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STOMACH TARGETED MUCOADHESIVE DRUG DELIVERY OF OFLOXACIN

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ABSTRACT

The Present study concerns the development and characterization of stomach targeted mucoadhesive tablets of ofloxacin in order to prolong the gastric residence time after oral administration. Ofloxacin is a synthetic fluoroquinolone antibacterial agent that inhibits the supercoiling activity of bacterial DNA gyrase, halting DNA replication and effective against both the gram positive and gram negative bacteria. Different types of polymers such as sodium carboxymethylcellulose, carbopol934P, hydroxypropylmethylcellulose K4M and polyethylene glycol 6000 were used to formulate the mucoadhesive tablets. The tablets were prepared by direct compression technique and were evaluated for parameters such as weight variation, drug content, thickness, hardness, surface pH, *in vitro* mucoadhesive strength, swelling index, and *in vitro* drug release. All the parameters evaluated for all formulations were satisfactory. Among all formulations, F3 with combination of carbopol934P and sodium carboxymethyl cellulose showed greater *in vitro* drug release of 98.86 after 24 hrs, better mucoadhesive strength and good swelling. Hence formulation F3 was optimized and the stability studies were carried out according to ICH guideline which showed that the formulation F3 was stable.

KEYWORDS: **Ofloxacin, Mucoadhesive drug delivery system, Sodium carboxymethylcellulose, bioadhesive polymers.**

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INTODUCTION

The principle of oral drug delivery system is to convey drugs for longer period of time to achieve better bioavailability[1]; oral route is most patient acceptance and cost effective because of its convenient, safe and ease of administration.[2] Hence oral drug delivery system is most widely used route of drug administration for systemic drug delivery.[3] Ofloxacin belongs to the class of organic compounds known as quinoline carboxylic acids. These are quinolines in which the quinoline ring system is substituted by a carboxyl group at one or more positions. A synthetic fluoroquinolone (fluoroquinolones) antibacterial agent that inhibits the supercoiling activity of bacterial DNA gyrase, halting DNA replication. It is used to treat the infections of respiratory tract, kidney, skin, soft tissue, UTI, urethral and cervical gonorrhea. Ofloxacin is a quinolone/fluoroquinolone antibiotic, its mode of action depends on blocking of bacterial DNA replication by binding itself to an enzyme called DNA gyrase, which allows the untwisting required to replicate one DNA double helix into two. Ofloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria.[4] It acts on DNA gyrase and toposiomerase IV prevents the excessive supercoiling of DNA during replication or transcription. By inhibiting their function, the drug thereby inhibits normal cell division. Bioavailability of ofloxacin in the tablet formulation is approximately 98%[20]. Elimination is mainly by renal excretion. Between 65% and 80% of an administered oral dose of ofloxacin is excreted unchanged via the kidneys within 48 hours of dosing. Four to eight percent of an ofloxacin dose is excreted in the feces. This indicates a small degree of biliary excretion of ofloxacin.[5,6] Bioadhesion means adhesion between two biological surfaces or biological and synthetic surface[7]; for extended period by interfacial forces. When adhesive attachment is to mucous membrane the phenomenon is referred to as mucoadhesion.[8] Mucoadhesive drug delivery systems in recent trend has increased interest in pharmacist for promoting dosage forms residence time along with prolonged contact time of drug with various biological membrane in the body.[9] Mucoadhesion keeps the delivery system adhering to the mucus layer.[10] Mucoadhesive drug delivery system gives rapid absorption and good bioavailability due to large surface area and blood flow. It bypasses the first-pass hepatic metabolism and avoiding the degradation of gastrointestinal enzymes.

The rate of mucus turnover can be affected by the presence of a mucoadhesive device and the nature of the surface presented to the mucoadhesive formulation can vary significantly depending on the body site and the presence of local or systemic disease.

MATERIALS AND METHODS

MATERIALS

Ofloxacin was obtained as gift sample from Cipla India Pvt. Ltd., Goa (India). Carbopol 934P, HPMC K4M were obtained from Hniosome Healthcare Pvt. Ltd., Punjab. Sodium CMC, PEG 6000, Magnesium state and Talc were procured from SD Fine Chemicals, Mumbai and Lactose DC was received from Cipla India Pvt. Ltd., Goa (India).

