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Formulation and Evaluation of pH and Enzyme - dependent Metronidazole Tablet for Colon Targeted Drug Delivery System

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ABSTRACT

In this study the formulation of safe and effective Ph and Enzyme dependent coated tablet of Metronidazole was prepared for the effectual treatment of Amoebic Dysentery, Inflammatory bowel diseases. Wet granulation method is used for the formulation of colon targeted pH and Enzyme dependent coated tablet of Metronidazole. Eudragit s-100, HPMCK 4M, Guar gum polymer and Eudragit s100 (pH dependent) This coating material is used for this tablet. This coated tablet evaluated for properties such as average weight, hardness and coat thickness, disintegration, drug content. The produced tablets were subjected to in vitro release experiments for two hr at 100 rpm using 0.1 N HCl and phosphate buffer 6.8 pH for three to five hr. After that 7.4pH phosphate buffer was used and the process was repeated for 24hr. Every formulation's % weight variation, percentage friability and drug molecule content fall within the bounds set by the united states pharmacopoeia (USP). According to the results, metronidazole would be a promising formulation to accomplish the goal of curing inflammatory bowel disorders and amoebic dysentery without causing any gastric irritation. This would be beneficial for individuals who have a history of ulcerative colitis.

Keywords: *Metronidazole, Amoebic dysentery, In- vitro dissolution, Eudragit s100 pH dependent coating, Guar gum , Stabilty study.*

1. INTRODUCTION

Drugs in the delivery systems designed to distribute medication into the colon must be shielded from harsh conditions of the stomach and small intestine. Colon illness includes amoebiasis, ulcerative colitis, Crohn's diseases and colon cancer must be treated topically with this target specific release. Furthermore, due to the colon's favourable environment compared to the upper gastrointestinal tract (GIT),[1](it holds great promise for the oral administration of therapeutic proteins Entamoeba histolytica is the cause of amoebiasis, an infection of the large intestines. According to current estimates, 34-50 million symptomatic infections are [2,14] caused annually by E. histolytica causing 40 and 100,000 deaths, making amoebiasis the second most common cause of protozoan parasites releated deaths after malaria. The intestinal epithelium may be invaded by E. histolytica trophozoites, resulting in amoebic colitis.[3] Metronidazole and tinidazole are the most used medications for the intestinal amoebiasis[4] several methods are available for colon specific drug delivery such as, I) Coating with PH dependent systems, II) Creating time- release dosage forms, and III) Using carriers that are only broken down by colonic bacteria. [5] Systems that rely on pH are made to allow the medicine to be released over a specific GIT pH since the Ph of the GIT varies greatly, it was well known that pH- dependent systems have poor site specificity. Timed-release systems after the prescribed amount of time, they discharge their load. [6]For these medications to effectively Comat E. histolytica, which is found in the lumen of the caecum and large intestine and adheres to the mucous and epithelial layers of the colon, they must be administered to the colon patient.

2. MATERIALS AND METHODS

Metronidazole (98-100% pure) were gift samples Aarti Drugs limited Gujrat (India)Guar gum was obtained from Dabur research foundation , India. Eudragit-s100, HPMC K4M, was obtained from SM Pharma and chemicals , Mumbai. Microcrystalline cellulose , Magnesium Stearate , talc was all purchased from SD fine chemicals, Mumbai(India)

3. FORMULATION OF COLON TARGETED TABLETS

1) **Preparation of core tablet:**

Metronidazole, various ratios of Eudragit S-100, HPMC K4-M, Guar gum, Avicel pH101(MCC), Magnesium Stearate, talc, PVPk-30 and water were weighed and out into a mortar using the table Formula. To get sluggy mass, thoroughly combine the granulating fluid.after going thoroughly combine the granulating fluid.after going through sieve number 18, this mass was dried for 30 minutes at 40ºC in a hot air oven. After drying , the granules were once more run through sieve number 18, yielding fine, nearly homogeneous particles. A 400mg tablet containing 200mg of metronidazole was immediately punched with an optimum combination and compressed using round-shaped punches in a rotary tablet compression machine. Ready compressed metronidazole tablets from various batches were gathered and kept in air tight containers (Table-1)[7]

