Original Research Article

Formulation and evaluation of sustained release bioadhesive tablets of ofloxacin using 3^2 factorial design

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Abstract

Background: Oral sustained release gastroretentive dosage forms offer many advantages for drugs having absorption from upper gastrointestinal tract and improve the bioavailability of medications that are characterized by narrow absorption window. The aim of current study was to design sustained release bioadhesive gastroretentive dosage form of ofloxacin. **Materials and Methods:** A 3^2 full factorial design was employed to systematically study the drug release profile and bioadhesive strength. Carbopol 934P and HPMC K100M were selected as the independent variables. Compatibility between drug and polymer was tested by fourier transform infrared (FTIR) and X-ray diffraction (XRD) techniques. Tablets were prepared by direct compression and were evaluated for tablet characteristics, swelling study, adhesion strength, percent drug released, radiographic imaging study and stability study. The optimized formulation was then compared with marketed formulation (Oflin OD®). **Results:** Tablets prepared showed good tablet characteristics, optimum swelling property, and good adhesion strength with high detachment force. Most of the formulations including the optimized formulation followed Higuchi kinetics and the drug release mechanism was found to be anomalous. Radiographic image proved that tablet remains intact in its structural integrity and shape in stomach up to 24 h. The short-term accelerated stability testing was carried out for the optimized formulation, and results revealed that drug content, *in-vitro* dissolution and all other parameters were within acceptable limits. **Conclusion:** Thus, the prepared bioadhesive gastroretentive ofloxacin tablet may prove to be a potential candidate which increases the bioavailability of ofloxacin for any intragastric condition.

Key words: Bioadhesion, gastroretentive dosage form, ofloxacin, radiographic imaging study

INTRODUCTION

Oral sustained (SR) systems continue to be the most popular ones among all the drug delivery systems.[1] Bioadhesive delivery systems offer several advantages over other oral SR systems by virtue of prolongation of residence time of drug in gastrointestinal (GI) tract, and targeting and localization of the dosage form at a specific site. Also, these bioadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, thereby resulting in high drug flux through the absorbing tissue.[2-6] Prolonging the gastric retention of a delivery system is sometimes desirable for achieving therapeutic benefit of drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT) or that are less soluble in or are degraded by the alkaline pH they encounter at the lower part of GIT. Gastroretentive drug delivery system (GRDDS) is thus beneficial for such drugs by improving their bioavailability, therapeutic efficacy and by possible reduction of dose. Apart from these advantages, these systems offer various pharmacokinetic advantages like maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels, minimizing the risk of resistance, especially in case of antibiotics.[7]

Ofloxacin is an antibacterial antibiotic. The mechanism by which it exerts this effect is by binding to and inhibiting topoisomerase II (DNA gyrase) and topoisomerase IV. These bacterial enzymes are responsible for the coiling and uncoiling of DNA, which is needed for bacterial cell repair and replication. Ofloxacin exhibits pH-dependant solubility. It is more soluble in acidic pH and slightly soluble at neutral or alkaline pH conditions (intestinal

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environment). The molecule exists as a zwitterions at the pH conditions in the small intestine and is easily absorbed there.[8,9]

The objective of the present work was to develop gastroretentive formulation, which releases drug in the stomach and upper GIT, and form an enhanced opportunity of absorption in the stomach and upper GIT rather than the lower portion of the GIT. Our work includes development of bioadhesive gastroretentive formulation of ofloxacin, and evaluation of tablet characteristics, swelling study, adhesion strength, percent drug release, radiographic imaging study and stability study. Hence, an attempt was made to develop GRDDS of ofloxacin which would increase the bioavailability of ofloxacin.

MATERIALS AND METHODS

Materials

Ofloxacin and Carbopol 934P were kindly gifted by Madras Pharmaceutical Ltd., Chennai. Hydroxypropylmethyl cellulose (HPMC K100M), potassium dihydrogen phosphate, and lactose were procured from Loba Chemical, Mumbai. All the other chemicals used were of analytical grade.

Methods

Identification of drug

Ultraviolet spectroscopy

25 μg/ml stock solutions of ofloxacin were prepared by weighing 25 mg of ofloxacin and dissolving in 1 l of different solvents (i.e. 0.1 N HCl, water and phosphate buffer, pH 6.8). Then, ultraviolet (UV) spectrum of 25 μg/ml solution of the ofloxacin was recorded in the range of wavelengths from 200 to 400 nm using UV-visible double beam spectrophotometer (V630, Jasco) [Table 1 and Figure 1]. Fourier transform infrared analysis.[10,11]

Infrared spectroscopic analysis of ofloxacin [Figure 2 and Table 2] was performed using Fourier transform infrared (FTIR) spectrophotometer 4100 (Jasco), with a resolution of 8 cm^{-1}, in the range of 4000–400 cm^{-1}, on a zinc selenide (ZnSe) crystal.