METHODS

Formulation of tablets

Using different polymers like carbopol 934P, HPMC K4M, SCMC and PEG 6000 based on the requirement ofloxacin tablets were prepared by direct compression technique. Table 1 shows the different formulations of the tablets. All the excipients were powdered and passed through mesh-60 sieve. Ofloxacin and mucoadhesive polymers were mixed by blending uniformly using glass mortar and pestle for a suitable time period. Then lactose DC, PFG6000 and magnesium sterate were added and blending was continued further for 2-3 minutes, then tablets were compressed with 9 mm punch. The weight of the tablets is kept constant. Each tablet contains 200mg of ofloxacin and tablet has an approximate weight of 750mg. Pre compression parameters were evaluated and summarized in the Table 2.

Table 1
Formulations of ofloxacin mucoadhesive tablets (F1-F6)

S. No.	Ingredients (mg)	Formulations					
		F1	F2	F3	F4	F5	F6
1	Ofloxacin	200	200	200	200	200	200
2	Carbopol 934P	200	250	300	-	-	-
3	HPMC K4M	-	-	-	200	250	300
4	Sodium Carboxy Methyl Cellulose	50	50	50	50	50	50
5	PEG 6000	100	100	100	100	100	100
6	Magnesium Stearate	5	5	5	5	5	5
7	Talc	2.5	2.5	2.5	2.5	2.5	2.5
8	Lactose DC	192.5	142.5	92.5	192.5	142.5	92.5

Table 2
Pre-compression Parameters For all the formulations (F1-F6)

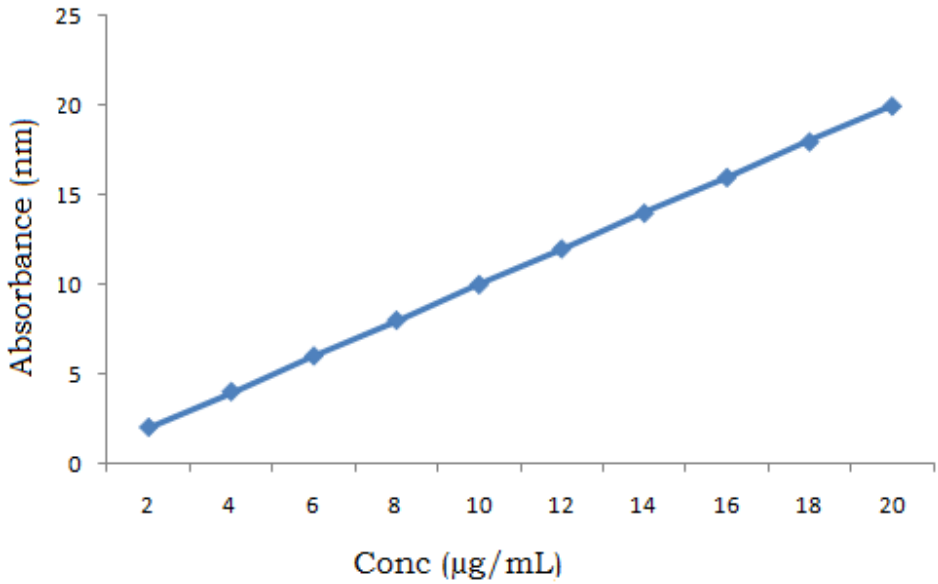
Sl. No.	Formulation Code	Angle of Repose (θ)	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's Index (%)	Hausner's Ratio (Hg)
1	F1	26.83	0.388	0.429	9.55	1.03
2	F2	25.16	0.405	0.429	5.59	1.05
3	F3	29.92	0.443	0.472	6.14	1.06
4	F4	24.73	0.419	0.452	7.30	1.05
5	F5	26.42	0.425	0.445	4.96	1.04
6	F6	27.92	0.453	0.509	4.75	1.04

Evaluation of tablets
The following standards or quality control tests were carried out on compressed tablets. The formulated tablets were evaluated for the following physicochemical parameters.

Physical appearance
Physical appearance plays an important role in consumer acceptance; this controls the uniformity between lots and between tablets. Physical appearance includes tablets size, shape color, odor, taste, surface texture, physical flows and consistency.[11]

Drug content
The drug content was evaluated by UV spectroscopy. A linear calibration curve was constructed with Beer's range of 2 to 20 µg/ml. Ofloxacin exhibits maximum absorbance at 294 nm (λmax). Figure 1 shows the calibration curve range for ofloxacin.

Figure 1
Calibration Curve for Ofloxacin



Correlation coefficient: 0.9996,
Slope: 0.9068,
Intercept: 0.009864

Hardness
Hardness was measured by Monsanto hardness tester.[12] Hardness of the tablet is the ability to withstand the mechanical hazardous during packing, transport and handling. The hardness was measured for all the formulations and results were summarized in the table 4. This shows that there is no significant deviation in all the prepared formulations. All the formulated tablets shown good hardness indicates that all the tablets exhibit good mechanical strength.

