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Formulation and evaluation of moxifloxacin loaded ocular *In-situ* gels

Velchuri Sirisha*[1], P Ram Babu[1], Sandeep Kumar G[2], Sarvepalli Revathi[3]

[1]Department of Pharmaceutics, College of Pharmaceutical Sciences and Research, Krishna University, Rudravaram, Machilipatnam-521 004, Krishna District, Andhra Pradesh, India

[2]Department of Pharmaceutics, St. Peter's Institute of Pharmaceutical Sciences, Vidya Nagar, Hanamkonda, Telangana 506001

[3]Department of Pharmaceutics, Ratnam Institute of Pharmacy, Pidathapolur (V), Muthukur (M), SPSR Nellore - 524001 Andhra Pradesh, India

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Abstract

Moxifloxacin, a fourth-generation broad-spectrum antibiotic, is at the heart of this research, aimed at treating infective ophthalmitis through sustained release via ion-sensitive ocular in-situ gels. The study emphasizes the importance of careful polymer and drug selection for effective oral in-situ gel formulation. Sodium alginate and HPMC were identified as compatible polymers with Moxifloxacin, as confirmed by IR and UV analyses. The concentration of these polymers significantly influences the gel's viscosity, spreadability, and drug release properties. Among the tested formulations, F4 emerged as superior, exhibiting the highest drug release and favorable rheological properties. This formulation not only showed good stability and uniformity but also resulted in better and faster patient improvement. Although the current results are promising, further pharmacokinetic studies are suggested. The F4 formulation outperformed others in efficacy, making it the most optimal choice. In vitro release studies validated the effectiveness of the Moxifloxacin gel formulations used in this research. The extended drug delivery system developed here has the potential to enhance the bioavailability of the medication, thereby improving patient efficacy, compliance, and overall therapeutic value.

∗Corresponding Author
Name: Velchuri Sirisha
Phone: +91 8978777928
Email: harshithananga27@gmail.com

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INTRODUCTION

Ophthalmic drug distribution is a difficult field because the eye's distinctive architecture limits drug absorption into the deeper tissues. The disadvantages of the available ophthalmic medication delivery methods, such as inserts, ointments, and suspensions, were patient compliance issues, impaired vision, and heterogeneity. Due to slower drainage from the cornea, increasing a drug formulation's viscosity in the precorneal region can boost bioavailability [1][2]. Several approaches for in-situ gelling

devices have been investigated to address this issue. Ion activation, pH, and temperature can all activate these systems. Insitu gels are created from polymers that experience phase transition as a result of environmental physicochemical change. They are easily injected into the conjunctival sac of the eye as a solution [3][4]. The polymer modifies its structure to form a gel when it comes into contact with the lachrymal fluid. Due to the gel formation, this delivery system has a long retention time and is as simple to use as an ophthalmic solution. Ion-sensitive in-situ gels have the capacity to produce a gel on the ocular surface by cross-linking with the cations found in tear fluid. Buffers can be used to manufacture them at the ideal pH for ocular delivery, and they can be precisely and quickly injected at room temperature. In order to increase the sustained delivery of Moxifloxacin, the present study's goal was to create and test ion-sensitive in-situ gels of Moxifloxacin utilising sodium alginate and HPMC K4M/ HPMC E50 LV.

MATERIALS AND METHODS

Moxifloxacin was obtained from Aurobindo pharma Ltd, Hyderabad India as a gift sample, HPMC E50, sodium alginate, HPMC-K4M and other chemicals came from Mumbai's SD Fine Chemicals. Analytical-grade materials and solvents were also used.

Preparation of In situ Gel

The dispersion process was used to create the polymeric solution. The necessary amounts of HPMC- K4M and sodium alginate were dissolved in water while being continuously stirred. Moxifloxacin solution was continuously stirred into the polymeric solution [5][6]. Agents for preservation and isotonicity were introduced. The solution's pH was determined to be 6.3–6.5.

EVALUTION PARAMETERS

Evaluation of Gels

Gels were evaluated for their clarity, pH, viscosity, spreadability, skin irritation test, drug content, in vitro diffusion studies and in vivo studies by using standard procedure [7][8][9]. All studies were carried out in triplicate and average values were reported.

Clarity

Visual inspection was used to assess the clarity of different formulations under black and white background and it was given the following grades: turbid (+), clear (++), and extremely clear (+++) [10].

pH

In 25 ml of purified water, 2.5 grammes of gel was precisely weighed and mixed. Digital pH metre was used to measure the pH of the dispersion [11][12]. (Systronics μ pH system 362).

Homogeneity

All developed after being placed in the container, the appearance of the gels and the presence of any aggregate were checked for homogeneity [13][14].

