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Development of floating matrix tablets of Ofloxacin and Ornidazole in combined dosage form: *in vitro* and *in vivo* evaluation in healthy human volunteers

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Abstract

Ofloxacin (OFX) is a synthetic broad spectrum analog of second generation fluoroquinolone antibiotic. It is used for the treatment of urinary tract, prostate, skin, urinary and respiratory tract infections. Ornidazole (ORN) is a nitroimidazole derivative. It is used in the treatment of bacterial vaginosis, trichomoniasis, amoebiasis, giardiasis and infections due to anaerobic bacteria. These drugs are highly soluble in acidic media and precipitates in alkaline media thereby losing its solubility. Hence we attempted to develop a gastro retentive floating matrix type drug delivery system for Ofloxacin and Ornidazole in combined dosage form with hydroxyl propyl methyl cellulose (HPMC) K15M, HPMC K100M and polyethylene oxide 18NF (PEO). The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy and differential scanning calorimetry. The results suggested no physicochemical incompatibility between the drug and the polymers. The prepared floating drug delivery systems were evaluated for physicochemical characteristics, mainly in vitro release and in vivo residence time by radiographic studies. The best formulation (F2) was selected based on in vitro release and physicochemical characteristics and used in vivo radiographic studies by incorporating BaSO4. These studies revealed that tablets 300 ± 30 minutes in healthy human volunteers in fasting state and indicated that the gastric retention was increased by floating principle. By fitting the data into zero order, first order and Higuchi models, it was concluded that drug release from matrix tablets followed Higuchi model and the mechanism of drug release was diffusion mediated. Based on the physical evaluation, in vitro drug release and in vivo characteristics, it was concluded that for potential therapeutic use, suitable for the development of a floating drug delivery system of Ofloxacin and Ornidazole in combined dosage form.

Keywords: Ofloxacin. Ornidazole. Gastro retentive. Floating tablets. Hydroxy propyl methyl cellulose. Poly ethylene oxide.

Introduction

Using current release technology, oral delivery for 24 h is possible for many drugs; however, the substance must be well absorbed throughout the whole gastrointestinal tract. A significant obstacle may arise if there is a narrow window for drug absorption in the gastrointestinal tract (GIT), if a stability problem exists in gastrointestinal fluids, or the drug is poorly soluble in the intestine or acts locally in the stomach. Thus, the real issue in the development of oral controlled release dosage forms is not just to prolong the delivery of the drugs for more than 12 h, but to prolong the presence of the dosage forms in the stomach or somewhere in the upper intestine until all of the drug is released over the desired period of time [1].

Controlled gastric retention of solid dosage forms may be achieved by the mechanisms of floating systems, swelling and expanding systems [2], bioadhesive systems, modified shape systems, high density systems or other delayed gastric emptying devices. The principle of buoyant preparation offers a residence time for the dosage form and sustained drug release [3].

The various buoyant preparations include microballoons [4, 5], granules, powders, capsules, tablets and laminated films [6]. Based on the mechanism of buoyancy, two distinctly different technologies, *i.e.*, non-effervescent and effervescent systems have been utilized in the development of floating systems [7]. Non-effervescent systems commonly use gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate, and polystyrene. Effervescent systems utilize matrices prepared with swellable polymers such as methocel or chitosan and effervescent compounds, *e.g.*, sodium bicarbonate and citric or tartaric acid [8, 9], or matrices containing chambers of liquid that gasify at body temperature.

Ofloxacin is a flouroquinolone, broad spectrum antibiotic, and is used in the treatment of urinary tract infections, prostatitis and gonorrhea. Ofloxacin is least absorbed from the lower part of the gastrointestinal tract and is better absorbed from the stomach. Ofloxacin is (±) - 9- fluoro-2, 3- dihydro-3-methyl-10-(4-methylpiperazine-1-yl) – 7-oxo -7H- pyrido [1, 2, 3-de]- 1, 4-benzoxazine-6-carboxylic acid [10]. Ornidazole is a nitroimidazole derivative. ORN is used in treating Bacterial vaginosis, Trichomoniasis, Amoebiasis, Giardiasis (lambliasis) and infections due to anaerobic bacteria (infections such as septicemia, meningitis, peritonitis, postoperative wound infections, puerperal sepsis, septic abortion, and endomentritis, with demonstrated or suspected involvement of susceptible bacteria). OFX and ORN have site-specific absorption in the stomach region of the GI tract and precipitated when enter into intestinal regions. OFX and ORN have biological half-life's of 5-6hrs and 12hrs respectively and shows high solubility in acidic medium (gastric acid) and favors development of a gastro retentive formulation in combined dosage form.

