ejpmr, 2020,7(10), 142-150

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

FORMULATION DESIGN AND EVALUATION OF METRONIDAZOLE ENTERIC COATED TABLETS FOR COLON TARGETING DRUG DELIVERY SYSTEM

Ibrahim M.E.[1], Fatehalrahman F. Magbool[2]*, Mahjoub. N.M. Ahmed[3], Dhia Eldin Elhag[3], Asim Halfawi[4], Zuheir Osman[2], Abdrhman Mahmoud Gamil[5] and Mohamed E. Adam[6]

[1]Al-Ribat National University, Khartoum, Sudan, Faculty of Pharmacy Khartoum, Sudan.
[2]Department of Pharmaceutics, Khartoum University, P.O. Box 1998, Sudan.
[3]Faculty of Pharmacy, University of Medical Sciences and Technology, Khartoum, Sudan.
[4]Department of Pharmacogency, Pharmacy Program, Nile College, Khartoum, Sudan. Department of Pharmacogency, Faculty of Pharmacy Khartoum, Sudan. Department of Pharmacogency, Faculty Pharmacy, Sudan International University, Department of Pharmacogency, Pharmacy Program, AlYarmouk College, Khartoum, Sudan.
[5]Associate professor of Pharmaceutics, Faculty of Pharmacy, Al-Neelain University – Sudan.
[6]Department of Chemistry, Faculty of Pharmacy, University of Khartoum, P.O. Box 1998, Khartoum, Sudan.

***Corresponding Author: Fatehalrahman F. Magbool**

Department of Pharmaceutics, Khartoum University, P.O. Box 1998, Sudan.

Article Received on 12/08/2020 **Article Revised on 02/09/2020** **Article Accepted on 22/09/2020**

BACKGROUND

Colon-targeted drug delivery has been the focus of numerous studies in recent years due to its potential to improve treatment of local diseases affecting the colon, while minimizing systemic side effects. *Method*s. Metronidazole core tablets were formulated using different polymers in different ratios and the core tablets were coated with an enteric polymer. The formulated enteric coated tablets were evaluated for their compatibility between the active ingredient and the excipients. The prepared tablets were evaluated for weight variation, hardness, friability, content uniformity and *in vitro* drug release. *Results*. The pre-compression aspect including determination of various flow property, compatibility testing for the active ingredient and the excipients was conducted using Fourier transform infrared spectrophotometer (FT-IR), all the formulations were passed the tests. The tablets were coated by using polymers, in post-compression aspect the coated tablets were subjected to pharmaceutical evaluation using official and non-official experiments. The overall pharmaceutical acceptability were satisfactory for the developed tablets regarding chemical and physical investigations. also drug content was in the range of 98.44 to 99.89 % indicating good content uniformity in the formulations. The tablets were passed all the tests. Among all the formulations F5 formula was found to be optimized and show better targeted site controlled drug delivery as it was retarded the drug release up to 6 hours and showed maximum of 98.32% drug release. The optimum formulation F5 was stable when it was stored at 45 ± 2°C /75% RH for 3 months. The formulation F5 was considered the most suitable formula for targeted the colon. The pharmaceutical evaluations and *in vitro* results showed that the Metronidazole tablets formulations can be a potential candidate for colon-targeted drug delivery, with better *in vitro* characteristics and physicochemical properties. As a result, colon-targeted drug delivery of Metronidazole appeared to be a promising alternative to traditional drug administration routes.

KEYWORDS: Metronidazole, Enteric coated tablets, Pre-compression aspect, *In vitro* drug release, Colon-targeted drug.

1. INTRODUCTION

Colon-targeted drug delivery has been the focus of numerous studies and received a lot of attention in recent years due to its potential to improve treatment of local diseases affecting the colon, while minimizing systemic side effects.

Targeted 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 treatment of colonic pathologies, and systemic delivery of protein and peptide drugs.[1,2]

The success of a colon-targeted drug delivery system depends significantly on the drug's physicochemical characteristics, the type of delivery system, factors which may influence the GI transit time, as well as the degree of interactions between the drug molecules and the GI tract.[3]

Colonic drug delivery may be achieved by either oral or rectal administration. Rectal dosage forms (enemas and suppositories), are not always much effective due to high variability in the distribution of drug administered by this route.[4] The major obstacle with the delivery of drugs by

oral route to the colon is the absorption and degradation of the drug in the upper part of gastrointestinal tract (GIT) which must be overcome for successful colonic drug delivery.[5]

In recent years, the targeting of drugs to the colon via the oral route could be achieved by different approaches including different formulation systems, for which the drug release is controlled by different pH conditions, transit time and intestinal micro flora. Colon is an ideal site for both systemic and local delivery of drugs. But oral conventional dosage forms basically dissolved in the stomach and gastro intestinal tract (GIT) and also absorption takes place from these regions depend upon the physico-chemical properties of the drug.

