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Formulation and In-vitro Evaluation metronidazole floating tablet using raft forming system

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ABSTRACT

The present article includes recent advance in floating drug delivery system for designing and development of Metronidazole floating tablet to increase the bioavailability and therapeutic effectiveness of the drug using raft forming system. This article shows controlled release of metronidazole for proper duration of action at a particular site and is planned to prolong the gastric residence time after oral administration. The natural and synthetic polymers used are Sodium alginate, Xanthan Gum, HPMC, HPMC K4M respectively as a raft forming agent. The different formulation batches (F1-F10) were and formulated for physical parameter, Raft strength and *in-vitro* drug release.

Key-words; Metronidazole floating tablet, raft forming agent

1. INTRODUCTION

Controlled release dosage forms deliver the drug for longer period and helps in producing the therapeutic effect for longer time for those drugs which are having low plasma half life. Drugs that have narrow absorption window in the gastrointestinal tract (GIT) will have poor absorption.[1] in the floating drug delivery system the mostly drug acting on GIT are used for the formulation and improve the gastric retention time.[2] ***Helicobacter pylori*** is a prevalent human specific pathogen, which is now believed to be the causative bacterium for chronic gastritis, peptic ulcer it requires high concentration of drug within the gastric mucosa for long duration.[3]

Metronidazole, chemically 2-(2-methyl-5-nitro-1*H*imidazol- 1-yl) ethanol, is a nitroimidazole anti-infective agent which has specific activity against anaerobic organisms and protozoa. Metronidazole is indicated for the treatment of Helicobacter pylori eradication therapy, as part of a multidrug regimen in peptic ulcer disease[4]. It is usually taken two or three times a day. Metronidazole is bactericidal, amoebicidal and trichomoncidal. The exact mode of action has not been fully elucidated. Metronidazole is reduced by low-redox-potential electron transfer proteins (e.g. nitroreductases such as ferredoxin) to unidentified polar product which lack the nitro group.[5] the reduction product appears to be responsible for the cytotoxic and antimicrobial effects of the drug which include disruption of DNA and inhibition of nucleic acid synthesis. In the present study, Metronidazole floating tablets were prepared using raft forming system to increase the gastric residence time and absorption of drug in stomach and the prepared tablets were evaluated.

2. MATERIALS AND METHODS

2.1 Materials

The chemicals used in this study were pure drug like Metronidazole and polymers like Sodium alginate, Xanthan gum, HPMC and HPMC K4M, other excipients like calcium carbonate, Magnesium stearate, Talc, Sodium bicarbonate all analytical grade chemical was purchased from

2.2 Preformulation study

Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product includes the FT-IR study, calibration curve of drug, and Organoleptic properties.[6]

2.3 Preparation and Characterization of granules

Weighed quantities of drug, polymer, calcium carbonate and sodium bicarbonate except magnesium stearate and talc as given in a Table No.1 were mixed properly in a mortar. Weight granulation was made by using 10% starch paste.[7] Wet mass was passed through sieve no 16# and prepared granules were dried hot air oven by maintain the temperature. Dried granules were again passed through sieve no 40#. The prepared granule was evaluated for Angle of Repose, Bulk Density, Tapped Density, Carr's Index and Hausner Ratio. [8, 9]

2.4 Formulation of Tablet

Development of the floating tablet in the present study was mainly based on wet granulation method. The prepared granules were lubricated with magnesium stearate and talc and compressed with the help of tablet machine using 12mm punch and formulate the various batches (F1-F8) using the different concentration of raft forming agent and sodium bicarbonate the natural and synthetic raft forming agent were used in the formulation of floating tablet and evaluate the every batches.

Table No.1: Composition of Tablet Batches F1-F8

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)
Metronidazole	200	200	200	200	200	200	200	200
Sodium Alginate	180	200	-	-	-	-	-	-
Xanthan Gum	-	-	180	200	-	-	-	-
HPMC	-	-	-	-	180	200	-	-
HPMC K4M	-	-	-	-	-	-	180	200
Calcium Carbonate	30	30	30	30	30	30	30	30
Sodium Bicarbonate	80	80	100	100	80	80	80	80
Magnesium Stearate	12	12	12	12	12	12	12	12
Talc	8	8	8	8	8	8	8	8
Starch Paste 10%	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