Experimental

Materials

OFX and ORN are generous gifts from Euro drugs, India. HPMC K15M and HPMC K100M were obtained from ISP, India. PEO 18NF was a generous gift sample from Dr. Reddy's Labs, India. Sodium bicarbonate, citric acid, talc and magnesium stearate (analytical grade) were purchased from S.D. Fine Chemicals Ltd. (Mumbai, India). All the other ingredients were of analytical grade.

Methods

Solubility study

Excess amount of OFX and ORN was placed in 0.1 N HCl, pH 4.5 acetate buffer, phosphate buffer pH 6.8 and pH 7.4 respectively in order to determine its solubility. The samples were shaken for 24h at 37 C in a horizontal shaker (HS 501 Digital, IKA-Labortechnik, and Staufen, Germany). The supernatant was filtered and the filtrate was diluted with the appropriate dissolution medium and assayed by UV-spectrophotometer at 293nm and 317nm for OFX and ORN respectively.

Simultaneous Spectrophotometric Estimation of OFX and ORN in tablet dosage form

Two simple, sensitive, accurate and economical spectrophotometric methods were developed for the estimation of Ofloxacin and Ornidazole simultaneously in tablet dosage form. First method is based on the simultaneous equations and second method is based on Q-analysis (absorbance ratio method). Ofloxacin and Ornidazole show absorbance maxima at 294 nm and 317 nm in N/2 acetic acid, respectively.

Development of combination of OFX and ORN necessitates developing and validating simple, rapid, accurate, spectrophotometric methods for simultaneous determination of Ofloxacin and Ornidazole in pharmaceutical dosage forms. Simultaneous Estimation of Ofloxacin and Ornidazole was carried out according to the methods described by Bhusari KP et al .

Preparation of Single Unit Floating Matrix Tablets of OFX and ORN

Accurately weighed quantities of polymer and MCC were taken in a mortar and mixed geometrically, to this required quantity of OFX and ORN 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 900mg was compressed into tablets with 13 mm capsulated punches at a hardness of 6-7 kg/cm^2.
The composition of various formulations was given in table1.

Evaluation of physicochemical properties

The formulated tablets were evaluated for weight variation, thickness, crushing strength, friability and content uniformity.

Weight variation

Twenty tablets were selected at random and the average weight of the tablets was determined. The weight of individual tablets was compared with the average weight.

Thickness

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using a Vernier Caliperse. The average thickness and standard deviation were reported.

Crushing strength and friability

Crushing strength of tablet was determined by Monsanto tester (Campbell Electronics, India) hardness tester. Friability test was carried out using Roche friabilator (Erection instrument & engineering, Ahmedabad, India). Ten tablets were weighed and subjected to the combined effect of attrition and shock by utilizing a plastic chamber. The friabilator was operated for 100 revolutions (4 min, 25 rpm). The tablets were dedusted and re-weighed to calculate the percentage of friability.

Drug content uniformity

Prepared tablets were accurately weighed and finely powdered by pestle in a mortar. A weighed portion of each powder equivalent to

mg of prepared tablet was transferred in to a volumetric flask and the drug was extracted with methanol as the solvent. The contents of the flask were sonicated for 10min and diluted with 0.1 N HCl as the solvent. The samples were analyzed spectrophotometrically at 294 nm and 317 nm for OFX and ORN respectively.

In vitro buoyancy studies

In vitro buoyancy studies were performed for all the twelve formulations as per the method described by Rosa *et al* [11]. The randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

In vitro dissolution studies

The release rate of OFX and ORN from floating tablets was determined using *United States Pharmacopeia* (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 ± 0.5 C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at predetermined time intervals and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N hydrochloric acid. Absorbance of these solutions was measured at 293 nm for OFX and 317 nm for ORN using a UV/Visible double beam spectrophotometer ((Elico, India). The percentage drug release was plotted against time to determine the release profile.