Table 1: λ^{max} of ofloxacin in different solvents

Ultraviolet spectroscopy	λ^{max} (nm)
0.1 N HCl	294
Water	288.4
Phosphate buffer, pH 6.8	287.2

Table 2: FTIR analysis of the drug

Reported wave number (cm^{-1})	Observed wave number (cm^{-1})	Assignments
1305	1305.85	Tertiary (C–N vibrations)
2786	2785.30	Piperazine C–H
1714	1714.77	(–COOH) C=O stretch
1145	1144.73	C–O–C
1622	1622.19	Pyridone C=O stretch
804	804.34	C–F

FTIR: Fourier transform infrared

Compatibility study of drug with polymers

FTIR analysis

Each polymer used in the formulation was mixed with drug at levels that are realistic with respect to the final dosage form. Drug–polymer mixtures were stored at 40°C and 75% relative humidity (RH) for a 3-month period. After 3 months, each mixture was tested for its stability by FTIR spectroscopy [Figures 3–5].[10,11]

Drug, polymers and their mixture (tablet triturated after compression) were analyzed by X-ray diffraction (XRD) in order to verify the effect of compression on crystallinity of components as well as to test any interaction between the excipients. Powder XRD patterns were obtained with an X-ray diffractometer (Model-MenifleX) at the following test conditions: time per step, 0.400 sec; step size, 2 = 0.020° (is incident angle); current, 30 mA at 40 kV; CuK rays (wavelength = 1.542 Å) [Figures 6–9].

Factorial design

A 3^2 randomized full factorial design was applied in the present study. In this design, 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all the 9 possible combinations. The amount of bioadhesive polymer, Carbopol 934P (X1), and the amount of release modifying polymer, HPMC K100M (X2), were selected as independent variables. The swelling index, bioadhesion strength, time required for 100% drug release and cumulative % drug released in 12 h, and mean dissolution time (MDT) were selected as dependent variables. The formulations using 3^2 randomized full factorial designs are as shown in Tables 3 and 4.[13-15]

Preparation of tablets

Drug ofloxacin and other excipients were passed through sieve #60 mesh separately and then all ingredients mixed uniformly.

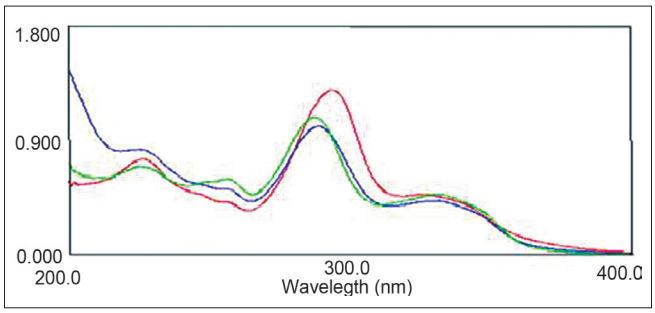

Figure 1: UV spectra of ofloxacin in 0.1 N aqueous HCl solution (---), in water (---) and in phosphate buffer solution, pH 6.8(---)

