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Research Article

FORMULATION AND EVALUATION OF FLOATING MATRIX TABLETS OF LEVOFLOXACIN HEMIHYDRATE USING HYDROXYPROPYL METHYLCELLULOSE K4M TO TREAT *HELICOBACTER PYLORI* INFECTION

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ABSTRACT

Objective: The aim of the study was to develop a floating drug delivery system of levofloxacin (LVF) hemihydrate for sustained drug delivery to improve the extended retention in the stomach, oral bioavailability, and local site-specific action in the stomach.

Methods: Preparation of LVF tablets using melt granulation method using hydroxypropyl methylcellulose (HPMC) K4M with sodium bicarbonate as gas generating agent. From LFTA1 to LFTA5, formulations were developed and evaluated for floating properties for swelling characteristics and *in vitro* drug release studies. *In vitro* dissolution was carried out using USP II paddle method using 0.1N HCl pH buffer at 50 rpm and samples were measured at 294 nm using ultraviolet-visible spectroscopy.

Results: Obtained Fourier-transform infrared charts indicated that there is no positive evidence for the interaction between LVF and ingredients of the optimized formula. *In vitro* drug release was performed and drug release kinetics were evaluated using the linear regression method and were found to be followed the zero-order release by diffusion controlled release. Optimized formula was found to be LFTA4 with 20% of a polymer with 99.03% of drug release with 12 h of floating time and 32 s floating lag time.

Conclusion: Matrix tablets (LFTA4) formulated employing 20% HPMC K4M are best suited to be used for gastroretentive dosage form of LVF.

Keywords: Levofloxacin hemihydrate, Buoyancy, Gastric retentive drug delivery system and floating matrix tablet.

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INTRODUCTION

Drug absorption from the gastrointestinal tract (GIT) is a complex process influenced by many variables. It has been reported that the extent of drug absorption from the GIT is related to contact time with the small intestinal mucosa. Gastroretentive drug delivery systems are designed to retain drug in the gastric region for several hours and assist in improving sustained delivery of orally administered drugs that have an absorption window in a particular region of the GIT [1]. Several approaches have been developed to achieve extended gastric residence time of the oral drug delivery systems such as bioadhesive system, swelling and expanding systems, floating systems, and delayed gastric emptying devices. Among these methods, floating drug delivery system (FDDS) preferred one that offers a simple and practical approach to achieve gastroretention [2]. Among these, the gastric FDDS (GFDDS) offers a number of applications for drugs with poor bioavailability because of a narrow absorption window in the upper part of the GIT. It retains the dosage form at the site of absorption and thus enhances the bioavailability [3,4]. Floating dosage forms have a bulk density lower than that of gastric fluids and therefore remain buoyant on the stomach contents to prolong the gastric retention time [5-8].

Helicobacter pylori (H. pylori) infection is the causative organism in chronic active gastritis, duodenal ulcers and gastric adenocarcinoma [9]. This bacterium is highly adapted for colonization in the human stomach; the majority of these bacteria are free living in the gastric mucus layer, although about 20% are in close contact with epithelial cells [10]. Levofloxacin (LVF) hemihydrate is a broad-spectrum third-generation fluoroquinolone antibiotic [11]. Some studies have demonstrated that LVF has a remarkable *in vitro* activity against *H. pylori* when its strains are resistant to clarithromycin and metronidazole [12]. LVF has shown promising results in different first-line triple regimens in several countries, with an eradication rate ranging from 72%–96% [13]. This study was conducted with an aim to develop floating gastroretentive tablet formulation incorporating 250 mg LVF into hydrophilic polymeric matrix which would release the drug in the stomach and upper part of GIT in a controlled manner [14]. LVF is a broad-spectrum third-generation fluoroquinolone antibiotic, which is rapidly and completely absorbed after oral administration. Peak plasma concentrations are usually attained 1–2 h after conventional dosing and the mean terminal plasma elimination half-life of LVF ranges from 6 to 8 h following single or multiple doses of LVF given orally [15]. In the treatment of infections, therapy requires constant levels of drug in the blood for an extended period, which can be achieved by design of controlled drug delivery system to deliver the drug through floating matrix tablets. The present study was undertaken with the objective to develop an optimized floating drug delivery of LVF to improve absorption and its oral bioavailability. In the current study, the effect of (hydroxypropyl methylcellulose [HPMC] K4M) polymer concentration on drug release behavior and the buoyancy properties of prepared formulations were evaluated.

