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FORMULATION, OPTIMIZATION AND EVALUATION OF BUCCOADHESIVE TABLET CONTAINING OFLOXACIN

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ABSTRACT

The aim of the work is to design Oral Buccoadhesive Tablet Containing Ofloxacin by using 3^2 factorial designs. The Total 9 experimental batches (F1…F9) of Buccoadhesive Tablet Containing Ofloxacin following design of experiment and optimized. The prepared formulations were subjected for various preformulation and post formulation parameter evaluations. The study reveals satisfactory results. Hence, the Buccoadhesive Tablet Containing Ofloxacin is expected to provide clinician with a new choice of safe and more bioavailable formulations.

KEYWORDS: Buccoadhesive Tablet, Ofloxacin.

INTRODUCTION

In recent years, the interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of drugs. Drug delivery via the buccal route using bio-adhesive dosage forms offers such a novel route of drug administration. Extensive first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via buccal route.[1]

Buccal delivery involves administration of desired drug through the buccal mucosal membrane lining of oral cavity. The mucosal lining of oral cavity offers some distinct advantages. It is richly vascularized and more accessible for the administration and removal of a dosage form. Additionally, buccal drug delivery has high patient acceptability compared to other non- oral routes of drug administration.[2]

Buccal delivery refers to drug release which can occur when a dosage form is placed in the outer vestibule between the buccal mucosa and gingiva. Various advantages and other aspects of this route are elucidated of the following.[3,4] Buccal tablets are small, flat, and oval shaped dosage form. Unlike conventional tablets buccal mucoadhesive tablets allow for drinking and speaking without major discomfort. They soften adhere to the mucosa and are retained in position until dissolution and/or release is complete. These tablets can be applied to different sites in the oral cavity including the palate the mucosa lining the cheek as well as between the lip and the gum.[5]

Ofloxacin is a quinolone/fluoroquinolone antibiotic. Ofloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. Ofloxacin is mainly eliminated by renal excretion, where between 65% and 80% of an administered oral dose of ofloxacin is excreted unchanged via urine within 48hours of dosing. About 4-8% of an ofloxacin dose is excreted in the feces and the drug is minimally subject to biliary excretion.[6] Hence it falls under BCS class IV. Because of all above reasons, buccal tablet of Ofloxacin was prepared for increasing bioavailability and therapeutic effect.

MATERIALS AND METHODS

Chemicals

The material used is analysed Ofloxacin was obtained from Shree swami Smarth Ayurvedic Pharmacy (Allopathic division) Jalgaon. Pluronic F-127, Gallen gum, Carbopol 940, Talc, Magnesium Stearate, Microcrystalline Cellulose, was obtained from Research Lab Fine Chem. Ltd. Mumbai.

Preparation of Tablet

All ingredients were weighed accurately and passed through sieve no.20. The blend was triturated in glass mortar pastel for 10 minutes and compression was done with 9 mm punch.

Table 1: Formulation table for Buccoadhesive Tablet Containing Ofloxacin.

Ingredient	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ofloxacin	100	100	100	100	100	100	100	100	100
Pluronic-F-27	50	50	50	60	60	60	70	70	70
Galen gum	60	70	80	60	70	80	60	70	80
Carbopol 940	20	20	20	20	20	20	20	20	20
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	7	7	7	7	7	7	7	7	7
Avicel	58	48	38	48	38	28	38	28	18
Total weight	300	300	300	300	300	300	300	300	300

Evaluation of pre-compression parameters

Dry powder blends of all formulations (F1- F9) were subjected for evaluation of pre-compression parameters such as Bulk Density,Tapped Density, Carr's Index, Hausner's Ratio, Angle of Repose as per the standard procedure given in IP. Drug excipients compatibility studies were done by FTIR and DSC.[7-14]

Density

Both the loose bulk density (*LBD*) and tapped bulk density (*TBD*) of prepared dry powder blends of all the formulations were determined. The quantity of 5 gm. Of powder blends from each formulation, previously lightly shaken to break any agglomerates formed; were introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface form the height of 2.5cm at second interval. The tapings were continued until no further changes in volume were noted. *LBD* and *TBD* of prepared powder blends of all Ofloxacin muco-adhesive formulations were calculated using the following formulas.