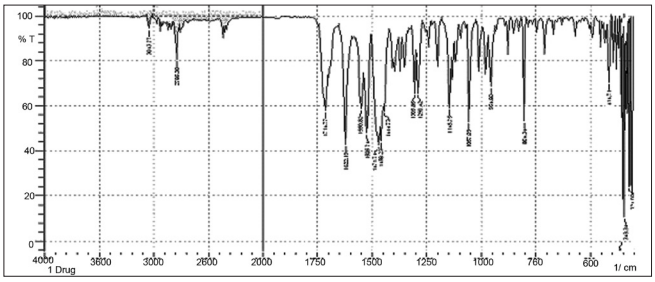

Figure 2: FTIR spectra of ofloxacin

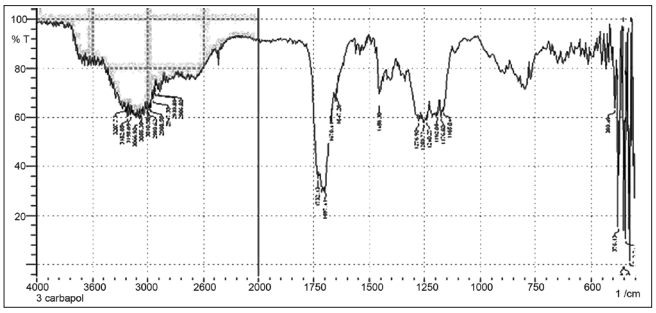

Figure 3: FTIR spectra of Carbopol 934P

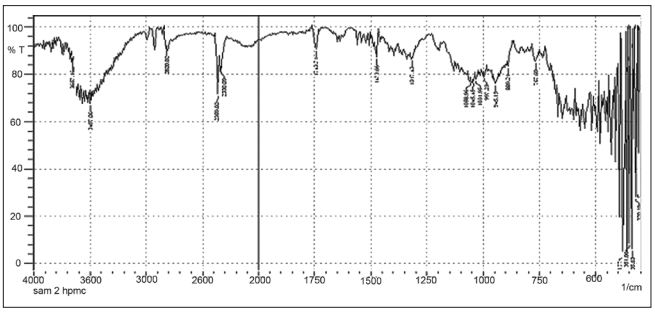

Figure 4: FTIR spectra of HPMC K100M

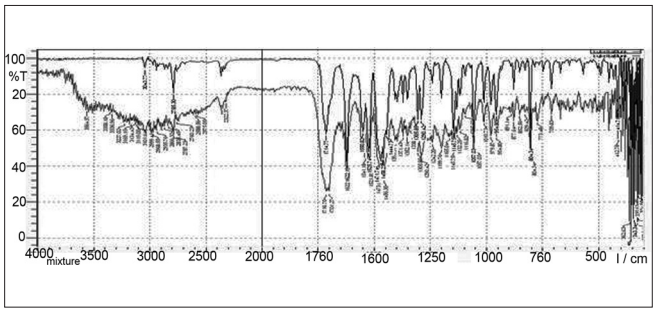

Figure 5: Overlay FTIR spectra of ofloxacin and polymer mixture

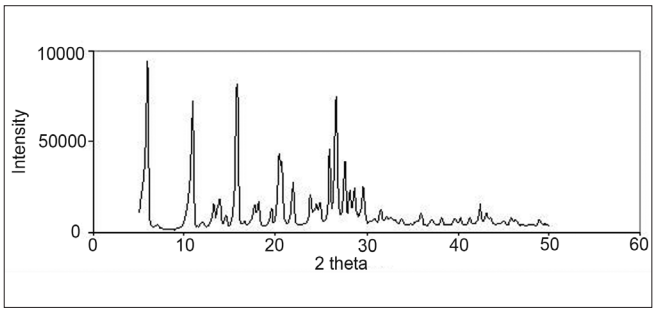

Figure 6: XRD spectra of ofloxacin

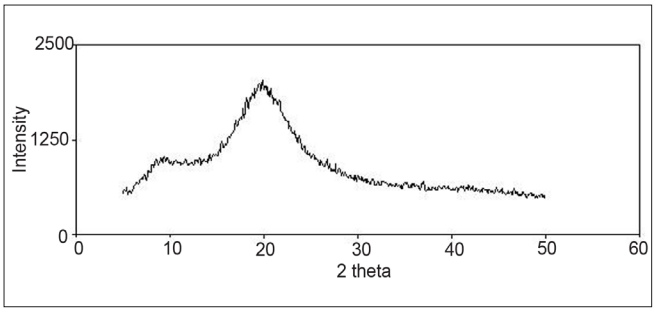

Figure 7: XRD spectra of HPMC K100M

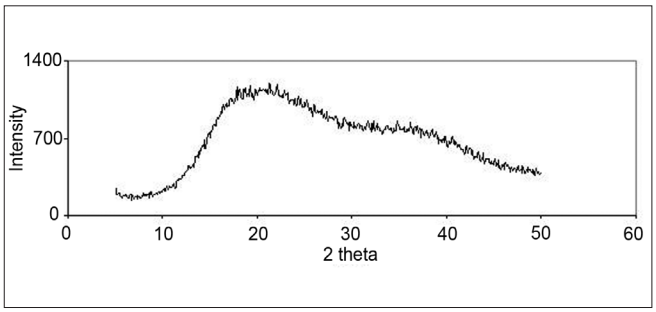

Figure 8: XRD spectra of Carbopol 934P

Table 3: Formulations using 3^2 randomized full factorial design

Variables	F1	F2	F3	F4	F5	F6	F7	F8	F9
X1	−1	−1	−1	0	0	0	1	1	1
X2	−1	0	1	−1	0	1	−1	0	1

Tablets were prepared by direct compression method using rotary press (Rimek, Mumbai India). Compression force for all the tablets was adjusted to get tablets of hardness 6–7 kg/cm^2. Hardness was measured by Monsanto hardness tester.

Characterization of powder blends of drug and excipients

The powder blend of formulations shown in Table 5 were evaluated for flow properties as follows and observations are reported in Table 6.[16]

Evaluation of tablets

Tablet characteristics

Formulated matrix tablets were evaluated for thickness by using Digital Vernier caliper (Mitutoyo), weight variation, hardness (Monsanto hardness tester), friability (Roche friabilator) and drug content.[17]

Drug content: Three tablets were weighed and finely powdered. The quantity equivalent to 400 mg of ofloxacin was weighed accurately and taken in a 100-ml volumetric flask. Fifty milliliters of 0.1 N HCl was added, sonicated for 30 min, made up to 100 ml with 0.1 N HCl and filtered. Two milliliters of the above solution was diluted to 100 ml in a volumetric flask and the drug concentration was determined at 293.8 nm by using UV spectrophotometer.

Swelling measurements

Swelling was measured by placing pre-weighed specimen tablets ($W1$) into the Type-I dissolution apparatus containing 900 ml of 0.1 N HCl at 37 ± 0.5°C. The medium was stirred continuously at 100 rpm. At different time intervals, the specimens were removed, wiped gently with a tissue paper to remove surface water and weighed ($W2$). Swelling index was determined using the equation:

$$\text{Swelling index} = (W2 - W1) \times 100/W1.$$[18]

Ex-vivo mucoadhesion measurement

Mecmesin Ultra tester (detachment force): Ex-vivo mucoadhesion studies were carried out on goat gastric mucosa. In evaluation of adhesion, it is important to use uniform surfaces that allow the formation of reproducible adhesive bonds. In the present study, goat gastric mucosa was used as model mucosal surface for bioadhesion testing. The goat stomach was cut into pieces and was mounted with mucus surface facing upward on wooden block specially prepared for holding mucosal tissues for bioadhesion testing. The wooden block was attached with double-sided adhesive tape to support the tissue on it. The thread was tied to firmly place the tissue on wooden block. The tablet was attached to the upper support using cynoacrylate glue [Figure 10]. The entire set was mounted on platform of test stand of Mecmesin Ultra Tester. Before the measurement, the mucus membrane was moistened with water. The upper support was lowered at a speed of 0.5 mm/sec until contact was made with the tissue at the predetermined force of 50 mN for a contact time of 5 min. Contact time is important because this period corresponds to a pre-swelling necessary for bioadhesive polymer chain disentanglement and establishment of intimate contact between polymer and mucin chains. At the end of contact time, the upper support was withdrawn at a speed of 0.5 mm/sec to detach the tablet from the membrane. The detachment force, i.e. the force required to separate tablet from tissue surface was reported as bioadhesive strength. The bioadhesive strength was reported in terms of miliNewton (mN).[18]

