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Preparation and evaluation of prolonged-release Levofloxacin floating tablets by direct compression method adopting the effervescent technique

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ABSTRACT

The recent study aimed to develop a gastric floating drug delivery system (GFDDS) containing levofloxacin and a floating gas-forming agent, sodium bicarbonate. This effervescent model approach was developed to prolong the action of gastric residence time for poor oral bioavailability drugs due to less gastric retention time and degradation in intestine alkaline pH.The floating effervescent tablet was prepared by adopting the direct compression method using various polymers like Karaya gum, Xanthan gum, and Carbopol at different concentrations. Sodium bicarbonate was used as a gas-forming agent, and other excipients used were lactose, magnesium stearate, and talc to enhance the binding, lubrication, and flow properties. The swelling nature, drug kinetics, in vitro drug release, and drug stabilities of the formulated tablets were all evaluated. The result of kinetic drug release revealed that F10 follow the Higuchi plot model, indicating According to a nonFickian diffusion kind of drug release pattern.

Keywords: Gastric floating, Levofloxacin, Gas-forming agent, Gastric retention time, Karaya gum, Xanthan gum, Carbopol, Higuchi plot model.

1. INTRODUCTION

The most convenient route to administer therapeutic agents at low cost is the oral route; it holds the highest level of patient compliance. Due to the poor absorption window all through the GIT, the oral controlled drug delivery system has experienced limited success in some developments. A controlled-release drug delivery system has more advantages over other drug delivery systems for improving GIT drug absorption by retaining the drug in the stomach for a long time. Hence, this system is favorable for drugs that get degraded in the intestine or that act locally in the stomach. Such gastric retention may increase the solubility of drugs, which are poorly soluble in the alkaline PH of the intestine. [1,2]

A floating drug delivery system is an advanced gastro-retentive drug delivery system for enhancing bioavailability and reducing fluctuations in plasma drug concentration. a low-density system with adequate buoyancy to float over GI fluids without affecting the gastric emptying rate, thus helping to produce prolonged action as well as increased gastric retention time. There are two types of floating drug delivery systems: effervescent and non-effervescent. The effervescent method uses gas-generating agents to produce carbon dioxide, which decreases the density of the system and makes it float on the gastric fluid. Some gas-generating agents are sodium bicarbonate, tartaric acid, and citric acid. On the other hand, the non-effervescent system uses swelling and bio adhesive techniques for buoyancy. Some excipients used are gel-forming materials and matrix-forming materials [3,4,5].

Levofloxacin is a synthetic fluoroquinolone (fluoroquinolone) antibacterial agent that inhibits supercoiling. (S)-9-fluoro-2, 3-dihydro -3-methyl-10-(4-methyl piperazine-1-yl) 7-oxo-7H-pyrido [1, 2, 3-de] 1,4-benzoxazine-6-carboxylic acid. Like all quinolones, it functions by inhibiting the topoisomerase enzymes. When administered orally, this drug quickly gets absorbed with a plasma concentration profile over time that is identical to intravenous administration of the same amount over 60 minutes. Subsequently, oral and intravenous formulations of levofloxacin are considered to be replaceable. [6]

2. MATERIALS AND METHOD

2.1. MATERIALS

Levofloxacin was received as a gift sample from Aurabinda Pharma Pvt. Ltd., Hyderabad. Karaya gum and xanthan gum were purchased from Yarrow Chemicals Ltd., Mumbai. Carbopol and sodium bicarbonate were purchased from Loba Chemicals, Mumbai. All other chemicals used in this study were of analytical grade.

2.2. METHOD

2.2.1. PREFORMULATION STUDIES

Solubility

The Solubility test was performed by adding little by little to the test tubes containing water, 0.1N Hcl, acetone, acetonitrile, and dichloromethane to find out the solubility

pH

The pH of Levofloxacin was determined by IP studies(between 3 and 4.5 in a 2.5% w/v solution).

