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FORMULATION AND *IN-VITRO* EVALUATION OF FLOATING TABLETS OF HYDROXYPROPYL METHYLCELLULOSE K4M AND CARBOPOL-934P USING METRONIDAZOLE AS A MODEL DRUG

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Keywords:

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ABSTRACT: In the present study, metronidazole was used for preparing floating dosage forms that are designed to retain in the stomach for a long time and have developed as a drug delivery system for better eradication of *Helicobacter Pylori* in peptic ulcer diseases. Hydroxypropyl methylcellulose (HPMC K_4M) and Carbopol-934P of different ratio were used to prepare Hydrodynamically Balanced Systems (HBS) by direct compression technique. The prepared HBS tablets were evaluated in terms of their pre-compression parameters and post-compression parameters like hardness, friability, weight variation, uniformity of drug content, percentage swelling, *in-vitro* floating studies, *in-vitro* drug release and short term stability studies. The floating properties and drug release characteristics were determined for the prepared HBS in 0.1 N HCl dissolution media. All the HBS formulations showed good *in-vitro* floating properties with an optimum concentration of gas generating agents; sodium bicarbonate and citric acid. The rate of drug release decreased with increased hardness of tablets. Optimum concentration of HPMC K_4M (140 mg) and Carbopol-934P (10 mg) along with excipients was found to be beneficial in improving the drug release rate and floating properties. Among the eight formulations, F8 was selected as the best formulation as its lag time was 10.3 seconds, percentage swelling 119.91% at 4^{th} hour and % drug release 75.62% at 8^{th} hour with buoyancy time >12 hours.

INTRODUCTION: Effervescent floating drug delivery systems generate gas (CO_2), thus reduce the density of the system and remain buoyant in the stomach for a prolonged period of time and released the drug slowly at a desired rate [1]. Floating Drug Delivery System (FDDS) has less density (<1.004gm/cm^3) than gastric fluid so they buoyant in fluid and show sustained release [2].

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Metronidazole is a nitroimidazole antibiotic medication used particularly for anaerobic bacteria and protozoa. Metronidazole is an antibiotic, amoebicidal and antiprotozoal. It is the drug of choice for first episodes of mild-to-moderate *Clostridium difficile* infection.

Metronidazole is indicated for the treatment of *Helicobacter pylori* eradication therapy, as part of a multi-drug regimen in peptic ulcer disease. It is usually taken two or three times a day [3]. Administration of prolonged release floating tablet will result in prolonged retention of the drug in the gastric fluid. Thus, resulting in complete dissolution of drug in extended period of time by

enhancing the drug absorption and thereby reduce the dosing frequency of the drug in therapy [4].

MATERIALS AND METHODS: Metronidazole, carbopol-934P, ethyl cellulose and microcrystalline cellulose was obtained from Yarrow Chem Products Mumbai. HPMC K_4M was gifted by BAL Pharma, Bommasandra, Bangalore, in the year of 2013. Chemicals were all used as received.

Method: Floating tablets of Metronidazole was prepared by direct compression method. All the weighed quantities of ingredients except Magnesium stearate were blended in glass mortar uniformly and were passed through sieve number 80 to get fine particles. After sufficient mixing of drug as well as other excipients, Magnesium stearate was added and further mixed for additional 2-3 minutes to get uniformly blended powder mixture. Powder thus obtained was compressed into tablets on a 10 station single punch rotary tablet compression machine in the pharmaceutics laboratory (machine room) of The Oxford College of Pharmacy, Bangalore.

Evaluation: Fourier Transform Infrared Spectroscopy (FT-IR) study was conducted to test the compatibility of drug with the polymer. The flow properties of blends (before compression) were characterized in terms of Angle of repose, Bulk density and Tapped density, Carr's index and Hausner's ratio [5].

