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Research article

Design and evaluation of floating gastro retentive tablets of fixed dose combination of ciprofloxacin and metronidazole

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Abstract

Gastro-retentive drug delivery systems offer the advantage in prolonging the gastric emptying time for drugs having a narrow absorption window in the gastrointestinal tract (GIT) resulting in poor absorption. Ciprofloxacin and metronidazole both have a short half-life resulting in increase in dosage regimen. Metronidazole is a nitro imidazole antibiotic and is ineffective on aerobic bacteria. Ciprofloxacin on the other hand is a broad spectrum fluoroquinolone antibacterial agent, the combination of both, is active against a broad spectrum of obligate anaerobic bacteria. The purpose of this study was to design, optimize and evaluate gastro- retentive floating tablet of Metronidazole and Ciprofloxacin hydrochloride combination to increase the residence time in the stomach and thereby giving prolong action of each drug individually. Screening of the various grades of HPMC polymer for optimization of matrix forming polymer, followed by optimization of the ratio of the polymer, and the quantity of the swelling agent guar gum. The micromeritic properties, tablet evaluation properties, floating behavior and drug release studies for ciprofloxacin and metronidazole were conducted as per guidelines and compared to the marketed product dissolution profile. The tablets showed acceptable physicochemical properties. The optimization showed that HPMC E10M and HPMC K100M in the ratio of 1:2 were the best suited polymers for the matrix whereas guar gum at 3.3 % was the ideal concentration for the desired floating and drug release profile. The optimized batch was subjected to stability studies at 40 °C/75% RH for 3 months and depicted a stable formulation.

Key words: Ciprofloxacin, metronidazole, gastro-retentive drug delivery systems, matrix forming polymer.

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1. Introduction

Drugs that have narrow absorption window in the gastro intestinal tract (GIT) will have poor absorption (1, 2). For these drugs, gastro-retentive drug delivery systems (GRDDSs) have been developed. GRDDSs help in maintenance of constant therapeutic levels for prolonged periods and produce therapeutic efficacy and thereby reduce the total dose of administration. This is the main reason why the oral sustained or controlled release dosage forms have come widely into application. Oral sustained or controlled drug delivery systems provide a release profile predominantly controlled by the design of the system itself (3). The major problem in achieving good absorption is the physiological variability such as gastrointestinal transit and gastric retention time in addition to other factors. The later plays a dominating role in the overall transit of the dosage form (4). Another problem associated with the performance of oral controlled release

systems is that even though the slow release can be achieved, the drug released after being absorbed at the target site (upper position of small intestine) is not fully utilized mostly because the Gastric Residence Time (GRT) of the delivery system is less than 12 hours. Hence, a prolonged gastric retention should not only control the time but also the space in the stomach by maintaining the delivery system placed at a steady site and thereby properly deliver the drug. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time(5). The desirable characters of prolonged gastric retention are that it improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment (6). GRDDSs include various drug delivery systems such as floating drug delivery systems, also known as hydro-dynamically balanced systems, swelling and expanding systems, polymeric bio-adhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices (7, 8). Ciprofloxacin is a broad-spectrum fluoroquinolone antibacterial agent that has most of its absorption from the stomach and the proximal part of the small intestine (9). This floating sustained release system is chosen for this drug primarily for this reason. It is freely soluble in water; its oral bioavailability is about 70% and reaches the peak plasma concentration to 2.5µg/ml in 1 to 2 h after administration of 500 mg equivalent but has a short half-life of 4 hrs. However, it shows a decrease in the absorption from the lower GIT. The drug is mostly used for indications like uncomplicated urinary tract infections (UTIs) (10,11) and for bone and joint infections, infectious diarrhoea, lower respiratory tract infections, hospital-acquired infections and meningococcal prophylaxis (12) Metronidazole, the prototype nitro-imidazole antimicrobial, was originally introduced to treat Trichomonas vaginalis, but is now used for the treatment of anaerobic and protozoal infections. Metronidazole given orally is absorbed almost completely, with bioavailability > 90% for tablets; absorption is unaffected by infection. Rectal and intravaginal absorption are 67 to 82%, and 20 to 56%, of the dose, respectively. Metronidazole is distributed widely and has low protein binding (< 20%). Metronidazole is metabolized in the liver by side-chain oxidation and glucuronide formation. The plasma elimination half-life of metronidazole is about 6-9 hours. (13) Because of its short elimination half-life, the controlled release of Metronidazole from numerous matrix-type and polymeric-coated formulations has been widely investigated. The present study focuses on designing, optimization and evaluation of a gastro-retentive floating tablet comprising of metronidazole and ciprofloxacin. The desired floating lag time was identified to be 75s and the floating duration was targeted more than 20h with not less than 90 % of drug release by 20 h. To optimize the formulation, the screening and optimization of polymer matrix and guar gum quantity was aimed followed by the study of process variables that affects drug release and identify the most optimized formulation and evaluate the same.