In vivo X-Ray study

The *in vivo* study was carried out by administering OFX and ORN floating matrix tablets to healthy human volunteers and monitoring them through a radiological method (X-ray study). To make the tablets X-ray opaque the incorporation of $BaSO_4$ was necessary. The amount of the X-ray opaque material in these tablets was sufficient to ensure visibility by X-ray, but at the same time this amount of $BaSO_4$ was low enough to enable tablets to float. Four healthy male subjects (mean age 27year; mean weight 60±10kg) participate after giving informed consent. The study approved by the Ethical Committee (UCPS, Kakatiya Univeristy, Warangal). The study was conducted by administering to each subject one floating tablet on fasted state, the subjects fasted overnight then swallowed the floating tablets with 150ml water. After wards the subjects were not allowed to eat or drink [12]. In each subject the position of the floating tablet was monitored by X-ray photographs (Konica Minolta, Siemens, Karlsruhe, Germany) of the gastric region at determined time intervals. All X-ray films were taken in anterior positions.

Stability studies

Stability studies were carried out for optimized formulation F3 according to the International Conference on Harmonization (ICH) guidelines. The samples were stored in closed HDPE bottles along with 1 g desiccant at 40 ± 2 C/75 ± 5% R.H. (Skylab Instruments and Engineering Pvt Ltd., Mumbai, India) for 3 months. Samples were withdrawn after 1, 2, and 3 months, and were evaluated for drug content and *in vitro* percentage drug release.

Results and Discussion

Solubility study

OFX and ORN is highly soluble in 0.1 N HCl, having quantitative solubility of 66.52 mg/ml and 10.68mg/ml of respectively. As pH increased solubility decreased drastically, i.e. pH 4.5 acetate buffer (28.24 mg/ml of OFX and 6.17mg/ml of ORN); pH 6.8 phosphate buffer (7.18 mg/ml of OFX and 3.12mg/ml of ORN), and pH 7.4 phosphate buffer (0.25mg/ml of OFX and 1.63 mg/ml of ORN). It shows pH dependent solubility, highly soluble in acidic pH but poorly soluble in alkaline pH. Precipitation of the Ofloxacin occurs in intestine, which adversely affects the absorption in the lower sections of the intestine [13]. The result was show in figure 1.

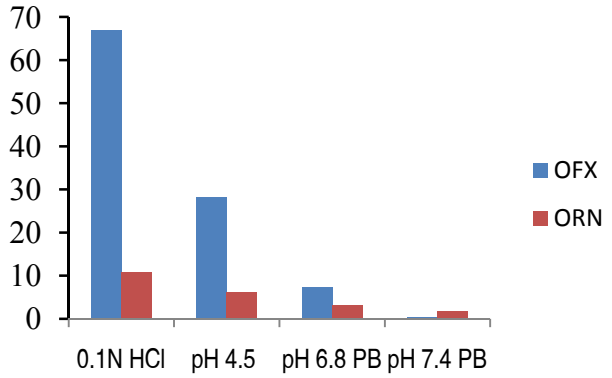


Figure 1: Solubilty of OFX and ORN in different mediums

Simultaneous Spectrophotometric Estimation of OFX and ORN in tablet dosage form

Simultaneous Estimation of Ofloxacin and Ornidazole was carried out according to the methods described by [14, 15] reported methods.

First method is based on the simultaneous equations and second method is based on Q-analysis (absorbance ratio method). OFX and ORN show absorbance maxima at 294 nm and 317 nm in N/2 acetic acid, respectively. The linearity was obtained in the concentration range of 2-10 µg/ml for Ofloxacin and 2-30 µg/ml for Ornidazole. In the first method, the concentrations of the drugs were determined by using simultaneous equations; and in the

second method, the concentrations of the drugs were determined by using ratio of absorbance at isoabsorptive point at 305nm. The results of analysis have been validated statistically and by recovery studies.

Table 1: Composition (mg) of OFX and ORN floating tablets

Formulation	HPMC K15M	HMPMC K100M	PEO 18NF	MCC
F1	90	--	--	115.5
F2	120	--	--	85.5
F3	150	--	--	55.5
F4	--	60	--	145.5
F5	--	90	--	115.5
F6	--	120	--	85.5
F7	--	--	120	85.5
F8	--	--	150	55.5
F9	--	--	180	25.5

All the tablets contain 200mg ofloxacin, 400mg ornidazole, 9 mg magnesium stearate and 9mg talc. HPMC – hydroxy propyl methyl cellulose, MCC – micro crystalline cellulose. The average weight of all the formulations was 900mg.