2) Preparation of metronidazole Coated tablet :

The Pan – coating process was applied to compressed tablets. Eudragit s-100 (6gm) , dibutyl phthalate(33.3%) as a plasticizer and 2% (to the weight of the polymer) of TiO_2 as an opacifying agent were dissolved in isopropyl alcohol to create the coating solution. After being mixed with isopropyl alcohol, Tio_2 was filtered. This is included in the solution of polymers. Volumetric additions of dibutyl phthalate were made to the specified amount with the remaining solvent mixture while meaning being continuously stirred for one hr. on a magnetic stirrer.Filtration was then performed.

Formulation batches	FB1	FB2	FB3	FB4	FB5	FB6	FB7	FB8	FB9
Metronidazole	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg
Eudragit S-100	50mg	75mg	100mg	---	--	--	--	--	--
HPMC K4M	--	--	--	50 mg	75mg	100mg	--	--	--
Guar gum	--	--	--	--	--	--	50mg	75mg	100mg
Avicel PH 101	131 mg	106 mg	81 mg	131 mg	106mg	81mg	131mg	106mg	81 mg
Magnesium stearate	4mg	4mg	4mg	4mg	4mg	4mg	4mg	4mg	4mg
PVPK30	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg
Talc	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
Total	400mg	400mg	400mg	400mg	400mg	400mg	400mg	400mg	400mg

Table 1: Formulation Table of Metronidazole

4. EXPERIMENTAL WORK

PREFORMULATION STUDY:

The organoleptic properties, solubility study, flow property, melting point and compressibility of the drug and excipients were determined.[9]

Bulk Density :

Using a funnel, the granules are precisely weighed and transferred into a 50ml measuring cylinder. It was determined how much of the unsettled visible volume the powder particles filled, to the nearest graded unit.

$$\rho_{bulk} = m/Vo$$, **m = is the mass of the blend, Vo=Untapped Volume**

Tapped Density:

After the bulk density was measured , the measuring cylinder containing a weighed quantity of powder granules was put into

a tapped density tester.(Electro lab USP II)for 500 taps.

ρ_t = m/Vt m= is the mass of the weighed granules, Vt=Final tapped volume of granules

Carr's Index: Compressibility index are a measure of the tendency for arch formation.

CI = ρt- ρbulk / ρt × 100 , ρbulk= Bulk Density, ρt=Tapped density

Hausner's Ratio :

He showed that Coarse spheres powder had proportion up to 1.2 : whereas extra cohesive, less free flowing granules such as flakes have value more than 1.6

Hausner's Ratio = ρt/ ρbulk × 100, ρbulk= Bulk density, ρt=tapped density

Angle of Repose:

The angle of repose of API as medication fall within the category of good flow and enhances flow characteristics.

Determination of Drug content:

Twenty tablets were ground into a fine powder, the amount equal to 200mg of metronidazole was precisely weighed and put into a 100ml volumetric flask with 50ml of methanol. To guarantee the drugs full solubility, this was left to stand for six hr. while being periodically, filtered, and made up to volume . a UV-visible spectrophotometer, (model Jasco V-730 spectrophotometer, Japan) was used to measure the metronidazole content λmax value 319nm.[10,15]

Disintegration test:

Without discs, the device runs for two hr. at 37ºC with simulated stomach juice(pH1.2).after being taken out, the tablets must show no signs of softening, breaking, or disintegration. Followings the additions of discs , the device is run using simulated intestinal fluid (pH7.4) at 37ºC for the duration specified in the monograph. When all of the tablets are broken apart, the product passes the test.

Weight Variation Test:

Twenty tablets were taken randomly and weighed individually .For weight variation test calculate average weight and check each tablet weight to the average weight.

Hardness: Tablet hardness of all the formulated tablets was measured using a Monsanto hardness tester.

Thickness :

The thickness of tablets shall not exceed a specified value variation of ± 5% digital vernier calipers were used to measures the thickness of each prepared tablet.