Oral dosage forms also allow for a greater degree of flexibility in their manufacturing processes, design, development, improved patient compliance and safe for administration.[6]

Metronidazole (Figure 1**)** is a synthetic antibacterial and antiprotozoal agent that belongs to the nitro-imidazole class, introduced in 1959 for *Trichomoniasis* and later found to be a highly active *Amoebicide*. It has broad *spectrumcidal* activity against *protozoa* including *Giardia amblia* and also many anaerobic bacteria such as *Bact, Fragilis, Fuso-bacterium, Clostridium perfringens, Cl. difficle, Helicobacterium pylori* and anaerobic *perfringens streptococci* are sensitive, and also effective in treatment of ulcerative colitis (UC) and irritable bowel syndrome (IBS).[7]

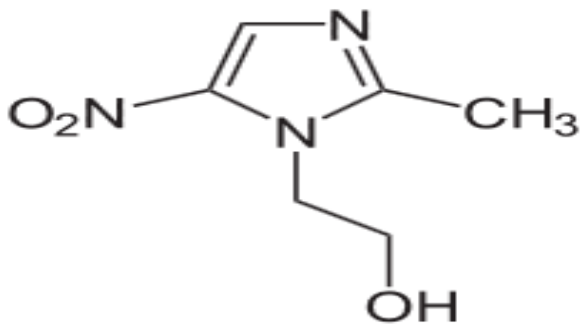

Figure 1: Chemical Structure of Metronidazole.

Thus, the approaches used in developing a colon-targeted drug delivery are aimed at delaying the drug release until the system reaches the colon, for the effective treatment of diseases of colon.

The present study is aiming to formulate and evaluate enteric coated tablets of Metronidazole for colon targeted drug delivery, so as to reduce the dosing frequency of the drug and to demonstrate its site specificity in the colon. The effect of different polymers in different concentrations on hardness, friability and also their effect on the drug release from the formulated tablets was also investigated.

2. MATERIALS AND METHODS

2.1. Materials

Metronidazole was obtained from Azal Industries, Khartoum, Sudan. Maize starch was obtained from Riddhi siddhi gluco boils limited, India. Talc was received from Golcha associated exports, India. Magnesium stearate was received from united pharma industries, China. Microcrystalline cellulose was received from Gujarat microwax private limited, India. Hydroxyl propyl methyl cellulose (606) obtained from Shin-etsu chemical co. LTD, Japan. Hydroxyl propyl methyl cellulose (E5) obtained from Shaudeng head co. LTD, China. Titanium dioxide and Propylene glycol 400 were obtained from Win coat colours and coating pvt. LTD, India. Potassium di hydrogen orthophosphate was procured from central drug house LTD, India. Sodium hydrogen orthophosphate, Acetic anhydride and Brilliant green were obtained from lab tech chemical Sodium chloride obtained from Al Nasr pharmaceutical chemicals Co. Egypt. Distilled water, in-house. Acetone was obtained from shiny hardware LTD, India. Anhydrous acetic acid and 0.1N perchloric acid were obtained from central drug house LTD, India.

2.2. Instruments

Fourier transform infrared spectrophotometer, Model no: FTIR-8400S, SHIMADZU, Columbia.Mini hand press, Model no: MHP-1, Shimadzu, Columbia.Fluid bed dryer, General mechanical industries, Model: JEBD-S, Serial number: 504, India.Multi mill, General mechanical industries, Model: GMB, Serial number: 543, India.High speed mixer granulator, General mechanical industries, Model: HSMG-10, Serial number: 543-99, India.Rotary tablet press, General mechanical industries, Model: JMP4-6-STNSerial number: 890, India.Hardness tester, Calibration ID; UQD/S3, BY; semuel, India.Friability tester, Electro lab ID; UQD-03-RPM, BY; Samuel, India.PH/ORP meter, Model no. H12211, Hanna instruments, India.Dissolution tester (USP), Model no. TDT-08L, Electrolab- India.Temperature controller, Model no. ETC-11L, Electrolab-India.UV-spectrophotometer, Model no. CE1020, CECIL instruments, UK.Electronic balance, ADAM, India.Electronic balance, Sartorious, Germany.Magnetic stirrer, IKA.RH basic-1, Germany.Beaker jugs, ISOLAB, USA.Mesh number 2 mm, 5mm and 425um.Spray gun, HVLP (max 45 psi 3 bar), USA. Yalimachine (multifunctional experimental pharmaceutical machinery), Shanghiyali machinery technology co. LTD, China.