2. Material and methods

Materials

Ciprofloxacin HCl (Taj Pharmaceuticals Ltd., India), Metronidazole (Ciron drugs, India), hydroxypropyl methylcellulose (HPMC K15M, HPMCK4M, HPMC E10M and HPMC K100M), (Shin-Etsu Chemical Corporation, Japan), Guar gum (alpha chemicals, India), Polyvinyl pyrrolidone K-30 (Glide chem. India), citric acid (Merck, Germany), sodium bicarbonate (Merck, Germany), Microcrystalline cellulose (Accent microcell Pvt. Ltd., India) magnesium stearate (S.D. Fine Chemical Pvt.)

Methodolgy

Analysis of Ciprofloxacin: Ciprofloxacin obtained from Taj Pharmaceuticals ltd. was characterized using IR spectra. The Ultra violet absorption maxima were determined in the range of 200-400 nm of a 5µg/ml of drug solution in 0.1N hydrochloric acid. The preparation of standard curve was undertaken in 0.1 N HCl at eight different concentrations 1-7 µg/ml and the absorbance was measured against blank at 275 nm. The solubility profile and partition co-efficient between octanol and water was also determined. Analysis of Metronidazole: Metronidazole obtained from Ciron drugs was characterized using IR spectra. The Ultra violet absorption maxima were determined in the range of 200-400 nm of

a 5µg/ml of drug solution in 0. 1N hydrochloric acid. The preparation of standard curve was undertaken in 0.1 N HCl at eight different concentrations 1-7 µg/ml and the absorbance was measured against blank at 289 nm. The solubility profile and partition co-efficient between octanol and water was also determined. Screening of polymer for desired polymer matrix. In order to evaluate the best matrix forming polymer from different polymer formulation such as HPMC K4M, HPMC K15M, HPMC K100M, HPMCE10M, 3 batches using each polymer at the ratio of 10%, 12.5% and 15% were formulated resulting in twelve batches F1-F12. All ingredients (except glidants, lubricant and PVP K-30) were passed through sieve No. 30 and mixed thoroughly in planetory mixer at 200 rpm. To this mixture MCC PH101 previously passed through sieve No. 44 was added and further mixing was carried in the planetory mixer. After thorough mixing granulation was carried using 6.5% w/v solution of PVP-K30 in isopropyl alcohol in the planetory mixer. The wet mass was subjected to drying on fluidized bed drier of 1 kg capacity, for a period of one hour at 40 ºC. The dried granules were then sized by sieve No. 22 and magnesium stearate was added as extra granular excipients to enhance flow property and lubrication. The granules thus obtained were compressed into tablets on a Cadmach 16-station, single rotatory, compression machine (D-tooling type). The powder blend for all the batches was studies for micromeritic properties and the formulated tablets were evaluated for hardness, friability, weight variation, drug content, floating lag time, floating duration and the drug dissolution for ciprofloxacin and metronidazole using 0.1 N HCl at 37±0.5 ^{0}C (900 ml using USP apparatus II at 50 rpm.). The composition of different excipients in formulations (F1-12) is listed in Table I.