Friability :

Twenty tablets were prepared for this test accurately weighed, and placed in the friabilator. The device ran for four minutes or 100 cycles. The tablets are then weighed and de-dusted. Weight loss is between 0.5 and 1% limit for non- coated , ordinary pills. The decrease in weight was measured using formula.

F(%)= weight loss/ initial weight × 100

5. IN VITRO DISSOLUTION STUDY

The USP dissolution testing apparatus 2(paddle) was used to measures the release rate of metronidazole from tablets.for the first two hr. of the test ,900ml of 0.1N HCl was used at 37±0.50ºC and 100 RPM After that a 7.4 pH phosphate buffer was added, and the process was repeated for 24hr .at regular intervals, a 5ml volume of liquor was removed and replaced with freshly diluted buffer. The samples were swapped out for fresh dissolving media. The absorbances of the samples and standard is used to calculate the drug release.[11].

6. FTIR ANALYSIS

Using a Jasco FTIR-4600, Japan drug and excipients in a 1: 1 ratio molar proportion were prepared in Kbr disc to obtain evidence of the viability of metronidazole molecular level interaction with constituents. The resolution was 1 cm^{-1} and the scanning area ranged from 4000cm^{-1} to 650 cm^{-1} and the resolution was 1cm^{-1} .[12]

