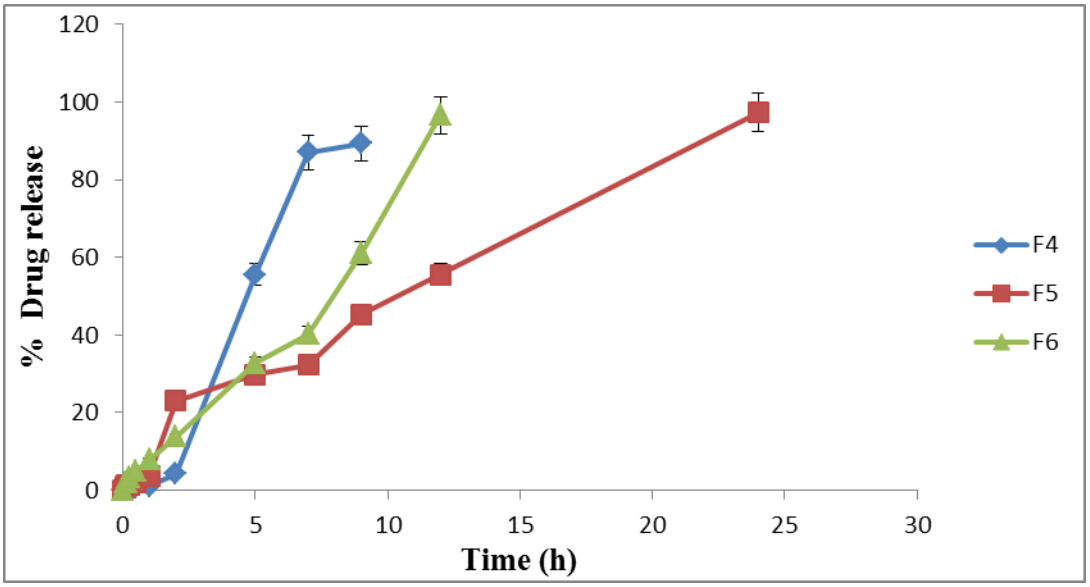
Time (h)	Formulation (F5)
0	0
0.062	0.33±0.6
0.125	0.53±0.2
0.25	0.6±0.8
0.5	0.9±0.3
1	1.2±0.5
2	2.20±0.4
5	42.28±0.9
7	56.25±0.3
9	87.6±0.5
12	99.9±0.5

Table 10: Drug release kinetics.

Formulation code	Zero order	First order	Higuchi	Korsmeyer-Peppas	"n" value
F1	0.9307	0.6731	0.7779	0.9570	1.1309
F2	0.9342	0.7242	0.7990	0.9563	2.2288
F3	0.9525	0.8445	0.9476	0.8786	2.5695
F4	0.9609	0.9456	0.9212	0.9123	0.7007
F5	**0.9756**	**0.9699**	**0.9563**	**0.9978**	**0.6741**
F6	0.9612	0.7309	0.8818	0.7098	0.4252



"Fig. 5" Percentage of drug release of Metronidazole mini-tablets from formulations (F1, F2, F3)



"Fig. 6" Percentage of drug release of Metronidazole mini-tablets from formulation (F4, F5, F6)

DISCUSSION

The aim of present study was to formulate Metronidazole core mini-tablets coated with Eudragit S 100 and Eudragit L 100 for site specific delivery for treatment of amoebiasis and to reduce risk of dose dumping, less inter and intra subject variability. The use of enteric polymer Eudragit S 100 coated tablets makes them able to release the drug at the particular pH of colonic fluid. The combination of these two polymers in a various ratios makes it possible to manipulate drug release within pH range of 6.0 to 7.0. FTIR analysis shows that the drug Metronidazole compatible with polymers used. There was no drug-excipient interaction in the physical mixture. All the prepared formulations possessed good flow properties as shown in Table 5 indicated by low values of angle of repose (22.45±2.4 to 28.52±1.2) and Carr's index (5.88±0.022 to12.0±0.05). Since, the flow properties of the powder mixture are important for the uniform of dose of the tablets. The core and coated tablets of different batches showed varied thickness of 3.97±0.58 to 3.99±0.53, 4.01±0.34 to 4.05±0.45 respectively and hardness 3.03±0.056 to 4.09±0.79 Kg/cm^2 and friability in the rage of 0.48±0.63 to 0.58±0.058 was shown in Table 6 and 7. The friability value below 1% were an indication of good mechanical resistance of tablets. The weight variation 48±0.03 to 55±0.03 of different batches of tablets was found within the prescribed limits. The drug content in all formulations (F1 to F5) was highly uniform in the range of 98.6 to 99.98%.

The drug release F1 coated with 2% of Eudragit L 100 was found to be 2.28% during 2 h and 14% during 5 h and maximum amount of drug release was found to be 99.71 during 12 h was recorded in Table 8. F2 coated with 4% of Eudragit L 100, the drug release was found to be 45% during 2 h and maximum amount of drug release was found to be 97.41% during 5 h. F3 coated with 6% of Eudragit L 100 the drug release was found to be 51.5% during 2 h and maximum amount of drug release was found to be 98.64% during 7 h was shown I Figure 5. F4 coated with 8% of Eudragit L 100 was found to be 13.82% during 2 h and maximum amount of drug release was found to be 96. 62% during 12 h. F5 coated with 12% of Eudragit S 100 and Eudragit L 100 found to be 1.5% during 2 h and maximum amount of drug release was found to be 97.32% during 24 h whereas with pectinase enzyme the drug release was found to be 99.3% within 12 h was shown in Table 9. F6 coated with 10% of Eudragit S 100 and drug release was found to be 12.5% during 2 h and maximum amount of drug release was found to be 96.62% during 12 h was shown in Figure 6.

From the results of release kinetics, it was observed that the optimized formulation follows korsemeyer-peppas. It has exhibited a correlation coefficient (R^2) it 0.9978. The 'n' value is 0.6741 non fickian diffusion (Table 10).

CONCLUSION

Colon drug delivery system was successfully developed by filling 5 mini-tablets weighing 50 mg into each an empty capsule which releases nearly the total dose for a period of 12 h. Metronidazole mini core tablets were prepared by direct compression method. The core tablets were coated with different ratios of pH sensitive polymer Eudragit S 100 Eudragit L 100 and combination of both polymers. The optimized formulation F5 core tablets is coated with 12% of polymeric solution of Eudragit L-100 and Eudragit S-100 for colonic drug delivery and drug release showed 97.32% in 24 h and in the presence of pectinase enzyme the drug release showed 99.70% in 12 h, following korsemeyer-peppas 0.9978 and 0.8850 respectively and non-fickian diffusion. Metronidazole mini-tablets coated with Eudragit can be promising system for the treatment of amoebiasis.

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