Table I: The composition of different excipients in formulations (F1-12)

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ciprofloxacin HCl	582.1	582.1	582.1	582.1	582.1	582.1	582.1	582.1	582.1	582.1	582.1	582.1
Metronidazole	500	500	500	500	500	500	500	500	500	500	500	500
HPMCK100M	150	200	250	0	0	0	0	0	0	0	0	0
HPMCK15M	0	0	0	150	200	250	0	0	0	0	0	0
HPMCK4M	0	0	0	0	0	0	150	200	250	0	0	0
HPMCE10M	0	0	0	0	0	0	0	0	0	150	200	250
Guar gum	52.9	52.9	52.9	52.9	52.9	52.9	52.9	52.9	52.9	52.9	52.9	52.9
PVP K 30	15	15	15	15	15	15	15	15	15	15	15	15
Citric Acid	20	20	20	20	20	20	20	20	20	20	20	20
NaHCO3	60	60	60	60	60	60	60	60	60	60	60	60
MCC PH 101	50	50	50	50	50	50	50	50	50	50	50	50
Mg. Stearate	10	10	10	10	10	10	10	10	10	10	10	10
Total wt.	1440	1490	1540	1440	1490	1540	1440	1490	1540	1440	1490	1540

Design and optimization of polymer ratio and guar gum content

In order to evaluate the effect of blend of polymer, and the optimization of guar gum quantity, a 2^3 full factorial design was implemented wherein the three factors at two levels viz. higher and lower were studied for the responses viz. floating lag time and the drug release profile of ciprofloxacin and metronidazole. Eight experiments (F-13 to F-20) were designed with statistical significance using the entire combinations of 66.6 mg and 133.3 mg of the two screened polymers and 50 and 100 mg of the guar gum quantity. The mathematical equation for a 2^3 full factorial design is as follows: $Y= \beta o + \beta_1 \cdot x_1 + \beta_2 \cdot x_2 + \beta_{12} \cdot x_1x_2 + \beta_3 \cdot x_3 + \beta_{13} \cdot x_1x_3 + \beta_{23} \cdot x_2x_3 + \beta_{123} \cdot x_1x_2x_3 + \varepsilon$. The powder blends obtained were studies for micromeritic properties and the

formulated tablets were evaluated for hardness, friability, weight variation, assay, floating lag time, floating duration and drug release profile for ciprofloxacin and metronidazole. Dissolution of the tablets was carried out using 0.1 N HCl at 37±0.5 ^{0}C (900 ml using USP apparatus II at 50 rpm.). The compositions of different excipients in formulations (F13-F20) are listed in Table II.

Table II: The composition of different excipients in formulations (F13-F20)

Ingredients (mg)	F13	F14	F15	F16	F17	F18	F19	F20
Ciprofloxacin HCl	582.1	582.1	582.1	582.1	582.1	582.1	582.1	582.1
Metronidazole	500	500	500	500	500	500	500	500
HPMCK100M	66.6	133.3	66.6	133.3	66.6	133.3	66.6	133.3
HPMCE10M	66.6	66.6	133.3	133.3	66.6	66.6	133.3	133.3
Guar gum	50	50	50	50	100	100	100	100
PVP K 30	15	15	15	15	15	15	15	15
Citric Acid	20	20	20	20	20	20	20	20
NaHCO3	60	60	60	60	60	60	60	60
MCC	50	50	50	50	50	50	50	50
Mg. Stearate	10	10	10	10	10	10	10	10
Total wt.	1403.7	1487	1487	1553.7	1470.3	1537	1537	1603.7

Evaluation of powder blend

1. Bulk and tapped densities of granules: The granules were poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark. Excess granules were removed using spatula and the weight of the cylinder with granules was determined. Weight of the granules required for filling the cylinder volume was calculated. The cylinder was then tapped on a tapped density apparatus until the time when there was no more decrease in the volume. Bulk density (ρ_b) was calculated as the quotient of the weight of the granules and the volume of the cylinder used. Tapped density (ρ_t) was calculated as the quotient of the weight of the granules and its final volume after tapping.
2. The flow properties were characterized in terms of Carr's index (I_c) and Hausner's ratio (HR).
3. Angle of Repose: The angle of repose is the angle formed by the horizontal base of the bench surface and the edge of a cone-like pile of granules. Funnel used was a glass funnel and the size of the orifice was about 10 mm and the height from the beginning of funnel to end of orifice was 110 mm. The funnel was fixed in place, 4 cm above the bench surface. The powder blend was allowed to flow freely from the funnel orifice onto the bench. After a cone from a 5 g of sample was built, height of the granules forming the cone (h) and the radius (r) of the base were measured. The angle of repose (θ) was calculated as follows:

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Evaluation of tablets

1. Weight variation: Twenty tablets were randomly selected from each batch and individually as well as collectively weighed. The average weight and standard deviation of 20 tablets was calculated.
2. Hardness of twenty tablets was measured using Schleuniger hardness tester. The instrument reads in both kilograms and Strong Cobb Unit (SCU).The mean value for breaking strength was reported in kg/cm^2.
3. Friability: Twenty tablets were weighed and placed in the plastic chamber of Roches Friabilator. After 100 revolutions the tablets

were removed and weighed again. Friability (%) = W_i-W_r/W_i x 100where, W_i was the initial weight of the tablets before friability testing, W_r was the weight of tablets after the testing.