Thickness
Thickness of the tablet was measured using Mitutoyo digital vernier caliper. The results were tabulated in table 4 and no significant deviation was observed in all the formulation.

Weight variation test
Twenty tablets were taken randomly from each batch and weighted individually. The average weight and standard deviation of twenty tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviates from average weight by more than the percentage shown in Table 3 and none deviate by more than twice the percentage shown.[13]

Table 3
% Deviation for weight variation

Average weight of tablets	Percentage deviation
130 or less	10
130-324	7.5
More than 324	5

Friability

Friability was evaluated using Roche friabilator; twenty tablets were weighed initially and were rotated at 25 rpm for 4 mins in Roche friabilator. After rotation tablets were taken and made them dust free and weighed again. The following formula was used to calculate percentage friability.[12]

$\%F = [1-(W_0/W)] \times 100$

Where,

%F= Percentage Friability

W_0= Initial weight of the tablets

W= Weight of the tablets after rotation

For all the formulations post compression parameters were evaluated and summarized in the table 4.

Table 4
Post-compression Parameters For all the formulations (F1-F6)

Sl. No.	Formulation Code	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight Variation (mg)	Drug Content Uniformity (%)
1	F1	4.2±0.03	5.8	0.71	724±0.04	98.35
2	F2	4.1±0.02	6.4	0.69	742±0.04	99.68
3	F3	4.1±0.03	6.9	0.65	744±0.03	99.89
4	F4	4.2±0.02	5.9	0.72	729±0.03	99.13
5	F5	4.1±0.03	6.2	0.71	738±0.02	99.29
6	F6	4.2±0.03	6.3	0.68	742±0.04	99.78

mm: milli meter
Kg/cm^2: killo gram per centimeter square
Mg: milligram

Mucoadhesive strength test

A modified physical balance was used to evaluate the mucoadhesive strength of the tablet.[14] In this balance right pan was replaced with glass slide and right pan weight made equal with left pan by additional weight. A Teflon block was kept with buffer 0.1N Hcl pH 1.2 in a beaker which was kept below the balance. A model membrane i.e. rat stomach mucosa was used and 0.1 N Hcl of pH 1.2 was used as a moistening fluid. Rat stomach mucosa was tied with teflon block and thread, buffer volume was maintained up to surface of the mucous in the beaker[11-15]. The formulated tablet was attached to the glass slide of the balance and then was made to come in contact with mucosa and tablet. 0-01gm load was kept on glass slide for some constant time (preload time) to form adhesion bond between mucosa and tablet. The preload time was kept constant for all the formulations. The preload was removed and 100 drops per minute were added to the bottle which was kept on left pan of the balance. Water drops was added until the mucoadhesive tablet was detached from the mucosa and stopped. Then water is weighed in grams. Force of adhesion was evaluated using the following the formula.

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength}}{100} \times 9.81$$

Wash off test

Mucoadhesive properties of formulated tablets were evaluated by wash off method. In this method pieces of mucosa were mounted on to the glass slide and connected with suitable support. Two tablets were attached on to the arm of a USP tablet disintegrating test machine which was given a slow regular up and down movement in the phosphate buffer pH 7.4 at 37°C. Time taken to detach both the tables was considered.[15,16]

Swelling index[11]

There is a increase in weight and volume because of absorption of liquid by the tablet excipients. This may be due to capillary spaces saturation with in particles or macromolecule hydration. Through pores liquid enters the particles and bind to large molecules, breaking the hydrogen bond and resulting in the swelling of particles. Swelling can be evaluated in terms of % weight gain by the tablet. Tablet was weighed and placed in a beaker filled with 900mL of distilled water and roated at 50 rpm maintained at 37 ± 5°C. At each interval of time the tablet was removed blotted to remove excess of water and weighed. This procedure was followed up to 12 hours.

$$\text{Swelling Index } \% = \frac{(Wt - Wo)}{Wo} \times 100$$

Where,
Wt = Weight of the tablet at the time t
Wo = Weight of the tablet before placing in the beaker.

***In vitro* dissolution studies:**

Dissolution of the tablets was evaluated using USP XXIII dissolution type II apparatus using paddle. The tablet was fixed to peddle by hydration mechanism. The dissolution vessel was filled with 900mL of buffer (0.1N Hcl) of pH 1.2 and temperature was maintained at 37 ± 0.5°C. Peddle speed was maintained at 100 rpm. 1mL of sample was taken out at predetermined intervals of time upto 12 hours and the same volume of fresh buffer was replaced to maintain vessel condition. The withdrawn samples were diluted to 10mL with 0.1N Hcl, filtred and analyzed on UV spectrophotometer at 294 nm using 0.1N Hcl as a blank. Percentage cumulative drug release was calculated.

