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Research Article

Formulation and In Vitro Evaluation of Sustained Release Floating Matrix Tablet of Levofloxacin by Direct Compression Method

Nidhi Kumari Pandey*¹, Sailesh Kumar Ghatuary¹, Amit Dubey¹, Prabhat Kumar Jain²¹RKDF School of Pharmaceutical Science, Bhopal (M. P.)²Scan Research Laboratories, Bhopal (M. P.)

ABSTRACT

The objective of the present work was to develop Gastro retentive dosage forms which would remain in the stomach and upper part of GIT for a prolonged period of time thereby maximizing the drug release at desired site within the time before GRDFs left the stomach and upper part of the GIT, has provoked a great deal of increased interest in the formulation of such drug as floating drug delivery systems. Levofloxacin, (BCS class I) is a fluoroquinolone anti-bacterial agent. The rationale for the formulation of floating matrix tablet are acidic solubility of levofloxacin, residence of *Helicobacter pylori* mainly in sub region of stomach and the overdosing associated adverse effect due to continuous intake of drug in acute infection. A simple visible spectrophotometric method was employed for the estimation of levofloxacin at 294 nm and Beer's law is obeyed in the concentration range of 2-10 µg /ml. Floating matrix tablet of levofloxacin was prepared by direct compression method using different polymers like hydroxyl propyl methyl cellulose (HPMC K4) and carbopol 934 as matrix formation polymers, sodium bicarbonate and citric acid was used as gas generating agents. The FTIR spectra of the levofloxacin and other excipients alone and in combination show the compatibility of the drug and excipients. Six formulations of different polymer percentages were formulated (F1-F6). Pre-compression parameters were evaluated. The influence of matrix forming agents and binary mixtures of them on levofloxacin release was investigated. The formulated tablets were characterized by hardness, friability, thickness, weight variation and *in vitro* drug release. The formulated tablets had acceptable physicochemical characters. The data obtained from the *in-vitro* dissolution studies of optimized batch F4 were fitted in different models. The optimized formulation F4 showed 99.25% drug content and swelling index of 79.85 %. Drug release mechanism was found to be first order kinetics. Levofloxacin floating tablets exhibited increased gastric residence time, there by improved bioavailability and therapeutic effect of the drug.

Keywords: Levofloxacin, Gastro retentive, Hydroxy propyl methyl cellulose, Carbopol, *Helicobacter pylori*, Direct compression method**Article Info:** Received 11 June 2019; Review Completed 23 July 2019; Accepted 28 July 2019; Available online 15 August 2019

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*Address for Correspondence:

Nidhi Kumari Pandey, RKDF School of Pharmaceutical Science, Bhopal (M. P.)

INTRODUCTION

Floating drug delivery system (FDDS) shows buoyancy in stomach for extended time period thus offers extended gastric residence time for the dosage form ensuring optimal bioavailability (BA) ¹. The residence time of the dosage form in the stomach depends upon various factors like pH, size of the dosage form, food intake, and biological factors which include age, body mass index, gender, posture, and diseased states (hepatic failure, diabetes, chronic disease). Other techniques for gastro retentive dosage forms involve swelling, mucoadhesion, sedimentation, microballoons ^{2,3} and low density systems. Out of all systems available, the floating beads, floating tablets and floating microspheres have gained major importance. FDDS possess lower bulk density than the gastric fluid exerting buoyancy in the

stomach leading to slow drug release in an extended manner before it reaches absorption window⁴. In this present formulation, dual benefits of buoyancy as well as sustained action are achieved with an intention to maintain the steady state of drug release⁵. Hydrophilic matrix system is one of the easiest approaches for developing modified and sustained release dosage forms. A polymer like hydroxyl propyl methyl cellulose (HPMC) function as a pH independent gelling agent and drug release is shown by swelling and erosion mechanism occurring simultaneously contributing to overall drug release⁶. Matrix system is the commonly used method for modulating the drug release⁷. The manufacture of matrix tablets by direct compression is cheaper, simpler process, broad regulatory acceptance, and allows flexibility in obtaining desirable release profiles⁸. Levofloxacin is a synthetic chemotherapeutic antibiotic of the

