ORIGINAL ARTICLE

Formulation and Evaluation of Floatable *In Situ* Gel of Ofloxacin

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Abstract

Aim: The main of our study is to formulate and evaluate the *in situ* gel of ofloxacin. **Materials and Methods:** The gift sample of drug was procured from Century Pharmaceuticals Limited Halol, Gujarat, India. The drug was identified by ultraviolet, infrared (IR), solubility, and on the basis of melting point. For the incompatibility studies, a drug-excipient study was performed. For the preparation of *in situ* gel of ofloxacin, Calcium carbonate (CaCO3), 0.1N HCl, and trisodium citrate were used. Now make solution of propylparaben and Methylparaben in purified Water in ration of 9:1 with aspartame. Now, different concentrations of HPMC-K 4 M, HPMC-K 15 M, and HPMC-K 100 M were added in respective batches. These solutions were mixed with the above solutions. The resulting alginate *in situ* gel solution containing ofloxacin was checked for lag time, viscosity, and amp, gelling property. **Results and Discussion:** Melting point was found to be 254–260°C. IR spectra of ofloxacin showed C=O, N-H, C-F, and O-H stretching which is similar to the standard drug sample. On the basis of results, P8 formulation was found to be best in respect of visual inspection, pH, viscosity, *in vitro* floating study, *in vitro* gelation study, determination of drug content, and *in vitro* drug release. **Conclusion:** In our experiment it is observed that if the final concentration of CaCO3 increases then it decreases the lag time for floating and if increase the concentration of sodium alginate and HPMC K4M the viscosity increases. It is proved by seeing all the results that ofloxacin *in situ* gel formulation has better performance than conventional formulation and also makes better compliance and improved efficacy.

Key words: Drug-excipient compatibility study, drug retention, in situ gel, melting point, ofloxacin

INTRODUCTION

In situ gel-forming systems have been widely investigated as vehicles for sustained drug delivery. Since administration of highly viscous formulations by a common spray device is difficult, it is preferred that a liquid-drug polymer formulation would gel at the site of administration since *in situ* gelling systems undergo reversible sol-gel transitions in response to temperature, pH, or ion composition of the fluids. Drug retention and bioavailability can be achieved by gelation.[1,2]

In general, a large dose of drug is difficult to incorporate using conventional dosage form and also to maintain constant plasma concentration. Gastroretentive *in situ* gelling system helps to increase bioavailability of drug compared to conventional liquid dosage form. The gel formed from *in situ* gelling system, being lighter than gastric fluids, floats over the stomach contents and produces gastric retention of the dosage form and increase gastric residence time, resulting in prolonged drug delivery in gastrointestinal tract.[3,4]

Ofloxacin is a synthetic fluorinated carboxyquinolone that has a broad spectrum of activity. It is highly soluble in acidic pH and has absorption window to upper part of GIT. 200–800 mg dose administered twice or thrice a day for 5–7 days depending on the severity of infection. Due to many reported side effects and decreased bioavailability of ofloxacin in gastric system, the main of our study is to formulate and evaluate the *in situ* gel of ofloxacin.[5,6]

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MATERIALS AND METHODS

Chemicals and reagents

All the solvents and chemicals (analytical grade) were purchased from Merck (India). The drug ofloxacin was received as gift samples from Century Pharmaceuticals Limited Halol, Gujarat, India.

Identification of drug

Melting point determination

Melting point is determined by capillary method in which compound is pushed in open end of capillary tube, and the closed end of capillary tube holds over dropping tube. Drop capillary tube into dropping tube. After placing tubes in oil bath or melting point apparatus, chamber starts to set temperature and sample should be observed continuously for accuracy and record the melting point range when sample first starts to melt and ends when the sample is completed melting.[7]

Infrared (IR) spectroscopy

The IR spectroscopy of the sample was carried out for the identification of drug. A pellet of 1-mm diameter of each drug was prepared by compressing 3–5 mg of the drug with 100–150 mg of potassium bromide in KBr press. The pellet was mounted in IR compartment and scanned between wavenumber 4000 and 600 cm^{-1}.[8]

Analytical estimation of drug

Ultraviolet (UV) visible spectroscopy

Estimation of absorption maxima (λ_{max})