2.3. Methods

2.3.1. Method of Preparation of Metronidazole Core Tablets

Matrix tablets of Metronidazole were prepared by the wet granulation technique. Accurate weights of metronidazole (1 kg) and micro-crystalline cellulose (0.166 kg) were mixed (in high speed mixer) for five minutes. A paste of maize starch was prepared by mixing maize starch (0.103 kg) with cold water (20 ml) in a

conical flask and then distilled water was added up to volume in paste kettle and allowed to boil. After that the solution of maize starch was added, and stirred well till a paste was formed. An accurate weight of hydroxyl propyl methyl cellulose was dissolved in water for 30 minutes, and added it with the maize starch paste to the mixed material placed in high speed mixer granulator (metronidazole and micro-crystalline cellulose), then mixed till obtain good granules. The wet granules were placed in fluid bed dryer for 30 minutes (with additional 15 minutes in some formulations) until complete drying, then milling the dry granules (in multi mill) using mesh number 2, finally talc (0.011 kg) and magnesium stearate (3.6 kg) were added to the meshed granules and mixed properly for 10 minutes. The powder was compressed (rotary tablet press) to tablets using punches and disc (size 18×8.5 mm). The different formulations prepared in this study which designated as K1, K2, F1- F5 are shown in the Table1.

Tablet 1: Composition of Metronidazole core tablets.

Ingredients	Formulation code						
	K1	K2	F1	F2	F3	F4	F5
Metronidazole	500	500	500	500	500	500	500
HPMC 606	-	200	-	25	75	-	-
HPMC E5	150	-	-	-	-	25	75
Maize starch	30	30	51.9	51.9	51.9	51.9	51.9
Microcrystalline cellulose	140	115	83.35	83.35	83.35	83.35	83.35
Sodium carboxy methyl cellulose	30	30	-	-	-	-	-
Talc	2	2	5.6	5.6	5.6	5.6	5.6
Magnesium stearate	2	2	1.8	1.8	1.8	1.8	1.8
Tablet Total	824	849	642.65	667.65	717.65	667.65	717.65

2.3.2. Method of Preparation of Enteric Coating of Metronidazole Tablets

Distilled water (900 ml) was placed in magnetic stirrer and mixed till vortex was formed. The coating material (Titanium dioxide) was added as fast as possible into the vertex without allowing the powder to float on the surface and was allowed to stir for 30 minutes and then propylene glycol was added and continued stirring for 10 minutes. The suspension was stirred gently while coating the tablets. The process parameters are shown in Table 2.

Table 2: Parameters of coating process.

Parameter of coating process	Range
Pan charge	1 kg
Pan speed	10-15 rpm
Exhaust air temperature	40^{o}C
Bed temperature	25-30^{o}C
Spray rate	35-45 g/min
Distance between spray gun and tablet bed	10-20 cm

2.3.3. Pre-formulation studies

Compatibility Study of Metronidazole and Excipients

The infrared spectra of drug alone (Metronidazole), and excipients were recorded in range from 400 to 4000 cm^{-1} on FTIR to detect the drug-excipients interactions. The IR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer. The resultant spectra were compared for any possible changes in the peaks of the spectra.[8]

2.3.3.1. Evaluation of Metronidazole Granules[9]

i. Angle of Repose

Angle of repose was determined using funnel method. The height of the funnel was adjusted in such a way that the tip of funnel just touches the heap of the blends. Accurately weighed blends are allowed to pass through the funnel freely on to the surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation;

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

Where;

tan θ - tangent of angle

r- Radius of base of the heap (cm) and

h - Height of the heap (cm).

ii. Determination of bulk density and tapped density

An accurately weighed quantity of the granules (W), was carefully poured into the graduated cylinder and the volume (V_0) was measured. Then the graduated cylinder was closed with lid, set into the density determination

apparatus. The density apparatus was set for 100 taps and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density, and tapped density were calculated using the formulae.[10] To calculate the densities the following equations were used;