Dissolution study

The release of ofloxacin from tablet was studied using USP Type I Dissolution apparatus; the dissolution medium was 0.1 N HCl, pH 1.2, the volume being 900 ml, the rotation speed was 100 rpm, and the temperature was maintained at 37°C.[19]

Dissolution studies were carried out for 24 h. Samples of 5 ml were taken at an interval of every 2 h up to 24 h. After collecting the sample, the dissolution medium was replenished with the same sample volume of fresh medium. Sample was analyzed using UV spectrophotometer at 293.8 nm.

Data treatment[20-22]*:* The dissolution data were subjected to different model-dependent and -independent treatments.

Table 4: Coded formulation

Coded level	−1	0	1
X1 (Carbopol 934P)	100	125	150
X2 (HPMC K100M)	50	75	100

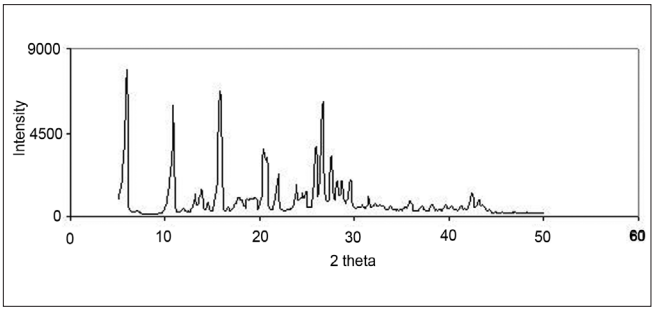

Figure 9: XRD spectra of the ofloxacin and polymer mixture

Figure 10: Mecmesin Ultra tester (detachment force)

Table 5: Formulation as per 3^2 factorial design

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ofloxacin	400	400	400	400	400	400	400	400	400
Carbopol 934P	100	100	100	125	125	125	150	150	150
HPMC K100M	50	75	100	50	75	100	50	75	100
Magnesium stearate	5	5	5	5	5	5	5	5	5
Lactose	100	75	50	75	50	25	50	25	00
Total	655	655	655	655	655	655	655	655	655

Table 6: Evaluation parameters of formulation F1–F9 powder blends

Formulation batch	Evaluation parameters					
	Angle of repose	Bulk density	Tapped density	Carr's index	Hausner ratio	Flow properties
F1	36.21 ± 0.201	0.6416 ± 0.023	0.8358 ± 0.068	23.24 ± 0.221	1.3026 ± 0.0202	Poor
F2	30.42 ± 0.134	0.6590 ± 0.014	0.8364 ± 0.098	21.21 ± 0.291	1.2691 ± 0.0573	Fair to pass
F3	28.71 ± 0.176	0.7314 ± 0.017	0.8531 ± 0.041	14.27 ± 0.124	1.1663 ± 0.0471	Good
F4	35.87 ± 0.147	0.632 ± 0.019	0.8393 ± 0.034	24.7 ± 0.012	1.328 ± 0.0224	Poor
F5	27.84 ± 0.242	0.726 ± 0.032	0.8615 ± 0.054	15.71 ± 0.201	1.1866 ± 0.0424	Good
F6	25.56 ± 0.227	0.7516 ± 0.043	0.8587 ± 0.056	12.48 ± 0.009	1.1424 ± 0.0221	Good
F7	32.86 ± 0.322	0.6248 ± 0.028	0.832 ± 0.098	24.96 ± 0.098	1.3316 ± 0.0421	Poor
F8	31.21 ± 0.228	0.6812 ± 0.017	0.8380 ± 0.016	18.72 ± 0.112	1.2301 ± 0.0521	Fair to pass
F9	25.02 ± 0.247	0.7104 ± 0.065	0.8498 ± 0.095	16.41 ± 0.139	1.1962 ± 0.0121	Good

Model-dependent methods

Zero-order kinetics: Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly can be represented by the following equation:

$Wo - Wt = Kt$,

where *Wo* is the initial amount of drug in the pharmaceutical dosage form, *Wt* is the amount of drug in the pharmaceutical dosage form at time *t* and *K* is a proportionality constant. Dividing this equation by *Wo* and simplifying we get:

$ft = K0t$,

where $ft = 1 - (Wt/Wo)$ and *ft* represents the fraction of drug dissolved in time *t* and *K0* the apparent dissolution rate constant or zero-order release constant.

First-order kinetics: $lnQt = lnQ0 - K1t$,

where *Q* represents the fraction of drug released in time *t* and *K*1 is the first-order release constant.

Higuchi model

$Qt = QHt^{1/2}$,

where *Qt* represents the fraction of drug released in time *t* and *QH* is the Higuchi dissolution constant.

