International Journal of Farmacia (IJF)
IJF |Vol.10 | Issue 4 | Oct - Dec -2024
www.ijfjournal.com
DOI : https://doi.org/10.61096/ijf.v10.iss4.2024.208-216
ISSN: 2231-3656

Research

Formulation and evaluation of gastro retentive floating tablets of metronidazole

Vipparthi Nithya Rani*[1], Dr. T. K. V. Kesava Rao [1], B. Deekshi Gladiola [1]

[1]*Department of Pharmaceutics, Pydah College of Pharmacy Patavala, Andhra University, Kakinada, Andhra Pradesh, India*

*Author for Correspondence: Vipparthi Nithya Rani
Email: nityalahari143@gmail.com

Published on: 19 Nov 2024

Published by:
DrSriram Publications

Abstract

The purpose of this work was to develop gastroretentive floating tablets of Metronidazole. Floating tablets were prepared by direct compression method using gas generating agents such as sodium bicarbonate and citric acid and polymers like HPMC K 100,Eudragit and Ethyl Cellulose. Formulations tried for different ratios of drug and polymers to get desired release profile. Prepared tablets M1- M9 were evaluated in term of precompression and post compression parameters. Metronidazole floating tablets were prepared direct compression method were found to be good with out chipping , capping and sticking. The drug content was uniform in all the tablet formulation indicating uniform distribution of drug within the matrices. All prepared tablets showed satisfactory floating lag time and total floating time found to be 12hrs. Among all formulations M5 showed the drug release most sustained manner and showed 99.56 % of in vitro drug release at end of 12hrs and selected as the best formulation. The release Kinetics was done for optimized formulation.

Keywords: Metronidazole Floating tablets HPMC K 100,Eudragit and Ethyl Cellulose

INTRODUCTION

Drug administration through the oral route is considered as the most appropriate, feasible, and the most convenient mode as far as the delivery of drugs is concerned, with numerous benefits such as safety, self-administration, cost economical, non-invasive, and improved patient compliance [1]. However, the oral route is sometimes associated with different issues that are major obstacles, e.g., patterns of gastric emptying, minimum drug residence, failure of drug targeting in specific area, and negligible drug release.[2]

Metronidazole has bactericidal effect and is efficacious to kill microorganisms, either facultative anaerobes or obligate anaerobes. It sits right in the cusp among medications selected for the management of Helicobacter pylori, i.e., it constitutes an important member of triple regimen therapy as an active adjunct . Metronidazole is a class 1 type of drug in the biopharmaceutical classification system. It undergoes absorption in

the stomach and possesses pH-independent effects . Conventionally, metronidazole exhibits a rapid and almost complete absorption when given orally .[3]

Helicobacter is a Gram-negative, facultative anaerobe which produces gastric mucosal irritation leading to chronic inflammation. Different people may show different episodes of inflammatory lesions which vary in intensity appreciably. This microbe constitutes about 50% of the world population epidemiologically, with over 90% of infected individuals being residents of developing countries .[4]