LBD= weight of the granules/volume of the packing
***T*BD= weight of the granules/ tapped volume of the granules**

Compressibility Index (Carr's index)

Compressibility index (Carr's index) is important parameters to determine the flow properties of powder and granules. Carr's index of prepared Ofloxacin muco-adhesive dry powder blends were calculated by following formula.

Carr s index (%)=(TBD-LBD/TBD)×100

Hausner's Ratio

Hausner's ratios is also another parameter to determine the flow properties of powder and Granules. The Hausner's ratios of prepared Ofloxacin muco-adhesive dry powder blends were determined by following formula.

Hausner's ratio=TBD/LBD

Angle of Repose

Angle of repose is an important parameter that is used to find out the flow properties of powder and that is indicated as maximum angle possible between the surface of a pile of powder and the horizontal plane. The dry powder blends from different formulations were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius (r) of the heap of powder formed. It is calculated by formula as.

$\tan \theta = h/r$

Fourier Transform Infrared (FTIR) spectroscopy

Fourier transform infrared (FTIR) study was performed to verify any physical or chemical interaction between the pure drug and the excipients used. The FTIR studies of pure drug Ofloxacin, HPMC K100M, carbopol 940, Magnesium stearate, Lactose and talc the formulation that contains all those ingredients (F1-F9) were carried out. It was performed by potassium bromide (*KBr*) pellet method. The samples were triturated with *KBr* and pellet was prepared by setting the pressure to 100 kg/cm2 for 2 min. The obtained pellet was analysed in FTIR 8400S, Shimadzu, Japan. The peaks that were obtained for the pure drug, polymers and formulation, characterised for the presence of different functional group and ensured that there was no extra peaks formed which usually indicates formation of new functional group.

Differential Scanning Calorimetric (DSC) analysis

In the present studies the DSC analysis of Ofloxacin and formulation that contains all the ingredients used for preparation buccal muco-adhesive tablets (F1-F9) were carried out using a Shimadzu DSC 60, Japan; to evaluate any possible polymer drug thermal interaction. Exactly weighed 5 to 6 mg samples were hermetically sealed in aluminium crucible and heated at constant rate of 10^{o}C/min over a temperature range of 40 to 300^{o}C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.

Evaluation of post-compression parameters[7-14]

Thickness

Ten tablets from each formulation of Ofloxacin muco-adhesive sustained release tablets were randomly selected and used for thickness determination. Thickness of each tablet was measured by using Vernier Callipers and the results were expressed as mean values of ten readings, with standard deviations. According to specification tablet thickness should be controlled within a ± 5% variation of standard value.

Hardness

Hardness of all the formulations of Ofloxacin muco-adhesive sustained release tablets were measured by using Monsanto hardness tester (Cad Mach). From each formulation the crushing strength of ten tablets with known weights were recorded in kg/cm^2 and average were calculated and presented with standard deviation. According to specifications of USP hardness values of 4-5 Kg for tablet is considered as acceptable limit.

Friability

Previously weighed ten Ofloxacin muco-adhesive sustained release tablets from each batch were taken in Roche friabilator (Roche friabilator, Secor India). After100 revolutions of friabilator tablets were recovered. The tablets were then made free from dust using a soft muslin cloth and the total remaining weight was recorded. Friability was calculated from the following formula.

%F= (wi-wf/wi)×100

Where *Wi* and *Wf* were the initial and final weight of the tablets before and after friability test. For any compressed tablet that the lose less than 0.1 to 0.5% and maximum up to 1% of the tablet weigh are consider acceptable.