100 mg of ofloxacin was accurately weighed and transferred to 100 ml of volumetric flask. The drug was dissolved in 0.1 N HCl, and the volume was made up to 100 ml to obtain a stock solution of 1000 µg/ml. 1 ml of this stock solution was again diluted with 0.1 N HCl up to 10 ml to obtain a solution of 100 µg/ml. Then, 0.5 ml was withdrawn from working solution and diluted up to 10 ml with 0.1 N HCl to obtained 5 µg/ml solution. The resulting solution was scanned between 200 nm and 400 nm in a double beam UV-visible spectrophotometer.[8]

Drug-excipient compatibility study

Fourier-transform infrared (FTIR) absorption spectra of pure drug and physical mixture were recorded in the range of 4000–400 cm^{-1} by KBr disc method using FTIR spectrophotometer.[9]

Preparation of *in situ* gelling solution

Take a beaker and amp, make a solution of Calcium carbonate (CaCO3) in water by dissolving it. Then, take 10 ml of 0.1N HCl solution and amp; dissolve 0.2 g of ofloxacin. Now, take another beaker and amp; add alginate into water which contains trisodium citrate with continuous stirring. Mix above three solutions. Now make solution of propylparaben and amp; methylparaben in purified Water in ration of 9:1 with aspartame. Now, different concentrations of HPMC-K 4 M, HPMC-K 15 M, and HPMC-K 100 M were added in respective batches. These solutions were mixed with the above solutions. The resulting alginate *in situ* gel solution containing ofloxacin was checked for lag time, viscosity, and amp, gelling property. In all batches, concentration of all ingredients were not changed only concentration of ingredients like Aspartame preservatives and amp; trisodium citrate was kept constant.[10,11]

Preliminary screening for selection of polymers, buoyancy materials, and their concentration

Preliminary batches were prepared using different polymers such as Na-alginate, HPMC-K 4 M, HPMC-K 15 M, and HPMC-K 100 M with their different concentrations using CaCO3 and NaHCO3 as Buoyancy material and optimum concentration were obtained. The concentration of trisodium citrate, methylparaben and amp, propylparaben (as preservatives), and aspartame (as sweetening agent) was constant. 10 batches had been prepared. The composition of 10 batches is shown in Table 1.[11]

Evaluation parameter of *in situ* floating gel[12,13]

Visual inspection

Visual inspection can be done for clarity of solution and amp; gel. For this purpose, black and amp and white background are used.

pH

At 25°C, calibrated pH meter was used for pH measurements. All measurements of pH were made in triplicate.

In vitro floating study

For floating study, 0.1 N HCl (pH 1.2) was taken in beaker. Accurately measured 10 ml of solution was added in 500 ml of solution of HCl. Floating lag time means time required for absorption on surface after adding solution and total floating time were measured.

Viscosity measurement of in situ gels

Brookfield viscometer was used for measurement of viscosity. 20 ml aliquot was used as sample. Temperature 25°C and spindle number 2 were taken for measurements. All measurements were made in triplicate.

In vitro gelation study

For gelling study, colored solution of *in situ* gel was used. The gelling capacity was evaluated on the basis of stiffness

Table 1: Composition of preliminary batches (P1 to P10)

Ingredients (mg)	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Ofloxacin	2700	2700	2700	2700	2700	2700	2700	2700	2700	2700
Sodium alginate	1000	250	500	500	750	1000	250	500	750	500
HPMC-K_4M	-	-	-	250	250	250	250	250	250	250
HPMC-K_{15}M	250	-	-	-	-	-	-	-	-	-
HPMC-K_{100}M	-	250	250	-	-	-	-	-	-	-
$CaCO_3$	500	500	500	400	400	400	750	750	750	1000
$NaHCO_3$	-	-	-	-	-	-	-	-	-	-
Trisodium citrate	250	250	250	250	250	250	250	250	250	250
Methylparaben	90	90	90	90	90	90	90	90	90	90
Propylparaben	10	10	10	10	10	10	10	10	10	10
Aspartame	250	250	250	250	250	250	250	250	250	250
Purified H_2OUpto (ml)	50	50	50	50	50	50	50	50	50	50

of formed gel and amp and time period for which formed gel remained as such.

Determination of drug content

UV absorbance of the sample was determined at a wavelength of 294 nm.