Bulk density = W/V_0

Tapped density = W/V_f

iii. Compressibility Index
Carr's index was calculated according to equation given below;

$$Carr's\ index = \frac{Tapped\ density - Bulk\ density}{Tapped\ density}$$

Hausner's Ratio
It is the ratio of tapped density to bulk density of the powder and measured by employing the following formula:

$$Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

2.3.4. Post-formulation studies
2.3.4.1. Evaluation of Enteric Coated Metronidazole Tablets[9]
a. Weight Variation Test
Weight variation test was performed according to USP, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The percentage deviation was calculated and checked for weight variation.

b. Thickness and Hardness Tests
Prepared matrix tablets were evaluated for thickness by using vernier calipers. Hardness of the tablets was evaluated using Monsanto hardness tester, which is expressed in kg/cm^2.

c. Friability
Friability of tablets was determined using Erweka Friabilitor. Twenty tablets were weighed and placed in a chamber. The friabilator was operated at 25 rpm for four minutes. The tablets were then dusted and reweighed and the percentage of friability was calculated by using the following formula;

$$F = Wi - Wf / Wi \times 100$$

d. *In–vitro* Drug Release Study
The Metronidazole matrix tablets were evaluated for its *in vitro* dissolution study. The *in vitro* drug release was studied by use of paddle apparatus (USP type II apparatus). In this studies, slight modifications with addition of another pH medium, based on different transit time present from stomach to colon, were carried out with different pH conditions similar to in vitro conditions (pH 1.2 for 2 hrs, pH 6.8 for 2hrs and pH 7.4 for 8 hrs) were maintained for the entire study. 900 ml of 0.1 N HCl was taken in a vessel, formulation was kept in basket after the media attained the temperature of 37 ± 0.5^{o}C. The basket rpm was maintained at 100. 5 ml of sample was withdrawn from the dissolution media at specific time intervals and replaced with a particular medium. After 2 hrs, the 0.1 N HCl was discarded and replaced with 6.8 phosphate buffer and it was maintained for 2 hrs after that pH 7.4 phosphate buffer was used for remaining 8 hrs. The amount of drug release was analyzed spectrophotometrically at λ_{max} of 319 nm.[11]

e. Uniformity of Drug Content[12]
For determination of drug content, five tablets from each formulation were triturated using mortar and pestle. An accurately weighed powder equivalent to 500 mg of drug was taken in 100 ml volumetric flask and diluted with 0.1M NaoH up to mark. Then the sample was sonicated for 1 hr and filtered. An aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically at 319 nm against blank. The test was done in triplicate and average drug content was estimated.

f. Stability Study
The best formulation was subjected to accelerated stability study according to ICH guidelines at temperature 45 ± 2°C and 75±5% RH (Relative Humidity) for 3 months in stability chamber. At the end of each month, content% and the physicochemical properties of tablets including organoleptic properties, average weight, hardness, friability were evaluated.

2.3.5. Statistical Analysis
The results obtained are expressed as a mean ± standard deviation calculated using Microsoft excel 2010 software. Statistical analysis was performed using SPSS version 20.0 for windows (SPSS Inc. Sep 2011).

3. RESULTS
Various approaches have been used for oral delivery of drug to the colon which includes pH-dependent delivery systems, time-dependent delivery systems, microbially-controlled delivery systems, pressure-dependent delivery systems, enzyme-based delivery systems. Hence the present study was aimed to develop Metronidazole matrix tablets for colon targeting using polymers HPMC 606, HPMC E5, Microcrystalline cellulose and Sodium carboxy methyl cellulose.

Table 3: FT-IR interpretation.

No.	Interpretation	FT-IR absorption bands		
		Pure drug	Drug + PHMC E5	Drug +HPMC 606
1	NO_2 stretching mode	1537.16	1537.16	1537.16
2	C-N stretching mode	1188.07	1186.14	1151.42
3	C=C stretching mode	1934.47	1639.38	1641.31
4	C-H Stretching mode	2948.96	2941.24	2929.67