Weight variation test

All formulated Ofloxacin muco-adhesive sustained release tablets were evaluated for weight variation as per USP monograph. Twenty tablets were weighed collectively and individually using an electronic balance. The average weight was calculated and percent variation of each tablet was calculated. According to USP monograph, the weight variation tolerance limit for the uncoated tablet having average weight 130mg or less is 10% whereas for average weight between 130-324mg is 7.5% and for average weight more than 324mg is 5%. For the tablet to be accepted, the weight of not more than two tablets deviate from the average weight by not more than 7.5% and no tablet deviates by more than 15%.

Content uniformity

Twenty Ofloxacin muco-adhesive sustained release tablets were taken and triturated to form powder and powder equivalent to dose of drug was taken and dissolved in 100 ml of phosphate buffer PH 6.8 and heated at 37 0C for 15 to 20 minutes with stirring. The solution was filtered, suitably diluted and the Ofloxacin content was measured by using UV Spectrophotometer at 279 nm. Each measurement was carried out in triplicate and the average drug content in each Ofloxacin muco-adhesive sustained release tablets was calculated.

Swelling index study

The extent of swelling was measured in terms of percentage weight gain by the tablet. The swelling indexes of all formulations were studied. One tablet from each batch was kept in a Petridis containing Phosphate buffer 6.8 at 37±1 °C. The tablet was removed after every one hour interval up to 8-10 hour and excess water blotted carefully using filter paper. The swollen tablets were re-weighed (*Wt.*). The swelling index (*SI*) of each tablet was calculated according to the following equation.

SI= (wt-w0/w0)×100

Where, *W0* = initial weight and *Wt* = weight after time t

Measurement of bio-adhesive force

Bio-adhesive force of the tablets was measured on a modified physical balance that is shown in figure. The apparatus consisted of a modified double beam physical balance in which a lighter pan had replaced the right pan and the left pan had been replaced by a glass slide (4 cm length and 2.5 cm width) with plastic hang suspended by Teflon rings and copper wire. The left-hand side of the balance was exactly 5 g heavier than the right side. The height of the total set-up was adjusted to accommodate a glass container of 6.6 cm height. In order to find out the bio-adhesion strength first buccal tablet (n = 3) was stacked to the glass slide with the help of the knob, which was situated at the base of the physical balance. Five grams weight from the right pan was then removed. This lowered the glass slide along with the tablet over the membrane with a weight of 5.0 g. This was kept undisturbed for 5 min. Then, the weights on the right-hand side were slowly added in increments of 0.1 g till the tablet just separated from the membrane surface.

The excess weight on the right pan, i.e. total weight minus 5 g was taken as a measure of the bio-adhesive strength.11, 13 by using this weight, bio-adhesive force for all the formulations of Ofloxacin buccal muco-adhesive tablets were calculated using following equations.

N = (W × g)/100

Where, *N* is bio adhesive force, *W* is the weight required for the detachment of two vials in grams and *g (g=9.81)* is the acceleration due to gravity.

In-vitro dissolution study

The *in-vitro* dissolution study was conducted for all the formulations using an eight station USP dissolution rate test apparatus type-II. A total volume of 900 ml of phosphate buffer PH 6.8 was taken as dissolution medium, which was maintain at 37°C± 0.5°C at 50 rpm. 1ml of aliquots was periodically withdrawn and the same volume was replaced with an equal volume of fresh dissolution medium. Samples were collected at 1 hour intervals and after filtering by Whatmann filter paper, were analysed spectrophotometrically at 279nm for determination of Ofloxacin that were released from muco-adhesive sustained release tablets.

Stability study of tablets

Formulation batch 5 has shown best results amongst all 9 batches. So stability study was carried out on formulation batch 9. Different tablets were kept on 25^{o}C and 40 ^{o}C

with humidity 60% and 75% respectively for the period on one month and evaluated after one month.