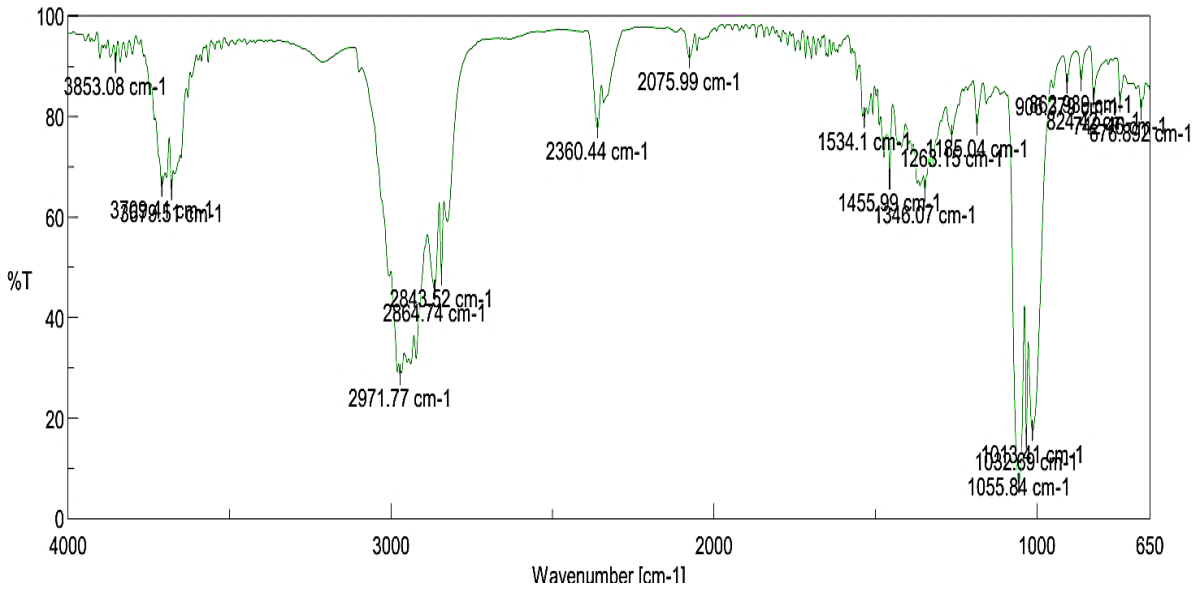

Fig 1 FTIR drug

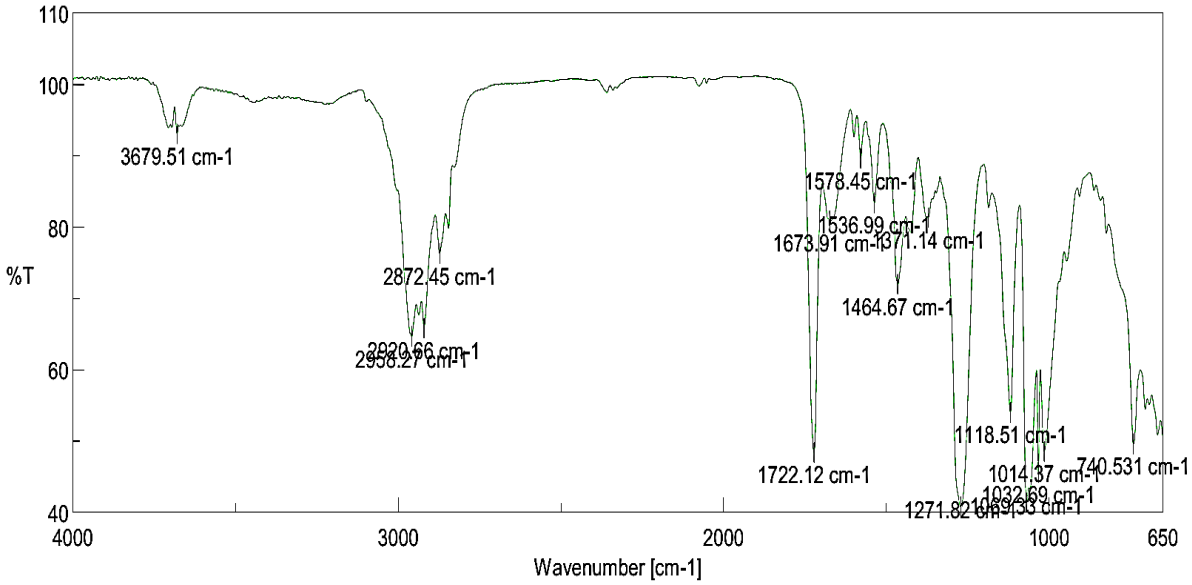

Fig .2 FTIR with Excipients

ASSAY (BY UV METHOD)

a) Determination of λmax : A Shimanzu double UV spectrometer was used to determine the λmax using a drug solution containing 10µg/ml in the 200-400nm range of wave length. As a blank, phosphate buffer 7.4 pH solution was utilized.

b) Calibration Curve Preparation:

1) **Phosphate buffer 7.4 pH solution:** Put in 250ml of potassium dihydrogen phosphate (0.2M) to create a phosphate buffer solution, add 393.4 of 0.1M sodium hydroxide.

2) Preparation of Standard drug solution:

Stock Solution: 10 mg of metronidazole was diluted in 10ml of phosphate buffer 7.4 pH to produce a 1000µg/ml concentration solution.

Standard Solution: Phosphate buffer 7.4 pH was added to 1 ml of stock solution for the metronidazole to 10ml, resulting in a concentration of 100µg/ml. a 10 ml volumetric flask was filled with aliquots of standard drug solution ranging in volume from 0.2,0.4,0.6,0.8,10ml. these were then diluted to the appropriate level