Floating drug delivery systems have paramount applications to achieve stomach specific action or local targeting of drug in the stomach. Such systems are divided into two sub-categories, i.e., effervescent and non-effervescent systems. Effervescent floating systems are made up of matrix of polymeric material of hydrophobic, expandable or polysaccharide nature with additional sodium bicarbonate or other gas-generating systems. Carbon dioxide generation due to reaction with the gastric acidic contents is a major determinant of floating behaviour of such systems. Non-effervescent systems, on the other hand, are chiefly composed of hydrophilic colloids that exhibit swelling upon reaction with the gastric contents, resulting in lowering of the specific density that allows upward movement of the fluid producing variations in the absence of gas production The suggested criteria for drugs to be formulated as floating drug delivery system include local action of drugs in stomach , drugs showing absorption window in stomach or upper part of the intestine , and candidates exhibiting poor solubility or instable nature in intestinal fluid . Floating drug delivery systems are peculiar to induce prolonged drug buoyancy in the stomach without having any specific effect in gastric emptying time alteration[5]. This results into desired retarded drug release rate from the system with prolonged gastric retention time, thus provides good control of drug plasma concentration variations. However, one major drawback or limitation of such systems is the provision of sufficient fluid saturation of stomach in order to keep the dosage form buoyant. For this issue, bioadhesive polymers are incorporated, e.g., carbopol, HPMC, dextran, tragacanth, chitosan, sodium alginate, polyethylene glycol, polyacrylic acid, and polylactic acid. These polymers stick to gastric mucosal lining due to their natural, peculiar behaviour. Their implication in dosage form development is responsible to cause improved bioavailability of drugs having an absorption window in the upper part of the GIT; as a result, frequency of drug administration is also reduced. Mucoadhesive delivery systems are designed to solve the issue of GIT transit time reduction. Such polymers are effective enough to enhance the dosage form adhesiveness owing to their bioadhesive potential. These polymers have beautified the literature consisting of both natural as well as synthetic mucoadhesive polymers .[6]

The current study was undertaken to develop and optimize the metronidazole based osmotically controlled bioadhesive floating drug delivery system by incorporating various muco-adhesive polymers based on buoyancy and bio-adhesion concepts. The aided benefits would be mirrored to offer *H. pylori* induced peptic ulcer healing along with improved patient compliance owing to a decreased administration frequency.[7]

The major disadvantage of the floating system is a requirement of a sufficiently high level of fluids in the stomach for the system to float. The floating DDS are effective only when the fluid level in the stomach is sufficiently high. Nonetheless, as the stomach empties dosage form reaches to the pylorus, the buoyancy of the dosage form may be impeded. Thus, bio-adhesive DDS are suffering from the effect of mucous turnover. The mucous secreted by the mucosa lining of stomach wall may detach the dosage form from the wall of the stomach which get emptied from the stomach along with its contents. This limitation can be over come by making the floating system eventually adhere to the mucous lining of the stomach wall Thus, FBDDS offers the advantage of increased gastric residence time of drugs over normal floating DDS. The FBDDS can be formulated by incorporating bio-adhesive polymers to normal floating DDS. Floating bio-adhesive systems can persist in the stomach for several hours and hence considerably extend the gastric residence time of therapeutics. Due to the extended gastric retention the delivery system enhances bioavailability. It has applications also for delivery of drug to the upper gastric tract. Floating and bio-adhesive delivery scar fold system helps

However, the United States Pharmacopoeia (USP) has accepted these dose forms as ODTs notwithstanding all the aforementioned terms. The term Oro dispersible tablets, which quickly dissolve in the tongue before being swallowed, is used in the European Pharmacopoeia. ODTs are solid dosage forms that include a medical substance or active substances that dissolve quickly in a matter of seconds when placed on the tongue, according to the United States Food and Drug Administration. Some drugs are absorbed from the pharynx, mouth, and oesophagus as the saliva travels down into the stomach in these cases, the drug's bioavailability is significantly higher than that observed with conventional tablets dosage. Oro dispersible tablets are those that dissolve instantly when placed on the tongue.Will eventually see a decline in their physiological and physical capacities. Fast dissolving drug delivery systems were thought of as a way to give patients access to traditional methods of taking their medications. Saliva in the mouth has the ability to dissolve, disintegrate, or suspend fast dissolving dosage forms.

When placed on the tongue, these Oro-dispersible tablets instantly dissolve, releasing the medication to dissolve or scatter in the saliva. Fast-dissolving tablets are beneficial for patients with conditions such as paediatric, geriatric, bedridden, or mental disabilities who may struggle to swallow conventional tablets or capsules, which can result in ineffective therapy, as well as for those who lead an active lifestyle and experience

persistent nausea, sudden episodes of allergic attacks, or coughing. When oral action in the mouth is desired, such as for local anaesthesia for toothaches, oral ulcers, cold sores, or teething, or for people who are unable to swallow whole sustained action, oral-dissolving tablets are also appropriate.