RESULTS

The muco-adhesive buccal tablet of Ofloxacin was formulated and evaluate for different parameter to ensure their therapeutic efficacy and accuracy. The preliminary examination of Ofloxacin like melting point obtained in ranges from 250°C to 255°C by capillary tube method and their calibration curve was taken in phosphate buffer pH 6.8 at 294 nm by U.V Spectrophotometer. Pre-formulation study confirms the purity drug through above tests. Blend of all tablet formulation were subjected for various evaluation such as Angle of repose, Bulk & Tapped density, Compressibility, Hausner's ratio, Car's index. Result of all pre compression parameters shows good flow characteristics, and compressibility index.

The pure drug of ofloxacin and the solid admixture of drug and various polymers used in the preparation of muccoadhesive tablet formulation were characterized by FT-IR spectroscopy and DSC to know the compatibility. There was no significant difference and characteristic peaks of pure drug were unchanged in spectrum of tablet formulation. The compatibility of Ofloxacin with polymers Pluronic-F-127, Gallen gum and Carbopol 940 the studies of IR shows that all above characteristic peaks of Ofloxacin observed near about their respective values so it has been concluded that there is no incompatibility between polymers and pure drug.

Table 2: Preformulation studies of formulation batch F1-F9.

Batch Code	Bulk Density (gm./ml)	TappedDensity (gm./ml)	Car's Ratio	Index (%) Hausner's	Angle of Repose (θ)
F1	0.53±0.04	0.64±0.09	15.9±1.23	1.15±0.08	20.7±2.3
F2	0.50±0.02	0.67±0.17	15.1±1.24	1.23±0.22	20.8±1.7
F3	0.54±0.04	0.63±0.12	13.2±1.12	1.16±0.11	19.6±2.1
F4	0.56±0.08	0.68±0.11	13.2±1.12	1.17±0.17	22.6±2.5
F5	0.52±0.06	0.69±0.16	14.1±1.3	1.18±0.23	21.7±1.9
F6	0.51±0.03	0.67±0.13	14.2±1.24	1.25±.019	20.8±1.8
F7	0.56±0.09	0.64±0.15	15.1±0.21	1.21. ±0.18	23.3±2.4
F8	0.54±0.06	0.62±0.13	14.1±1.19	1.17±0.16	22.6±1.7
F9	0.55±0.08	0.65±0.17	13.1±1.25	1.14±0.25	22.4±2.9