4. Drug content: Twenty tablets of each formulation were crushed to powder in mortar-pestle and powder equivalent to average weight was added in 50 ml of 0.1N hydrochloric acid. The resultant solution was stirred at 100 rpm using a magnetic stirrer for a period of 2h. The solution was filtered through 0.45 um membrane, diluted suitably and analyzed for drug content spectrophotometrically at 275 nm for ciprofloxacin and 289 nm for metronidazole using 0.1N hydrochloric acid as blank.
5. In vitro floating study: The buoyancy lag time and the duration of buoyancy were determined by beaker method using 0.1 N hydrochloric acid with 0.02% w/v tween 20 incorporated to simulate gastric fluid. The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium was taken as buoyancy lag time and the duration of buoyancy was observed visually.
6. In vitro drug release studies: Drug release was studied using six-station dissolution apparatus USP, II (paddle method) in 900 ml 0.1N hydrochloric acid at 37 □ 0.5□ C and 50 rpm, the difference being that although stirring was carried out using paddle shaft, the tablets were kept into sinker (USP baskets closed at both extremes) prior to their exposure into dissolution medium and the sinker was then placed horizontally at bottom. Moreover, the paddle height was adjusted at 3.5 cm form the hemispherical bottom to avoid friction between the paddle shaft and sinker, which else may lead to erratic results. This ensured a complete exposure of tablet to the dissolution medium throughout the study. The study was performed in triplicate for a period of 24 hours. 5 ml aliquots of sample were withdrawn at regular intervals and an equal volume of pre-warmed (37±0.5 ^{0}C) fresh dissolution medium was replaced. The samples withdrawn were filtered using 0.45 um membrane, suitably diluted with 0.1N hydrochloric acid and analyzed for drug content using Thermospectronic-1 UV/Vis spectrophotometer at 276 nm for ciprofloxacin and 289 nm for metronidazole. The cumulative percentage drug release was plotted against time to determine the release profile.
7. Calculation of F2 value (Similarity Factor):A similarity factor (F2) directly compares the difference between the percent drug dissolved per unit time for a test and a reference and is calculated using the formula:

$$F_2 = 50 \log \frac{100}{1+\frac{\sum_{i=1}^{n} T_t - R_t}{n}}$$

Where, T_t = percent drug release of test formulation at time "t"
R_t = percent drug release of reference formulation at time "t"
n = number of time points selected in the dissolution study.

The purpose of F2 value calculation is to be able to compare entire curves and not time points. F2 value between 50 and 100 signifies that the two dissolution profiles are similar.

3. Results and discussion

Analytical profile of Ciprofloxacin: The identity of the Ciprofloxacin HCl was confirmed by verification of presence of functional groups by IR spectroscopy which showed sharp band at 3490, 3320, 2930, 1696, 1605 and 1480 cm^{-1} to O-H stretch, N-H stretch, aliphatic C-H stretch, C=O stretch of carboxyl group, C=O stretch of quinoline, C-N stretch. The UV absorption of 5 µg/ml of drug solution in 0.1 N hydrochloric acid was determined to be 275 nm in 0.1N HCl. The standard curve for Ciprofloxacin HCl in 0.1 N HCl was found to obey Beer's law within the range of 0 to 7 µg/ml with the correlation coefficient of 0.9982 and the line equation of y= 0.11 x + 0.0064 as depicted in figure I.