Spreadability

Glass slide and wooden block measuring tools were used to determine it. Excess sample was put for the spreadability test between two glass slides and squeezed to a uniform thickness for 5 minutes with a 1000 g weight and 83. 50 g of weight was put to the pan. The spreadability was measured by the time it took to separate the two slides, or when the upper glass slide moved over the bottom plate

Table 1 Formulation Design of Insitu Gelling System

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Drug	2	2	2	2	2	2	2	2
Sodium alginate	600	1100	1100	600	1600	600	-	-
HPMC K4M	600	1100	600	1100	600	1600	600	1100
Ethyl cellulose	-	-	-	-	-	-	1000	500
Calcium carbonate	2100	2100	2100	2100	2100	2100	2100	2100
Methylparaben	199	199	199	199	199	199	199	199
Distilled water (up to 100ml)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

(S) [15][16]. Spreadability was determined using the following formula:

$$S = ML/T$$

Viscosity measurement

Using a Brookfield DV-II + Pro viscometer and a tiny sample adaptor with the spindle number SC4-18/13R, the viscosity of the gels was measured. The torque applied to the gel ranged from 10% to 100%. The "Rheocal" software was used to determine the viscosity [17][18].

Drug content

The Moxifloxacin 50 cc of phosphate buffer pH 6.8 were used to dissolve 100 mg of gel. To obtain full drug solubility, the volumetric flask holding the gel solution was agitated on a mechanical shaker for two hours. This solution underwent filtering and spectrophotometer estimation [19][20].

Extrudability

The Pfizer hardness tester was used to conduct the extrudability test [21][22]. The aluminum tube was filled with 15gm of gel. To adequately secure the tube, the plunger was adjusted. For 30 seconds, 1 kg/cm^2 of pressure was applied. Weighing was done on the gel that was extruded. At three equally spaced locations along the tube, the process was repeated. A test was conducted in triplicates.

DRUG DIFFUSION STUDY

Through Dialysis sac

The device is a cylindrical glass tube with an internal diameter of 22 mm and a height of 76 mm that was opened on both ends [23]. One end of the tube was fixed to the dialysis sac, which had previously been soaked in water for 15 minutes, and 100 mg of the gel formulation equivalent to 1 mg of Moxifloxacin—was evenly disseminated on the surface. The preparation now fills the inner circumference of the tube. The assembly was adjusted so that the lower end of the tube carrying the gel barely touched (1-2 mm depth) the surface of the diffusion medium, which was a 250 ml beaker containing 200 ml of phosphate buffer with a pH of 6.8 that was kept at 37.2°C in a water bath. The contents were swirled using a magnetic stirrer at a speed of 100 ± 10 rpm. The dialysis sac serves as a barrier between the gel phase and water (the sink phase). At intervals of 1, 2, 3, 4, 6, 8, 10 and 12 hours, 5ml samples of the receptor fluid were taken. A spectrophotometer set at 280 nm was used to estimate the release of the medication, and 5 ml of pH 6.8 phosphate buffer was changed out right away after each estimate.

Drug Release Kinetics

The results of in vitro release profiles obtained for all formulations were fitted in to three kinetics models of data treatment as follows:

Cumulative percentage drug release versus time (Zero-order kinetics model).

Log Cumulative percentage drug remaining versus time (First-order kinetics model).

Cumulative percentage drug released versus square root of time (Higuchi's).

Log cumulative percentage drug released versus log time (Korsmeyer-peppas equation).

Drug release kinetics for prepared Moxifloxacin *In-situ* Gel [24]

Data from the in vitro release was plotted in several kinetics models to evaluate the kinetics of release.

Zero order equation: The graph was drawn as percent medication release vs days of time.

$C = K_0 t$

First order equation: Log cumulative % medication remaining was used to depict the graph against time in days.

$\log C = \log C_0 - Kt/2.3$

Higuchi kinetics: The cumulative% drug release vs square root of time was used to produce the graph.

$Q = Kt^{1/2}$

Korsmeyer –Peppas equation: To evaluated the mechanism of drug release, which was then plotted as log cumulative% drug release vs. time in Peppa's equation.

$M_t/Ma = Kt^n$ and $\log Mt/Ma = \log K + n \log t$

Table 2 Different Types of Diffusion Release Mechanisms

n value	Mechanism
0.5	Fickian diffusion
0.5<n<1	Non Fickian diffusion
1	Class II transport

Table 4 FTIR interpretation data of Moxifloxacin and mixture of all compounds

Functional Groups	Moxifloxacin		Mixture of compounds	
	Observed peak	Characteristic peak	Observed peak	Characteristic peak
O-Hstrech (Monometric alcohol)	3009.0	3000-3100	3009.0	3000-3100
C-H Bend in plane (Alkanes)	1338.0	1330-1540	1500.0	1330-1540
-C-Ostrech (Alcohol,ethers)	1225.4	800-1300	1005.4	800-1300

STABILITY STUDY

Moxifloxacin *In-situ* Gel Stability tests were run on the formulas developed for this investigation [25]. Stability research on the best formulation F4 was carried out in accordance with ICH recommendations under various humidity and temperature conditions for 3 or 6 months.