Korsmeyer–Peppas model

$Q = Kpt^n$,

where *Kp* is a constant incorporating the structural and geometric characteristics of the drug dosage form, *n* is the release exponent, indicative of the drug dissolved fraction at time *t*. This equation was further simplified and proposed by Ritger and Peppas as

$Mt/M = Kt^n$,

where *Mt* is the drug released at time *t, M* is the amount of drug released at infinite time, *K* is a kinetic constant, and *n* is the diffusional exponent.

The value of *n* indicates the drug release mechanism. For a slab, the value $n = 0.5$ indicates Fickian diffusion and values of *n* between 0.5 and 1.0 or $n = 1.0$ indicate non-Fickian mechanism. In case of a cylinder, the values are $n = 0.45$ instead of 0.5, and 0.89 instead of 1.0 [Table 7].

Table 7: Interpretation of diffusional release mechanism from polymeric films[20]

Release exponent (*n*)	Drug transport mechanism
0.5	Fickian diffusion
$0.5 < n > 1.0$	Anomalous transport
1.0	Case-II transport
Higher than 1.0	Super Case-II transport

Determination of bioadhesive property by radiographic imaging technique

The *in vivo* behavior of the gastroretentive bioadhesive tablet of optimized formulation F9 in the rabbit stomach was observed in real time using a radiographic imaging technique. A healthy male albino rabbit weighing 2 kg was used throughout the study. Also, to assess the formulation *in vivo*, a specialized formulation with barium sulfate was prepared, i.e. optimized formulation F9 using barium sulfate.

The prepared F9 formulation using barium sulfate was administered to the rabbit by intubation method. After that, 10–12 ml water was given immediately. During the experiment, the rabbit was not allowed to eat any food, but water was available *ad libitum*. Then, the radiographic images were taken at various time intervals.[23]

Stability study

The optimized formulated tablets were wrapped in aluminum foils and then were subjected to temperature of 40°C and 75% RH for a period of 1 month. The tablets were then analyzed for organoleptic characteristics, hardness, drug content and drug release.[24]

RESULTS AND DISCUSSION

Compatibility study of drug with polymers

FTIR analysis

The spectrum remained unchanged at the end of 3 months. The overlay spectra of the drug and the mixture are shown in Figures 2–5. Therefore, the active molecule is not altered by the addition of polymer substances. This study helps in assuming the stability of drug and in further development of dosage form.

XRD study

Ofloxacin was found to be crystalline in nature as it showed sharp peaks in X-ray diffraction spectrum, as shown in Figures 6–9. No sharp peaks were observed in the XRD spectra of Carbopol 934P and HPMC K100M; this indicates that both the polymers are amorphous in nature and this finding is in accordance with the literature reports. Peak intensities of Carbopol and HPMC K100M were less as compared to ofloxacin. The peak intensities of Carbopol and HPMC K100M were weak in the spectrum of the compressed mixture. This may be due to dilution of the polymers by drug since the drug composed 55% by weight of the whole mixture while the polymers were 40% by weight of the whole mixture.

Characterization of powder blends of drug and excipients

Particle size of drug and polymer affects flow characteristics, compression as well as release from delivery system. Individually drug powder, with a crystalline nature, has good flow property, but Carbopol and HPMC show poor to passable flow properties. But when mixed together with glidant, it shows passable to good flow property. The difference in compressibility of the mixture may be due to the difference in particle nature of ingredients [Table 6].

Tablet characteristics

Hardness of tablets was in the range of 6–7 kg/cm^2. Percent weight loss in the friability test was found to be less than 0.4% in all the formulations. Content uniformity was found within 100 ± 2% of 400 mg of ofloxacin.

Determination of swelling index

The swelling index of all formulations was in the range of 111.44–241.20%. The study of swelling behavior of all formulations showed that swelling is increased up to 24 hours; but initially swelling is slow up to 6 hours and at the end of 24 hours swelling increases as the time increases. From the results, it is also seen that as the concentration of polymers increases, % swelling index also increases [Table 8 and Figure 11].

Ex-vivo mucoadhesion measurement

Mecmesin Ultra tester (detachment force)

The results of the detachment force of ofloxacin bioadhesive tablets are given in Table 9. In all the formulations, as the polymer concentration increases, the detachment force increases. Increasing the concentration of polymer may provide more adhesive sites and polymer chains for interpenetration with mucin, resulting consequently in the augmentation of bioadhesive strength. The polymer in the tablet first gets activated by moistening and gets adhered to mucus membrane and after that formation of intimate contact between mucus and polymer chains takes place leading to formation of bonds and strengthening the adhesive joints. Very strong bioadhesion could damage the epithelial lining of the mucosa, so the concentration of polymer should be optimum because high concentration may cause inflexible confirmation of polymer coils that cannot participate actively in adhesion with mucus macromolecule [Figures 12 and 13].