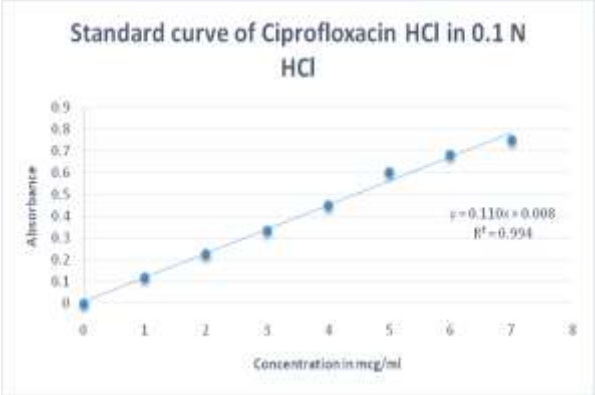

Figure I: The standard curve for Ciprofloxacin in 0.1 N HCl

The solubility profile depicted free solubility in DMSO, Aqueous solution (pH 4-5), sparingly soluble in 0.1N HCl, methanol and aqueous solution (pH>9) and insoluble in ethanol and water. The octanol/ water partition coefficient was found to be 1.0825± 0.23.

Analytical profile of Metronidazole: The identity of metronidazole was confirmed by verification of presence of functional groups by IR spectroscopy like a sharp band at 3648 cm^{-1} (O-H stretching), 3221-3101 cm^{-1} (N-H Stretching), 2982 – 2937cm^{-1} (C-H Stretching), 1354 – 1265cm^{-1} (C-O stretching), 1428 – 1368cm^{-1} (C-H bending (in plane)), 1340 cm^{-1} (C-C stretching). The UV absorption of 5µg/ml of drug solution in 0.1 N hydrochloric acid was determined to be 289 nm in 0.1 N HCl. The standard curve for Metronidazole in 0.1 N HCl was found to obey Beer's law within the range of 0 to 7 µg/ml with the correlation coefficient of 0.9919 and the line equation of y= 0.02x + 0.0037 and represented in figure II.

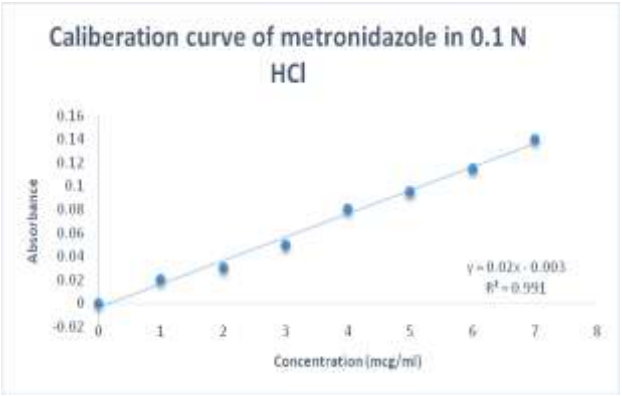

Figure II: The standard curve for Metronidazole in 0.1 N HCl

The solubility profile depicted free solubility in DMSO, 0.1N HCl, methanol, water and ethanol while sparingly soluble in DMF and chloroform. The octanol/ water partition coefficient was found to be -0.15± 0.02. Screening of the polymer matrix to be used in the final formulation. The micromeritic properties of F1-F12 are depicted in table III.

Table III: The micromeritic properties of F1-F12

Powder Blend	Angle of repose (°)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Carr's Index (%)	Hausner's ratio
F1	29.52	0.631	0.762	19.25	1.29
F2	28.79	0.622	0.759	18.87	1.23
F3	28.35	0.633	0.764	21.63	1.27
F4	27.68	0.588	0.758	20.11	1.18
F5	26.49	0.596	0.725	16.78	1.2
F6	27.21	0.602	0.735	17.69	1.27
F7	27.87	0.611	0.742	17.84	1.28
F8	28.32	0.597	0.522	18.63	1.26
F9	28.15	0.684	0.763	18.98	1.25
F10	29.45	0.676	0.784	19.55	1.22
F11	29.16	0.652	0.736	18.75	1.27
F12	28.14	0.637	0.766	18.69	1.24

The angle of repose for all the batches depicts excellent flow property with values between 25-30°**.** All the batches except for F5, shows fair to passable flow which typically lies in the range of 17-21 % whereas F5 shows good flow property with a Carr's index less than 17. Batches F1, F3, F6, F7, F8 and F11 depicted poor flow properties as per the Hausner's ratio whereas F2, F4, F5, F9, F10 and F12 depicted good flow properties as their Hausner's ration was found to be below 1.25.