Accelerated stability studies

The stability studies were done in compliance with ICH guidelines. The Thermo lab TH 90S stability chamber was used to evaluate the stability studies. The temperature and relative humidity selected was 42 ±2°C and 75±5% for a period of three months.[17] Table 5 summarizes the stability parameters of formulation F3.

Table 5
Stability Parameters for Optimized Formulation F3

Sl. No.	Parameter	Data after three months
1	Hardness	6.9
2	Bioadhesive Strength	25.52
3	Swelling Index	241
4	Surface pH	7.1
5	*Invitro* Dissolution	98.78

RESULTS AND DISCUSSION

Mucoadhesive strength

The mucoadhesive strength was evaluated for all the formulated formulations. Fig.2 shows the mucoadhesive strength for all the formulated formulations. Modified balance method was used to evaluate the mucoadhesive force (Fig.3). Constant time of 15mins was maintained during evaluation. Polymer viscosity and concentration plays an important role in mucoadhesion. By evaluation of the mucoadhesive strength of all the formulations it was concluded that by increasing the concentration of Carbopol 934P, mucoadhesive strength can be increased. High molecular weight and high viscosity polymers will have the higher adhesive strength.[18]

Figure.2
Mucoadhesive strength of all the formulations (F1-F6)

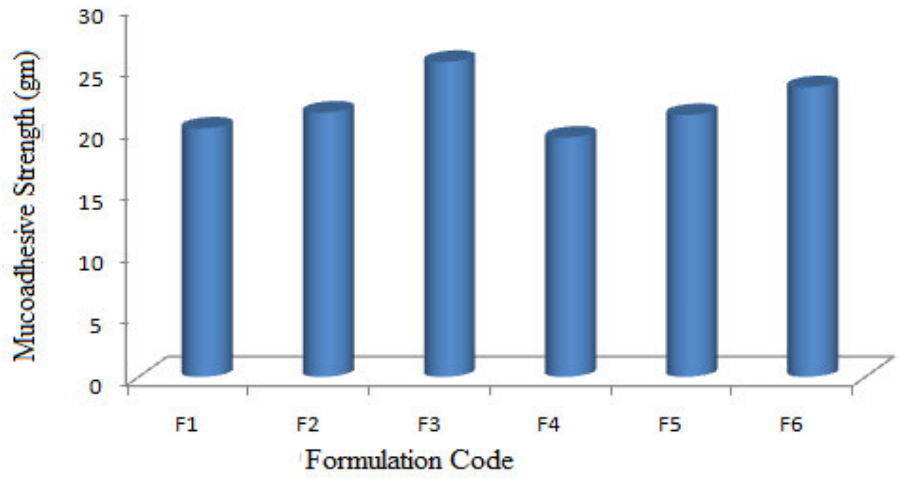
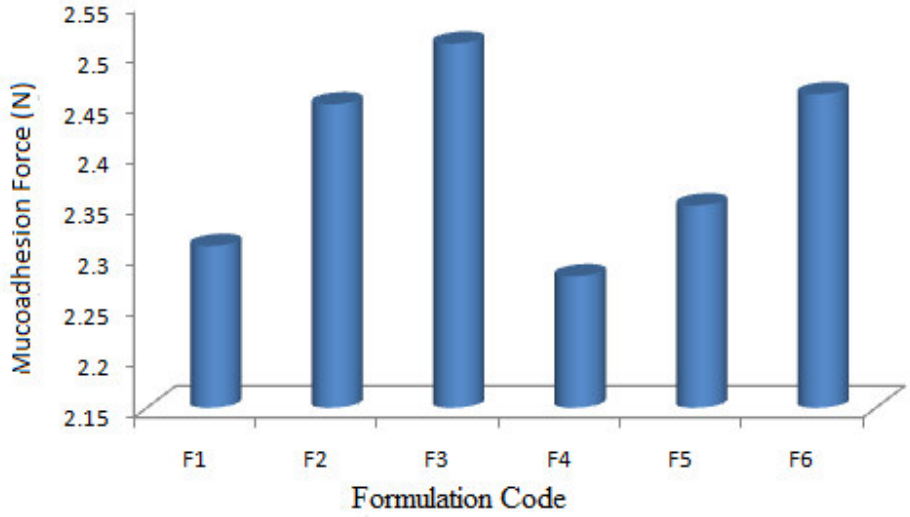