Physical evaluation of Metronidazole Floating Tablet [5]: Hardness of the tablets was tested using a Monsanto hardness tester. Friability of tablets was determined in Roche friabilator. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

1. **The buoyancy lag time (BLT) and total floating time (TFT) [6]:** Tablets were kept in 0.1N HCl solution at 37±0.5°C and the time taken for tablet to float was noted down as BLT and the total time tablet floated was noted down as TFT.

2. **Drug content estimation:** For drug content estimation 5 tablets from each formulation were taken and crushed to powder. Powder weight equivalent to 50 mg drug was taken and dissolved in 50 ml of 0.1 N HCl. From the first solution, 1 ml solution was taken in 100 ml volumetric flask and the volume was made up to 100 ml with 0.1 N HCl. Solution was then filtered and absorbance was measured spectrophotometrically at 276 nm against 0.1 N HCl as a blank.

3. **Swelling study [7]:** The swelling property of all drug containing formulations were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml of 0.1 N HCl at 37± 0.5 ^{o}C. The tablets were removed periodically from dissolution medium and after draining free from water by blotting paper, these were measured for weight gain. Swelling characteristics were expressed in terms of percentage swelling calculated using the given formula;

Percentage Swelling =

$$\frac{\text{Weight of tablet at time t} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100\ \%$$

4. ***In-vitro* Dissolution studies:** The release profile of Floating tablet of Metronidazole was determined using USP dissolution test apparatus II (basket type) at 50 rpm using 0.1 N HCl as dissolution medium at temperature of 37±0.5°C. 1 ml of the sample was withdrawn at an hour interval for 8 hours and replaced with the same volume of fresh dissolution medium. The withdrawn samples were diluted to 10 ml using 0.1 N HCl. Absorbance of these solutions was measured at 276 nm using a UV Visible spectrophotometer. The cumulative percentage drug release was plotted against time to determine the release profile.

5. ***In-vitro* drug release kinetic studies [8]:** The dissolution data were of all the batches were fitted to various kinetic models like zero order, first order, Higuchi square root, Korsmeyer-Peppas model to ascertain exact mechanism of drug release from the tablets.

6. **Short term stability studies:** The formulation (F8) was selected for stability studies on the basis of *in-vitro* buoyancy and *in-vitro* drug dissolution studies. The tablets were investigated at 25±2°C/ 60±5% RH for 1st

month and at 40±2°C/ 75±5% RH for 2nd month. Various tablet properties were analysed after the stability test.

RESULTS AND DISCUSSION: In the present study, floating tablets of Metronidazole were prepared by using HPMC as a matrix binding agent, carbopol as a gelling agent and sodium bicarbonate and citric acid as effervescent agent. Floating tablets of metronidazole were developed to increase the gastric residence time of the drug, so that they can be retained in stomach for longer time resulting in controlled release of drug. A total number of eight formulations (**table 1**) were prepared by direct compression technique after the confirmation of compatibility of Metronidazole drug with the selected polymer done using FT-IR study. The pre-formulation studies such as bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio were evaluated which were found to be within prescribed limits and indicated excellent flowing property (**table 2**).

The data obtained from physicochemical parameters such as hardness, friability, weight variation, drug content were in acceptable range (**table 3**). The swelling percentage of all the formulations was more than 90% thus revealed the better swelling behavior of all the tablet (**table 4** and **figure 1**).

TABLE 1: FORMULATION TABLE OF FLOATING TABLETS OF METRONIDAZOLE

Ingredients	F_1	F_2	F_3	F_4	F5	F6	F7	F8
Metronidazole	200	200	200	200	200	200	200	200
HPMC K_4 M	100	110	90	120	80	130	70	140
Carbopol-934	50	40	60	30	70	20	80	10
Sodium Bicarbonate	50	50	50	50	50	50	50	50
Citric acid	20	20	20	20	20	20	20	20
Ethyl Cellulose	20	20	20	20	20	20	20	20
MCC	30	30	30	30	30	30	30	30
Magnesium Stearate	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10
Total Weight (mg)	490	490	490	490	490	490	490	490