2.5 Evaluation of Tablet

A) Physicochemical Evaluation

The prepared tablets were evaluated for their physicochemical parameters like weight variation, hardness, friability, thickness and drug content.[10, 11]

B) Floating Lag Time

This test was performed in beaker containing 100 ml 0.1 N HCL as a testing medium maintained at 37^0C. The time required for the tablet to rise to the surface and float was determined as floating lag time.[10]

C) Raft Strength

A tablet powder equivalent to unit dose was transferred to 250 ml beaker add 150 ml 0.1 N HCL and maintained at 37°C in a 250 ml glass beaker. Each raft was allowed to form around an L-shaped wire probe (diameter: 1.2 mm) held upright in the beaker throughout the whole period (30 min) of raft development, Raft strength was estimated using the modified balance method. Water was added drop wise to the pan and the weight of water required to break the raft was recorded.[12]

D) Dissolution Studies

An *In-Vitro* drug release study for all the formulations was carried out by using USP type-I dissolution test apparatus at 50 rpm. The dissolution rate was studied using 900 ml of 0.1 N Hydrochloric acids (pH 1.2) for 10 hrs. The temperature was maintained at 37±0.5^{0}C. Samples of 2 ml each were withdrawn at 1 hr time intervals, filtered through Whatman filter paper and replaced with an equal amount of fresh dissolution medium. Samples was suitably diluted and analyzed for metronidazole content using UV spectrophotometer (aligant carry UV 1700) and was measured the absorbance at 278 nm.

3. RESULTS AND DISCUSSION

3.1 Preformulation study

A) Organoleptic characterization and Solubility analysis

Test	Observation
Colour	Pale yellow
Odour	Odourless
Taste	Bitter
Melting point	160 –165^{0}C

Solvent	Solubility
Distilled water	Soluble
0.1N HCL	Soluble
Methanol	Freely soluble

The solubility of pure drug was carried out in 10 ml of solvent and meting point was carried out using open capillary method.

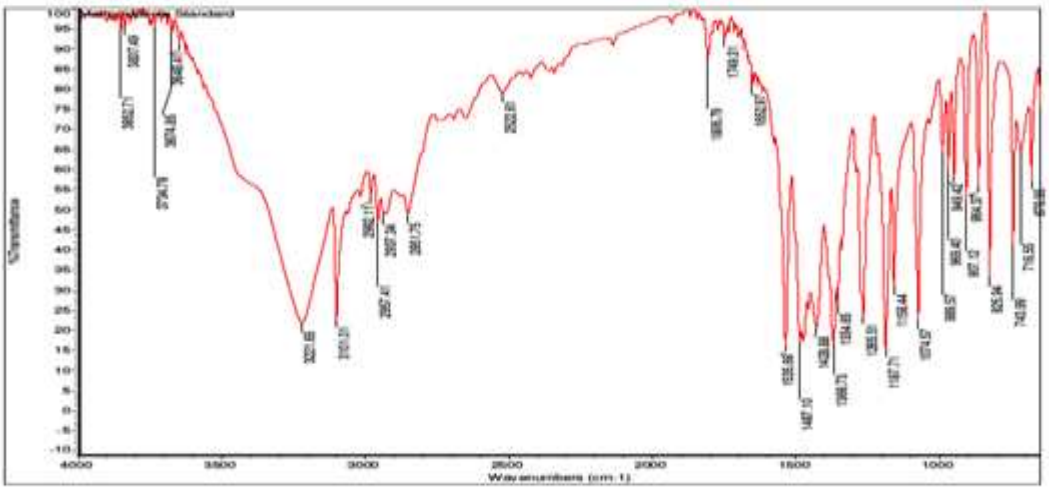

Fig.1: Infra-Red spectra of metronidazole

C) Calibration curve of Metronidazole

Table No.2: Absorbance for metronidazole

Sr.No	Concentration µg/ml	Absorbance at 278nm
1	2 µg/ml	0.2981
2	4 µg/ml	0.3877
3	6 µg/ml	0.4726
4	8 µg/ml	0.5219
5	10 µg/ml	0.5849