Evaluation of physical properties of pre-compressed granules

The physical properties like Compressibility index (CI), Angle of repose and Haunser's ratio were calculated and tabulated in table 2. The results of the physical properties of many of the blends were in the limits and comply with the standards.

Table 2: Physical properties of final blend

Formulation	CI	Angle of repose	Haunser's ratio
F1	12.1	27.7º	1.15
F2	15.8	26.5º	1.13
F3	12.5	29.2º	1.18
F4	15.4	28.4º	1.17
F5	12.3	29.5º	1.15
F6	11.2	28.4º	1.18
F7	13.7	29.8º	1.08
F8	12.2	27.5º	1.18
F9	14.8	29.4º	1.14

Evaluation of physicochemical properties

The tablets of OFX and ORN were prepared by direct compression technique using HPMC K15M, HPMC K100M and PEO 18NF. Magnesium stearate and talc were used as lubricant and glidant respectively. The data of physical parameters like thickness, drug content, weight variation, hardness, friability and *in vitro* buoyancy properties, of all the formulations is enclosed in table 3. All the parameters lie within the limits. The average weight of the tablets was 900mg and the weight variation for every batch was less than ± 5%. The hardness was maintained as 6.5 to 7 kg/cm^2 in all the formulations. The friability of all the formulations falls in the acceptable limit. The drug content in the range of 96.54±2.5% to 98.56±2.5% for ORN and 97.67±2.6% to 99.65±1.4% for OFX.

In vitro buoyancy studies

The prepared floating matrix tablets buoyant for 12 h with a lag time of less than 95 seconds. The optimized concentration of the gas-generating agent (sodium bicarbonate) contributed to the buoyancy of all tablets. Buoyancy results of floating matrix tablets are shown in table 3.

In vitro dissolution studies

An ideal controlled release system should be able to release the drug immediately to attain the therapeutic level at a faster rate and maintain this drug level for a prolonged period of time. *In vitro* drug release studies revealed that the release of ofloxacin and ornidazole from different formulations varies with characteristics and composition of matrix forming polymers as shown in figure 2a.

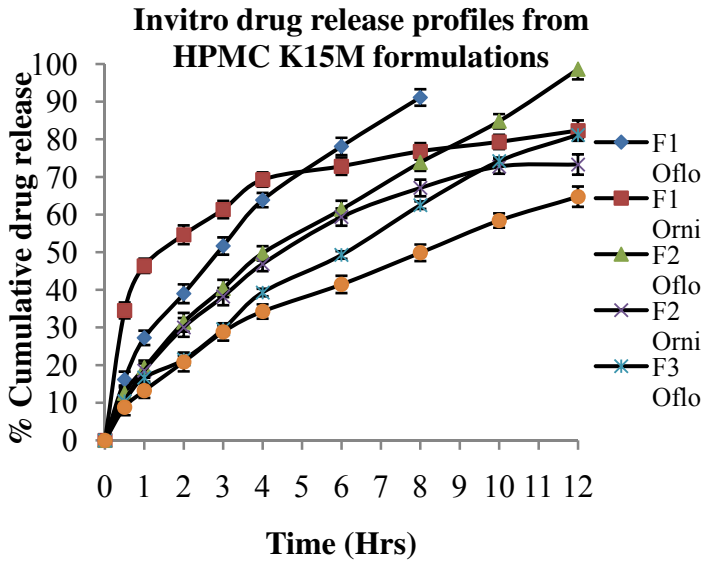


Figure 2a: *In vitro* dissolution of ofloxacin and ornidazole from HPMC K15M floating matrix tablets

The release rate of ofloxacin from formulations F1, F3 and ornidazole F1, F2, and F3 was decreased with increasing concentration of HPMC K15M. The release rate of ofloxacin and ornidazole from F2 formulations were found to be 98.64 ±1.34% and 73.31±1.74% in 12h respectively. Upon increasing the concentration of polymer the release rate of ofloxacin from formulations F1 and F3 were found to be 91.14±1.27% in 8h and 81.19±2.01% in 12h and ornidazole were found to be 82.34±0.97%

and 64.76±1.84% in 12h from the observations of physical parameters the formulation F2 exhibit controlled and prolonged release of drugs.