fluoroquinolone drug class and is used to treat severe or life-threatening bacterial infections or bacterial infections that have failed to respond to other antibiotic classes⁹. Levofloxacin is a broad-spectrum antibiotic, inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, which is an enzyme necessary to separate replicated DNA, thereby inhibiting cell division¹⁰. The bioavailability of levofloxacin is above 99% with a plasma half-life of 6–8 h. It is freely soluble in pH 0.6 to 5.8 ranges. Above pH 5.8, the solubility increases rapidly to its maximum at pH 6.7 and above which the solubility decreases and reaches a minimum value at a pH of approximately 6.9. Thus solubility of the drug is reduced in intestinal alkaline pH¹¹ hence, it was selected in the present investigation as a suitable candidate for the design of gastric floating drug delivery system for improved retention time and bioavailability. The present study is to develop a floatable drug delivery system of levofloxacin using hydroxy propyl methyl cellulose, carbopol for sustained drug delivery and gastric retentive property. Thus the study aims to improve the oral bioavailability of the drug and to achieve extended retention in the stomach which may result in prolonged absorption.

MATERIALS AND METHODS

Materials

Levofloxacin was received as a gift sample from Ajanta Pharmaceuticals, Mumbai. Hydroxy Propyl Methylcellulose, Magnesium stearate, Sodium bicarbonate, Talc, Carbopol, were procured from S. D. Fine Chem. Ltd, Mumbai, India. All other solvents and reagents were purchased from Merck (Germany) and were of analytical grade.

Methods

Determination of λ_{\max} of levofloxacin

The λ_{\max} of levofloxacin was determined by analyzing the drug solution in double beam ultraviolet spectrophotometer.

Accurately weighed 10 mg of drug was dissolved in 10 ml of 0.1 N HCl solutions in 10 ml of volumetric flask. The resulted solution was 1000 μ g/ml of strength and from this solution 1 ml solution was pipette out and transfer into 10 ml capacity of volumetric flask and volume was made upto 10 ml with 0.1 N HCl solutions. This solution was scan at wavelength 400-200 nm on UV spectrophotometer. The higher absorption peak was obtained at 294 nm which was the λ_{\max} of drug.

Preparation of calibration curve of levofloxacin

Previously prepared stock solution (1000 μ g/ml of strength) of Levofloxacin was use to prepare suitable dilution into concentration range of 2-10 μ g/ml. 0.2, 0.4, 0.6, 0.8 and 1.0 ml of solution was taken in different volumetric flask having 10 ml of capacity and dilute upto 10 ml with 0.1 N HCl to obtained 2, 4, 6, 8 and 10 μ g/ml of solution. The absorbance of these solutions was taken at 294nm using UV-spectrophotometer (Labindia-3000 Plus). Graph between absorbance and concentration was plotted followed linearly regressed on Microsoft excel.

Preparation of floating tablets of levofloxacin

Levofloxacin matrix floating tablets were prepared by direct compression method employing sodium bicarbonate as gas-generating agent. HPMC and Carbopol were used as rate controlling polymers. The concentrations of the excipients were optimized as showed in table 1. The drug was mixed with the rate retarding polymers and other excipients in ascending order of their weights. The powder mix was blended for 20 min to have uniform distribution of drug in the formulation. Then magnesium Stearate and Talc were added. About 450 mg of the powder mix was weighed accurately and fed into the die and compressed using 10 mm round surface punches¹². The composition of formulation was given in table 1.

Table 1 Composition of SR matrix floating tablet of levofloxacin

Excipients(mg)	F1	F2	F3	F4	F5	F6
Levofloxacin	250	250	250	250	250	250
HPMC K 4	80	90	100	80	90	100
Carbopol	20	20	20	30	30	30
NaHCO ₃	15	15	15	15	15	15
Mg(C ₁₈ H ₃₅ O ₂) ₂	15	15	15	15	15	15
Talc	15	15	15	15	15	15
Lactose	55	45	35	45	35	25
Total Weight	450	450	450	450	450	450

Evaluation of levofloxacin floating matrix tablets

Pre-compression parameters

Angle of repose

The angle of repose of blends was determined by the funnel method. The accurately weighed blend was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the blend. The blend was allowed to flow from the funnel on the surface. The diameter and height of the heap formed from the blend were measured. The angle of repose was calculated using the following formula¹³.

$$\tan \theta = h/r$$

Where, "h" is the height of the heap and "r" is the radius of the heap of granules.