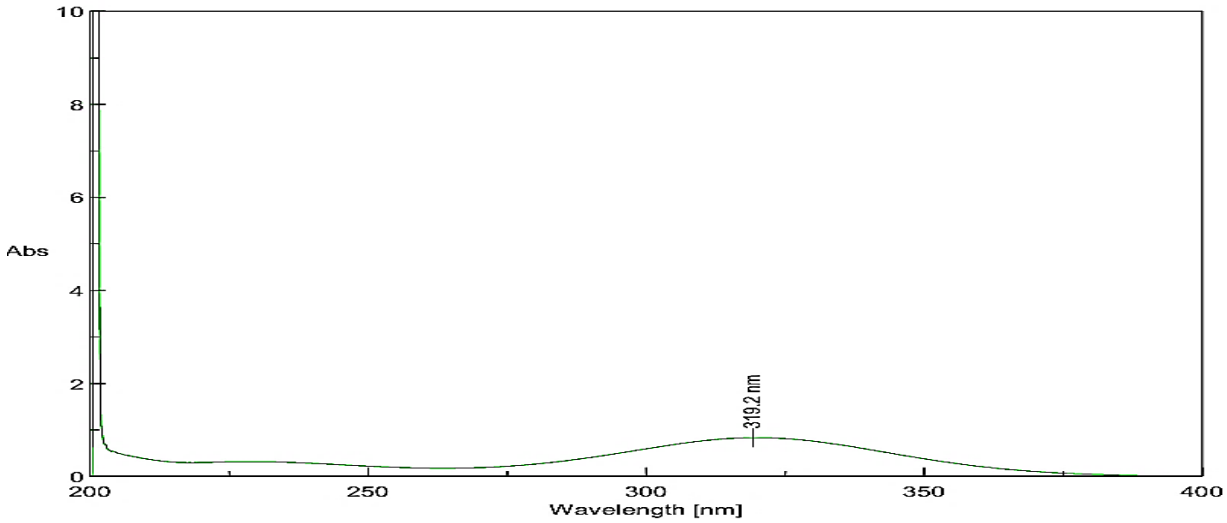

Fig 3

Uv spectral Analysis in Phosphate buffer 7.4 pH λmax 319nm

using phosphate buffer 7.4pH.as a result, the final concentration falls between 2 and 10µg/ml.a blank of phosphate buffer 7.4 pH was used to measure the absorbance was done.

Construction of calibration Curve: A stock solution of 100mcg/ml of metronidazole separately in phosphate buffer 7.4 pH and the using phosphate buffer 7.4 pH appropriately dilute the stock solution create quality solutions ranging from 2 to10µg/ml. using a Jasco V-730 double beam spectrophotometer, the absorbances of the resultant solutions were measured spectrophotometrically at the solvents greatest absorbances.[13]

SOLUBILITY STUDY OF METRONIDAZOLE (Table 2):

Sr no.	Solvent	Saturation Solubility(mg/ml)	Inferences
1.	0.1N HCl	8.7	Slightly soluble
2.	Phosphate buffer 7.4 pH	2.69	Freely Soluble
3.	Phosphate buffer 6.8 pH	9.4	Freely Soluble
4.	Distilled water	9.02	Soluble

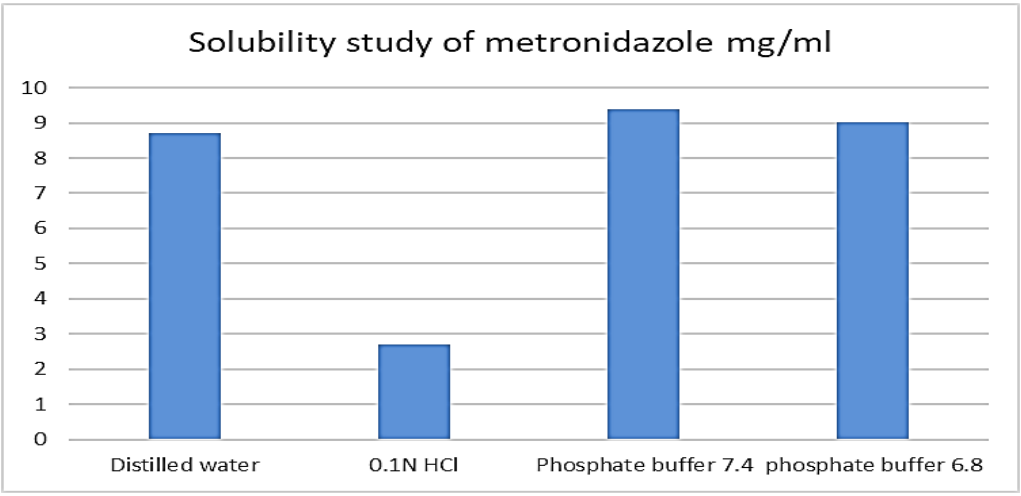

Fig: 4 Solubility of Metronidazole

7. RESULT AND DISCUSSION

Table 3: Evaluation of Granules:

Batch	Bulk density (g/ml)	Tapped density(g/ml)	Angle of repose(º)	Hausner's Ratio	Carr's Index(%)
F1	0.52±0.02	0.63±0.02	29.03±1.31	1.23±0.03	14.92±1.00
F2	0.54±0.10	0.68±0.01	32.51±2.37	1.24±0.04	16.13±0.34
F3	0.56±0.01	0.71±0.01	24.76±0.04	1.20±0.05	20.90±0.50
F4	0.50±0.02	0.61±0.02	27.35±0.35	1.25±0.07	13.85±0.62
F5	0.52±0.04	0.64±0.01	30.12±1.23	1.26±0.05	18.03±1.17
F6	0.56±0.62	0.70±0.02	31.31±0.20	1.25±0.02	15.25±2.18
F7	0.58±0.01	0.67±0.04	27.48±0.50	1.29±0.04	13.67±4.56
F8	0.60±0.01	0.78±0.01	35.15±1.15	1.34±0.09	13.85±0.62
F9	0.53±0.06	0.71±0.01	28.18±1.29	1.26±0.05	16.13±0.34

Table 4 : Evaluation of Uncoated Tablet:

Batch	Hardness kg/cm^2	Friability(%)	Thickness(mm)	Weight Variation(mg)	Disintegration Time (min)
FB1	**5.8±0.37**	**0.53±0.01**	**4.48±0.14**	**398±1.05**	**218.65±1.98**
FB2	**6.08±0.13**	**0.56±0.02**	**4.53±0.10**	**397±3.46**	**225.88±1.61**
FB3	**5.74±0.15**	**0.61±0.03**	**4.46±0.08**	**399±3.16**	**219.76±3.50**
FB4	**6.1±0.29**	**0.71±0.01**	**4.53±0.05**	**398±1.16**	**223.69±1.98**
FB5	**6.36±0.15**	**0.64±0.02**	**4.56±0.19**	**399±0.98**	**235.64±2.54**
FB6	**6.27±0.24**	**0.57±0.02**	**4.40±0.13**	**397±3.46**	**225.89±1.61**
FB7	**6.62±0.11**	**0.59±0.01**	**4.46±0.08**	**398±0.18**	**238.67±2.56**
FB8	**7.11±0.20**	**0.47±0.03**	**4.66±0.06**	**400±2.13**	**248.29±3.58**
FB9	**6.78±0.27**	**0.52±0.02**	**4.53±0.10**	**398±1.05**	**230.82±2.25**

Table 5: Evaluation of coated tablet

Batch	Hardness kg/cm^2	Friability(%)	Thickness(mm)	Weight Variation(mg)	Disintegration Time(min)	Drug Content(%)
FB1	**6.1±0.40**	**0.48±0.01**	**4.70±0.15**	**414±1.10**	**284.25±2.40**	**90.21%**
FB2	**6.4±0.14**	**0.50±0.02**	**4.75±0.11**	**417±3.60**	**283.67±3.85**	**92.33%**
FB3	**6.1±0.16**	**0.55±0.03**	**4.68±0.09**	**415±3.30**	**290.27±3.85**	**94.70%**
FB4	**6.6±0.31**	**0.64±0.01**	**4.75±0.06**	**414±1.22**	**300.80±2.38**	**96.81%**
FB5	**7.0±0.17**	**0.58±0.02**	**4.79±0.20**	**417±1.03**	**330.00±2.85**	**97.71%**
FB6	**6.9±0.26**	**0.52±0.02**	**4.62±0.14**	**414±0.09**	**332.66±1.93**	**87.85%**
FB7	**7.3±0.12**	**0.53±0.01**	**4.68±0.09**	**417±3.60**	**334.14±2.85**	**92.31%**
FB8	**7.5±0.22**	**0.42±0.03**	**4.89±0.07**	**420±2.25**	**335.15±2.70**	**98.27%**
FB9	**6.6±0.31**	**0.64±0.01**	**4.75±0.06**	**414±1.22**	**330.80±2.38**	**97.34%**

IN -VITRO DISSOLUTION STUDY:

Table 6: 0.1 NHCl

% Cumulative Drug Release in 0.1 N HCl									
Time	**F1%**	**F2%**	**F3%**	**F4%**	**F5%**	**F6%**	**F7%**	**F8%**	**F9%**
1hr	6.12	3.96	2.88	4.32	3.24	2.16	7.71	9.52	9.89
2hr	7.72	8.64	5.76	8.64	7.92	6.73	9.53	9.78	10.06