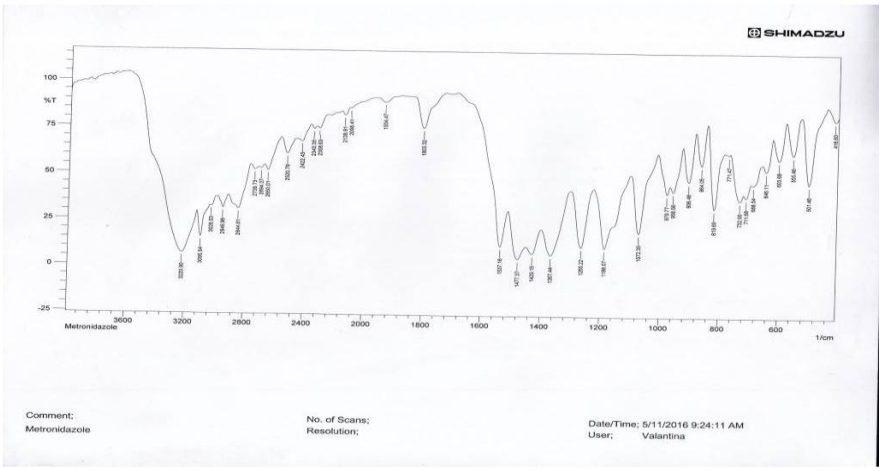

Figure 2: FT-IR Spectra for Metronidazole.

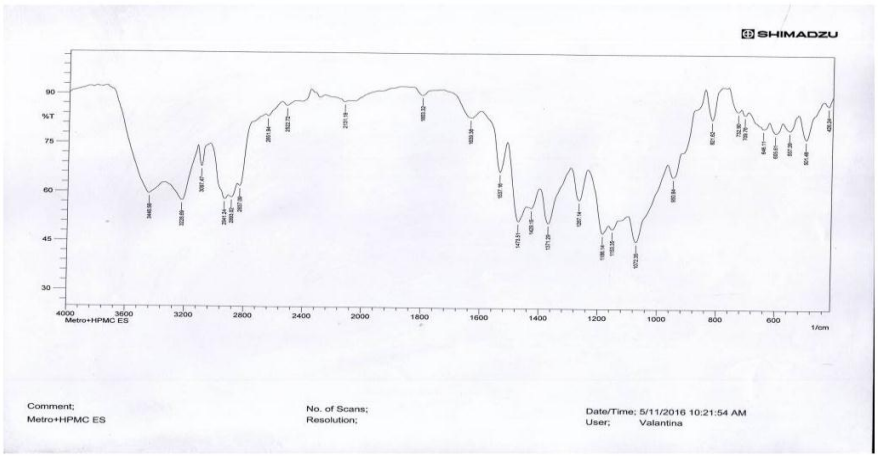

Figure 3: FT-IR Spectra for Metronidazole and HPMC E1.

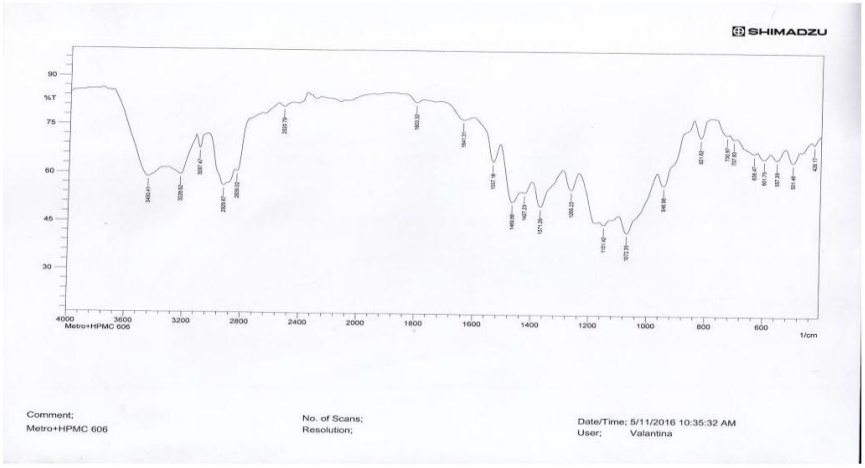

Figure 4: FT-IR Spectra for Metronidazole and HPMC 606.

Table 4: Results of evaluation of Metronidazole granules.

Formulation code	Bulk density (gm/cc	Tapped density (gm/cc)	Compressibility index (%)	Hauser's ratio	Angle of repose
K1	0.43	0.55	27.9	1.27	24.33
K2	0.51	0.59	15.68	1.15	28.81
F1	0.46	0.56	21.39	1.19	25.42
F2	0.59	0.68	13.04	1.15	29.19
F3	0.49	0.57	14.04	1.16	30.40
F4	0.43	0.49	12.24	1.14	26.72
F5	0.55	0.64	14.06	1.16	26.21

Table 5: Results of evaluation of enteric coated Metronidazole tablets.