Bulk density (BD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The BD of powder blends was determined using the following formula¹⁴.

$$\text{Bulk density} = \text{Total weight of powder} / \text{Total volume of powder}$$

Tapped bulk density (TBD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was

noted which gave the tapped volume. The TBD of powder blends was determined using the following formula¹⁵.

TBD = Total weight of powder/Total volume of tapped powder

Carr's compressibility index

The Carr's compressibility index was calculated from bulk density (BD) and tapped density of the blend. A quantity of 2 g of blend from each formulation, filled into a 10 ml of measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5 cm. The tapped frequency was 25 ± 2 /min to measure the tapped volume of the blend. The BD and tapped density were calculated by using the bulk volume and tapped volume.

Carr's compressibility index was calculated using the following formula^{16,17}.

Carr's compressibility index (%) = [(Tapped density-Bulk density) \times 100]/Tapped density

Hausner's ratio

It is the measurement of frictional resistance of the drug. The ideal range should be 1.2-1.5, it was determined by the ratio of tapped density and bulk density.

HR = Tapped Density/ Bulk Density

Post-compression parameters

Shape of tablet

Directly compressed tablets were examined under the magnified lens for the shape of the tablet.

Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier caliper¹⁸.

Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

Friability test

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, de dusted and reweighed. The friability was calculated as the percentage weight loss.

% friability was calculated as follows

% Friability = $(W_1 - W_2) \times 100/W_1$

Where W_1 = Initial weight of the 10 tablets, W_2 = Final weight of the 10 tablets after testing.

Friability values below 0.5-1% are generally acceptable [19].

Weight variation test

To study weight variation individual weights (W_1) of 20 tablets from each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

Swelling index

Swelling study of individual polymers and combinations was carried out using eight-stage USP type 1 (basket) Dissolution Test Apparatus (Lab India, DS 8000) at 50 rpm, and 0.1 N HCl was used as medium, and the temperature was maintained at $37 \pm 0.5^\circ\text{C}$. Weight of individual tablet was taken prior to the swelling study (W_1). The tablet was kept in a basket. The weight of tablet was taken at time interval of 2, 4, 8, 12 hours (W_2). Percent hydration (swelling index) was calculated as shown in Table using the following formula:

Swelling index = $(W_2 - W_1) \times 100/W_2$,

Where W_1 is the initial weight of tablet and W_2 is the weight of hydrated tablet

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 10mg of drug was transferred to 10ml standard flask. The powder was dissolved in 5 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45μ membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at λ max of 294nm using of 0.1 N HCl as blank.

Dissolution rate studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was set into the dissolution flask maintaining the temperature of $37 \pm 0.5^\circ\text{C}$ and rpm of 75. One levofloxacin tablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 10 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 2 hours using 10ml pipette. The new disintegration medium (37°C) was supplanted each time with a similar amount of the sample and takes the absorbance at 294.0 nm using spectroscopy.

Kinetic analysis of dissolution data

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent. Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets.

$$C = K_0 t \quad (1)$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\text{Log}C = \text{Log}C_0 - K_1 t / 2.303 \quad (2)$$

Where, C_0 is the initial concentration of drug and K_1 is first order constant.

$$Q = KHt^{1/2} \quad (3)$$

Where, KH is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = KHC t \quad (4)$$

Where, Q_t is the amount of drug remained in time t , Q_0 is the initial amount of the drug in tablet and KHC is the rate constant for Hixson-Crowell rate equation.

The following plots were made using the in-vitro drug release data

Cumulative % drug release vs. time (Zero order kinetic model); Log cumulative of % drug remaining vs. time (First order kinetic model); Cumulative % drug release vs. square root of time

(Higuchi model); and cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. time (Hixson-Crowell cube root law) ²⁰.

RESULTS AND DISCUSSION

λ_{max} of levofloxacin was found to be 294 nm by using U.V. spectrophotometer ((Labindia-3000 Plus)) in linearity range 2-10 $\mu\text{g/ml}$ Fig.1.

Tablet powder blend was subjected to various pre-compression parameters Table 2. 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 0.428 to 0.439 (gm/ml) showing that the

powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.531 to 0.548 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 18.704 to 20.438 which show that the powder has good flow properties. All the formulations have shown the Hausner's ratio ranging between 1.230 to 1.257 indicating the powder has good flow properties.