Compatibility Studies

The obtained drug and polymer were subjected to IP studies. In the present study, the potassium bromide disc (pellet) method was employed, and the obtained IR spectra were compared with the reference spectrum of levofloxacin (Table -1). [7,8]

Table – 1: FT-IR Spectra data: Drug and Drug with polymers

Groups and mode of vibrations	Frequency (in cm^{-1})		
	Drug	Drug with Polymers	Expected Range
NH stretching	3327.32	3356.45	3500-3300
C-N stretching	1327.07	1354.23	1350-1000
C-F stretching	1379.15	1390.26	1400-1000
C=C stretching	1712.54	1720.12	1720-1708
C=O carboxylic stretching	1728.33	1698.57	1730-1700
C-H stretching	3084.28	3054.18	3050-3010
O-H carboxylic stretching	2976.26	3010.43	3400-2400

Table – 2: Composition of Levofloxacin floating tablets

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Levofloxacin	100	100	100	100	100	100	100	100	100	100
Karaya Gum	20	20	40	40	40	60	60	60	60	-
Carbopol	40	60	40	20	60	20	40	60	-	60
Xanthum Gum	60	40	40	60	20	40	20	-	60	60
Sodium bicarbonate	60	60	60	60	60	60	60	55	55	55
Lactose	20	20	20	20	20	20	20	25	25	25
Talc	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5	5

2.2.2. PREPARATION OF LEVOFLOXACIN FLOATING TABLETS

Levofloxacin was passed through sieve no. 20, and other excipients Karaya gum, Carbopol, Xanthan gum, and sodium bicarbonate) were passed through sieve no. 40; talc was passed through sieve no. 60 and collected in separate clean bowls. Finally, magnesium stearate was passed through sieve no. 60 and collected. For 10 minutes, levofloxacin was geometrically mixed with Karaya gum, Carbopol, Xanthan gum, and sodium bicarbonate. After that, talc was added and mixed for 5 minutes. After sufficient mixing of the drug and another component, magnesium stearate was added and mixed for another 2 minutes for lubrication. A rotary tableting machine was used to compress the lubricated granules. The weight of the tablet was kept constant for all formulations (Table - 2).[9]

3. EVALUATION STUDY

3.1. Pre-Compression Parameters:

Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined for prepared granules. LBD and TBD were calculated by using the following formula:

LBH = weight of granules/volume of packing.

TBH = granule weight or tapped volume of packing

Compressibility Index

The percent compressibility of granules as determined by Carr's compressibility index was calculated by the following formula:

Carr's Index = TBD – LBD/ TBDx 100

Hausner's Ratio

The following formula was used to calculate the Hauser ratio:

Hausner's ratio = TBD/LBD

The Angle of Repose

The angle of repose is used to measure the frictional forces in loose powder and granules. The prepared granules were allowed to pass through the funnel, which was fixed to a stand at a particular height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed. Tan θ = h/r, θ = tan-1 (h/r) Where θ = angle of repose. [10]

Post-Compression Parameters:

Drug Content

Ten tablets from each batch were weighed and powdered. accurately weighed, dissolved in a suitable amount of 0.1 N HCl, and filtered up to 100 ml. 2 ml of filtrate made with 0.1 N HCl up to 100 ml The absorbance of the resulting solution is measured by a UV spectrophotometer at 276 nm.[11]

Floating Test

The prepared tablets were placed in a 100-ml beaker containing 0.1 N HCl. The duration for which the dosage form remains buoyant was measured. Total floating time (TFT) refers to the total amount of time that the dosage form remains buoyant. [12]

Swelling Study

The study was done by immersing the dosage form in 0.1 N HCl at 37°C and determining these

factors at regular intervals of up to 8 hours. Water uptake was measured in terms of percent weight gain, as given by the equation. [13]

WU = (Wt – Wo) x 100 / Wo

In-vitro Dissolution Studies:

The in-vitro drug release profile of levofloxacin was evaluated using the paddle method (900 ml of 0.1 N HCl at 370.5 oC and 50 rpm). Aliquots of samples were withdrawn after the 1st, 2nd, 4th, 8th, 10th, and 12th hours. The withdrawn aliquots were filtered and suitably diluted with 0.1 N HCl to obtain a concentration of 10µg/ml and their absorbance was measured spectrophotometrically at 276 nm to determine drug release.[14]

Kinetics of Drug Release

The data obtained from in vitro dissolution studies were subjected to analysis to determine the release kinetics of the formulations. The obtained data were put through a zero-order kinetics model (cumulative percentage release against time), a first-order kinetics model (log cumulative percentage release against time), the Higuchi model (cumulative percentage release against a square root of time), and the Korsmeyar&Peppa's model (log cumulative percentage release against log time) to identify release mechanisms. [13]