The quality control tests for tablets are shown in table IV. The hardness and friability of all the batches is well within limits. The % standard deviation for the weight variation test for all the batches is under 5 % which compiles for the test of weight variation for tablets above 250 mg. All the batches are very much within the designated assay range of 90-110 %. Floating lag time of batches F1, F2, F3, F10, F11 and F12 are very close to the desired floating lag time of 75s while others deviate from the desired floating lag time. Floating duration for most of the batches except F4, F6, F7 and F9 is greater than 20 h.

The drug release profile of ciprofloxacin and metronidazole for batches F1-F12 are depicted in figure III, IV respectively.

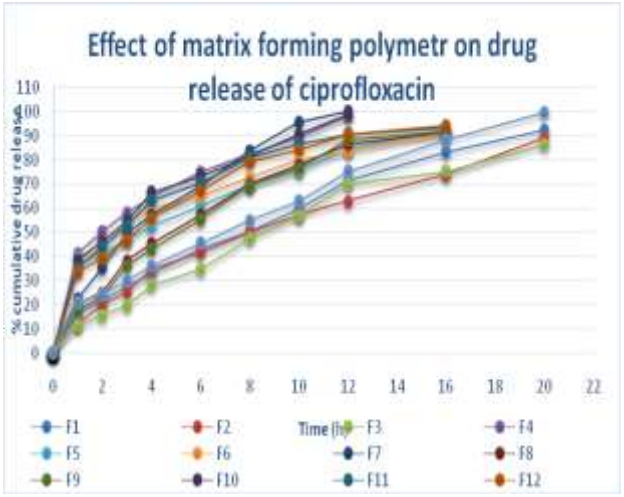

Figure III: Effect of matrix forming polymer on drug release of ciprofloxacin on batches F1-F12 and targeted profile

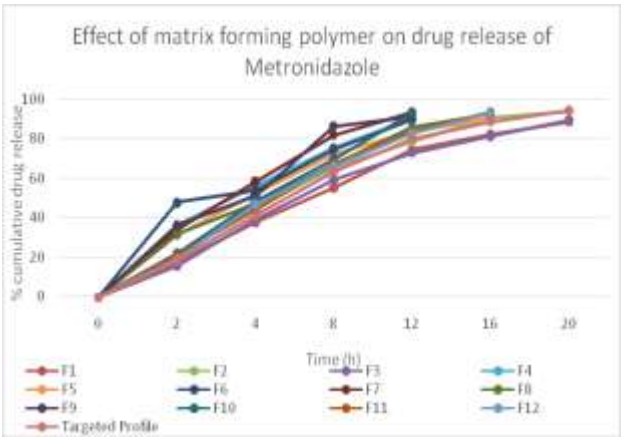

Figure IV: Effect of matrix forming polymer on drug release of metronidazole on batches F1-F12 and targeted profile

Using HPMCK100M, the floating properties of the tablet was as per the desired levels, whereas the drug release was sustained, fulfilling the floating and sustained release requirements of the formulation. The floating properties of batches using HPMCK15M was reasonable and up to the desired levels but the release was much faster than required, thus not fulfilling the sustained release property. The batches prepared using HPMCK4M depicted faster release thus not achieving the desired floating property and sustained drug release. Using HPMCE10M, the floating properties of the tablet increased whereas the drug release was sustained fulfilling the floating and sustained release requirements of the formulation. Based on micromeritics properties of the granules, floating lag time, floating time and the drug release profiles of the tablets, HPMCK100M and HPMCE10M were screened as the polymer matrix to be used for further optimization of the formulation.

Evaluation of optimization of the ratio of polymer quantities and guar gum quantity

The ratio of the screened polymers and the guar gum quantity was optimized using 2^3 full factorial design using Minitab 17.3.1. The micromeritic properties of F13-F20 are depicted in table V. The angle of repose for all the batches depicts excellent flow property with values between 25-30°**.** The loose bulk density and tapped bulk density for the batches are comparable without any major variation. The Carr's index for F13, F14 and F18 shows good flow properties which is depicted by Carr's