Table 8: Swelling study of blended formulation

Formulation	% Swelling index		
	6 h	12 h	24 h
F1	24.13	70.90	111.44
F2	36.25	92.62	153.98
F3	48.35	110.68	190.35
F4	44.02	78.55	150.23
F5	58.28	101.20	159.61
F6	72.62	132.95	172.71
F7	60.85	106.66	181.96
F8	82.09	142.11	199.33
F9	96.44	183.54	241.20

Table 9: *Ex-vivo* mucoadhesion measurement of blended formulation

Formulation	Force of detachment (mN) Mean ± SD (*n* = 3)	Adhesion time (h)
F1	194 ± 5.32	19
F2	218 ± 3.73	20
F3	251 ± 6.23	20
F4	312 ± 5.57	21
F5	325 ± 5.45	21
F6	343 ± 6.72	23
F7	429 ± 7.32	24
F8	463 ± 9.61	25
F9	501 ± 6.28	27

Dissolution study

Drug release profile

Carbopol and HPMC are hydrophilic polymers. When tablets containing these polymers come in contact with water, it allows gradual hydration of the tablet matrix, leading to swelling of the tablets. Water decreases the glass transition temperature of the polymers to the experimental temperature. At this temperature, glassy polymer is transformed into a rubbery state. Mobility of polymeric chains is enhanced in this state. This favors the transport of water into tablet and consequently transport of the dissolved drug from tablet core to the dissolution medium. Drug release from matrix tablet is determined by drug characteristics, delivery system and destination (site of drug release). Drug content of each tablet was 400 mg and 900 ml of dissolution medium was used for dissolution studies. Ofloxacin has a solubility of 76 mg/ml in 0.1 N HCl at 25°C.[1,26] Maintaining sink condition is important during the dissolution experiment for consistent and accurate measurement of the dissolution rate. According to the United States Pharmacopeia (USP, 2005), sink condition is established when the saturation solubility is at least three times more than the drug concentration in the dissolution medium. Thus, sink conditions could be maintained throughout

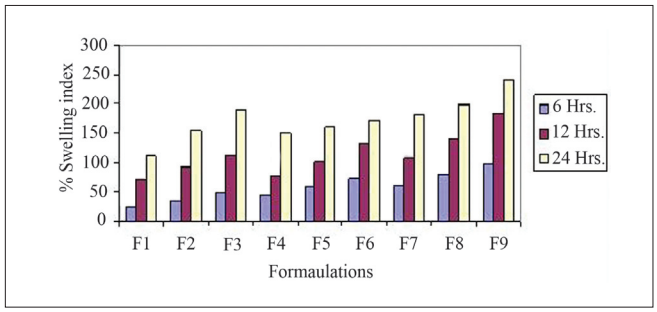

Figure 11: Swelling index of formulations

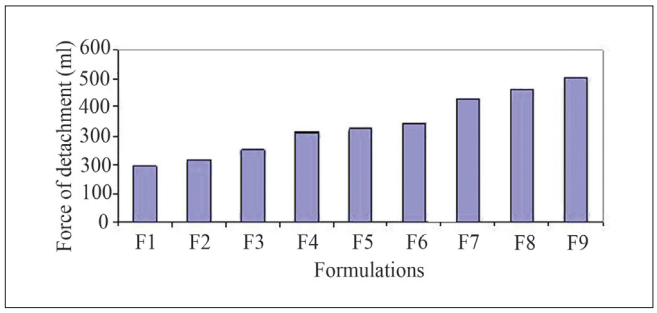

Figure 12: Force of detachment of formulations

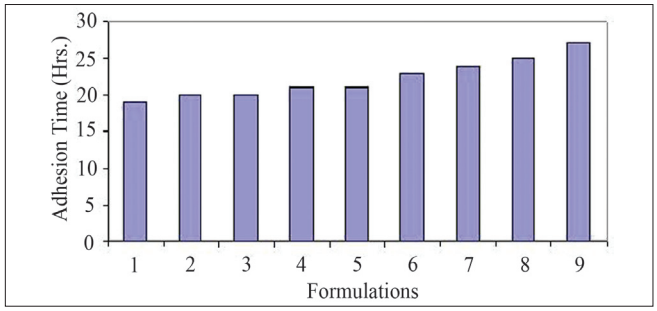

Figure 13: Adhesion time of formulations

Table 10: Drug release profile of blended formulations

Time (h)	Cumulative drug release (%)[a]								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	23.30 ± 0.57	23.14 ± 0.47	18.76 ± 0.47	21.79 ± 1.24	22.13 ± 2.1	21.96 ± 1.63	20.61 ± 1.88	20.36 ± 1.67	18.51 ± 0.79
4	40.03 ± 1.04	38.34 ± 0.94	38.65 ± 0.69	37.41 ± 0.7	33.87 ± 1.75	33.45 ± 0.68	30.49 ± 0.8	26.79 ± 0.78	25.18 ±.69
6	58.11 ± 0.79	52.37 ± 0.6	51.00 ± 0.35	50.67 ± 0.8	48.46 ± 0.98	45.76 ± 0.91	44.81 ± 1.61	35.27 ± 1.28	33.74 ± 1.59
8	71.40 ± 1.67	67.56 ± 1.12	67.53 ± 0.68	66.11 ± 0.46	64.06 ± 1.01	52.59 ± 1.03	52.31 ± 1.26	48.10 ± 1.02	45.97 ± 2.24
10	84.59 ± 1.67	82.84 ± 1.14	72.37 ± 0.56	72.79 ± 0.48	75.95 ± 1.41	95.49 ± 1.14	62.03 ± 1.03	53.08 ± 1.17	50.69 ± 1.38
12	95.08 ± 0.74	91.81 ± 1.81	83.63 ± 1.29	83.13 ± 0.81	81.17 ± 0.90	69.49 ± 0.91	69.61 ± 0.92	62.81 ± 0.58	59.64 ± 1.32
14	103.09 ± 1.35	99.30 ± 2.17	93.69 ± 0.52	91.25 ± 0.92	88.77 ± 1.14	79.89 ± 0.92	81.86 ± 1	70.39 ± 1.34	66.62 ± 1.51
16	–	104.47 ± 1.9	100.35 ± 1.05	99.66 ± 1.86	93.21 ± 0.68	88.58 ± 1.13	85.34 ± 1.22	79.28 ± 1.01	73.13 ± 1.9
18	–	–	–	104.16 ± 2.43	98.85 ± 0.92	93.60 ± 0.99	89.01 ± 0.76	82.84 ± 0.48	78.92 ± 1.33
20	–	–	–	–	102.42 ± 0.69	97.98 ± 1.25	92.77 ± 0.83	86.40 ± 0.72	84.571 ± 2.22
22	–	–	–	–	–	101.54 ± 1.63	96.81 ± 0.61	90.74 ± 0.63	88.901 ± 1.55
24	–	–	–	–	–	–	100.53 ± 0.84	94.01 ± 0.49	93.08 ± 1.06