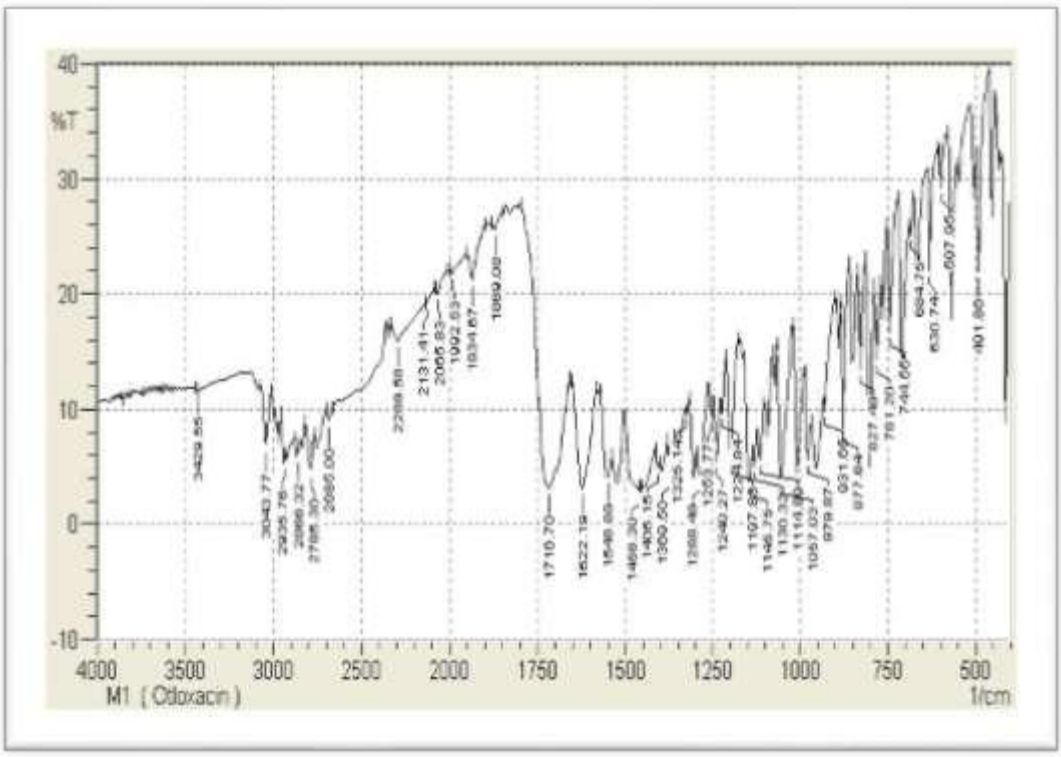

Figure 1: IR Spectra of Ofloxacin.

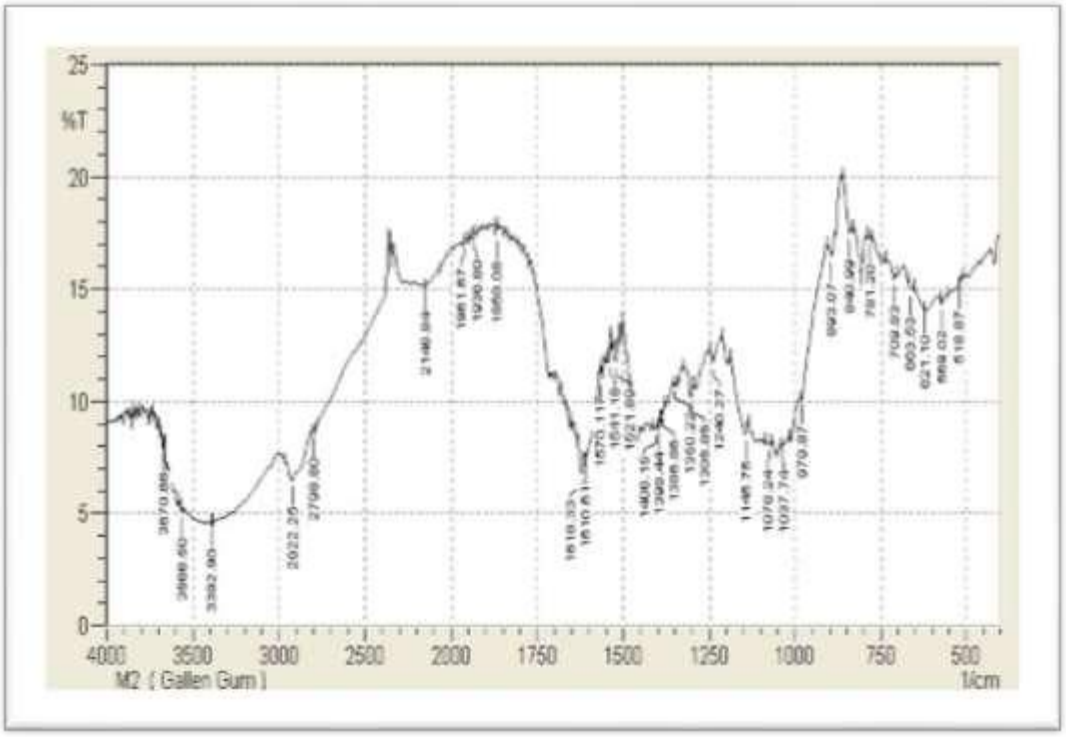

Figure 2: IR Spectra of Ofloxacin with Gallen gum.