TABLE 2: PRE-COMPRESSION STUDY DATA

Formulation code	Angle of repose (°) ±SD	Compressibility Index (%)	Hausner's Ratio	Flow Property
F1	28.16 ± 1.030	08.68 %	1.09	Excellent
F2	24.58 ± 0.899	10.17 %	1.11	Excellent
F3	25.16 ± 0.612	12.09%	1.14	Excellent
F4	24.71 ± 1.306	10.63%	1.12	Excellent
F5	25.36 ± 0.465	10.50%	1.12	Excellent
F6	29.563±1.446	11.2%	1.13	Excellent
F7	26.15±1.905	10.57%	1.14	Excellent
F8	24.26±1.235	12.5%	1.11	Excellent

TABLE 3: POST-COMPRESSION STUDY DATA

Formulation code	Weight variation (mg) ±SD	Hardness (kg/cm^2) ±SD	Friability (% loss) ±SD	Thickness (mm)	Drug content (%)
F1	482.7±5.22	4.26±1.36	0.415±0.048	4.02±0.01	97.71
F2	482.75±4.55	5.9±0.79	0.23±0.013	4.04±0.02	100.57
F3	480.6±5.16	6.66±0.288	0.449±0.046	4.04±0.00	99.71
F4	483.05±4.22	4.03±0.33	0.049±0.034	4.02±0.00	109.90
F5	484.95±6.14	5.83±0.288	0.534±0.07	4.04±0.00	94.85
F6	481.95±4.28	7.1±1.014	0.036±0.046	4.02±0.00	95.71
F7	484.85±4.53	4.66±0.763	0.519±0.152	4.03±0.01	103.90
F8	484.45±4.70	4.33±0.208	0.232±0.053	4.02±0.00	101.33

TABLE 4: PERCENTAGE SWELLING TABLE FOR F1-F8

Formulation code	15	30	60	120	240
F1	28.51145	46.4049	61.90766	80.15381	99.92982
F2	10.86815	49.24518	70.59565	78.22612	103.8123
F3	55.50933	55.29607	73.6144	86.15062	102.7313
F4	20.70958	49.17945	65.97686	79.81906	123.5402
F5	18.92734	42.39038	54.02336	69.1511	83.61179
F6	29.55112	50.21686	65.05932	81.0084	111.396
F7	27.79882	38.77314	49.58849	62.85871	78.50495
F8	22.68451	46.51887	64.38412	82.70529	119.9171

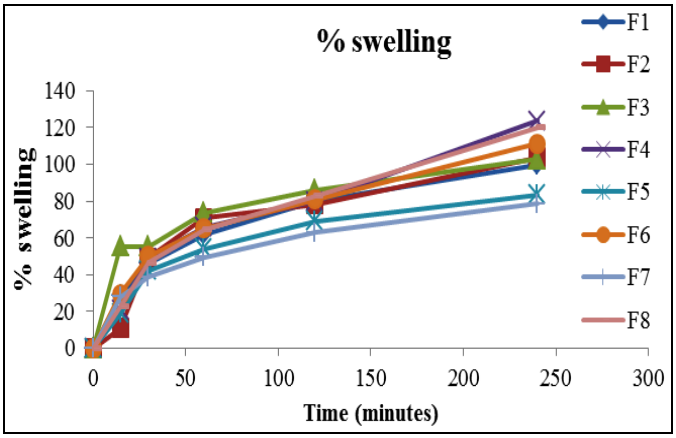

FIGURE 1: PERCENTAGE SWELLING GRAPH FOR F1-F8

From *in-vitro* drug dissolution profile of floating tablets of Metronidazole, it was found that the formulation F8 containing 140 mg of HPMC K_4M and 10 mg of carbopol-934P showed highest drug release (75.6245%) in comparison with other formulations (**figure 3**). Tablets of batch F8 have considerable *in-vitro* drug release, and also showing good floating lag time (10.7 ± 2.00 seconds) and good buoyancy time (>12 hours) (**table 5**). Thus the formulation F8 was selected as the most satisfactory formulation.