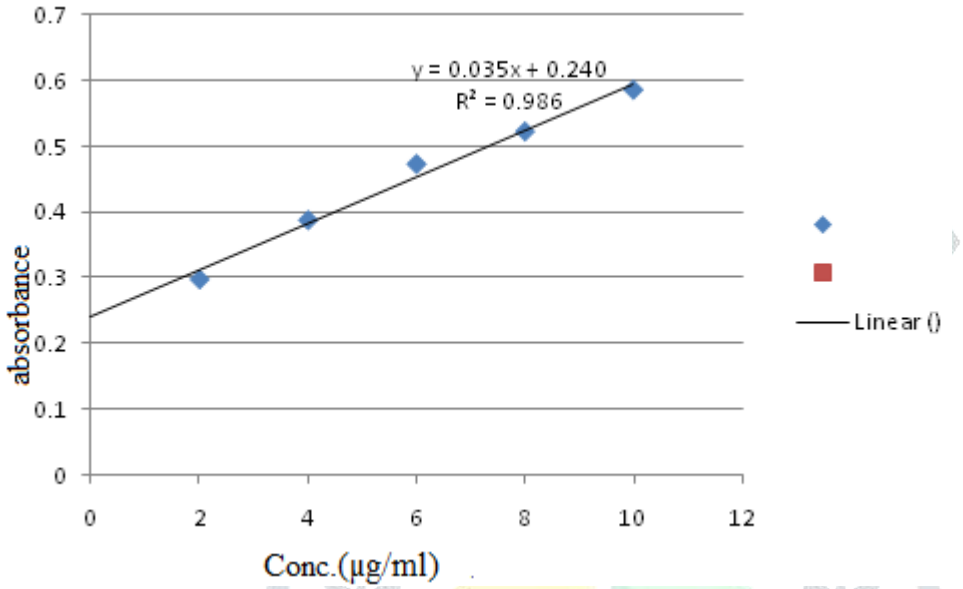

Fig.2: Calibration curve of Metronidazole in 0.1 N HCL

100mg of drug was dissolved in 0.1N HCL and the volume was made up to 100ml using 0.1N HCL From this solution 1ml was withdrawn and diluted to 100ml with 0.1N HCL From this stock solution serial dilutions were made to obtain the solutions in concentrations ranging from 2-10µg/ml. The absorbance was measured at 278nm using spectrophotometer.