Stability studies

The prepared floating tablets of levofloxacin were placed in plastic tubes containing desiccant and stored at ambient humidity conditions at room temperature, at oven temperature (40±2oC), and in the refrigerator (2-8oC) for 60 days. The samples kept for stability were evaluated after 15, 30, 45, and 60 days for selected batches. [14]

4. RESULTS AND DISCUSSION

Hydrodynamically balanced tablets of Levofloxacin were prepared and evaluated for their use as a Gastroretentive drug delivery system. The formulation study result shows levofloxacin is soluble in water and 0.1N HCL (pH-3.7). FT-IR studies prove that excipients and levofloxacin are compatible. (Shown in Figure 1 and Figure 2). The bulk density, compressibility index, Hauser ratio, and angle of repose values indicate the prepared formulation has good flow properties. The post-compression parameters result shows the percentage drug content of the ten formulations was found to be 97.53%–100.40%, which indicates dose uniformity. The results of floating lag time for all ten formulations were found to be with in 1 minute. The total floating time for F1, F4, and F9 is more than 10 hours, and it is more than 14 hours for F2, F3, F5, F6, F7, F8, and F10. According to the swelling study, the swelling of all formulated tablets increased for 4-6 hours (Shown in table 3) before decreasing. The in-vitro drug release of Formulation F10 shows the maximum dissolution rate and % of dissolution was found to be 95.32% (Shown in table 4).. The other Formulations F1-90.20, F2 – 83.36%, F3 – 73.30%, F4-79.50,F5-74.20, F6- 85.20, F7- 74.40, F8-86.38, F9-80.98.F10was found to be satisfactory with the dissolution profile results and are retained for

further research (shown in figure 3 and 4). The results of the dissolution studies were fitted to various drug release kinetic equations. The regression coefficient (R2) value was highest for the Higuchi plot release equation in F10.[15] The data obtained from the release kinetics fitted with the Higuchi model. The n value obtained from the Korsmeyar-Peppa's model showed that the release mechanism was non-Fickian. The stability study results reveal no significant changes in appearance, floating test, drug content, or drug release.

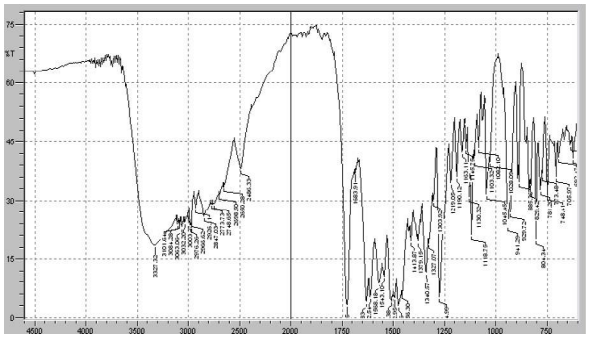

Figure – 1: FT-IR spectrum of pure drug Levofloxacin.

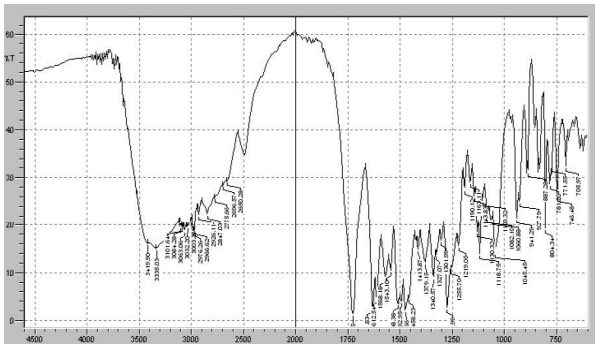

Figure – 2: FT-IR spectrum of Levofloxacin with Polymers.

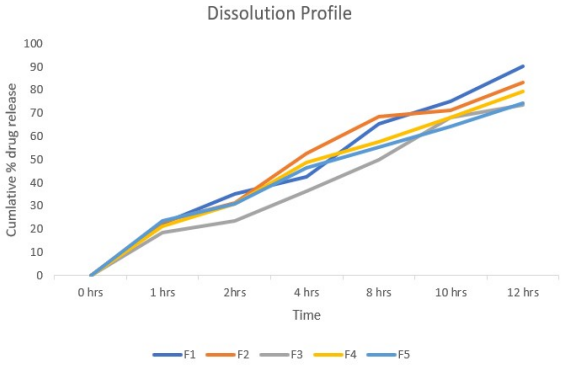

Figure – 3: In-*Vitro* drug Release study of Levofloxacin Floating Tablets (F1-F5).