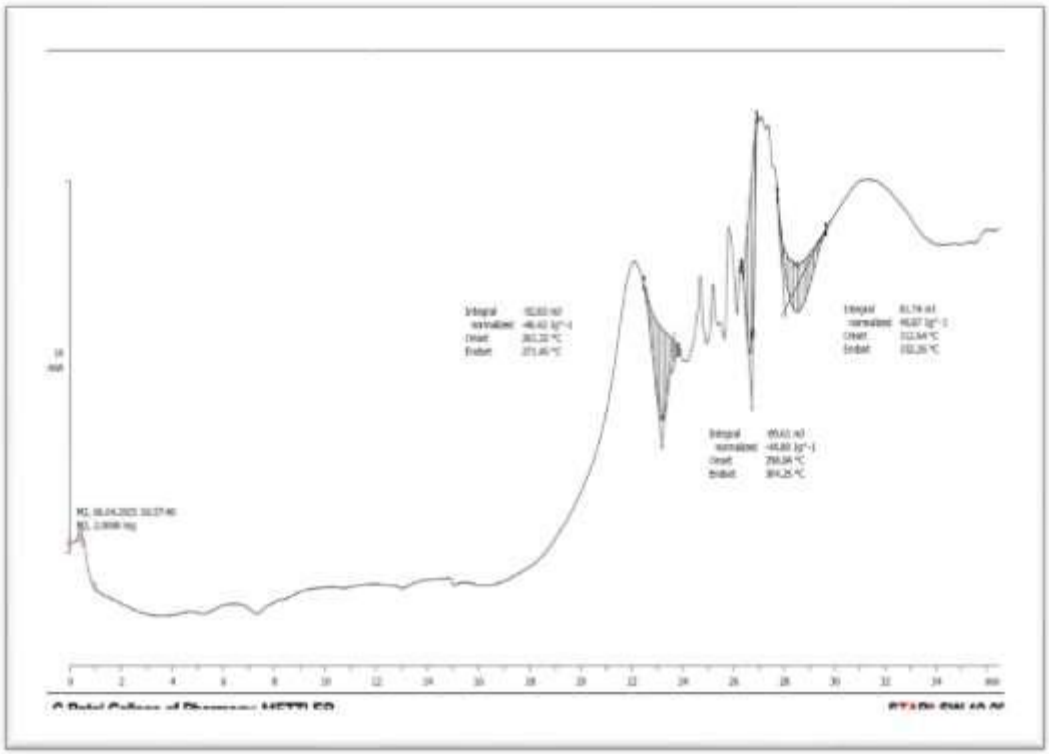

Figure 3: DSC of drug excipients compatibility Analysis.

Post-formulation Evaluation

Thickness

Thickness of formulation batches was found in between 3.08 to 3.30 mm. The individual data of all batches are given in table 3 for optimized batches respectively.

Hardness

The hardness of all 09 batches (F1-F9) was found in the rage of 4.85 to 5.10 kg/cm2. The details of hardness values are given in table 3 for optimized batches respectively.

Friability
The percentage friability was found in the range of 0.35 to 0.64% of all 09 batches. The details of friability are given in table 3 for optimized batches respectively.

Weight Variation
The weight variation of all 09 formulation batches was found in between ±1.5 to ±4.67 and details are given in table 3 for optimized batches respectively.

Drug Content Uniformity
To evaluate the tablet potential for their efficacy, the amount of drug in the tablet need to be monitored from tablet to tablet and batch to batch. The average of drug content was found in range of 90.51 to 97.25%. The detail values summarized in table 3 for optimized batches respectively.

Surface pH
The surface pH values were found to be in the range of 6.23 to 6.93 for all formulations were almost within the range of salivary pH i.e. 6.0 to 7.5. To see details of values refer the table 3 for optimized batches respectively.

Swelling Index
The percentage swelling index of all formulations was found in the range of 44.62 to 87.33%. The details of values are given in table 3 for optimized batches respectively.