In vitro dissolution study of formulations F4, F5 and F6 prepared with HPMC K100M were done in 0.1N HCl and the percent of ofloxacin and ornidazole drug release from formulations F5 and F6 was 96.89±2.12%, 81.96±1.73% and 72.81±1.64%, 62.53±2.21% in 12 h respectively. Formulation F5 and F6 unable to sustain the drug release desired period of time. This is because of change in polymer concentrations used in these formulations compared to K15M. Formulations F6 failed to meet the desired drug release profile. Formulation F5 obtained the desired drug release profile and floated with a lag time of 95 sec, for these reasons it was considered as the best formulation among all the four formulations. The release profile from all these formulations were followed diffusion controlled release complying with higher correlation coefficient values of Higuchi. Formulation F5 was considered as best formulation among all the four formulations as it showed good buoyancy properties (floating lag time: 95 sec & floating time >12 hrs) (figure 2b)

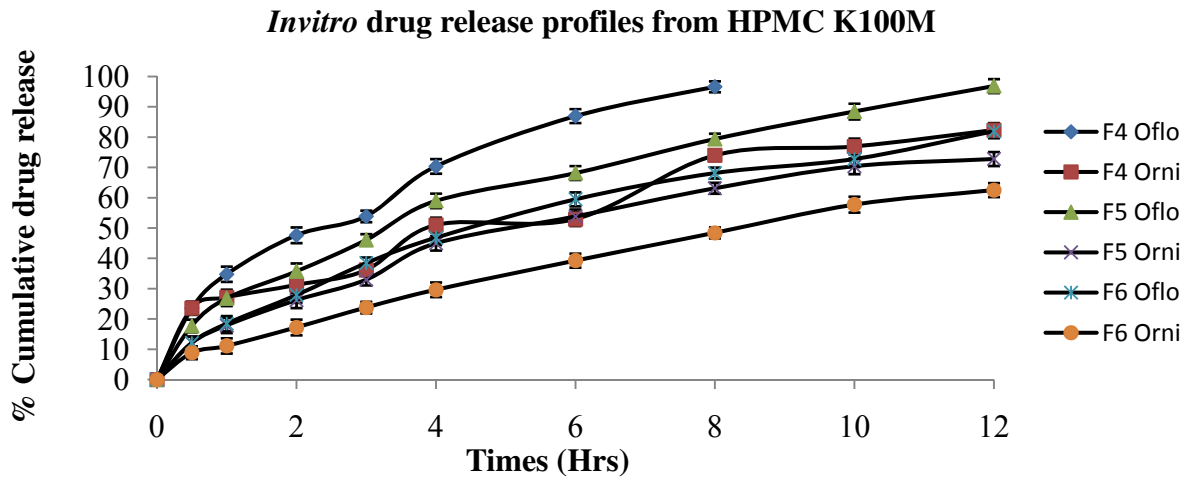


Figure 2b: *In vitro* dissolution of ofloxacin and ornidazole from HPMC K100M floating matrix tablets

and sustained the drug release for desired period of time (12 hrs). *In vitro* dissolution study of formulations F7 to F9 were also done in 0.1N HCl and the percent drug released was calculated (figure 2c). These three formulations prepared with PEO

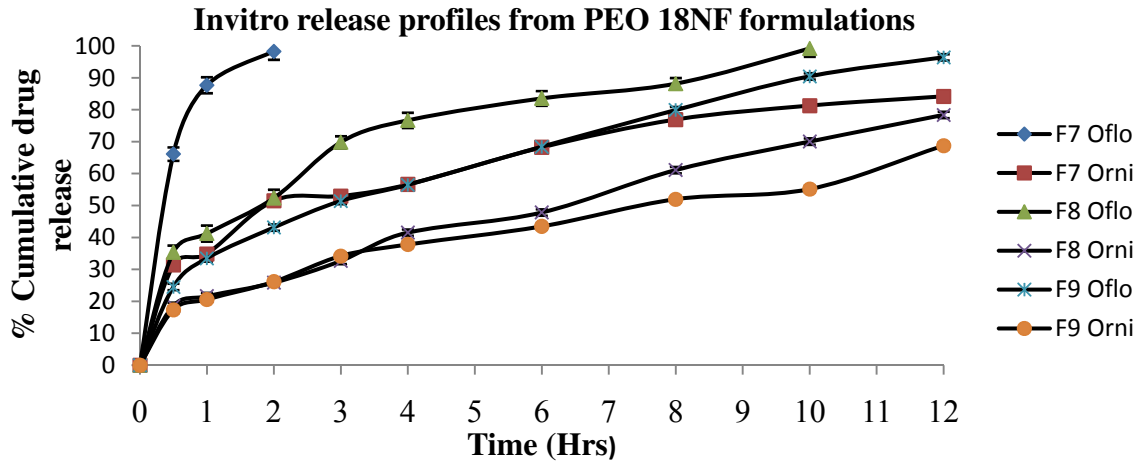


Figure 2c: *In vitro* dissolution of ofloxacin and ornidazole from PEO 18NF floating matrix tablets