MATERIALS

Metronidazole-Procured From Dr. Reddy's Laboratories Ltd., New Delhi. Provided by SURA LABS, Dilsukhnagar, Hyderabad, HPMC K 100-Merck Specialities Pvt Ltd, Mumbai, India, Eudragit-Merck Specialities Pvt Ltd, Mumbai, India, Ethyl Cellulose-Merck Specialities Pvt Ltd, Mumbai, India, Citric acid-Merck Specialities Pvt Ltd, Mumbai, India, Sodium bicarbonate-Merck Specialities Pvt Ltd, Mumbai, India, Talc-Merck Specialities Pvt Ltd, Mumbai, India, Mg Stearate-Merck Specialities Pvt Ltd, Mumbai, India, Lactose-Merck Specialities Pvt Ltd, Mumbai, India.

METHODOLOGY

Analytical method development
Determination of absorption maxima
A solution containing the concentration 10 µg/ mL drug was prepared in 0.1N HCL UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Preparation calibration curve
10mg Metronidazole pure drug was dissolved in 10ml of methanol (stock solution1) from stock solution1. 1ml of solution was taken and made up with10ml of 0.1N HCL (100µg/ml). From this 1ml was taken and made up with 10 ml of 0.1N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 10, 20, 30, 40, 50µg /ml of per ml of solution. The absorbance of the above dilutions was measured at 340nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis.

Drug – Excipient compatibility studies
Fourier Transform Infrared (FTIR) spectroscopy
The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany(Alpha T).The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 550 cm^{-1}.

Preformulation parameters
The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose
The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:
$\tan \theta = h / r$ $\tan \theta$ = Angle of repose
h = Height of the cone , r = Radius of the cone base

Bulk density
Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:
Bulk Density = M / V_o
Where, M = weight of sample
V_o = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

Tap = M / V
Where, Tap= Tapped Density
M = Weight of sample
V= Tapped volume of powder

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\text{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100$$

Where, b = Bulk Density
Tap = Tapped Density

Formulation development of floating Tablets

For optimization of sodium bicarbonate concentration, granules were prepared by direct compression method.

Procedure for direct compression method:

1) Drug and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Optimisation of Sodium bicarbonate

Sodium bicarbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of sodium bicarbonate were employed; floating lag time and floating duration were observed. Based on the concentration of sodium bicarbonate was finalized
and preceded for further formulations.

Table 1: Optimisation sodium bicarbonate concentration

Ingredients	DO1	DO2	DO3
Metronidazole	100	100	100
Eudragit	25	50	75
Citric acid	15	15	15
Sodium bicarbonate	10	10	10
Talc	5	5	5
Mg Stearate	5	5	5
Lactose	240	215	190
Total Weight	400	400	400

All the quantities were in mg.

Based on the floating lag time and floating duration the concentration of sodium bicarbonate was optimised.

Formulation of tablets

Table 2: Formulation composition for Floating tablets

Ingrediants	M1	M2	M3	M4	M5	M6	M7	M8	M9
Metronidazole	100	100	100	100	100	100	100	100	100
HPMC K 100	25	50	75	-	-	-	-	-	-
Eudragit	-	-	-	25	50	75	-	-	-
Ethyl Cellulose	-	-	-	-	-	-	25	50	75
Citric acid	15	15	15	15	15	15	15	15	15
Sodium bicarbonate	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Mg Stearate	5	5	5	5	5	5	5	5	5
Lactose	240	215	190	240	215	190	240	215	190
Total Weight	400	400	400	400	400	400	400	400	400

All the quantities were in mg

RESULTS AND DISCUSSION

Analytical Method

Determination of absorption maxima

The standard curve is based on the spectrophotometry. The maximum absorption was observed at 340nm.

calibration curve

Graphs of Metronidazole was taken in 0.1N HCL (pH 1.2).