In vitro drug release study

The release rate of ofloxacin was determined using USP apparatus 1 (basket covered with muslin cloth/cellophane paper) at 50 rpm. The given rpm is enough to avoid the breaking of gel formulation and was maintaining mild agitation condition which is available inside the body. The dissolution medium used was 900 ml of 0.1 N HCl, and temperature was maintained at 37°C. A sample was withdrawn at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, and 16 h of dissolution. The sample was analyzed, and percentage cumulative release was calculated.

Stability study of optimized formulation

Physical stability was done for appearance, and the chemical stability was estimated by percentage drug release. The samples for this purpose were withdrawn regularly at the interval of 1 month, and it was analyzed in UV spectrophotometrically at 294 nm.[14]

RESULTS AND DISCUSSION

Identification of drugs [Table 2]

Melting point: By capillary method [Table 3]

Melting point was measured by the help of capillary tube methods and it was found to be 254-260oC [Figure 1].

FT-IR spectra of ofloxacin

FT-IR spectra of ofloxacin denotes the presence of various functional groups which indicates the purity of drug. On the observation of FT-IR spectra, we found that Frequency (cm^{-1}) of ofloxacin was found to be very close to the reference [Figure 2].

Analytical estimation of drug [Table 4]

UV Absorption maxima of ofloxacin in 0.1 N HCl [Figure 3].

Drug-excipient compatibility study

All the above peaks present in physical mixture confirm the presence of ofloxacin peak in the physical mixture without any interaction. Hence, drug and polymer are compatible.

Justification for the selection of promising batch

From the all observation tables, results shows that proper stiff gel is done with 1% concentration of sodium alginate, while in below 1% concertration, it is found that gel was formed but gets ruptured. At 0.5% concentration, HPMC-K_{15}M gave viscous solution while HPMC-K_{100}M makes non-pourable solution at 0.5% concentration. HPMC-K_4M at low concentration (0.5%) forms proper viscous solution along with enough gel strength. High concentration of sodium bicarbonate makes dosage form dumping and fragmentation of gel within 4–5 h, while low concentration of CaCO3 gives poor cross-linking due to insufficient concentration of Ca2+ ions [Table 5].

Here, in batches P1, P2, and P3, gel was formed but it was ruptured and showed fragmentation in 2–3 h due to poor cross-linking of sodium ion due to the low concentration

Table 2: Melting point of ofloxacin

Theoretical range (The Merck Index)	Practically obtained
250–257°C	254–260°C

Table 3: Comparison of vibration frequencies of FTIR Spectra

Functional group	Frequency (cm^{-1})	
C=O stretching	1750–1700	1750–1700
N-H bending	1650–1600	1650–1600
C-F stretching	1050–1000	1050–1000
O-H stretching	3000–2950	3000–2950

FTIR: Fourier-transform infrared

Table 4: Vibrational frequencies of ofloxacin and physical mixture

Functional group	Frequency (cm^{-1})	
	Pure Ofloxacin	Physical mixture
C=O stretching	1750–1700	1710.74
N-H bending	1650–1600	1600.34
C-F stretching	1050–1000	1010.63

of sodium bicarbonate. Here, in case of batch P1, solution was highly viscous due to HPMC $K_{15}M$. At the same time, batches P2 and P3 were non-pourable due to HPMC $K_{100}M$. The sissolution study was performed only for P1, P2, and P3 batches, and the result of release profile is shown in Table 6.

Drug release profile of selected batches

Among all these batches (from P1 to P10), batch 8 has optimum viscosity and it has enough gel capacity. P8 showed maximum drug release in 16 h among selected batches. Hence, on bases of these evaluation parameters and release profile, P8 has been selected as promising batch.

Stability study of optimized batch

The optimized formulation was subjected at 40 ± 2.0°C temperature and 75 ± 5 % RH for 1 month to check the stability. The results of physical appearance and drug release after 1 month storage of prepared floating *in situ* gel were noted. There was no drastic change in physical appearance of gel during storage condition [Table 7].