MATERIALS AND METHODS

Materials

LVF was obtained as a gift sample from Ajanta Pharmaceuticals, Mumbai. HPMC K4M was obtained from Orchid Health Care, Chennai. Microcrystalline cellulose was obtained from Moly Chemicals Ltd., Mumbai. Polyvinylpyrrolidone (PVP K30) was obtained from Fisher Scientific, Mumbai. All other reagents and solvents used were of analytical grade.

Preparation of floating gastroretentive tablets
Out of the two conventional tablet preparation methods such as wet granulation [16-18] and direct compression [19], a wet granulation method was chosen to achieve the better tablet physical properties. Tablets were prepared by a conventional wet granulation method using HPMC K4M as a release retardant, and sodium bicarbonate as gas generating agent. Compositions of designed nine formulations are listed in Table 1. All ingredients (except gas generating agents and magnesium stearate) were passed through a sieve no. 60 and mixed in a poly bag for 10 min and granulated using PVP K30 using isopropyl alcohol as binding solvent. The wet mass was passed through sieve number 14 and dried in hot air oven at 50°C for 1.5 h. Dried granules were mixed with the remaining ingredients and compressed using multistation rotary tablet press (Cadmach Machinery Co. Pvt. Ltd., Mumbai) using 12 mm flat punch to obtain controlled release floating gastroretentive matrix tablets containing 250 mg of LVF.

Drug excipient compatibility
The infrared spectra of pure drug, binary mixture of drug and each excipient (1:1), optimized formulation, and placebo were recorded between 600 and 4000 cm^{-1} by Fourier-transform infrared (FT-IR) spectrometer using the potassium bromide pellet technique.

Weight variation of tablets
The weight variation test was conducted by weighing 20 randomly selected tablets individually [20]. The average weight and standard deviation were calculated.

Friability
For each formulation, the friability of 10 tablets was determined using Roche friabilator, respectively [21]. In friability, test tablets were subjected to the combined effect of abrasion and shock using a plastic chamber that resolves at 25 rpm droppings. The tablets fall from a distance of 6 inches with each revolution. Previously weighed 10 tablets were placed in friabilator, which is then set for 100 revolutions. Then, the tablets were dusted and weighted.

Friability=Weight loss/initial weight of tablet ×10

Content uniformity test
A total of 10 tablets of the chosen formula were randomly selected and weighed. Each one was crushed individually and dissolved in 50 ml 0.1 N HCl. The volume was adjusted to 50 ml using 0.1 N HCl and then filtered. Samples were assayed for LVF content spectrophotometrically at predetermined λ_{max} 294 nm, and the drug concentration in each tablet was calculated, after suitable dilution. The drug content in each tablet was compared to the label claim. The drug content for the other formulations was calculated from their corresponding absorbance values at 24 h during the release study. Drug content of the selected formulation was also tested by crushing 20 tablets, and the blend equivalent to 250 mg of LVF was weighed, dissolved in 0.1 N HCl, filtered, and suitably diluted. The drug content was analyzed spectrophotometrically at λ_{max} 294 nm [22].

***In vitro* buoyancy test**
In vitro buoyancy was determined by measuring buoyancy lag time and total floating duration. The buoyancy test was performed using the USP dissolution apparatus II containing 900 ml of 0.1 N HCl as the dissolution medium was maintained at 37 ± 0.5°C. The measurements of both floating lag time and total floating time were carried out for each formulation. The floating and the settled tablets were also observed visually, and the results were presented as % floating after 4 h. Matrix integrity was also observed throughout the *in vitro* buoyancy studies [23].

***In vitro* drug release test and modeling of drug release profiles**
Tablets containing 250 mg LVF were placed in 900 ml 0.1 N HCl as a dissolution medium was maintained at 37 ± 0.5C. Drug release was performed using a USP type II apparatus at 75 rpm for 12 h. Aliquots of 5 ml were withdrawn at specified intervals of time, filtered and replenished with 5 ml fresh dissolution medium. Samples absorbance was measured at λ_{max} 294 nm after suitable dilution [24]. The studies were performed in triplicate. The cumulative % of LVF released was calculated at each time interval. Drug release data were analyzed according to the zero-order, first-order, Higuchi, and Peppas [25,26]. The model with the highest coefficient of determination was considered to be the best fitting one.