[a]Values are expressed as mean ± SD, n = 3

Table 11: Correlation coefficient (*R*) values in various kinetic models tested

Formulation	Zero order		First order		Higuchi		Korsmeyer–Peppas	
	R	*K*	*R*	*K*	*R*	*K*	*R*	*n*
F1	0.9915	6.7084	0.9390	−0.1109	0.9925	35.085	0.9925	0.7704
F2	0.9936	6.5336	0.9008	−0.1496	0.9962	33.369	0.9952	0.7521
F3	0.9830	5.2551	0.9633	−0.0844	0.9977	30.852	0.9864	0.7898
F4	0.9874	5.1201	0.8507	−0.1334	0.9987	29.955	0.9950	0.7184
F5	0.9778	4.8582	0.9378	−0.0992	0.9930	27.681	0.9855	0.6927
F6	0.9972	4.4519	0.9388	−0.0780	0.9966	25.669	0.9979	0.6577
F7	0.9900	4.4128	0.9762	−0.0653	0.9961	24.151	0.9910	0.6606
F8	0.9962	4.1042	0.9847	−0.0503	0.9944	23.055	0.9876	0.6680
F9	0.9963	3.8829	0.9786	−0.0465	0.9965	22.822	0.9929	0.6937

Table 12: Comparison between optimized versus marketed formulation

Time (h)	Cumulative drug release (%)[a]	
	Oflin OD	Optimized formulation
2	25.49 ± 1.41	21.11 ± 1.72
4	32.80 ± 1.39	28.73 ± 1.79
6	41.32 ± 2.44	36.30 ± 0.94
8	54.93 ± 2.17	50.31 ± 0.88
10	63.15 ± 1.70	58.42 ± 1.52
12	73.10 ± 1.40	64.81 ± 1.44
14	78.64 ± 2.22	75.60 ± 1.93
16	86.23 ± 1.57	79.47 ± 1.26
18	91.07 ± 1.69	85.04 ± 0.55
20	94.01 ± 0.94	90.64 ± 1.41
22	96.62 ± 0.95	94.83 ± 1.02
24	99.83± 0.84	98.79 ± 0.63

[a]Values are expressed as mean ± SD, *n* = 3

the dissolution study and drug solubility could not be a factor responsible for retardation of drug release from the formulations studied. Hence, retardation of drug release from the formulations could be attributed to the properties of polymers used in the formulations as shown in Table 10 and Figure 14.[25,26]

Data treatment

The correlation coefficient (R) value was used as criteria to choose the best model to describe drug release from the mucoadhesive sustained release tablets. The R-value in various models is given in Table 11. The R-values (R>0.9925) obtained for fitting the drug release data to the Higuchi equation, indicated that the drug release mechanism from these tablets was diffusion controlled.

Comparison: Optimized vs. Marketed

Dissolution profiles comparison of marketed product (Oflin OD) and optimized formulation is given in Table 12 and Figure 15. Also Correlation Coefficient (R) Values in Various Kinetic Models Tested for marketed and optimized formulation shown in Table 13.

From the radiographic images in Figure 16, it is proved that

Table 13: Correlation coefficient (*R*) values in various kinetic models

Formulation	Zero order		First order		Higuchi		Korsmeyer –Peppas	
	R	*K*	*R*	*K*	*R*	*K*	*R*	*n*
Oflin OD	0.9782	3.52	0.8854	−0.092	0.9932	23.37	0.9924	0.6
Optimized formulation	0.9869	3.62	0.9502	−0.662	0.9956	23.84	0.9944	0.6634

