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FORMULATION AND EVALUATION OF FLOATING TABLETS OF METRONIDAZOLE

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ABSTRACT

The goal of the present investigation was to prepare and evaluate floating tablets of Metronidazole which is an Amoebicide inhibits the bacteria nucleic acid synthesis, used frequently in case of Amoebiasis, vaginitis, trichomonas infections, giardiasis, treponemal infections etc. Hydroxy propyl methyl cellulose (HPMC K4M, K15M, K100M) hydrophilic polymers used as control release of the drug, polyvinylpyrrolidine (PVP K30) used as binder, Microcrystalline cellulose (MCC) used as diluents, Sodium bicarbonate were used as source of carbon dioxide in effervescent tablets, Talc were used as glidant, Magnesium stearate used as lubricant. Three processes involved in the manufacturing of Floating tablets were direct compression, Dry granulation and wet granulation. The FTIR spectra of drug and different polymers showed no shift in peak, hence no interaction. Preformulation studies of drug and excipients were carried out and showed satisfactory results. The Floating tablets were evaluated for their hardness, friability, weight variation, thickness, assay, floating lag time, Total floating time and *In-vitro* dissolution. The in-vitro release study showed controlled and maximum drug release of 97.8%, 99.8%, and 95.1% within 12 hrs from formula F4, F7 and F9 respectively. Among these three formulations F7 shows least floating lag time of 84 sec and maximum drug release. The post FTIR spectra showed no shift in peaks. From the floating lag time data, release study and stability studies formulation F7 showed satisfactory results. Hence this study showed that direct compression is the best technique to formulate floating tablets.

KEYWORDS: Metronidazole, floating tablets, Dry granulation, wet granulation, Direct Compression.

INTRODUCTION

Introduction of oral drug delivery

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first Avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration, and cost-effective manufacturing process. For many drug substances, conventional immediate-release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient.

Orally administered drugs are mainly absorbed in the small intestine (duodenum, jejunum, and ileum) and in the large intestine (colon); however, other regions, such as buccal cavity, stomach, and rectum, also can be considered potential sites for drug absorption. However, the potential for oral dosage form development is sometimes limited for therapeutic agents that are poorly absorbed in the gastrointestinal (GI) tract and unstable to various enzymes, in particular, to proteolytic enzymes, such as peptide and protein drugs. The overall process of oral delivery is frequently impaired by several physiological and pharmaceutical challenges that are associated with the inherent physicochemical nature of the drugs and/or the variability in GI conditions, such as pH, presence of food, transit times, expression of P-Glycoprotein (P-Gp) and CYP3A, as well as enzymatic activity in the alimentary canal. Manipulation of these problems and challenges is considered an important strategy for improving oral drug delivery, and requires thorough understanding and appropriate integration of physicochemical principles, GI physiology and biochemistry, polymer science, pharmacokinetics, and pharmacodynamics. Over the last three decades, much research effort has been made in this area to address various biological and technological issues. Research has opened many novel avenues for the more effective, sustained, or rate-controlled oral delivery of both existing and new therapeutic agents, including peptide and protein drugs emerging from the biotechnology arena. Furthermore, the oral route offers an attractive approach of drug targeting at the specific sites within GI tract for the treatment of certain pathological conditions, such as gastroesophageal reflux disorder, gastroduodenal ulcers,

inflammatory bowel disease, and stomach and colon cancers. Oral drug delivery systems (ODDS) can be classified into three categories: immediate-release (IR) preparations, controlled-release (CR) preparations, and targeted-release preparations.

Aim and objective of the study

The purpose of this research is to prepare gastro-retentive effervescent floating tablet consisting of polymers like HPMC K4M, HPMC K15M, HPMC K100M and the drug is Metronidazole, by direct compression method and to evaluate their gastro-retentive and controlled-release properties. The effect of various formulations and process variables on the in - *vitro* floating behavior, and *in- vitro* drug release was studied.

Hence, the objectives of the present work include:

1. Preparation of Metronidazole floating tablets using different viscosity grades of HPMC by direct compression technique.
2. Physical parameters like hardness, friability, weight variation, drug content estimation.
3. Evaluation of drug loaded floating tablet for pre and post compression parameters.
4. To develop suitable formulae and procedure for the manufacture of Metronidazole floating tablets in a relatively economical way.
5. *In vitro* evaluations of floating tablets for the release characteristics.
6. To develop an optimized formulation.