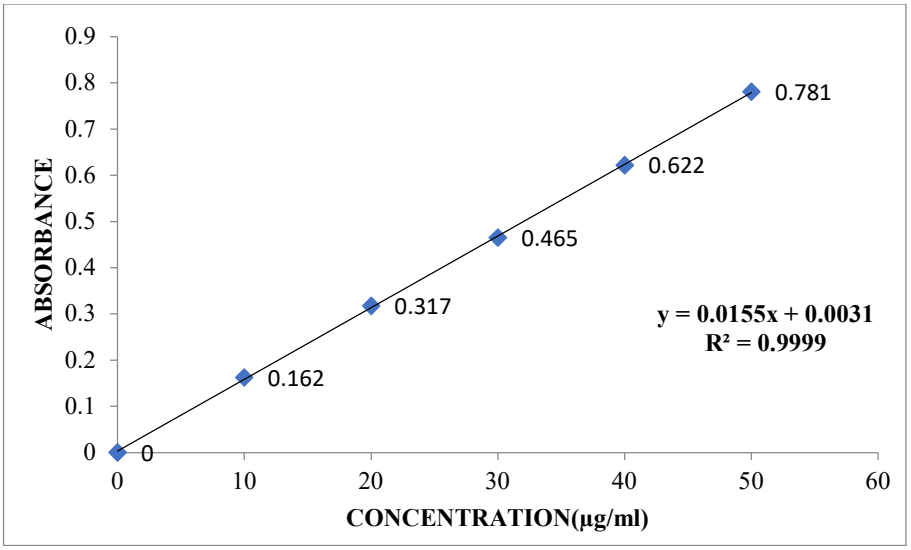

Fig 1: Standard graph of Metronidazole in 0.1N HCL

Standard graph of Metronidazole was plotted as per the procedure in experimental method and its linearity is shown in Table and Fig. The standard graph of Rosiglitazone Malate showed good linearity with R^2 of 0.999, which indicates that it obeys "Beer- Lamberts" law.