Formulation code	Hardness (kg/cm^2) *	Weight variation (%)*	Friability (%)	Content uniformity (%)
K1	5.2±2	-	-	-
K2	5.4±3	-	-	-
F1	5.8± 2	642.65± 3	0.98	98.64
F2	5.9± 1	667.65± 3	0.43	99.16
F3	6.0± 1	717.65± 2	0.24	98.44
F4	6.2± 2	667.65± 2	0.21	99.89
F5	6.5± 3	717.65± 2	0.16	99.35

*Mean value ± SD

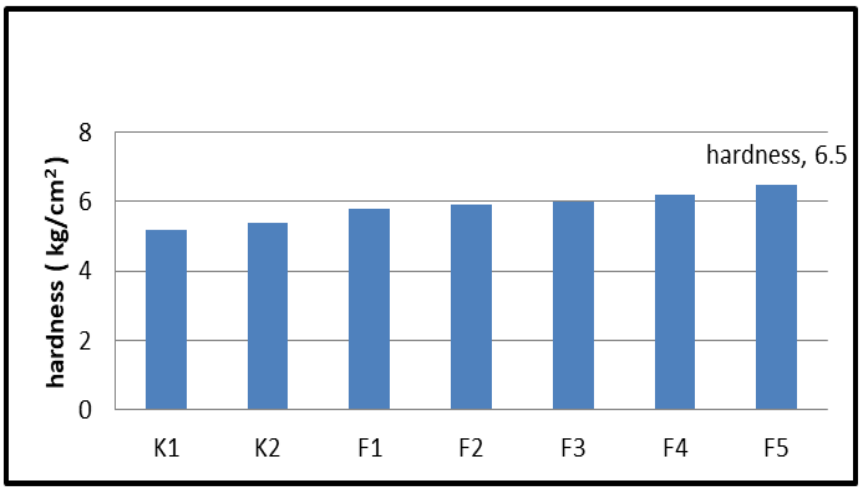

Figure 5: Hardness of all formulations.

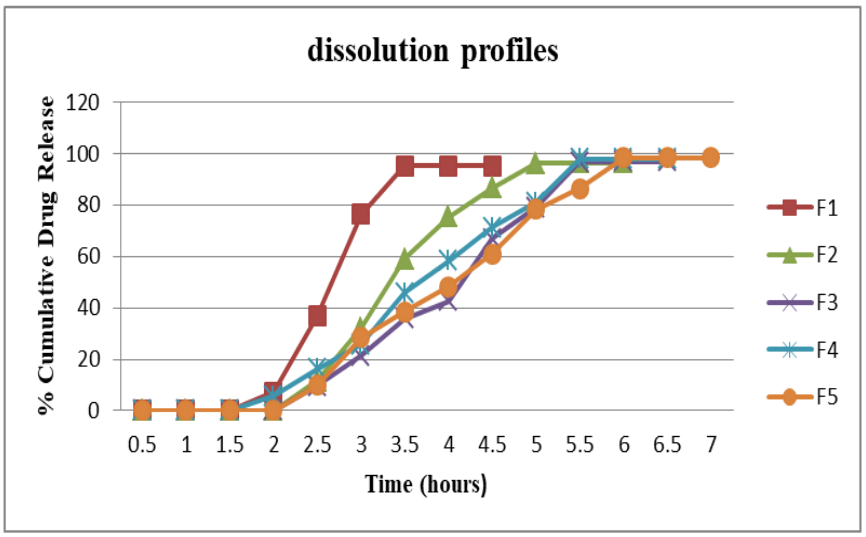

Figure 6: Dissolution profile for the formulations (F1, F2, F3, F4 and F5).

Table 6: *In- vitro* release profiles of formulations F1- F5.