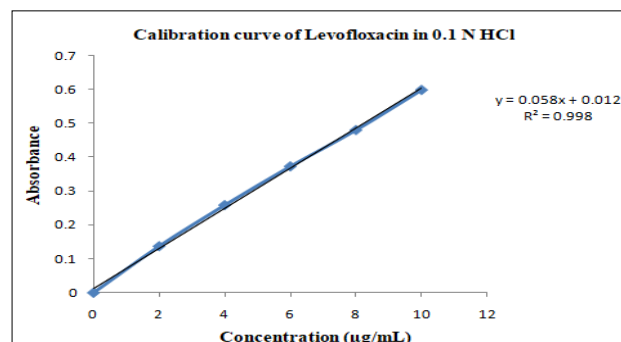


Figure 1 Calibration curve of levofloxacin in 0.1 N HCl at 294nm

Table 2 Result of pre-compression properties of levofloxacin GR tablets

F. Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner's ratio
F1	0.432	0.539	19.852	1.248
F2	0.441	0.543	18.785	1.231
F3	0.436	0.548	20.438	1.257
F4	0.432	0.536	19.403	1.241
F5	0.439	0.540	18.704	1.230
F6	0.428	0.531	19.397	1.241

The results of post-compression parameters such as the uniformity of weight, hardness, thickness, friability, swelling index and disintegration time of the tablets are given in Table 3. All the tablets of different batches complied with the official requirements of uniformity of weight. The hardness of the tablets ranged from 5.1 ± 0.3 to 5.6 ± 0.1 kg/cm² and the friability values were less than 0.9% indicating that the

matrix tablets were compact and hard. The thickness of the tablets ranged from 3.21 to 3.45 mm. All the formulations satisfied the content of the drug as they contained 98.78 to 99.56 % of levofloxacin and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control.

Table 3 Results of post compression properties of levofloxacin FGR tablets

F. code	Thickness (mm)	Hardness (kg/cm ²) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3
F1	3.25	5.2±0.2	445±5	0.898±0.025	99.22±0.022
F2	3.26	5.4±0.2	455±4	0.852±0.023	98.89±0.021
F3	3.45	5.6±0.1	450±6	0.987±0.014	99.56±0.026
F4	3.25	5.5±0.3	452±5	0.569±0.015	99.25±0.041
F5	3.22	5.2±0.2	442±4	0.852±0.021	98.78±0.032
F6	3.21	5.1±0.3	440±3	0.745±0.015	99.12±0.025

Swelling study of individual polymers and combinations was carried out using eight-stage USP type 1 (basket) Dissolution Test Apparatus (Lab India, DS 8000) at 50 rpm, and 0.1 N HCl was used as medium, and the temperature was maintained at $37 \pm 0.5^\circ\text{C}$. Results was given in table 4

Table 4 Results of swelling index of levofloxacin matrix tablets

F. Code	% Swelling Index			
	2 hrs.	4 hrs.	8hrs.	12hrs.
F1	22.36	43.56	63.25	73.25
F2	24.36	44.58	68.89	75.65
F3	23.45	43.36	65.52	74.58
F4	28.89	54.57	69.98	79.85
F5	29.45	55.45	70.23	80.21
F6	26.45	56.74	72.45	78.25

The tablets were evaluated for in vitro dissolution studies in Phosphate buffer 0.1N HCl for 12 hrs. The results of the optimized formulation F4 showed maximum drug release i.e. 98.78 % at the end of 12 hrs. The results of release studies of formulations F4 was shown in Table 5 & Fig 2. The *in vitro* drug release data of the optimized formulation F4 was subjected to goodness of fit test by linear regression analysis

according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of first order was maximum i.e. 0.989 hence indicating drug release from formulations was found to follow first order release kinetics Table 6 & Fig 3-6.