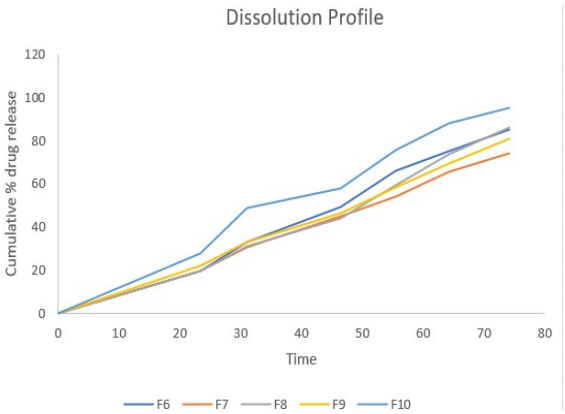

Figure – 4: In-*Vitro* drug Release study of Levofloxacin Floating Tablets (F6-F10).

Table – 3: Swelling Index of Levofloxacin Floating Tablets

Code	Percentage of swelling inTime (Hours)				
	1	2	4	6	8
F1	151.38±1.25	161.72±1.85	169.92±2.32	163.11±3.22	117.18±2.94
F2	130.14±2.45	147.33±2.97	155.44±3.36	155.42±3.92	127.93±3.12
F3	124.54±1.60	132.51±1.94	146.41±2.24	148.23±2.92	139.87±2.22
F4	149.27±0.79	160.51±1.12	161.41±1.75	168.17±2.24	140.16±1.86
F5	131.28±2.37	144.72±2.98	164.28±3.12	157.45±3.87	129.24±2.32
F6	132.22±1.99	149.06±2.13	157.14±2.64	166.75±3.15	130.42±2.18
F7	134.04±1.25	151.42±1.90	141.75±2.35	147.80±3.23	129.71±2.75
F8	142.32±2.75	154.91±2.97	158.40±3.30	151.04±3.76	139.42±2.67
F9	138.74±1.86	149.04±2.26	168.35±2.61	174.12±3.15	133.50±2.54
F10	151.12±2.25	162.47±2.76	170.72±2.97	179.74±3.26	141.28±2.14

Table - 4: In-*vitro* drug Release study of Levofloxacin Floating Tablets

Batch No	Cumulative percentage of drug release					
	1 hrs	2hrs	4 hrs	8 hrs	10 hrs	12 hrs
F1	22.29	35.30	42.40	65.40	75.20	90.20
F2	23.32	31.40	52.70	68.40	71.20	83.36
F3	18.70	23.72	36.21	49.97	67.98	73.70
F4	21.10	30.80	48.80	57.60	68.20	79.50
F5	23.40	31.00	46.50	55.50	64.20	74.20
F6	20.00	33.23	49.23	66.05	75.20	85.20
F7	19.90	31.00	45.07	54.34	65.62	74.40
F8	20.00	31.05	44.10	59.50	73.76	86.38
F9	22.02	33.20	46.40	58.70	69.34	80.98
F10	28.00	49.00	58.00	75.62	88.32	95.32

Table - 5: Kinetics of drug release of R^2 value for F2, F5, F8, and F10

Batch No.	Regression Coefficient (R^2)				
	Zero Order	First Order	Higuchi	Korsmeyar - Pappas	
				$_R2$	n
F2	0.9760	0.9611	0.9920	0.9834	0.612
F5	0.9820	0.9714	0.9868	0.9918	0.633
F8	0.9727	0.9642	0.9918	0.9840	0.542
F10	0.9466	0.9701	0.9937	0.9879	0.521

5. CONCLUSION

Hydrodynamically balanced tablets of Levofloxacin can be formulated to increase gastric residence and thereby improve drug bioavailability (Shown in table 2). A direct compression technique was used to create floating tablets of Levofloxacin using sodium bicarbonate and sodium oxonate as gas-generating agents and natural gums as polymers. The dissolution study formulation F10 had a good release, and found to be excellent (Shown in table 3). Data obtained from kinetic treatment revealed that F 10 follows the Higuchi model release kinetics. The 'n' value obtained from 0.521 to 0.633 indicates the non-Fickian diffusion (shown in figure 4). The results of stability studies indicated that the most suitable storage The Formulations was Subjected to Stability Studies for 3 Months. The Obtained results of stability studies had shown that there were no Significant changes at different storage Conditions.

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