D) Compatibility study of drug and polymer

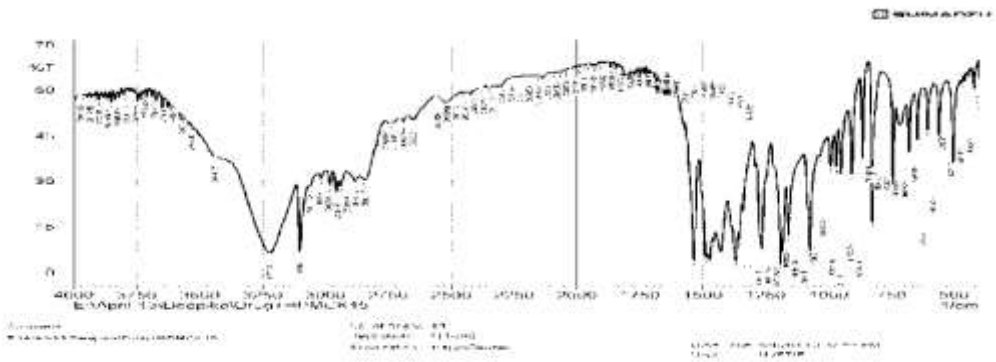

Fig.3: Infra-Red spectra of metronidazole with sodium alginate

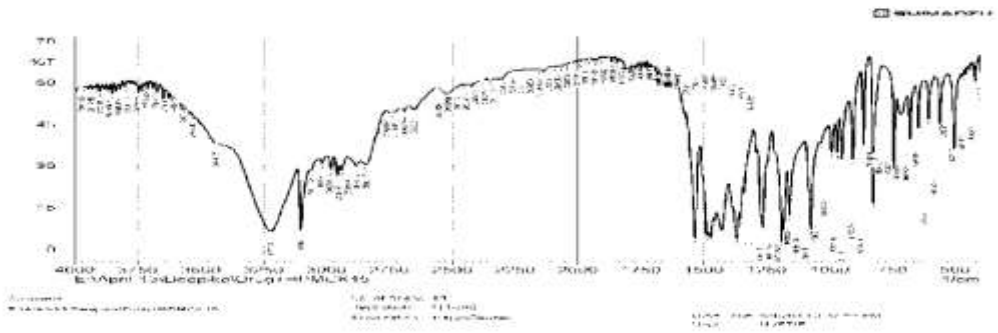

Fig.4: Infra-Red spectra of metronidazole with Xanthan gum

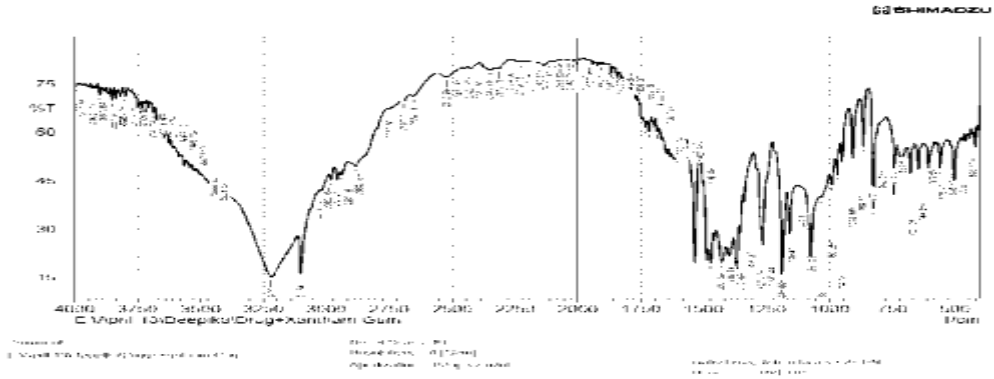

Fig.5: Infra-Red spectra of metronidazole with HPMC

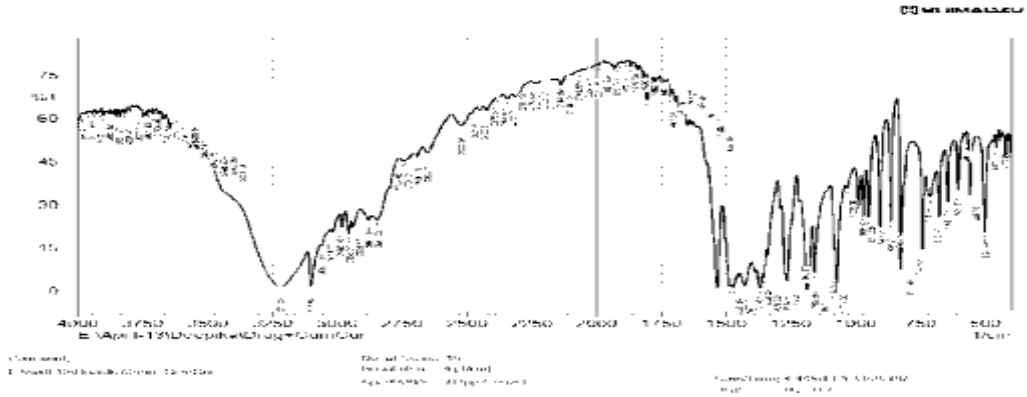

Fig.6: Infra-Red spectra of metronidazole with HPMC K4M

E) Characterization of granules

Table No.3: Evaluation of prepared metronidazole powder blend

Formulation Batches	Angle of Repose (degrees)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner Ratio
F1	$30^0 12' \pm 1.63$	0.623±0.004	0.689±0.007	8.89±0.05	1.19±0.11
F2	$29^0 21' \pm 0.45$	0.657±0.005	0.715±0.004	8.49±0.03	1.17±0.06
F3	$25^0 89' \pm 2.31$	0.679±0.006	0.779±0.004	10.57±0.05	1.18±0.05

F4	$27^0$50'±1.27	0.667±0.004	0.697±0.002	4.42±0.06	1.21±0.02
F5	$27^0$26'±1.23	0.719±0.003	0.837±0.004	14.51±0.04	1.24±0.07
F6	$27^0$87'±1.64	0.691±0.005	0.776±0.008	10.61±0.07	1.22±0.09
F7	$27^0$29'±0.85	0.703±0.003	0.739±0.003	5.57±0.09	1.19±0.10
F8	$30^0$15'±1.50	0.735±0.006	0.827±0.003	11.17±0.04	1.21±0.08

All the values except angle of repose represent mean ± Standard deviation (n=3)

3.2 Evaluation of tablet

A) Physicochemical Evaluation

It includes the weight variation, hardness, friability, drug content and thickness was carried out and it was found weight variation between 510 to 550 mg is not more than 7.5%, hardness values of the formulation ranged from 4.6 to 5.3 kg/cm^2, friability values of all the formulation were less than 1%, drug content ranged from 96.36±1.27% to 99.79±0.71%. and thickness was found between 4.50±0.16 mm to 4.76±0.20 mm.