METHODOLOGY

Drug-Excipient compatibility studies

Fourier Transform Infrared spectroscopy

The Fourier transform infrared (FTIR) spectra of samples were obtained using FTIR spectrophotometer (Perkin Elmer). Pure drug, individual polymers and optimised formulations were subjected to FTIR study. About 2–3 mg of sample was mixed with dried potassium bromide of equal weight and compressed to form a KBr disk. The samples were scanned from 400 to 4000 cm^{-1}.

Evaluation of final blend

The Final blend of all formulations was evaluated for Bulk density, Tapped density, % Compressibility Index (CI), Hausner ratio and Angle of repose.

Formulation Development

preparation of sigle unit floating matrix tablets of Metronidazole

Technology Applied: Direct compression.

Accurately weighed quantities of polymer and MCC were taken in a mortar and mixed geometrically, to this required quantity of Metronidazole was added and mixed slightly with pestle. Accurately weighed quantity of Sodium bicarbonate was taken separately in a mortar and powdered with pestle. The powder is passed through sieve no 40 and mixed with the drug blend which is also passed through sieve no 40. The whole mixture was collected in a plastic bag and mixed for 3 minutes. To this Magnesium stearate was added and mixed for 5 minutes, later Talc was added and mixed for 2 minutes. The mixture equivalent to 400mg was compressed into tablets with 9.0mm capsulate punches at a hardness of 6 kg/cm^2. The composition of various formulations was given in Table.

Evaluation of single unit floating matrix tablets of Metronidazole

Weight variation, Thickness, Hardness, Friability, Floating time, Floating lag time, Drug content, In vitro drug release.

In- vitro *Drug Release Studies*

The *in vitro* drug release study was performed for the single- & multiple-unit tablets using USP Type II dissolution apparatus under the following conditions.

Dissolution test parameters

Medium	**:**	900ml of 01.N HCl
Rotation speed	**:**	50 rpm
Temperature	**:**	37±0.5ºC
Sampling Volume	**:**	5ml
Sampling Time	**:**	0.5, 1, 2, 3,4,5,6,7,8,9,10,11,12 hours

At predetermined time intervals samples (5 ml) were collected and replenished with same volume of fresh media. The drug content in the samples was estimated using UV-spectrophotometer at 277 nm.

RESULTS AND DISCUSSION

FTIR is one of the most widely used methods for the identification of the drug and checking the compatibility between drugs and excipients. metronidazole, excipients and optimized formulations were analyzed using infrared spectrophotometer.

Compatibility of metronidazole with polymers, individual excipients and physical mixture of main formulation was established by Fourier-Transform Infrared Absorption Spectral Analysis (FTIR). Any changes in the chemical composition after combining with the excipients were investigated with IR spectral analysis.

Drug polymer interaction (FTIR) Study IR spectroscopy was performed on Fourier transformed infrared spectrophotometer (840, Shimadzu, Japan). The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 min on KBr-press and the spectra were scanned in the wave number range of 4000 - 500 cm^{-1}. FTIR study was carried on metronidazole, physical mixture, and formulations.

All the samples were scanned at the resolution of 4 cm^{-1} over the wave number region 4000-400 cm^{-1} using KBr disk method. This KBr disks were prepared by taking drug and KBr in a ratio of 1:100 respectively. Then this mixture was mixed well in mortar for three to five min. A very small amount of this mixture was uniformly spread and pressed using KBr pellet press at a pressure of 20,000 psi for 1 min. The pressure was then released and pellet was placed into the pellet holder and thus scanned in the IR region.

The selected formulation shows the characteristics peak similar to that obtained in the pure metronidazole indicating that there is no incompatibility between the drug and the excipients used.

The IR spectrum of metronidazole was estimated for characteristic absorption bands in the following region of 800 to 4000 cm^{-1}.

Pre-compression properties of prepared powder blend

The physical properties like % Compressibility index (CI), Angle of repose and Hausner ratio were calculated and tabulated. The results of the physical tests of many of the blends were in the limits and comply with the standards.

Evaluation of physical parameters of single unit floating tablets of metronidazole

All the prepared formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeias limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good results of the physical tests of many of the formulations were in the limits and comply with the standards.

All the formulations were tested for floating properties like floating lag time and total floating time. The results of the tests were tabulated. All the batches showed good in vitro buoyancy. The results of the in vitro buoyancy study were shown in Table.

Tab: Formulation trails with HPMC K4M alone.

INGREDIENTS Weight in mg	FORMULATIONS			
	F1	F2	F3	F4
DRUG	100	100	100	100
HPMC K4M	50	100	150	200
HPMC K15M	-	-	-	-
HPMC K100	-	-	-	-
PVP K30	20	20	20	20
MCC	174	124	74	24
NaHCO3	48	48	48	48
Mg sterate	4	4	4	4
Talc	4	4	4	4

*****equivalent to 100 mg of Metronidazole; Total tablet weight: 400mg.

Tab: Formulation trails with HPMC K15M alone.