Table 3: Physical Evaluation parameters:

Formulation	Weight variation (mg)[a]	Hardness (kg/cm^2)[b]	Thickness (mm)	Friability	Drug Content (%)[c] ORN	OFX	Floating lag time (sec)	Floating time (hr)
F1	903±4.3	6.8±0.5	6.7±0.06	0.23	98.5±2.5	99.6±1.4	81±2.1	>12
F2	902±4.5	7±0.3	6.8±0.03	0.48	98.2±3.6	99.1±1.9	79±1.9	>12
F3	903±3.7	6.5±0.5	6.7±0.04	0.51	97.9±2.9	98.6±1.4	76±2.8	>12
F4	902±4.7	6.8±0.5	6.6±0.05	0.35	97.4±2.7	99.5±2.4	99±3.2	>12
F5	901±3.9	7±0.2	6.5±0.25	0.38	97.6±2.4	98.6±2.1	95±2.8	>12
F6	903±4.5	6.8±0.5	6.5±0.04	0.41	97.3±3.4	98.4±3.4	105±2.4	>12
F7	901±4.6	7±0.3	6.5±0.07	0.25	97.4±3.5	98.5±2.5	40±01.9	>12
F8	900±4.8	7.2±0.1	6.4±0.04	0.28	97.9±3.7	99.3±3.1	42±1.8	>12
F9	905±4.6	6.8±0.2	6.6±0.06	0.39	96.4±2.5	97.7±2.6	48±2.5	>12

(a=20, b=6, c=20)

18NF. The polymer should have the lower viscosity than the methocel polymers. The results indicated that higher viscosity grade of polymer concentrations drug release was retarded greatly. Formulations F7 and F9 release the ofloxacin in 6h and 10h respectively. This was ascertained due to the insufficiency of the polymer to form a rigid gel barrier around the tablet ultimately leading to loss of matrix integrity. Increasing the polymer level (F8 and F9 formulations) resulted in sustaining the release rate of ofloxacin upto 12h. The release rate of ornidazole from formulations was decreased with increased concentration of polymer in 12h. Among these formulations F8 should release the 96.43±2.04% % and 68.76±2.16% of ofloxacin and ornidazole respectively with a floating lag time of 48seconds.

Data of the *in vitro* release was fit into kinetic models to explain the release kinetics from floating tablets [16]. The kinetic models used were zero-order equation, first-order equation, and Higuchi [17, 18] and Korsemeyer-Peppas models. The cumulative amount of the drug released from the tablets, when plotted against square-root of time the release profiles of drug seemed to follow Higuchi model as it was evidenced by correlation coefficients (r2 = 0.98 to 0.99) better than zero order (r2 = 0.93 to 0.98) and first order (r2 = 0.52 to 0.57). The data was further treated as per the following equation for Korsemeyer-Peppas models [19, 20]

$$M_t/M = K.t^n$$

Where, M_t/M is the fractional release of the drug, M_t is the amount released at time *t*, M is the total amount of drug contained in the matrix tablet, *t* is the release time, *K* is a kinetic constant, and *n* is the diffusional release exponent indicative of the operating release mechanism. The n values obtained were below 0.5 indicative of Fickian diffusion (table 4).