RESULTS AND DISCUSSIONS

Drug-polymer interaction using FTIR
Spectra's of drug and drug, polymer mixtures were given in Figs. 1-3. No interaction was observed between drug and polymer. Drug showed

Table 1: Formula for LVF floating tablets with HPMC K4M

Ingredient	LFTA1	LFTA2	LFTA3	LFTA4	LFTA5
LVF	250	250	250	250	250
HPMC K4M	25	50	75	100	125
Sodium bicarbonate	75	75	75	75	75
PVP K 30 (2%)	10	10	10	10	10
Magnesium stearate (1%)	5	5	5	5	5
Talc (1%)	5	5	5	5	5
MCC	130	105	80	55	30
Total weight (mg)	500	500	500	500	500

MCC: Microcrystalline cellulose, HPMC: Hydroxypropyl methylcellulose, PVP: Polyvinylpyrrolidone, LVF: Levofloxacin

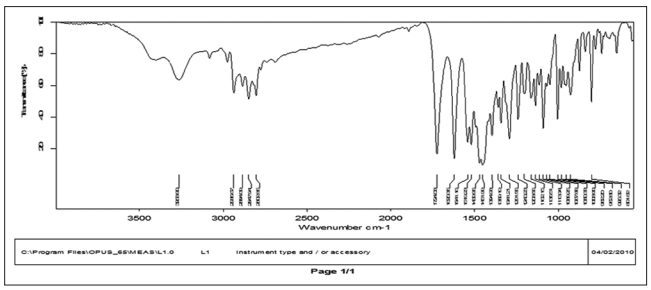

Fig. 1: Fourier-transform infrared spectrum of pure drug levofloxacin hemihydrate

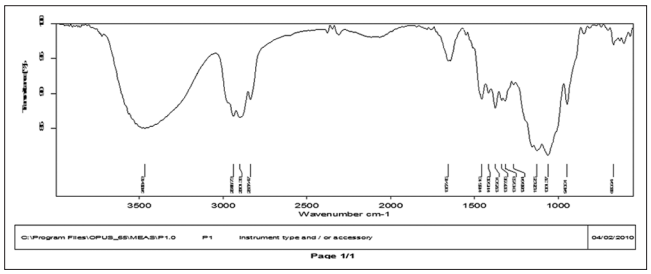

Fig. 2: Fourier-transform infrared spectrum of hydroxypropyl methylcellulose K4M

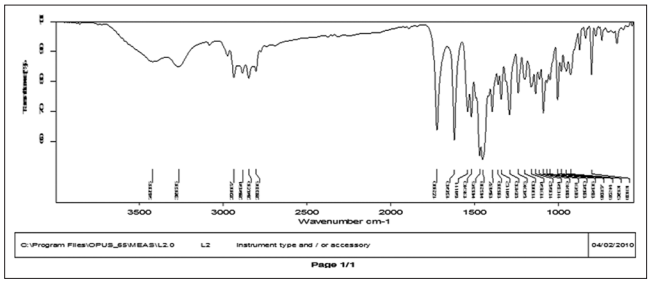

Fig. 3: Fourier-transform infrared spectrum of levofloxacin hemihydrate with hydroxypropyl methylcellulose K4M

Table 2: Physical evaluation of LVF matrix tablets with HPMC K4M

Formulation code	Hardness (Kg/cm²)	Weight variation (%)	Friability (%)	Assay (%)	Floating lag time (s)	Floating time (h)
LFTA1	4±0.63	0.826±0.03	0.24±0.14	96.14±0.45	66	12
LFTA2	4±0.75	1.23±0.09	0.53±0.11	96.86±0.57	61	12
LFTA3	4-±0.85	1.96±0.08	0.42±0.14	98.73±0.90	59	12
LFTA4	4±0.76	0.987±0.12	0.58±0.14	99.02±0.63	50	12
LFTA5	4±0.89	1.227±0.06	0.43±0.08	97.75±0.55	52	12