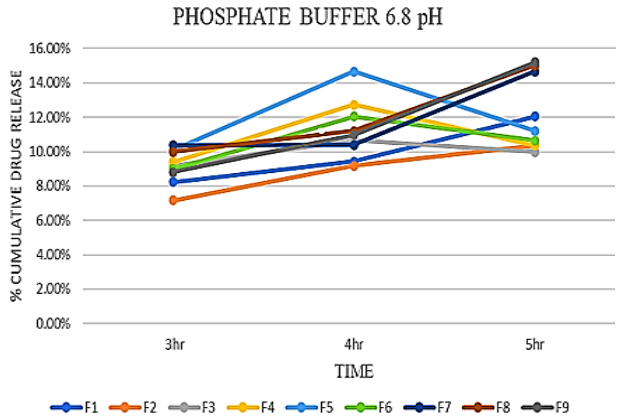

Fig 5: 0.1N HCl

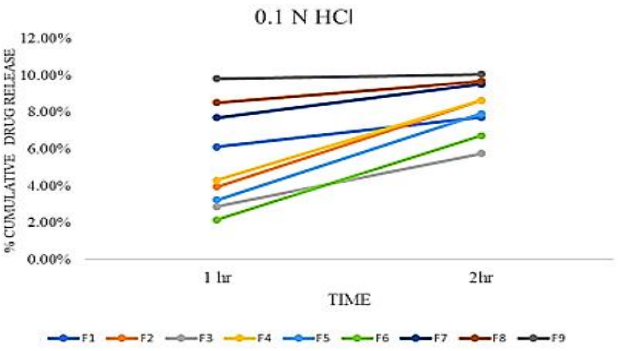

Fig 6: Phosphate buffer 6.8 pH

Table 7: Phosphate buffer 6.8pH

% Cumulative Drug Release in Phosphate buffer 6.8 pH									
Time	**F1%**	**F2%**	**F3%**	**F4%**	**F5%**	**F6%**	**F7%**	**F8%**	**F9%**
3hr	8.23	7.17	9.19	9.41	10.11	9.00	10.36	9.98	8.81
4hr	9.44	9.18	10.66	12.74	14.67	12.05	10.40	11.22	10.97
5hr	12.05	10.36	9.98	10.36	11.22	10.66	14.67	15.01	15.21

Table 8: Phosphate buffer 7.4pH

% Cumulative Drug release in Phosphate buffer 7.4 pH										
Batch	**6hr**	**8hr**	**10hr**	**12hr**	**14hr**	**16hr**	**18hr**	**20hr**	**22hr**	**24hr**
F1	22.59%	27.54%	29.83%	34.83%	43.33%	48.91%	55.80%	62.53%	78.34%	90.26%
F2	21.60%	26.50%	28.89%	33.39%	37.03%	39.33%	43.42%	51.48%	67.45%	92.87%
F3	20.65%	23.71%	27.94%	30.10%	33.30%	36.94%	51.49%	62.75%	85.78%	94.74%
F4	21.56%	23.56%	25.45%	33.40%	40.34%	46.78%	60.20%	78.34%	82.34%	93.67%
F5	30.23%	40.34%	42.35%	53.47%	63.38%	65.76%	71.67%	83.40%	90.45%	95.78%
F6	31.26%	45.56%	49.34%	55.75%	62.34%	73.56%	77.45%	80.10%	84.34%	90.89%
F7	22.45%	26.50%	28.78%	31.24%	67.56%	75.67%	82.45%	85.67%	87.45%	91.65%
F8	20.56%	23.45%	30.24%	42.35%	60.45%	78.89%	82.48%	87.56%	90.55%	96.67%
F9	24.48%	30.45%	33.40%	54.34%	62.43%	70.56%	82.38%	85.67%	87.78%	92.89%