index below 17 whereas other batches shows fair flow property as the Carr's index is between 17-21%. Hausner's ratio of all the batches depicts good flow properties whereas, batches F15 and F20 shows bad flow property. The quality control tests for tablets are shown in table VI. The hardness and friability of all the batches is well within limits of hardness test. The % standard deviation for the weight variation test for all the batches is under 5 % which compiles for the test of weight variation for tablets above 250 mg. All the batches complies the assay range of 90-110 % both for ciprofloxacin and metronidazole. The order of floating lag time for ratio of polymers is F14>F17>F15, F20>F18>F19>F13>F16 indicating F14 to be the ideal formulation as far as floating lag time is concerned. The drug release profile of ciprofloxacin and metronidazole for batches F13-F20 and target profile CifranOD and Flagyl ERare depicted in figure V and VI respectively. The order of drug release for ciprofloxacin is F14>F13>F19>F15>F18>F20>F17>F16 indicating F14 having similar drug release profile as target profile. The order of drug release for metronidazole is F14>F13>F19>F15>F18>F20>F17>F16 indicating F14 having similar drug release profile as target profile. F2 values for the formulations (F13-F20) followed the sequence: F14>F13>F16>F19>F18>F15>F17>F20. All of the F2 Values are above 50 which represent a similar dissolution profile, while that of F14 is nearing 100 indicating an identical dissolution profile as compared to the reference drug Cifran OD and Flagyl ER. The micromeritic properties, tablet evaluation properties, floating lag time and floating duration was found to be the best in F-14. Moreover, drug release profile both for Ciprofloxacin and Metronidazole is almost similar to that of the target profiles and hence it can be very well concluded that F14 is the optimized batch. This would further conclude that the best suited ratio between the polymers HPMCK100M and HPMCE10M would be 2:1 and the levels of the polymers best suited for the ideal formulation would be 133.3mg and 66.6mg for HPMCK100M and HPMCE10M respectively. Optimum Guar gum quantity is required for desired swell ability and buoyancy of the formulation and hence plays a major role in achieving the desired floating lag time and floating time of the formulation. The design of experiment was found to be statistically significant and from this design of experiment it is clear that the optimum quantity of guar gum would be 50 mg.

Table IV: The quality control tests for tablets of batches F1-F12

Batch Number	Hardness (Kg/cm2) (n=10)	Friability (%) (n=6)	Weight variation(mg) (avg±%SD) (n=20)	Assay (90-110%) (n=3)	Floating lag Time (Sec)	Floating Time (hrs)
F1	4.5±0.05	0.44±0.26	100.2±0.024	99.2±0.21	76	>20
F2	4.8±0.12	0.47±0.18	99.8±0.86	98.8±0.64	75	>20
F3	5.1±0.04	0.51±0.29	99.9±0.91	101.2±0.38	78	>20
F4	4.1±0.22	0.39±0.15	100.3±1.05	98.4±0.54	96	19
F5	4.3±0.17	0.52±0.11	100.1±0.75	98.3±0.14	79	>20
F6	4.2±0.06	0.39±0.18	99.8±1.2	97.5±1.04	104	19
F7	4.5±0.34	0.52±0.26	99.8±0.36	101.7±0.74	68	15
F8	4.3±0.21	0.39±0.18	99.7±1.79	98.4±0.39	70	>20
F9	5.0±0.19	0.44±0.26	100.1±0.23	97.6±0.87	101	17
F10	4.9±0.01	0.52±0.26	99.9±1.54	99.1±0.14	79	>20
F11	4.5±0.08	0.43±0.29	99.8±1.58	98.6±0.63	76	>20
F12	5.1±0.04	0.51±0.29	99.8±0.98	98.6±0.98	78	>20

Table V: The micromeritic properties of F13-F20

Powder Blend	Angle of repose (°)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Carr's Index (%)	Hausner's ratio
F13	28.37	0.679	0.729	16.27	1.25
F14	27.64	0.634	0.714	16.59	1.22
F15	27.29	0.654	0.753	19.51	1.27
F16	25.83	0.613	0.737	17.93	1.21
F17	26.71	0.668	0.768	17.44	1.23
F18	25.68	0.654	0.726	16.28	1.21
F19	27.59	0.689	0.741	17.21	1.18
F20	26.21	0.613	0.792	17.63	1.26