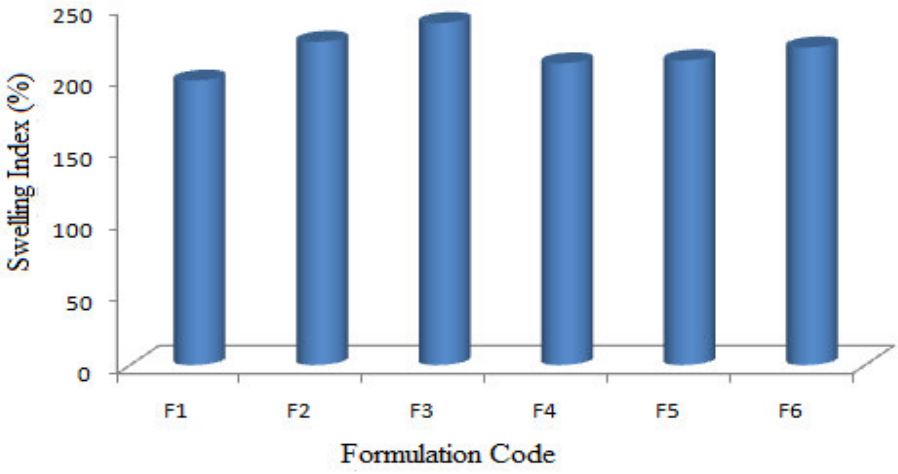
Figure.3
Adhesion force of all the formulations (F1-F6)



Swelling Index

Tablet of F3 formulation show high swelling index which contains Carbopol 934P with SCMC. Matrix integrity, viscosity and adhesion capacity of polymer plays a major role in swelling process. Decrease in percentage of polymer carbopol 934P showed the decrease in swelling value of the formulations.[19] Figure 4 shows the polymer with higher concentration and viscosity had a lower swelling value because this restricts the movement of polymers.

Figure. 4
% swelling index of all the formulations (F1-F6)



In vitro dissolution studies

From dissolution study was conducted for all the formulations F1-F6 and it was found that the increased viscosity and quantity of carbopol 934P shows the decrease in rate of drug release. A higher viscosity particle swells more slowly and produces smaller volume of swollen particles. At higher polymer level formation of tightly swollen gel layer results in decreased mobility of insoluble drug particles in swollen matrices which causes decreased dissolution rate. Increased viscosity and quantity of mucoadhesive polymer decrease in the drug release. Table 6 shows the drug release profile for all the formulations.

Table 6
In vitro dissolution profile for all the formulations (F1-F6)

Sl. No.	Formulation Code	Cumulative % drug release after 24 hours
1	F1	92.85
2	F2	94.68
3	F3	98.86
4	F4	92.12
5	F5	94.31
6	F6	96.86

peppas is found to be 0.615 indicates F3 followed the fickian release. The formulations were fitted to zero order, first order, higuchi's model and korsmeyer peppas model and from the respective values of slope, intercept and r^2 value was calculated. These values are shown in table 7. The model that best fits the drug release data was evaluated by correlation coefficient (r). The n-value of korsmeyer.

Table 7
Kinetic data of all the formulations (F1-F6)

Sl. No.	Formulation Code	Zero Order	First Order	Higuchi's	Krosmeyer Peppas	
		Correlation Coefficient 'r'	Correlation Coefficient 'r'	Correlation Coefficient 'r'	Correlation Coefficient 'r'	Slope 'n'
1	F1	0.974	0.782	0.991	0.981	0.588
2	F2	0.984	0.798	0.989	0.983	0.602
3	F3	0.985	0.881	0.998	0.988	0.615
4	F4	0.976	0.784	0.992	0.982	0.592
5	F5	0.979	0.796	0.993	0.986	0.598
6	F6	0.987	0.798	0.996	0.988	0.608

CONCLUSION

Stomach targeted mucoadhesive tablets of ofloxacin which were prepared by direct compression technique using carbopol 934P, HPMC K14M, SCMC and PEG6000. Tablets were subjected to various evaluation parameters such as weight variation, Hardness, Friability, drug content, Swelling index, *in vitro* drug release study, in vitro mucoadhesive strength study. It was discovered that tablets of all batches had acceptable physical parameters. It was revealed that increase in the polymer concentration will increase swelling index and mucoadhesive strength. The optimized formulation F3 has better *in vitro* drug release than the other formulations, and kinetic study shows that the drug was released by fickian diffusion. The F3 formulation has shown good short term stability. Long term stability studies and *in vitro* studies in human subjects need to be carried out in order to manufacture formulations that can be commercialized.

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