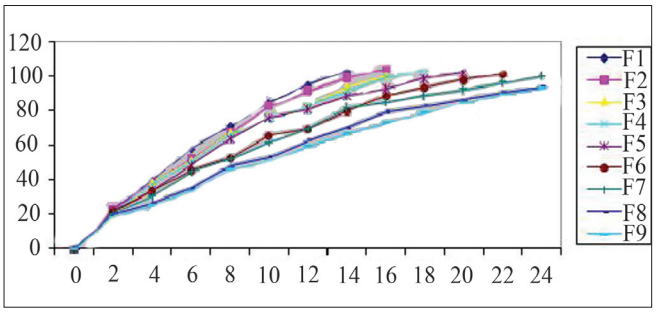

Figure 14: Comparison of drug release of formulations F1–F9

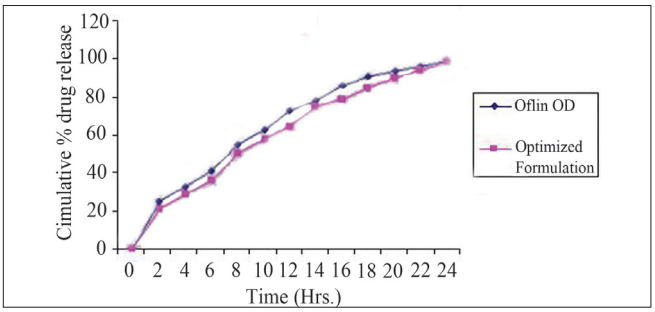

Figure 15: Comparison between optimized versus marketed formulation

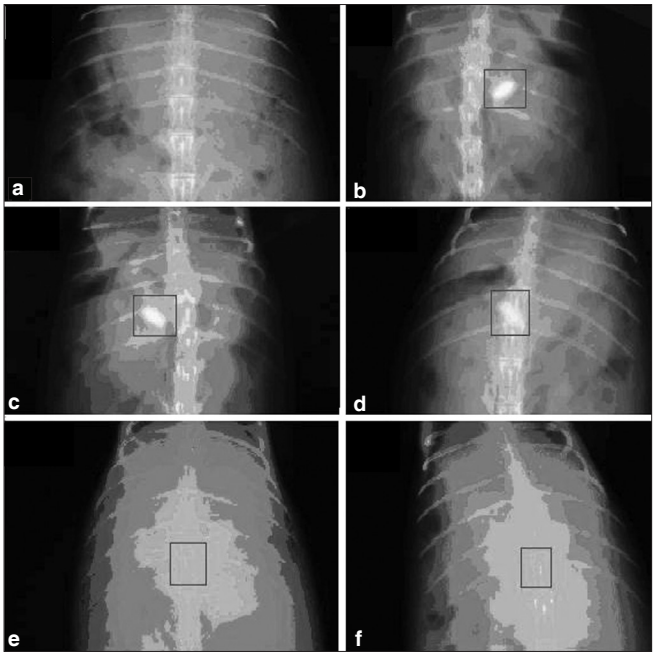

Figure 16: Photograph shows: (a) X-ray without tablet, (b) X-ray after 30 min administration of tablet, (c) X-ray after 1 h, (d) X-ray after 6 h, (e) X-ray after 12 h, (f) X-ray after 24 h

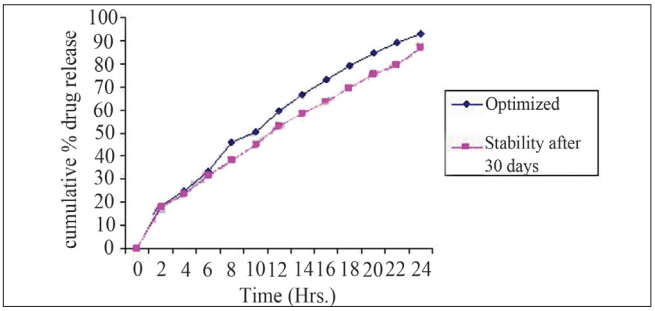

Figure 17: Stability study of optimized formulation

tablet remains intact in its structural integrity and shape in stomach. The changes in position of tablet in Figure 16b and c at 30 min and 1 h, respectively, provide the evidence of bioadhesive nature of tablets in rabbit's stomach. At 30 min and 1 h, the swelling of tablet is observed very clearly with centre core and a small swelling layer around it. So, it provides the swelling property of this formulation. Then, the unchanged position of tablet starts from 12th h and is maintained throughout up to 24th h, indicating the bioadhesive property of the developed formulation (i.e. it remained in the stomach for 24 h which may be due to bioadhesiveness). As the swelling continues, the core and outer swelling get diminished and size reduction along with slight modulation in structure at 24th h indicates structural integrity retaining capacity of developed formulation in stomach for 24 h.

Stability study of optimized formulation

The short-term-stability testing was carried out for the optimized formulation. The results for the dissolution profile are as depicted in the graph. Short-term accelerated stability data obtained for optimized formulation revealed that drug content, *in-vitro* dissolution and all other parameters were within acceptable limits [Figure 17]. Thus, the formulation can be said to be stable. The stability may be attributed to the polymers.

CONCLUSION

Carbopol and HPMC K100M can be promising polymers for gastroretentive bioadhesive drug delivery system. High bioadhesive strength of the formulation is likely to increase its GI residence time, and eventually improve the extent of bioavailability. Swelling studies indicated significant water uptake and contributed in drug release; swelling could also help in gastroretention. The optimized formulation sustained the release up to 24 h, followed Higuchi kinetics, while the drug release mechanism was found to be of anomalous type, and controlled by diffusion through the swollen matrix. Sustained drug release with high bioadhesive strength was observed in case of optimized formulation. The swollen tablet also maintained its physical

integrity during the drug release test. The optimized formulation was found to stable in short-term accelerated stability testing at 40°C at 75% RH for a period of 1 month.

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