Time (hours)	F1	F2	F3	F4	F5
0.5	0	0	0	0	0
1	0	0	0	0	0
1.5	0	0	0	0	0
2	7.2	0	0	0	0
2.5	36.82	11.69	9.62	16.21	9.83
3	76.23	32.14	21.44	25.69	28.54
3.5	95.09	59.02	35.81	45.85	38.56
4	95.21	75.26	42.71	58.27	48.15
4.5	95.19	86.67	66.83	71.28	60.87
5	-	96.22	78.91	81.01	78.31
5.5	-	96.28	96.73	97.86	86.41
6	-	96.26	96.83	97.89	98.32
6.5	-	-	96.80	97.88	98.37
7	-	-	-	-	98.35

Table 7: The accelerated stability study test for the optimized formula (F5).

Test time	Average weight (mg) *	Hardness (kg/cm^2) *	Friability (%)	Content %
Zero Time	717.65± 20	6.5± 30	0.16	99.35
1 month	717.65± 20	6.6± 10	0.16	99.35
2 months	712.65± 40	6.5± 50	0.16	99.10
3 months	713.65± 30	6.9± 20	0.17	98.80

*Mean value ± SD

4. DISCUSSION

4.1. Compatibility Studies

The compatibility testing for the active ingredient and the excipients was conducted using Fourier transform infrared spectrophotometer (FT-IR) from which the IR spectra of individual Metronidazole and the combination of drug with excipients (different hydroxy propyl methyl cellulose) are determined which are shown in the Figures 2-4 and in the Table 3.

IR spectra of individual Metronidazole and the combination of drug with polymers (different HPMCs) indicate that there was no interactions between the drug and both HPMC.

4.2. Evaluation of Metronidazole Granules

Table 4 shows the results of Angle of repose, Bulk density, Tapped density, Carr's index, and Hausner's ratio for granules of all formulae. The results of granules evaluation summarized in (Table 4) indicate good flow properties of prepared granules for all formulae. This is observed from the obtained results of angle of repose (24.33^o - 30.40^o) which indicate good flow properties of prepared granules. According to table 4, the compressibility index values for the formulations (F2, - F5 and K2) ranged from 12.24 to 15.68 which reflected their good compression properties whereas the formulations (F1 and K1) showed fair compression properties as compressibility index exceeded 21.[9] The Hauser's ratio values for the formulations (K2, F2- F5) had values within 1.14 - 1.16 which indicated good compressibility and flowability as they are below 1.18,[9] however the F1 and K1 showed possible flow properties.[9]

4.3. Evaluation of Enteric Coated Metronidazole Tablets

Metronidazole core tablets was formulated using different polymers in different ratios and the core tablets were coated with an enteric polymer. Table 5 shows the results of weight variation test, hardness test, friability test, and thickness test for prepared Metronidazole colon targeted matrix tablets of all formulas.

The results indicate that the weight variation for different formulations is found to be within the pharmacopeia limit of 5% as per USP standard.[9] Also, the thickness is uniform and reproducible.

The measured hardness of formulations (K1 and K2) was below the recommended range 5.8 therefor it failed to pass (Table 5 and Figure 5). The formulations (F1- F5) were ranging from 5.8 – 6.5 kg/cm^2 which show a good hardness.[9] The results indicated that as the amount of hydroxyl propyl methyl cellulose increased, the hardness increased as shown below in the figure 5.

The friability values were found to be less than 1% in the formulated tablets (F1- F5) which are considered to be acceptable.[9] The result indicated that the friability decreased as the amount of hydroxy propyl methyl cellulose increased. This showed that all the tablet formulations could withstand abrasion without loss of tablet integrity. Also all formulated tablets show uniform diameter.

4.4. *In–vitro* Drug Release Study

The release profile of Metronidazole from the enteric coated tablets of different formulations were investigated. Upon using 0.1 N HCl as dissolution medium, for 2 hours. No drug release was recorded during this time from F2-, F5 but there was drug release recorded in F1. Then the same formulations were subjected to *in vitro* dissolution test with of phosphate buffer for next 6 hrs. It was found that the release of drug in F5 which contain hydroxyl propyl methyl cellulose (HPMC E5) gave the best release. From the results of *in vitro* dissolution studies, it was clear that drug release depends upon the type of polymer and concentration of polymer.[11] The results obtained were in agreement with the fact that formulations having higher percentage of HPMC E5 as a matrix former show much more retardation of drug release as compared to the formulations having lower percentage of HPMC E5.[11] The sustainability of the drug in Formulation F5 was found to show better targeted site controlled drug delivery, as it showed 98.32% drug release for 6 hours (Table 6 and Fig. 6) in dissolution study illuminating the effect of HPMC E5 concentration in the formulations. This may be due to the fact that the presence of HPMC E5forms a much more viscous layer around the tablet allowing less seepage of fluid into the tablet to prolong the drug release. Higher concentration of HPMC E5 provides gel layer which was more viscous as compared to that formed by lower concentration of HPMC E5.