Drug – Excipient compatability studies
Fourier Transform-Infrared Spectroscopy

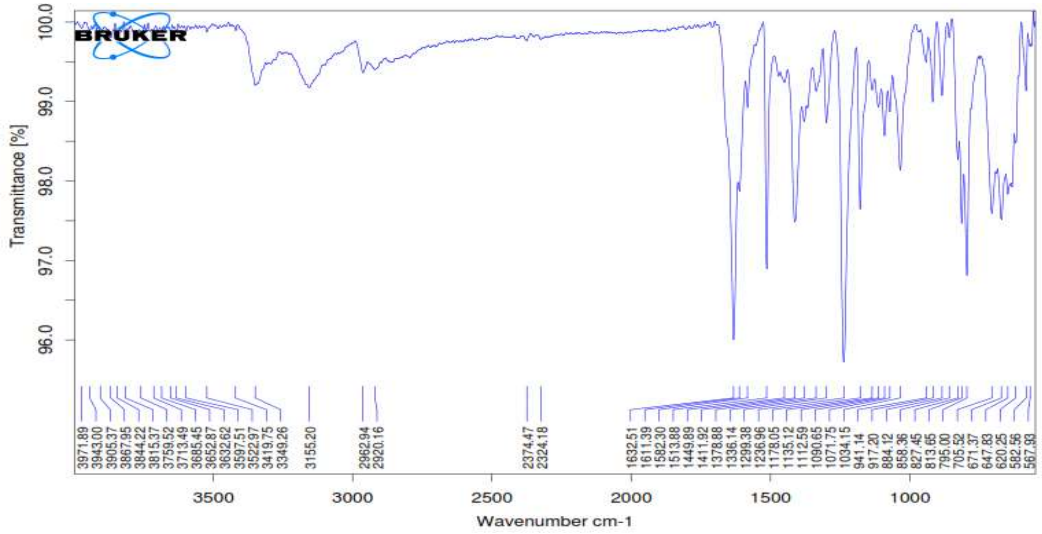

Fig 2: FTIR Spectrum of pure drug

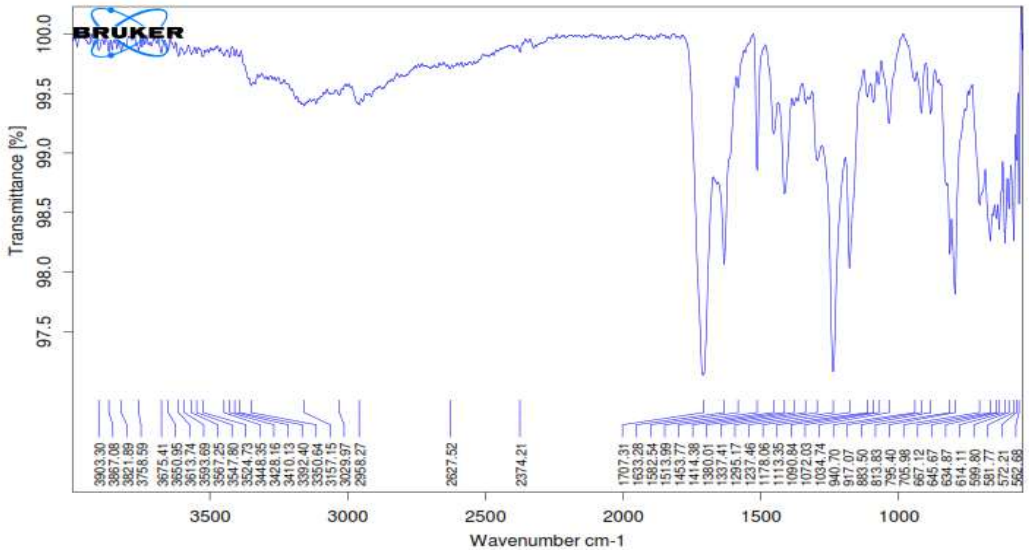

Fig 3: FTIR Spectrum of optimized formulation

From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence they were compatible.

Preformulation parameters of powder blend

Table 3: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
M1	29. 2	0.326	0.377	1.15	13.63
M2	20.14	0.355	0.394	1.11	10.12
M3	28 .1	0.391	0.451	1.15	13.33
M4	24.10	0.409	0.425	1.04	10.07

M5	23.17	0.365	0.429	1.19	14.99
M6	24.19	0.245	0.269	1.09	8.80
M7	28.5	0.361	0.423	1.16	14.82
M8	25.11	0.375	0.441	1.17	14.63
M9	22.47	0.404	0.455	1.12	11.10

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.245 to 0.409 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.269 to 0.455 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 1.04 to 1.19 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 8.80 to 14.99 indicating the powder has good flow properties.

Optimization of sodium bicarbonate concentration

Three formulations were prepared with varying concentrations of sodium bicarbonate by direct compression method and three more formulations were prepared by Direct Compression method to compare the floating buoyancy. The formulation containing sodium bicarbonate in 10 mg, Citric Acid in 15 mg concentration showed less floating lag time in Direct Compression method and the tablet was in floating condition for more 12 hours.

Quality Control Parameters For tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, Drug content and drug release studies were performed for floating tablets.

Table 4: *In vitro* quality control parameters

Formulation codes	Average Weight (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Flaoting lag time (min)	Total Floating Time (Hrs)
M1	399	4.12	0.47	2.36	99	3.12	12
M2	401	4.56	0.42	2.12	98	3.48	12
M3	398	4.32	0.38	2.22	97	4.52	12
M4	397	4.41	0.25	2.28	99	4.36	12
M5	400	4.38	0.22	2.08	99	4.28	12
M6	402	4.25	0.39	2.31	98	4.36	12
M7	397	4.39	0.51	2.39	98	3.62	12
M8	399	4.42	0.35	2.35	97	3.29	12
M9	398	4.55	0.43	2.29	99	3.31	12

All the parameters such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

***In Vitro* Drug Release Studies**

Table 5: Dissolution data of Floating Tablets (M1- M3)