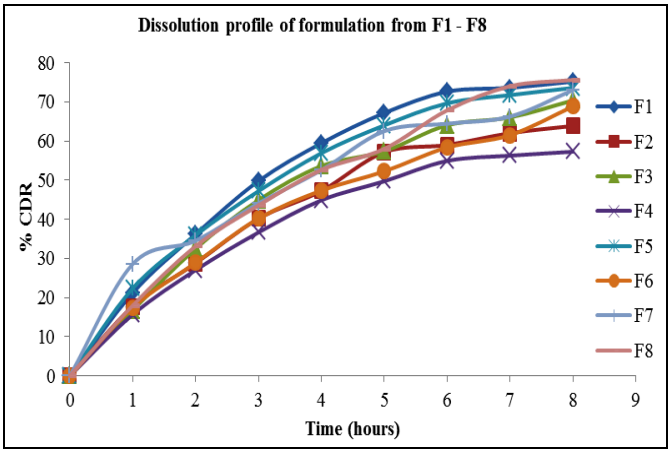

FIGURE 2: *IN-VITRO* DISSOLUTION GRAPH OF METRONIDAZOLE FLOATING TABLETS

TABLE 5: RESULTS OF *IN-VITRO* BUOYANCY STUDY OF METRONIDAZOLE FLOATING TABLETS

Formulation Code	Buoyancy Lag (seconds)	Total Floating Time (hours)
F1	42.0 ± 13.076	>12
F2	28.0 ± 08.185	>12
F3	38.0 ± 11.135	>12
F4	18.7 ± 04.725	>12
F5	51.3 ± 15.82	>12
F6	16.5±03.25	>12
F7	55.6±3.23	>12
F8	10.3±2.0	>12

The most satisfactory formulation F8 was fitted into various *in-vitro* drug release kinetic models and best fit model was found to be first order in case of all formulations than zero order (**table 6** and **figure 3-5**). The drug release kinetics follows Higuchi model and the mechanism of drug release was found to be non Fickian/anomalous. Release pattern from formulations followed both membrane erosion and diffusion process.

TABLE 6: KINETIC RELEASE DATA OF DIFFERENT MODEL FOR FORMULATION F8

Model	Slope	R^2
Zero Order	11.009	0.9009
First Order	-0.0777	0.9917
Higuchi's	32.329	0.9939