Table No. 4: Standard physical tests for floating tablets

Batches	Weight variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity (%)	Thickness (mm)
F1	509.2±0.81	4.70±0.14	0.83±0.01	98.10±1.17	4.50±0.16
F2	529.8±0.32	4.76±0.12	0.89±0.03	98.23±1.28	4.63±0.12
F3	529.9±0.35	4.93±0.20	0.78±0.06	99.58±1.27	4.66±0.26
F4	550.4±0.44	4.70±0.08	0.78±0.03	99.79±0.71	4.76±0.20
F5	509.4±0.63	4.83±0.09	0.93±0.05	97.85±1.22	4.56±0.20
F6	530.03±0.87	5.06±0.12	0.70±0.03	96.36±1.27	4.60±0.29
F7	509.8±0.47	4.9±0.16	0.56±0.05	97.82±2.45	4.53±0.28
F8	530.2±0.86	5.0±0.14	0.54±0.04	99.72±1.40	4.63±0.30

All the values represent mean ± standard deviation (n=3)

Table No. 5: Raft strength and floating lag time tests for floating tablets

Formulation Batches	Raft Strength (gm)	Floating lag time (sec)
F1	6.41±0.27	217±2
F2	7.40±0.45	225±4
F3	5.26±0.12	231±2
F4	6.46±0.26	247±2
F5	1.73±0.24	213±6
F6	1.70±0.29	217±4
F7	4.30±0.35	207±5
F8	5.10±0.21	204±3

All the values represent mean ± standard deviation (n=3)

B) Floating lag time

The floating lag time was found between 204±3 sec to247±2 sec, it indicates the good floating property.

C) Raft strength measurement

Raft was measured by in-house vitro method it indicates the breaking property of gel (raft) it was found in between the range of 1.70±0.29 gm to 7.40±0.45gm.

Fig 7: Formation of raft and Measurement of raft strength

D) Dissolution studies

Table No.6: *In-vitro* dissolution data of F1, F2, F3, and F4 formulation

Time (Hrs)	F1	F2	F3	F4
1	6.87±0.11	16.70±0.34	9.44±0.38	10.33±0.63
2	14.94±0.47	29.67±0.54	14.08±0.30	20.26±0.76
3	22.32±0.12	42.03±0.44	21.15±0.17	30.95±0.31
4	40.30±0.50	54.87±0.33	27.92±0.25	44.78±0.43
5	50.12±0.27	60.55±0.38	43.15±0.27	53.21±0.59
6	61.12±0.34	73.89±0.21	55.81±0.34	64.85±0.44
7	68.59±0.28	81.16±0.69	74.78±1.23	74.13±0.46
8	74.97±0.19	84.30±0.19	85.69±1.17	83.97±0.22
9	81.62±0.53	86.39±0.43	90.74±0.44	91.08±0.76
10	89.11±0.81	93.17±0.81		

All the values represent mean ± standard deviation (n=3)