INGREDIENTS Weight in mg	FORMULATIONS			
	F5	F6	F7	F8
DRUG	**100**	**100**	**100**	**100**
HPMC K4M	**-**	**-**	**-**	**-**
HPMC K15M	**50**	**100**	**150**	**200**
HPMC K100	**-**	**-**	**-**	**-**
PVP K30	**20**	**20**	**20**	**20**
MCC	**174**	**124**	**74**	**24**
NaHCO3	**48**	**48**	**48**	**48**
Mg stearate	**4**	**4**	**4**	**4**
Talc	**4**	**4**	**4**	**4**

*****equivalent to 100 mg of Metronidazole; Total tablet weight: 400mg.

Tab: Formulation Trails With HPMC K 100M alone.

INGREDIENTS Weights in mg	FORMULATIONS F9	F10	F11	F12
DRUG	100	100	100	100
HPMC K4M	-	-	-	-
HPMC K15M	-	-	-	-
HPMC K100	50	100	150	200
PVP K30	20	20	20	20
MCC	174	124	74	24
NAHCO3	48	48	48	48
Mg stearate	4	4	4	4
Talc	4	4	4	4

*equivalent to 100 mg of Metronidazole; Total tablet weight: 400mg.

Tab: Absorbance of Metronidazole against different concentrations at λ_{max} 277 nm.

S.NO.	Concentrations(µg/ml)	Absorbance
1	4	0.143
2	8	0.296
3	12	0.431
4	16	0.632
5	20	0.772
6	24	0.964

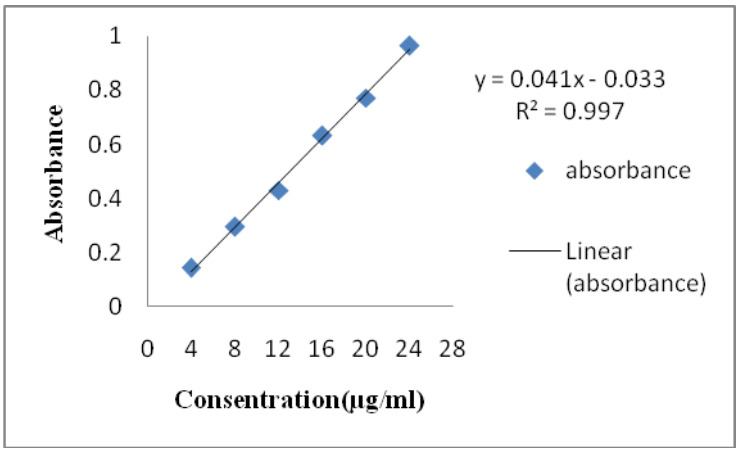
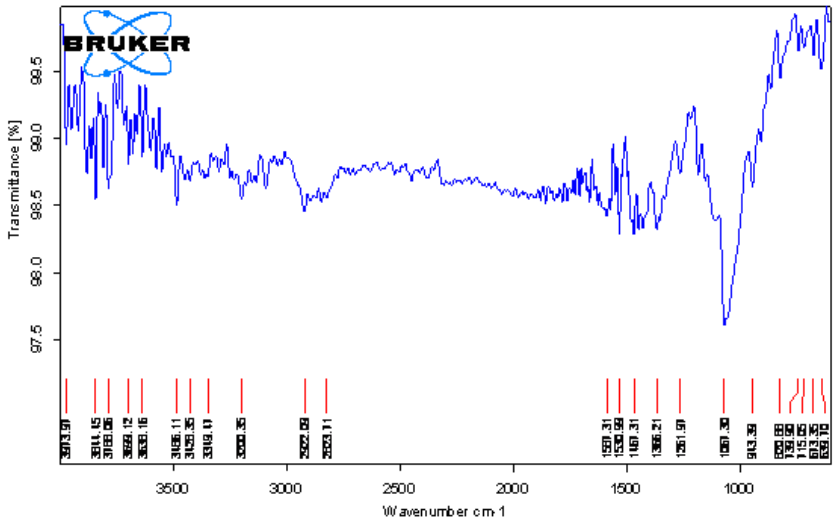


Fig: standard graph of Metronidazole6.2 Identification of Metronidazole by FTIR studies (drug excipient compatability).

Tab: Characteristic absorption band frequency of Metronidazole.