*Mean percent of levofloxacin hemihydrate released ($\bar{x}$±SD) (n=3). HPMC: Hydroxypropyl methylcellulose, LVF: Levofloxacin, SD: Standard deviation

Table 3: *In vitro* drug release studies of floating tablets

Time (h)	LFTA1	LFTA2	LFTA3	LFTA4	LFTA5
0.5	70.71±0.76	24.84±0.14	7.58±0.11	7.23±0.31	7.12±0.87
1	100.09±0.23	32.06±0.32	11.32±0.91	12.32±0.22	10.09±0.74
2	-	42.89±0.54	21.01±0.33	19.60±0.72	17.10±0.32
3	-	61.44±0.26	26.60±0,78	26.13±0.94	23.09±0.61
4	-	70.05±0.98	31.75±0.61	30.98±0.41	28.10±0.72
5	-	79.44±1.09	48.02±0.32	38.82±0.75	34.09±0.46
6	-	92.68±0.28	61.86±0.76	58.02±0.92	49.37±0.73
7	-	101.67±0.31	70.66±0.14	66.67±0.38	57.05±0.95
8	-	-	78.65±0.32	72.12±0.71	66.09±0.88
9	-	-	86.87±0.21	75.19±0.54	71.09±0.43
10	-	-	95.76±0.22	81.73±0.76	76.03±0.21
11	-	-	99.075±0.32	90.46±0.91	81.75±0.11
12	-	-	-	99.03±0.93	94.23±0.68

* Mean percent of levofloxacin hemihydrate released (x±SD) (n=3). SD: Standard deviation

Table 4: Correlation coefficient (r) values in the analysis of release data as per the zero, first, and Higuchi models

Formulation code	Zero-order plot	First-order plot	Higuchi plot
LFTA1	0.972	0.999	0.999
LFTA2	0.980	0.964	0.993
LFTA3	0.995	0.894	0.962
LFTA4	0.992	0.965	0.964
LFTA5	0.994	0.982	0.961

characteristic peaks at the wavenumber of 3420.55, 3266.25, 2935.67, 2884.34, 2847.39, and 2803.36 cm^{-1}. These peaks were also observed in the case of drug-polymer mixture. No shifting in drug peaks was observed in mixtures. It was confirmed that no interaction was observed between drug and polymer.

Physical evaluation of tablets

Matrix tablets each containing 250 mg of LVF could be prepared employing HPMC K4M in different proportions (5%, 10%, 15%, 20%, and 25% strengths in the formulae) by the wet granulation method. Hardness of the tablets was in the range of 4–6 kg/sq.cm. Weight loss in the friability test was <1% of all the cases. All the matrix tablets prepared contained drug in the range of 98–102% of the labeled LVF. All the tablets were found to be non-disintegrating in acidic pH of 1.2 and alkaline fluids so that they are considered suitable for a gastroretentive drug delivery system. Physical evaluation of floating matrix tablets was shown in Table 2.

***In vitro* buoyancy studies**

The *in vitro* buoyancy with maximum floating lag time was 66 s. All the tablet formulations were remained buoyant for more than 12 h, except the tablets prepared with HPMC K4M up to 15% polymer in simulated gastric fluid (SGF) of pH 1.2. Tablets prepared with HPMC K4M at 20% polymer maintained buoyancy time up to 12 h.

Drug release profiles of matrix tablets

LVF release was relatively rapid in the case of matrix tablets prepared employing 5% HPMC K4M and a floating time of 1h was seen for a 100% drug release for these tablets. When 10% of HPMC K4M was used in the formula, the release at the end of the 7 h was 100%. The matrix tablets containing 15% HPMC K4M released 99.18% drug by the end of the 11 h while the matrix tablets having 20% HPMC K4M released 99.03% by the end of the 12 h. The matrix tablets having 25% of HPMC K4M showed minimum release of just 94.23% by the end of the 12 h. LVF release from the matrix tablets prepared was studied in 0.1N HCl for 12h. Drug release profiles of LVF matrix tablets are given in Table 3 and are shown in Figs. 4 and 5. The drug release parameters are summarized in Table 4 and 5. LVF release from the prepared matrix tablets was fast in low polymer concentrations, and release was decreased with an increase in polymer concentration up to some extent and with further increase in the polymer concentration did not decrease the release.