4.5. Content Uniformity

Drug content was determined (Table 5) and described which was in the range of 98.44 to 99.89 % which indicating good content uniformity in the all formulations.[12,13]

4.6. Stability Study

The result of accelerated stability studies, carried out according to ICH guidelines, indicated that there was no significant change in physical parameters organoleptic characteristics and percentage drug content, during the study period. Study was performed at a raised temperature of 45ºC and 75 % RH for 3 month. The content was found above 98% at the end of 90 days (Table 7). This indicated that the optimized formula (F5) exhibited good physical stability and acceptable potency at accelerated storage condition for 3 months.

5. CONCLUSION

The study had successfully formulated enteric coated tablets of Metronidazole for oral administration, with a view of targeting the drug to lower part of gastro intestinal tract.

The pharmaceutical evaluations and *in vitro* results showed that the Metronidazole tablets formulations can be a potential candidate for colon-targeted drug delivery, with better *in vitro* characteristics and physicochemical properties. As a result, colon-targeted drug delivery of Metronidazole appeared to be a promising alternative to traditional drug administration routes.

Abbreviations

BP	British Pharmacopeia
USP	United State Pharmacopeia
FT-IR	Fourier Transform InfraRed
HPMC	Hydroxyl Propyl Methyl Cellulose
ICH	International Conference on Harmonization

Data Availability

All data underlying the results are available as a part of the article, and no additional sources are required.

Competing Interests

The authors declare that they have no competing interests.

Author's Contributions

All authors have worked equally for this work.

ACKNOWLEDGEMENTS

The authors are thankful to wish to Azal Industries, Khartoum, Sudan, for providing the gift sample of Metronidazole (standard).

REFERENCES

1. Philip AK, Dabas S, Pathak K. Optimized prodrug approach: a means for achieving enhanced anti-inflammatory potential in experimentally induced colitis. J Drug Target, 2009; 17(3): 235-241.
2. Oluwatoyin AO, John TF. In vitro evaluation of khaya and albizia gums as compression coating for drug targeting to the colon. J Pharm Pharmacol, 2005; 57: 63-168.
3. Das S, Deshmukh R, Jha A. Role of natural polymers in the development of multiparticulate systems for colon drug targeting. Syst Rev Pharmacy, 2010; 1(1): 79–85. doi: 10.4103/0975-8453.59516.
4. Patel M, Shah T, Amin A, Therapeutic opportunities in colon specific drug delivery system, Crit Rev Ther Drug Carrier Syst, 2007; 24: 147-202.
5. Lee VHL. Changing needs in drug delivery in the era of peptide and protein drugs. In: Lee VHL. (Eds.). Peptide and protein drug delivery. Marcel Dekker Inc., New York, pp. 1-56.
6. Leuva VR, Patel BG, Chaudhary DJ, Patel JN, Modasiya MMK. Oral colon-specific drug delivery system. J Pharm Res, 2012; 5(4): 2293–7.
7. Tripathi KD. , essential of medical pharmacology, 5TH edition, 2003; 12: 750. jaypee brothers medical publishers ltd, new Delhi, India.
8. Liu J, Xiao Y, Allen C. Polymer–drug compatibility: a guide to the development of delivery systems for the anticancer agent, ellipticine. J Pharm Sci, 2004; 93(1): 132-143.
9. United States Pharmacopeia and National Formulary (USP 41-NF 36). Rockville, MD: United States Pharmacopeial Convention, 2016; 277: 674, 731.

10. Ashutosh M, Parikh RK, Parikh MC. Formulation, development and evaluate; on of patient friendly dosage forms of metformin. Asian J Pharm, 2008; 2: 177-181.
11. Patel J, Patel N, Shah SH, Formulation and *in-vitro* evaluation of mesalamine matrix tablets using chitosan for colonic drug delivery. J Pharm Res, 2009; 2(7): 1319-1323.
12. Ratnakumari T, Chetty CM, Reddy Dwarkasnadha, Ramyakrishna P, Formulation and evaluation of aceclofenac matrix tablets for colon drug delivery, J Global Trends Pharmaceut Sci, 2010, 1(1): 53-60.
13. British pharmacopeia (2012), the stationary Office, London, UK.