S.No	Types of Vibrations	Group frequency in wave number (cm^{-1})
1	C-H bending	1351
2	C-N vibrations	1261
3	C=N stretching	1587
4	C=C stretching(aromatic)	1531
5	O-H stretching	3547



Fig, FTIR Graph of pure Drug of Metronidazole.

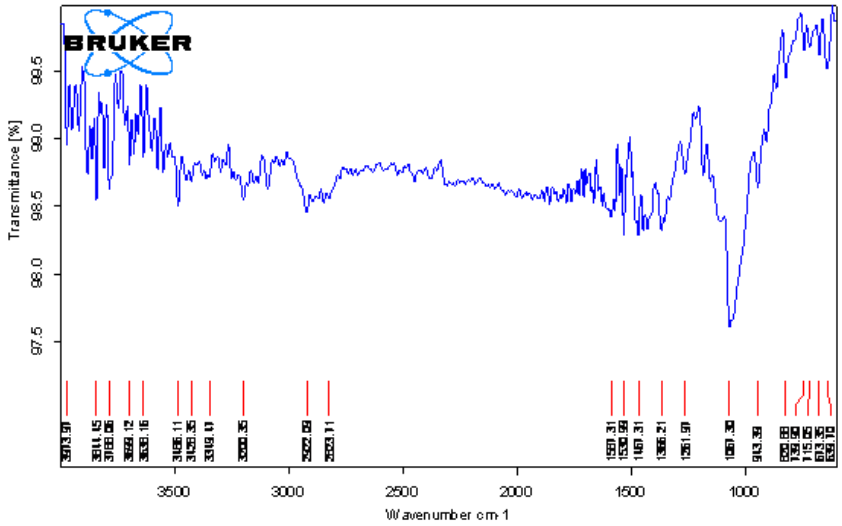


Fig. FTIR Graph of Physical mixture (F7).

Tab: Physical properties of powder blends of single unit tablet formulations.

Formulations	% CI	Angle of repose	Hausner ratio
F1	15.7	29.4^{o}	1.18
F2	12.4	28.5^{o}	1.14
F3	11.2	29.4^{o}	1.13
F4	15.7	29.4^{o}	1.02
F5	12.4	28.5^{o}	1.14
F6	11.2	29.4^{o}	1.13
F7	13.6	28.4^{o}	1.02
F8	12.5	26.9^{o}	1.16
F9	14.6	27.5^{o}	1.15
F10	12.6	27.1^{o}	1.17
F11	13.6	28.4^{o}	1.02
F12	14.6	27.5^{o}	1.15

Tab: Physical parameters of single unit floating matrix tablets of Metronidazole.

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F1	400.38±3.84	6.8±0.5	6.84±0.05	0.22	99.65
F2	399.52±2.87	5.9±0.2	6.76±0.06	0.37	98.65
F3	402.23±2.73	6.8±0.5	6.86±0.03	0.23	98.45
F4	398.6±2.13	6.8±0.4	6.76±0.04	0.29	99.64
F5	400.19±3.48	6.8±0.5	6.63±0.06	0.23	98.45
F6	397.2±1.19	6.8 ±0.5	6.68.005	0.37	98.12
F7	399.71±2.3	5.9±0.2	6.65 ±0.06	0.29	99.64
F8	399.46±2.27	6.5±0.3	6.55±0.25	0.23	99.72
F9	400.67±3.84	6.8±0.5	6.506±0.4	0.29	98.45
F10	398.38±3.84	6.7±0.2	6.62±0.07	0.37	99.64
F11	398.6±2.13	6.8±0.4	6.76±0.04	0.29	99.64
F12	400.19±3.48	6.8±0.5	6.63±0.06	0.23	98.45

Tab: Floating properties of single unit matrix tablets.

Formulation code	Floating Lag time (sec)	Total floating time (hrs)
F1	88	>12
F2	97	>12
F3	102	>12
F4	99	>12
F5	96	>12
F6	87	>12
F7	84	>12
F8	86	>12
F9	94	>12
F10	81	>12
F11	84	>12
F12	89	>12

Initial **At 84 secs (F7)** **At 12 hrs**

Fig. Floting Behaviour of Tablets at initial and sustained time interval.