To check the similarity between drug release profiles for promising formulation at different time intervals, i.e., 0 month and 1 month, similarity factor was calculated using the following equation.

$$f_2 = 50 \times \log\left\{1+\left[\left(\frac{1}{n}\right)\right]\sum_{i=1}^{n}\left[(R_i - T_i)^2\right]^{-0.5} \times 100\right\}$$

Table 5: Evaluation parameters of batches P1–P10

Evaluation parametlers	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Lag time (s)	108.7±5.688	69.0±2.832	104.3±7.047	68.76±2.091	90.66±2.86	91.66±4.99	39.43±1.97	59.0±2.95	73.76±3.94	49.76±2.319
pH	7.28±0.067	7.29±0.059	7.29±0.058	7.23±0.059	7.20±0.06	6.53±0.06	7.93±0.09	7.46±0.06	7.50±0.09	7.36±0.27
Gelling time (min)	6.7±0.173	7.63±0.152	6.26±0.057	9.73±0.152	8.56±0.28	7.93±0.12	12.46±0.28	10.26±0.12	8.96±0.28	9.96±0.152
Gel capacity	+++	+++	+++	++	++	++	++	+++	+++	+++
Viscosity (cp)	324.0±3.464	421.6±2.886	470.0±5.00	106.0±3.464	122.6±1.14	134.6±3.05	201.3±2.39	241.3±3.05	272.0±2.0	265.3±1.154
TFT (h)	>16	>16	>16	<8	<8	<8	<8	>16	>16	>16
Drug content (%)	93.13±2.127	95.96±2.543	108.7±3.820	96.32±2.607	83.58±2.81	87.74±1.78	92.93±0.55	98.62±2.17	93.01±1.92	85.28±1.392

Table 6: Release profile of preliminary batches

Time (h)	P1 (%)	P2 (%)	P3 (%)	P8 (%)	P9 (%)	P10 (%)
0.5	6.36±0.698	9.68±0.512	8.02±0.216	8.08±0.824	7.48±0.256	7.12±0.306
1.0	13.82±0.573	15.14±0.108	12.77±0.336	14.90±0.672	12.32±0.419	15.74±1.126
2.0	19.54±0.289	22.70±0.352	20.12±0.888	23.53±0.116	21.66±0.823	22.48±0.807
3.0	26.12±0.364	27.93±0.687	24.82±0.560	31.15±0.229	28.92±0.788	33.95±0.989
4.0	33.95±1.213	33.38±0.639	30.96±0.560	38.66±0.824	39.04±0.144	41.16±0.554
6.0	43.61±0.573	40.78±1.012	35.42±0.114	46.78±1.123	46.83±0.470	48.27±0.110
8.0	52.74±0.289	46.22±0.512	41.48±0.197	54.44±0.791	51.14±0.782	55.97±0.238
10.0	62.32±0.986	51.17±0.732	46.24±0.372	63.80±0.720	60.38±0.250	64.22±0.306
12.0	68.10±0.875	55.43±1.012	49.98±1.430	72.28±0.382	67.50±0.732	75.30±0.744
14.0	74.18±0.364	61.92±0.352	55.05±0.658	84.35±0.402	75.16±1.204	82.08±0.509
16.0	79.87±0.698	64.64±0886	61.36±0.743	94.72±0.155	88.82±0.484	90.62±0.681

Table 7: Drug release data after stability study

Time (h)	% cumulative release of drug	
	At 0 day	After 30 days
0.0	0.000±0.000	0.000±0.000
0.5	8.936±0.816	6.988±1.233
1.0	15.36±0.936	13.06±0.687
2.0	25.05±0.637	22.66±0.445
3.0	33.17±0.987	31.13±0.778
4.0	41.18±0.897	38.29±0.325
6.0	53.97±0.656	49.78±1.011
8.0	64.13±0.897	61.44±0.687
10.0	71.45±0.395	69.54±1.011
12.0	80.48±0.845	76.68±0.023
14.0	88.93±0.715	84.36±0.208
16.0	97.84±0.740	93.16±0.445

*Values are mean±SD, (*n*=3)

Where n is the number of dissolution time, and Ri and Ti are the reference and test dissolution values at time t. Two release profiles are considered similar when the F2 value is in between 50 and 100. Similarity factor F2 was found to be 64.67 which indicates similarity between release profiles before and after stability study revealing that films are stable.