In-vitro Mucoadhesive Strength
The mucoadhesive strength of all 9 formulation batches (F1-F9) were found in the range of 7.5 to 13.5 gm. The detail values of mucoadhesive strength are put in table 3 for optimized batches respectively

Ex-vivo Residence Time
The ex-vivo residence time on gout buccal mucosa ranged from 5.49 to 6.46hrs. The detail values are given in table 3 for optimized batches respectively.

Table 5: Post compression parameter for formulation batch F1-F9.

Batch Code	Thickness (mm) Mean ± SD	Hardness(kg/cm^2)	Friability (%)	Weight variation (%) Mean ± SD	Drug Content (%)	Swelling Index	In-vitro Muco-adhesive Strength	Ex-vivo Residence Time
F1	3.24±0.15	5.10	0.52±0.08	299.8±2.04	90.51%	51.43	9.7	6.46
F2	3.13±0.05	5.00	0.64±0.11	297.66±4.67	94.75%	53.24	10.2	6.34
F3	3.18±0.03	4.99	0.42±0.03	296.16±3.06	93.75%	59.81	10.8	5.26
F4	3.20±0.10	4.92	0.54±0.12	299.16±1.94	97.25%	44.62	11.1	5.49
F5	3.08±0.02	5.05	0.42±0.05	302.66±1.5	97.25%	56.89	12.2	6.30
F6	3.30±0.01	5.02	0.44±0.06	301.00±2.2	91.49%	68.41	13.5	6.02
F7	3.20±0.01	4.95	0.35±0.03	294.66±3.6	91.75%	59.66	6.8	5.43
F8	3.21±0.00	5.03	0.60±0.14	298.16±1.72	95.25%	75.83	7.5	6.36
F9	3.22±0.01	4.85	0.59±0.07	298.16±1.32	96.25%	87.33	8.2	5.56

In-vitro Dissolution Studies
The dissolution study of Optimized batches was performed in USP dissolution test apparatus, the release of drug is ranges from 75.93 to 98.51%. The formulation batch FB5 shows best drug release. The details of values of drug release data are given in table 4.

Table 5: In-vitro of dissolution studies of formulation batch F1-F9.

Batch Code	Time								
	30 min	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
F1	1.04	2.89	6.26	11.49	23.38	35.51	50.14	73.92	98.51
F2	1.52	3.77	7.47	13.90	24.0	35.43	50.06	66.45	83.89
F3	0.4	1.2	3.13	8.75	17.59	29.00	41.86	58.01	75.93
F4	1.76	4.58	8.51	15.83	29.57	43.87	58.74	74.49	93.53
F5	0.8	3.05	7.23	13.58	22.82	33.58	48.61	66.45	91.68
F6	0.8	2.16	4.17	9.08	18.48	30.13	44.83	65.65	92.00
F7	0.8	2.33	4.58	8.43	15.42	26.51	21.54	63.08	87.74
F8	1.28	2.97	2.90	9.80	19.04	32.30	48.53	68.54	93.37
F9	0.96	3.21	6.50	12.77	21.37	30.93	43.23	59.22	83.49

Stability Study
Stability study is carried out on formulation batch (F1) according to ICH guidelines. The tablet did not show any physical changes during the study period and the drug content was found to be 94.06 % for Ofloxacin at the end of 1 month on stability condition which has shown in table 5

Table 5: Stability study of formulation batch F1.

Temprature	Time in month	Mucoadhesive strength (mg)	Mucoadhesive Time (mg)	Swelling index %	Surface pH	% Drug Release
25°C ± 2°C 60% RH	1	9.78	6.46	51.42	6.24±0.0 2	98.51
40°C ± 2°C 75% RH	1	9.78	6.45	51.43	6.22±0.0 2	96.58

CONCLUTION

In conclusion, we reported here the formulation of Buccoadhesive Tablet Containing Ofloxacin produced following design of experiment and optimized with the help of response surface methodology. The formulation F 1 was found to be optimized with desirable properties.

Therefore, Ofloxacin can be conveniently administered orally in the form of Buccoadhesive Tablet with lesser occurrence of its side effects and with improved bioavailability.

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