Table VI: The quality control tests for tablets of batches F13-F20

Batch number	Hardness (Kg/cm^2) (n=10)	Friability (%) (n=10)	Weight variation(mg) (avg±%SD) (n=20)	Assay (90-110%) (n=3)	Floating lag Time (Sec)	Floating Time (hrs)
F13	4.5±0.19	0.39±0.58	99.7±1.57	97.6±1.8	62	>20
F14	4.7±0.53	0.41±0.91	100.1±0.89	97.1±2.7	75	>20
F15	4.8±0.81	0.48±0.53	99.8±1.15	101.7±0.9	69	>20
F16	4.8±0.46	0.51±0.15	99.8±1.07	98.2±1.3	60	>20
F17	5.0±0.27	0.45±0.47	100.2±2.34	99.3±1.1	79	>20
F18	4.6±0.89	0.51±0.12	100.1±2.5	97.1±2.3	81	>20
F19	4.7±0.29	0.45±0.19	99.9±1.2	98.7±1.4	83	>20
F20	4.8±0.31	0.43±0.21	99.8±1.6	101.5±2.8	69	>20

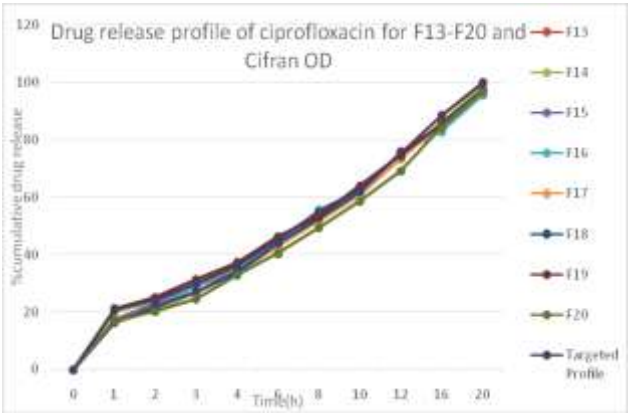

Figure V: Drug release profile of Ciprofloxacin of batches F13 to F20 along with Cifran OD

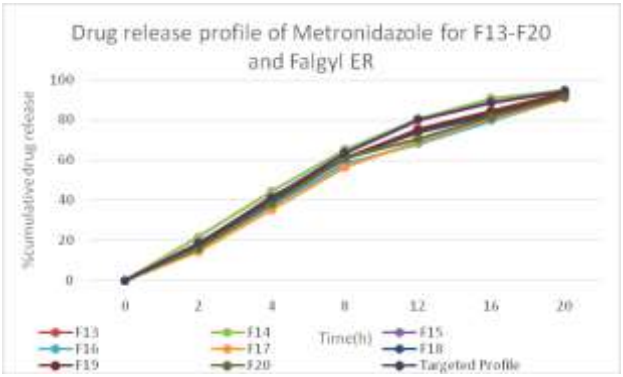

Figure VI: Drug release profile of Metronidazole of batches F13 to F20 along with Flagyl ER

Conclusion

A combination of ciprofloxacin with an antimicrobial agent active against anaerobes, such as metronidazole, could prove an efficient way of treating mixed aerobic/ anaerobic infections. Moreover, the combination has proved to be more potent than individual drug administration. Most of the marketed combination drugs do not provide a sustained release pattern and thus increase the frequency of drug administration to the patient. Development of gastro retentive dosage form can be advantageous and could provide prolonged gastric retention and an increased efficacy of the dosage form. For accomplishments of the target, the experimentation included the selection of polymers, screening of polymers, optimization of the ratio of polymers and optimization of guar gum quantity, to achieve a floating lag time of 75 seconds and the floating duration of more than 20 hours with not less than 90 % of drug release by 20 hours. From the screening study evaluation, it was concluded that based on the floating lag time, floating duration, and drug release profiles, HPMC K100M and HPMC E10M were the ideal HPMC polymers to form the polymer matrix. Further a 2^3 full factorial design with three factors and two levels of each factor was carried out to optimize the polymer ratio and to optimize the guar gum quantity. Most of the experiments carried out showed a linear and parallel release profile but F14 shows the desired floating lag time of 75 seconds along with a floating time of more than 20 hours. The drug release profile for both ciprofloxacin and metronidazole also showed similar to that of the marketed brands Cifran OD and FlagylER. This further concluded that the best suited ratio between the polymers HPMCK100M and HPMCE10M would be 2:1 and the levels of the polymers best suited for the ideal formulation would be 133.3 mg and 66.6 mg for HPMCK100M and HPMCE10M respectively and the optimum guar gum quantity was 3.3 %. F2 value of F-14 was nearing 100 which indicated a close resemblance with point to point dissolution profile of the test batch to the target profile

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