DISCUSSION

A research study was done on the topic "Formulation and Evaluation of Floatable *in situ* gel of Ofloxacin." Formulation of *in situ* gel was done by mixtures of polymers and thickening agents. Formulation gives the property of sol-gel phase transition when taken orally many factors such as concentration of polymer and thickening agents affect the drug release.[15] Drug with excipient compatibility was analyzed by FTIR. It showed that there was no chemical interaction between the drug and excipient. For the preliminary trials, 10 batches (P1–P10) were taken to select a proper concentration of polymer and buoyancy material. Sodium alginate (1.0 %), HPMC K_4M (0.5 %), and CaCO3 (1.5 %) were optimized. They were characterized for appearance, clarity, pH, gelling

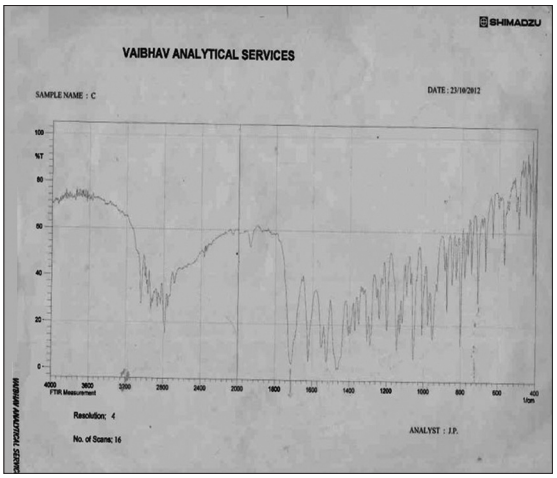

Figure 1: Fourier-transform infrared spectra of ofloxacin

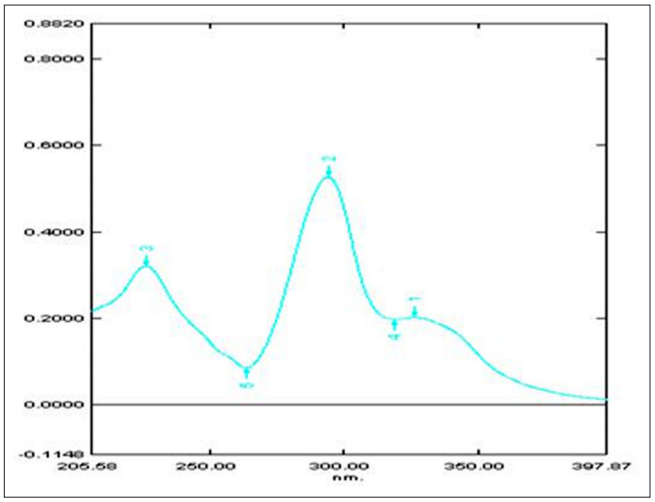

Figure 2: Ultraviolet absorption maxima of ofloxacin in 0.1 N HCl

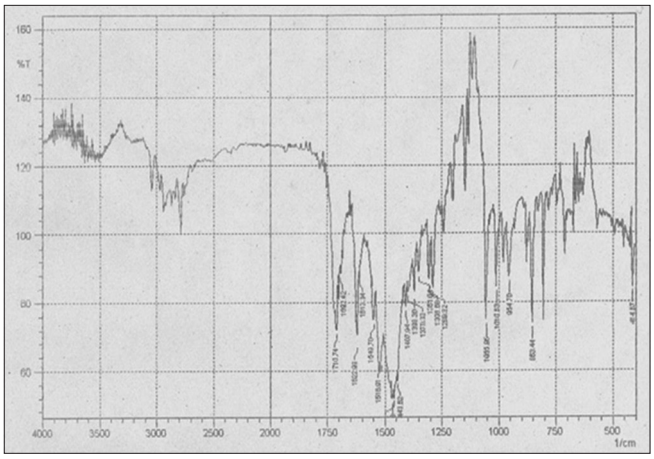

Figure 3: Excipient compatibility study

capacity, floating lag time, viscosity, and *in vitro* release in simulated gastric fluid.[16] P8 showed maximum drug release in 16 h (94.72%) along with optimum viscosity and enough gel capacity. Stability study of optimized batch was carried out at 40 ± 2°C and 75 ± 5% RH for 1 month, and it was found that no statistically significant difference was found in *in vitro* drug release before and after stability study.[17]

CONCLUSION

For retention of formulation in gastric fluid for 16 h, the ofloxacin was formulated as floatable *in situ* gel. In our experiment it is observed that if the final concentration of CaCO3 increases then it decreases the lag time for floating and if increase the concentration of sodium alginate and HPMC K4M the viscosity increases. By varying all three excipient contents, we can adjust drug release and viscosity. It is proved by seeing all the results that ofloxacin *in situ* gel formulation has a better performance than conventional formulation and also makes better compliance and improved efficacy.

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