TIME	CUMULATIVE PERCENT DRUG RELEASED								
(hr)	M1	M2	M3	M4	M5	M6	M7	M8	M9
0	0	0	0	0	0	0	0	0	0
0.5	10.12	14.88	18.52	12.02	16.82	13.19	11.56	17.25	14.52
1	15.08	19.72	23.66	17.14	24.65	18.78	16.17	25.66	22.83
2	21.31	25.38	29.94	23.91	32.85	29.23	22.75	31.86	28.98
3	28.22	32.21	36.89	28.62	41.45	35.13	27.36	38.94	35.17
4	33.85	38.66	42.55	31.92	48.26	42.28	31.13	42.29	39.55
5	39.96	43.92	47.23	36.34	56.88	47.37	39.65	46.33	44.09
6	46.52	49.85	55.16	44.74	67.86	53.28	42.51	57.85	51.93
7	51.37	53.49	64.81	49.48	72.18	61.32	47.66	62.38	56.98
8	57.23	62.35	69.98	56.95	79.32	66.74	52.69	73.07	68.23
9	63.18	67.22	75.57	64.27	85.54	73.97	61.99	79.21	75.18

10	68.39	73.62	84.42	72.97	92.85	82.03	69.41	83.26	81.61
11	75.72	82.76	91.26	81.38	95.10	91.39	78.06	91.63	87.28
12	83.32	89.29	95.63	88.75	99.56	96.29	85.22	97.52	94.84

Formulations prepared with HPMC K 100 M1 to M3 Formulations Does not retard the drug release upto 12hrs. These formulations also did not take into consideration. In that M3 Formulation Showed better drug release (95.63 %) in 12 hours. Formulations prepared with Eudragit M4 to M6 Formulations Does not retard the drug release upto 12hrs. These formulations also did not take into consideration. In that M5 Formulation Showed better drug release (99.56 %) in 12 hours. Formulations prepared with Ethyl Cellulose M7to M9 Formulations Does not retard the drug release upto 12hrs. These formulations also did not take into consideration. In that M8 Formulation Showed better drug release (97.52 %) in 12 hours. Among all formulations M5 formulation was considered as optimised formulation. It was shown 99.65% drug release at 12hrs.

Application of Release Rate Kinetics to Dissolution Data for optimised formulation

Table 6: Application kinetics for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	**0**	0			2.000				100	4.642	4.642	0.000
16.82	0.5	0.707	1.226	-0.301	1.920	33.640	0.0595	-0.774	83.18	4.642	4.365	0.276
24.65	1	1.000	1.392	0.000	1.877	24.650	0.0406	-0.608	75.35	4.642	4.224	0.418
32.85	2	1.414	1.517	0.301	1.827	16.425	0.0304	-0.483	67.15	4.642	4.065	0.577
41.45	3	1.732	1.618	0.477	1.768	13.817	0.0241	-0.382	58.55	4.642	3.883	0.759
48.26	4	2.000	1.684	0.602	1.714	12.065	0.0207	-0.316	51.74	4.642	3.726	0.915
56.88	5	2.236	1.755	0.699	1.635	11.376	0.0176	-0.245	43.12	4.642	3.507	1.135
67.86	6	2.449	1.832	0.778	1.507	11.310	0.0147	-0.168	32.14	4.642	3.179	1.462
72.18	7	2.646	1.858	0.845	1.444	10.311	0.0139	-0.142	27.82	4.642	3.030	1.612
79.32	8	2.828	1.899	0.903	1.316	9.915	0.0126	-0.101	20.68	4.642	2.745	1.897
85.54	9	3.000	1.932	0.954	1.160	9.504	0.0117	-0.068	14.46	4.642	2.436	2.205
92.85	10	3.162	1.968	1.000	0.854	9.285	0.0108	-0.032	7.15	4.642	1.926	2.715
95.1	11	3.317	1.978	1.041	0.690	8.645	0.0105	-0.022	4.9	4.642	1.698	2.943
99.56	12	3.464	1.998	1.079	-0.357	8.297	0.0100	-0.002	0.44	4.642	0.761	3.881