Table 4: Regression coefficient (r^2) values of different kinetic models of OFX and ORN floating matrix tablets

Code	Zero order (r^2)		First order (r^2)		Higuchi (r^2)		Korsmeyer (r^2)		n value	
	OFX	ORN	OFX	ORN	OFX	ORN	OFX	ORN	OFX	ORN
F1	0.945	0.897	0.526	0.523	0.988	0.912	0.923	0.912	0.509	0.536
F2	0.968	0.923	0.559	0.526	0.999	0.991	0.931	0.920	0.541	0.533
F3	0.98	0.96	0.605	0.588	0.976	0.981	0.904	0.892	0.293	0.382
F4	0.928	0.915	0.476	0.45	0.986	0.973	0.902	0.917	0.422	0.389
F5	0.92	0.931	0.466	0.539	0.991	0.990	0.963	0.932	0.501	0.539
F6	0.928	0.979	0.484	0.633	0.997	0.974	0.946	0.903	0.538	0.562
F7	0.933	0.802	0.534	0.352	0.948	0.958	0.932	0.953	0.716	0.536
F8	0.976	0.956	0.361	0.504	0.925	0.983	0.972	0.913	0.522	0.518
F9	0.906	0.917	0.421	0.462	0.992	0.985	0.921	0.937	0.529	0.513

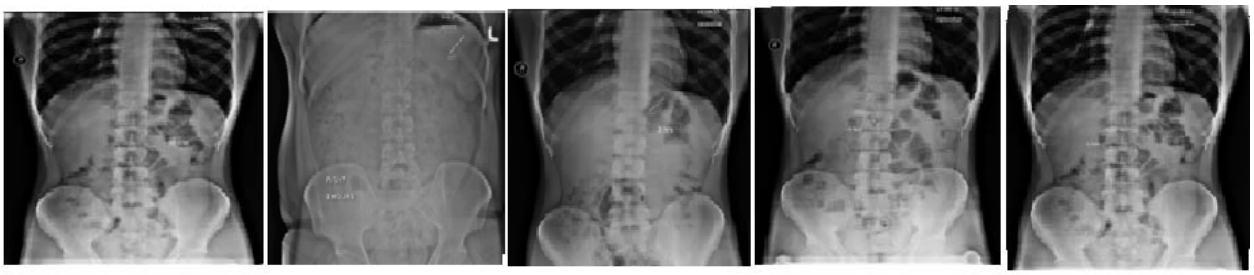
Comparing the two different grades of methocel (K15M and K100M) and PEO 18NF, it was found that low-viscosity grade methocel K15M provided better-controlled release characteristics with excellent drug release and *in vitro* buoyancy. Formulation F2 selected has optimized from the observations of physical

parameters, in vitro buoyancy properties, in vitro dissolution study and regression analysis, hence it selected for in vivo X-ray study.

In vivo radiographic studies

The optimized formulation was selected based on the correlation factor (r^2) values of all formulations and dissolution parameters and physical characteristics of formulation. Formulation (F2) selected as optimized and *in vivo* X-ray studies revealed that tablets remain float in stomach for 300minutes in healthy human volunteers in fasting conditions and results show in figure 3.

Figure 3: Intra-gastric behavior of the Floating Tablets



Stability studies

In view of the potential utility of the floating matrix formulation, stability studies were conducted as per ICH guide lines and the results were represented in table 5. Drug content and *in vitro* drug release results reveal that after 3 months of the stability studies there was no significant difference in drug content and *in vitro* drug release.

Table 5: Stability study of the optimized floating matrix tablet (F2) for three months

Time	Hardness	Floating	Drug content (mg)		% drug released	
(days)	(kg/cm^2)	lag time (sec)	OFX	ORN	OFX	ORN
0	6.8 ± 0.54	74±1.5	197.8 ± 1.63	395.2 ±1.58	98.9 ± 1.59	71.2 ± 1.53
30	7.0 ± 0.5	81±2.2	196.9 ± 1.59	395.4 ±1.73	98.45 ± 1.72	69.9 ± 1.83
60	6.4 ± 0.7	76±2.1	197.2 ± 1.68	396.1 ±1.64	98.6 ± 1.61	71.2 ± 1.72
90	6.7 ± 0.65	69±1.6	197.3 ± 2.13	395.8 ±1.85	98.65 ± 1.91	71.9 ± 1.63

Conclusion

The effervescent-based floating drug delivery is a promising approach to achieve *in vitro* buoyancy. The addition of gel-forming polymer (HPMC K15M, HPMC K100M and PEO 18 NF) and gas generating agent (sodium bicarbonate) was essential to achieve *in vitro* buoyancy. Formulation F2 showed controlled drug release and adequate floating properties. The kinetics of drug release was best explained by Higuchi model. The tablets remain floated in stomach should be 5hrs in fasting human volunteers and indicated that gastric retention time was increased by the floating principle.

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