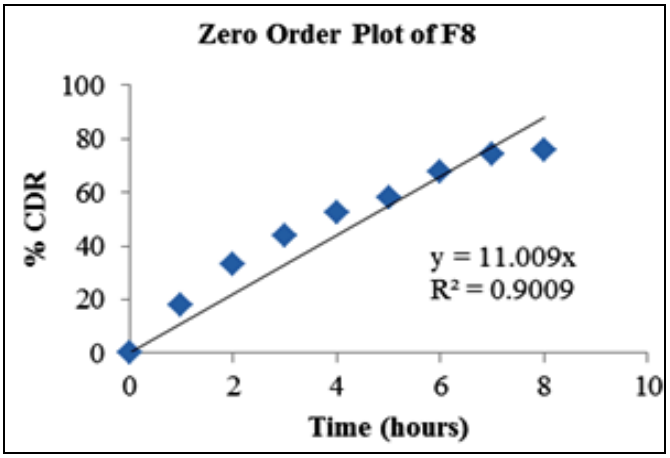

FIGURE 3: ZERO ORDER PLOT OF METRONIDAZOLE (F8) FORMULATION

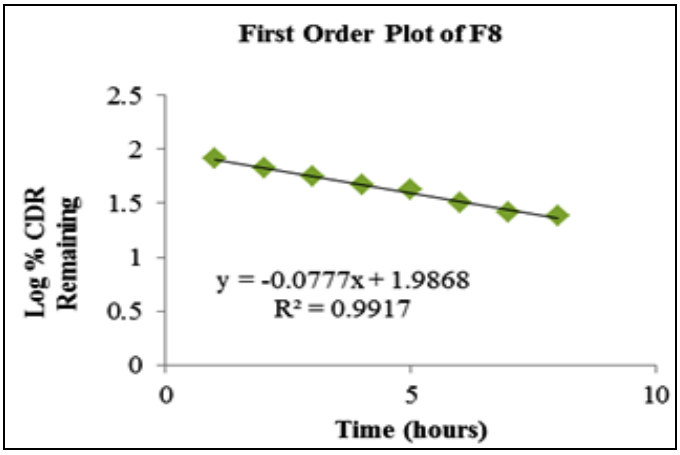

FIGURE 4: FIRST ORDER PLOT OF METRONIDAZOLE (F8) FORMULATION

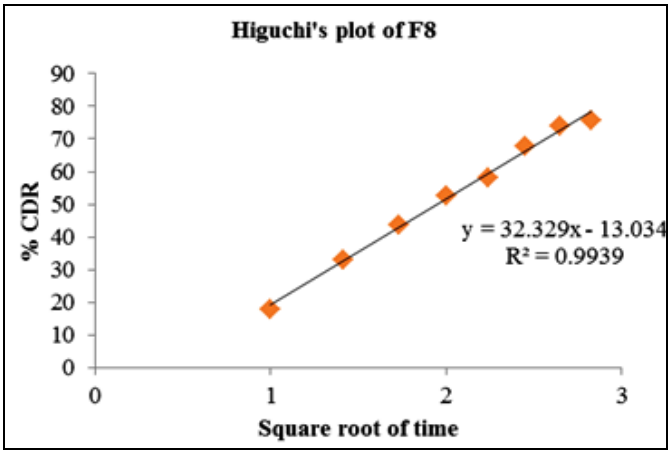

FIGURE 5: HIGUCHI PLOT OF METRONIDAZOLE (F8) FORMULATION

The most satisfactory formulations F8 was subjected to the short term stability studies by placing in varied conditions for sixty days. The *in-vitro* drug release and other formulation property of F8 showed no significant changes confirming that the formulations are stable after a period of sixty days (**table 7**).

TABLE 7: STABILITY STUDY OF FORMULATION F8

Parameters	1st month 25°C ± 2°C/ 60% RH ± 5%	2nd month 40°C ± 2°C/ 75% RH ± 5%
Physical Appearance	White, convex faced	White, convex faced
Weight Variation (mg)	484.45±4.70	484.45±4.90
Hardness (Kg/cm^2)	4.33±0.208	4.30±0.308
Drug Content (%)	101±0.03	100±0.65
Floating Lag Time (sec)	10.3±2.0	10.3±41.0
Total Floating Time (hours)	>12	>12
In-vitro Release (%)	75.65±0.011	75.63±0.041
Buoyancy on disturbing	Float	Float

CONCLUSION: This study discusses the preparation of floating tablets of Metronidazole. The effervescent-based floating drug delivery was a promising approach to achieve *in-vitro* buoyancy. The addition of polymer HPMC, Carbopol, Ethyl Cellulose and gas-generating agent sodium bicarbonate was essential to achieve *in-vitro* buoyancy. Addition of citric acid, to achieve buoyancy under the elevated pH of the stomach caused an enhancement in drug release. The polymer composition affects the drug release rate and the mechanism. Polymer swelling is crucial in determining the drug release rate and is also important for floatation. A lesser FLT and a prolonged floating duration could be achieved by varying the amount of HPMC and Carbopol and was found to be best in formulation F8 which shows a floating duration (>12hrs) having a controlled release characteristic (75.62%) in 8 hours. Good stability was observed for 2 months during stability studies. Since the formulation showed sufficient release for prolonged period, the dosing frequency can be reduced and possible incomplete absorption of the drug can be avoided.

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