CONCLUSION

From the above studies it is concluded that gastro retentive floating tablets of Metronidazole can be formulated using gas generating agents such as sodium bicarbonate and citric acid and polymers like HPMC K 100, Eudragit and Ethyl Cellulose with respect to drug in formulation affected the water uptake efficiency, in vitro buoyancy and in vitro drug release rate of formulations. As concentrations of polymers was increased in formulations the water uptake efficiency and total floating time increased and also the drug release in more sustained way The formulation have medium concentration of 50 mg of Eudragit showed maximum drug release of 99.56% for 12hrs.

REFERENCES

1. Gambhire, M.N.; Ambade, K.W.; Kurmi, S.D.; Kadam, V.J.; Jadhav, K.R. Development and in vitro evaluation of an oral floating matrix tablet formulation of diltiazem hydrochloride. AAPS PharmSciTech 2007, 8, 313. [CrossRef] [PubMed]
2. Ugurlu, T.; Karaçicek, U.; Rayaman, E. Optimization and evaluation of clarithromycin floating tablets using experimental mixture ˘design. Acta Pol. Pharm. Drug Res. 2014, 71, 311–321.
3. Emara, L.H.; Abdou, A.R.; El-Ashmawy, A.A.; Mursi, N.M. Preparation and evaluation of metronidazole sustained release floating tablets. Int. J. Pharm. Pharm. Sci. 2014, 6, 198–204.
4. Prasanthi, C.H.; Prasanthi, N.L.; Manikiran, S.S.; Rao, N.R. Focus on current trends in the treatment of helicobacter pylori infection: An update. Int. J. Pharm. Sci. Rev. Res. 2011, 9, 9.
5. Youssef, N.A.H.A.; Kassem, A.A.; El-Massik, M.A.E.; Boraie, N.A. Development of gastroretentive metronidazole floating raft system for targeting Helicobacter pylori. Int. J. Pharm. 2015, 486, 297–305.

6. Krishnaiah, Y.S.R.; Raju, P.V.; Kumar, B.D.; Jayaram, B.; Rama, B.; Raju, V.; Bhaskar, P. Pharmacokinetic evaluation of guar gum-based colon-targeted oral drug delivery systems of metronidazole in healthy volunteers. Eur. J. Drug Metab. Pharmacokinet. 2003, 28, 287–294. [CrossRef]
7. Arora, S.; Budhiraja, R. Effect of polymers and excipients on the release kinetics, bioadhesion, and floatability of metronidazole tablet. Asian J. Pharm. 2011, 5, 215.
8. Balata Design and Evaluation of Gastroretentive Floating Tablet of Nizatidine: A Trial to Improve Its Efficacy. Int J Pharm PharmSci, 6(5): 2014: 423-429.
9. Basak SC, Rahman J, Ramalingam M. Design and in vitro testing of a floatable gastroretentive tablet of metformin hydrochloride. Pharmazie, 2007; 62(2): 145–148. [PubMed].
10. Benet LZ, Cummins C.L, Ad. Drug. Del. Rev, 2001; 50(Supplement 1): S3-S11.
11. Bultman JM; Multiple Compaction of Microcrystalline cellulose in Roller compactor. Eur. J. pharm. Biopharm., 2002; 54: 59-64.
12. Chain Y.W. In encyclopedia of pharmaceutical technology, J. Swarbrick and J.C. Boylan, Ed; Marcel Dekker, New York, 1990; 280-313.
13. Chien Y.W. In Novel Drug delivery Systems, Y.W. chien, Eds. Marcel Dekker ,New York, 1992; 139-196.
14. Chungi V.S, L.W Dittert, and R.B. Smith, Int.J.Pharm, 1979; 4: 27-28.
15. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm, 2010; 67(3): 217–223. [PubMed].