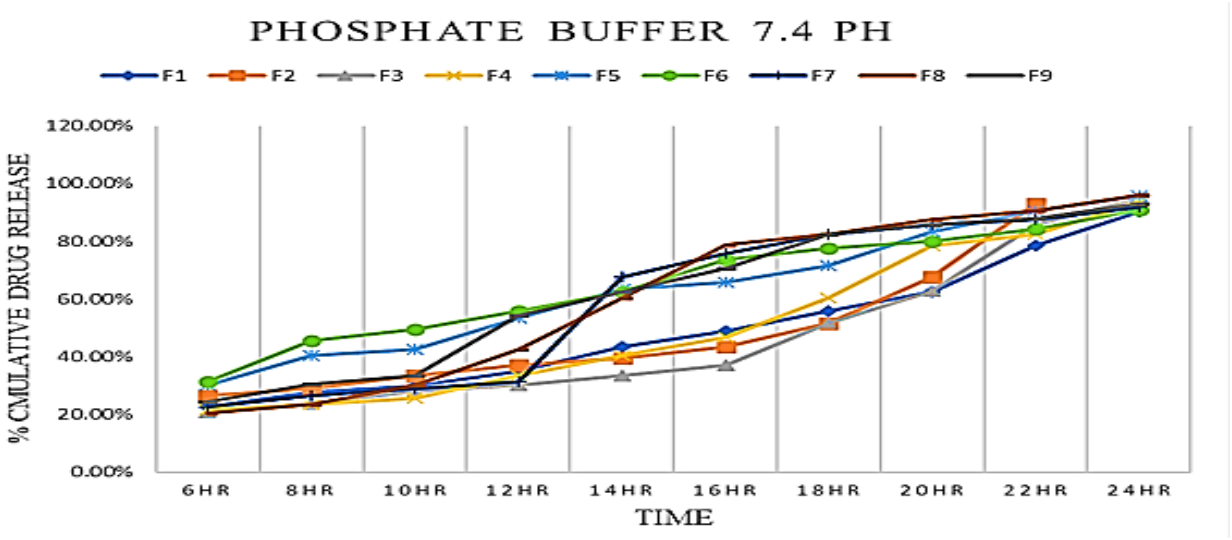

Fig 7: Phosphate buffer 7.4 pH

Angle of repose of metronidazole:

35.15 ±1.15 was the predicted angle of repose of API. As a result, the medication falls within the category of good flow and needs glidants to enhance its flow characteristics.

Bulk density and tapped density metronidazole:

The Average bulk density tapped density were determined to be **0.60±0.01 to 0.78±0.001 g/ml** respectively.

Powder compressibility and hausner's ratio:

According to Hausner's ratio **1.34±0.09** and the compressibility index **13.85±0.62** . Metronidazole (API) has good flow properties.

8. STABILITY STUDIES

The formulation F8 batch was selected for stability studies on the basis of their high cumulative % drug release and also result of invitro disintegration time studied. The stability studies were carried out at 40±2ºand 75± 5% relative humidity for the selected formulation up to 3 months. For every 1-month time interval the tablets were analysed for drug appearance, Hardness, Disintegration time, % drug Release up to three months. The results obtained in table below;

Table 9: Stability study

Formulation	Parameters	Initial	After 2 month	After 3 month
F8 Batch	**Appearance**	Pale yellow Crystalline powder	Pale yellow Crystalline Powder	Pale yellow Crystalline powder
	Hardness	7.5±0.22	7.4±0.22	7.1±0.17
	Disintegration	334.14±2.85	332.12±2.80	330.10±2.75
	In vitro drug release	96.12%	95.17%	93.15%

9. CONCLUSION

The formulation and evaluation of metronidazole tablet aimed at treating amoebiasis caused by Entamoeba Histolytica.Efficacy of metronidazole is one of the most effective medications for intestinal amoebiasis, which is a significant health concern due to its prevalence and associated mortality rates. Need for effective drug delivery systems to ensure that metronidazole reaches the colon, where E. histolytica resides, to maximize therapeutic effect. The study explores various formulation techniques for colon specific drug delivery. These include coating with Ph- dependent systems, creating time release dosage forms. In vitro dissolution studies conducted using the USP dissolution testing apparatus demonstrated the release profile of metronidazole from the tablets. The result indicates that the drug was effectively released in controlled manner, which is essential for achieving the desired therapeutic outcomes.

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