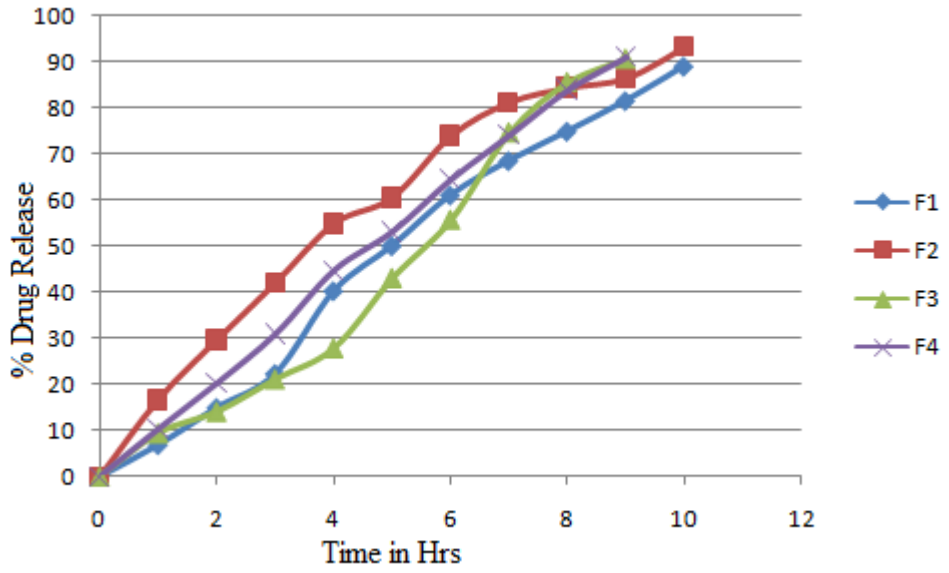

Figure.8: *In-vitro* dissolution profile of F1, F2, F3 and F4 formulation

Table No.7: *In-vitro* dissolution data of F5, F6, F7, and F8 formulation

Time (Hrs)	F5	F6	F7	F8
1	21.71±0.74	30.48±0.81	10.91±0.55	15.16±0.61
2	65.67±1.11	69.07±0.54	11.15±0.28	20.54±1.03
3	96.40±1.85	95.48±1.09	21.52±0.45	28.92±0.71
4			41.13±0.73	50.24±0.56
5			53.88±0.40	52.41±0.51
6			69.06±0.71	73.06±0.73
7			81.51±0.74	74.71±0.90
8			82.69±1.06	81.53±0.75
9			87.28±0.50	83.18±1.28
10			90.07±0.76	92.08±0.60

All the values represent mean ± standard deviation (n=3)

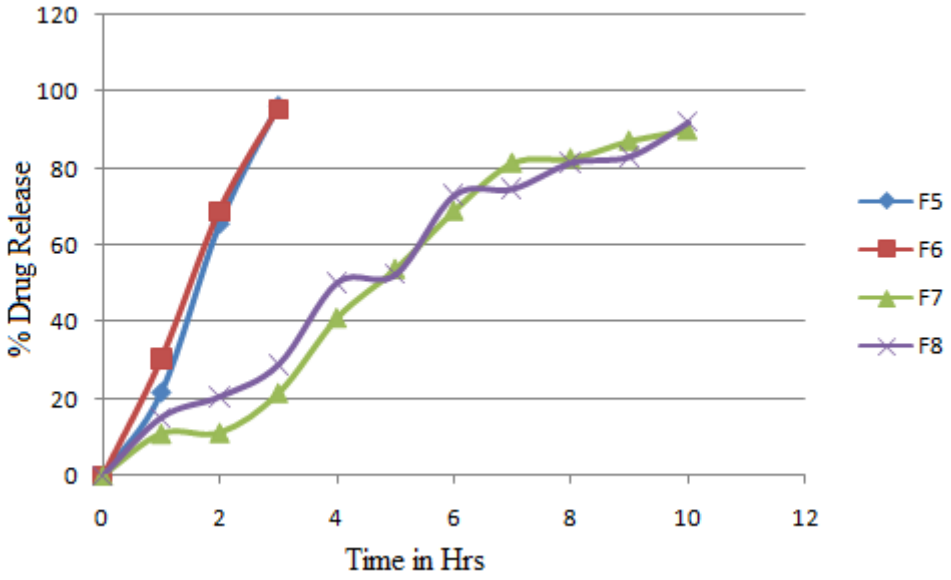

Figure.9: *In-vitro* dissolution profile of F5, F6, F7, and F8 formulation

4. CONCLUSION

Tablets of batch F2 was found that increase in the sodium alginate concentration will increase the raft strength, increases floating duration and drug release. Floating tablets using raft forming system containing metronidazole was prepared successfully by using wet granulation technique. Tablets were subjected to various evaluation parameters such as Weight variation, Hardness, Friability, Drug content, raft strength, floating lag time, *in vitro* drug release study. It was discovered that tablets of all batches was acceptable physical parameters. FT-IR studies discovered that there was no interaction between metronidazole and other excipients used in the tablets.

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