Table 5 *In-vitro* drug release study of GRF tablets

Time (hr)	% Cumulative Drug Release					
	F1	F2	F3	F4	F5	F6
0.5	33.25	32.25	30.14	25.56	20.36	18.56
1	45.56	40.23	39.98	32.25	26.65	22.25
1.5	65.56	60.58	59.88	46.69	40.23	39.98
2	88.89	79.98	78.89	58.89	51.12	49.98
3	98.89	87.52	85.56	69.98	60.23	55.56
4	-	93.32	92.23	76.12	71.45	69.78
6	-	98.85	99.12	88.56	79.98	78.89
8	-	-	-	92.23	86.65	83.32
12	-	-	-	98.78	90.12	89.98

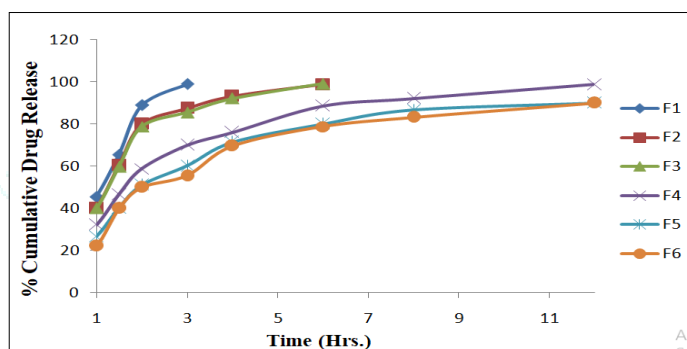


Figure 2 *In-vitro* drug release study of GRF tablets

Table 6 Regression analysis data of levofloxacin floating matrix tablets

Batch	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
	r ²	r ²	r ²	r ²
F4	0.788	0.989	0.916	0.946

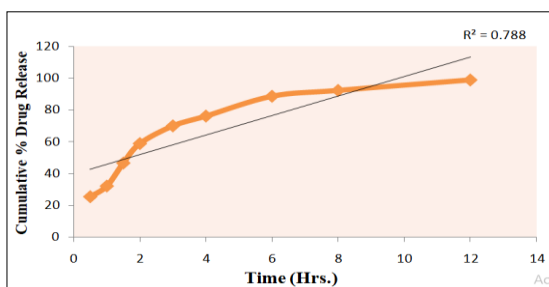


Figure 3 Zero order release kinetics

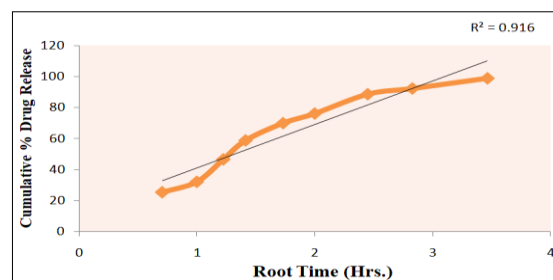


Figure 5 Higuchi release kinetics

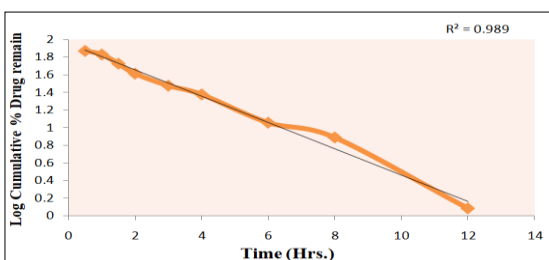


Figure 4 First order release kinetics

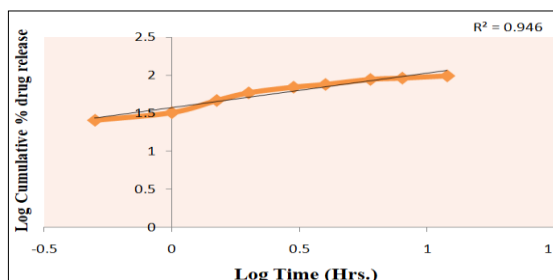


Figure 6 Korsmeyer-Peppas release kinetics

CONCLUSION

Gastro-retentive controlled drug delivery system of levofloxacin was prepared to increase the therapeutic effect of the drug by releasing the drug at the proximal part of the small intestine. Levofloxacin is used in eradication of *Helicobacter Pylori* and other bacterial infections. Levofloxacin floating tablets were prepared using of carbopol and hydroxy propyl methyl cellulose in various ratios by direct compression technique employing sodium bicarbonate as gas-generating agent. According to the above results, formulation F4 offered best controlled release along total floating time of 12 h and in-vitro drug release of 98.78% at the end of 12 h.

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