Drug release kinetics and mechanism

The drug release data were analyzed as per the zero-order, first-order, Higuchi, Erosion, and Peppa's equation models. The correlation coefficient (r) values in the analysis of the release data as per different kinetic models are given in Table 4. Analysis of release data as per the zero-order and first-order kinetic models indicated that the LVF release from the matrix tablets followed the first-order kinetics. The correlation coefficient (r) values were higher in the zero-order models than in the first-order model. In the case of drug release study of the optimized formula in SGF, the release followed the zero-order kinetics. Plots of percent release versus the square root of time were found to be linear with r values >0–9. Hence, it was concluded that with all the tablets prepared. Drug release from these matrix tablets was diffusion controlled. When the release data were analyzed as per Peppa's equation, the release exponent "n" was in the range of 0.37–0.50 in the case of formulating matrix tablets employing HPMC K4M indicating non-Fickian (anomalous) diffusion as the release mechanism. As such, these matrix tablets formulated employing 20% HPMC K4M are considered suitable for gastroretentive dosage form.

CONCLUSION

From the drug release study, it was concluded that the F4 formula of HPMC K4M matrix tablets has given the controlled release up to 12 h by showing increased release with floating lag time of 65 s. Non-Fickian diffusion was the drug release mechanism from the matrix

Table 5: LVFs release characteristics of matrix tablets

Formulation code	Polymer concentration (%)	T_{50} (h)	T_{80} (h)	K_0 (mg/h)	K_1 (h^{-1})	"n" in Peppas equation
LFTA1	5	-	-	100	2.45	0.5
LFTA2	10	2.51	4.98	13.160	0.374	0.54
LFTA3	15	5.19	7.81	9.38	0.336	0.882
LFTA4	20	5.62	8.91	8.20	0.188	0.799
LFTA5	25	5.91	9.93	7.49	0.145	0.819

LVF: Levofloxacin

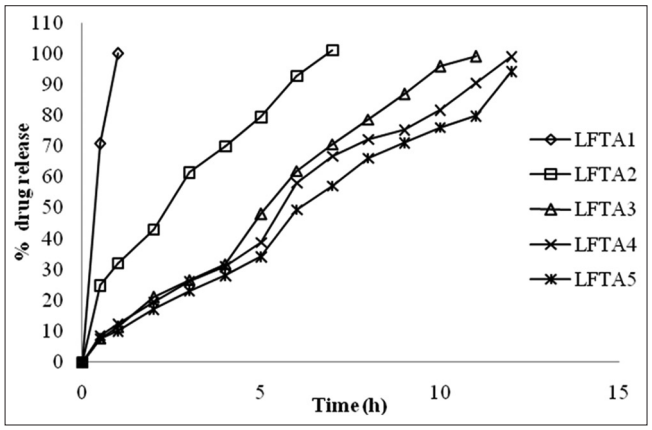

Fig. 4: Percent drug release versus time (h) profiles of tablets containing hydroxypropyl methylcellulose K4M

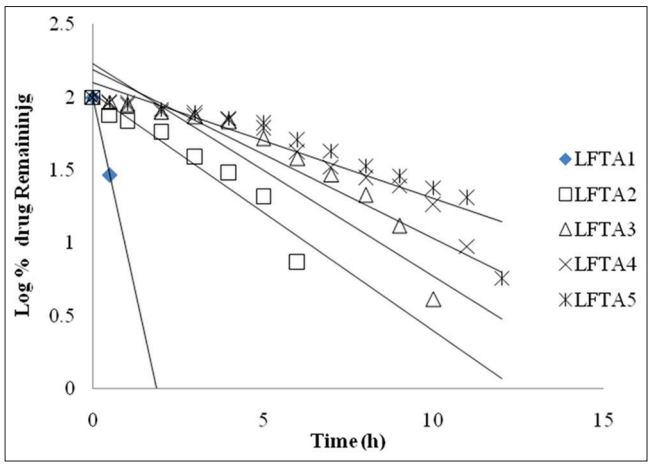

Fig. 5: Log % drug remaining versus time (h) plots of tablets containing hydroxypropyl methylcellulose K4M

tablets formulated employing HPMC K4M. Matrix tablets (LFTA 4) formulated employing 20% HPMC K4M are best suited to be used for gastroretentive dosage form of LVF.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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