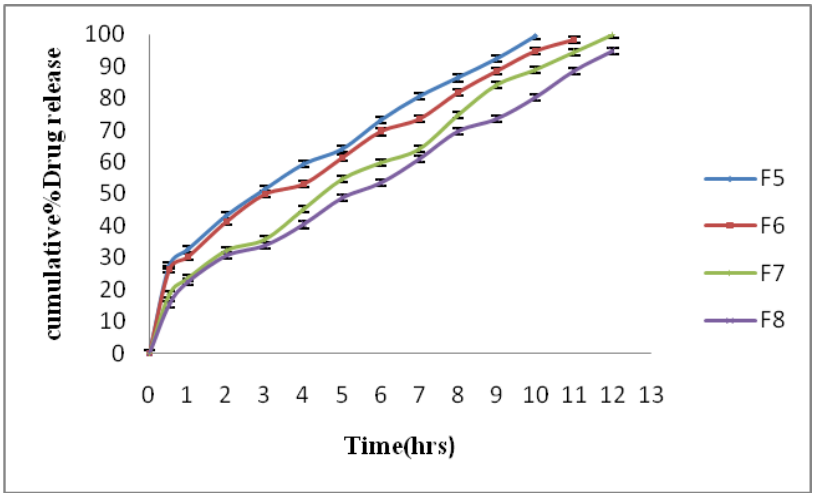


Fig. Dissolution profile of the formulations F5, F6, F7 and F8.

Dissolution profile of the formulations F1, F2 and F3, F4

Formulation F1 to F4 observed that that the polymer HPMC K4M has sustaining effect on the release of drug from the floating matrix tablet. The percent of drug release from formulations F1, F2, F3 and F4 was 105.6, 102.6,100 and 97.8 in 8, 10, 10 and 12 hr respectively.

In Formulation F1 Drug and HPMC K4M were taken in the ratio of 1:0.5.In F 2 formulation the drug and HPMC K4 were taken in the ratio 1:1.In F3 formulation the drug and HPMC K4 were taken in the ratio of1:1.5.In F4 formulation the drug and HPMC K4M were in the ratio of 1:2.

Among the four formulations the F4 formulation was shows high sustained release of drug within 12 hrs and observed that when drug and polymer ratio will be increased to improve the more retention of drug release.

The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. All these four formulations floated for 12 h.

Formulation F4 was considered as best formulation among all the four formulations as it showed good buoyancy properties (floating lag time: 101sec & floating time >12 hrs) and sustained the drug release for desired period of time (12 hrs).

From the above figure it is evident that the polymer HPMC K15M has sustaining effect on the release of drug from the floating matrix tablet. The percent of drug release from

formulations F5, F6, F7 and F8 was 99.68, 98.4, 99.8 and 94.6 in 10,11,12 and12 h respectively.

In Formulation F5 Drug and HPMC K15M were taken in the ratio of 1:0.5.In F6 formulation the drug and HPMC K15M were taken in the ratio 1:1.In F7 formulation the drug and HPMC K15 were taken in the ratio of1:1.5.In F8 formulation the drug and HPMC K15M were in the ratio of 1:2.

Among the four formulations the F7 formulation was shows high sustained release of drug within 12 hrs and observed that when drug and polymer ratio will be increased to improve the more retention of drug release.

The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. All these four formulations floated for 12 h.

Formulation F7 was considered as best formulation among all the four formulations as it showed good buoyancy properties (floating lag time: 84sec & floating time >12 hrs) and sustained the drug release for desired period of time >12 hrs).

Dissolution profile of the formulations F9, F10, F11 and F12

From the above figure it is evident that the polymer HPMC K100M has sustaining effect on the release of drug from the floating matrix tablet. The percent of drug release from formulations F9, F10, F11 and F12 was 95.1, 90.13, 85.23 and 78.8, in 12 h respectively. In Formulation F9 Drug and HPMC K100M were taken in the ratio of 1:0.5.In F10 formulation the drug and HPMC K100M were taken in the ratio 1:1.In F11 formulation the drug and HPMC K100 were taken in the ratio of1:1.5.In F12 formulation the drug and HPMC K100M were in the ratio of 1:2.

Among the four formulations the F9 formulation was shows high sustained release of drug within 12 hrs and observed that when drug and polymer ratio will be increased to improve the more retention of drug release. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. All these four formulations floated for 12 h. The cumulative percent drug release from various formulations was represented in tables 19. Formulation F9 was considered as best formulation among all the four formulations as it showed good buoyancy properties (floating lag time: 94sec & floating time >12 hrs) and sustained the drug release for desired period of time >12 hrs).

From the above all observations and results, formulation F4,F7,F9 was found to be an optimized one with a least floating lag time (99,84,94 sec), total floating time of >12hrs, and a maximum drug release of 97.8,99.8,95.1% in 12 hrs interval.

From the above three formulations F4,F7 and F9.The F7 was found to be an optimized one with a least floating lag time (,84 sec), total floating time of >12hrs, and a maximum drug release of 99.8, % in 12 hrs interval.

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