Table 3 Stability Study Storage Condition

Study	Storage condition
Long term	25^{0}C ± 2 ^{0}C/60%RH± 5% RH
Intermediate	30^{0}C ± 2 ^{0}C/65%RH± 5% RH
Accelerated	40^{0}C ± 2 ^{0}C/75%RH± 5% RH

The samples were withdrawn after periods of 3, 6 months and were analyzed for its Clarity; Spreadability; Viscosity; Drug content and In-vitro drug release. The results revealed that no significant changes in Clarity; Spreadability; Drug content and In-vitro drug release for F4 formulation.

RESULTS AND DISCUSSION

Pre-Formulation Studies

The first stage in creating any formulation is to conduct pre-formulation investigations. The main objective of this investigation was to determine whether the medicine was compatible with the polymers that were being employed.

Studies on drug-polymer compatibility

FTIR was used to conduct investigations on drug-polymer compatibility (Fourier Transform Infrared Spectroscopy). Pure drug's FTIR absorption spectra Moxifloxacin, Sodium alginate, HPMC K15M, Calcium carbonate, Methyl parabbin, alone and when the medicine is combined with the recipients. 200 mg of IR grade KBR and 2 mg of sample were combined in a silicon motor, and the resulting mixture was then pressed into a disc. Disk was carefully maintained in an FTIR position. The scanning range for infrared (IR) spectra was 4000 to 400-1. All these spectrums are show in figs.

FT-IR spectroscopy

To study the possible interactions between the Moxifloxacin and Moxifloxacin best formulation.

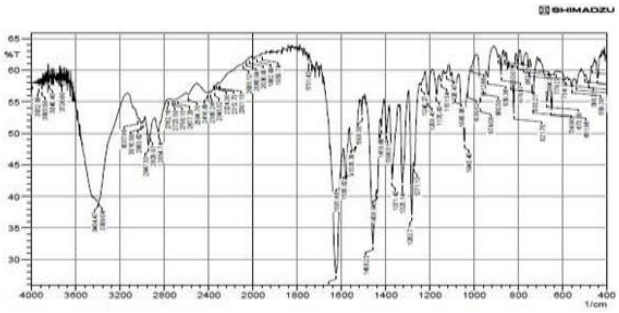

Figure 1 FT-IR spectra of pure Moxifloxacin

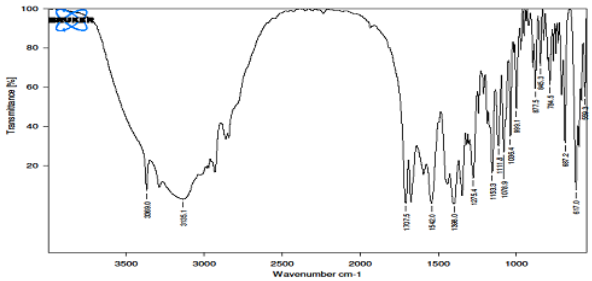

Figure 2 FT-IR spectra of pure Moxifloxacin

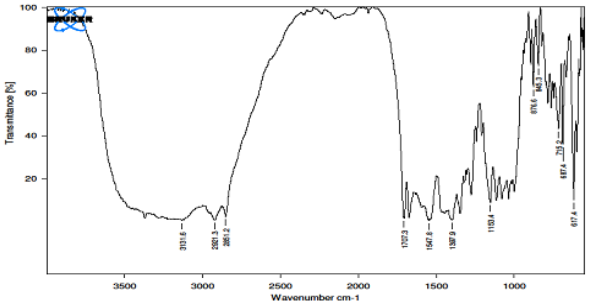

Figure 3 FT-IR Physical Mixture of all Ingredients (formulation F4)

Table 5 Values of created gel's evaluation metrics

F.Code	Clarity	pH	Homogenity	Spreadability (G.Cm/S)	Viscosity (Cps)	%Drug release	Skin irritation	Extrudability
F1	+	6.5	Good	19.01	8798	102.47	-	+
F2	+	6.5	Good	26.22	8556	99.75	-	+
F3	++	6.7	Good	19.71	9331	98.14	-	++
F4	+	6.6	Good	28.26	8765	96.30	-	+
F5	+	6.8	Good	19.02	8987	99.64	-	+
F6	+	6.7	Good	23.11	8882	99.34	-	+
F7	+	6.5	Good	20.12	9324	99.72	-	+
F8	+	6.3	Good	19.07	9890	99.69	-	+

DISCUSSION

The main peaks that were obtained for the combinations were nearly identical to those of the medication. Pure materials' IR spectra did not significantly differ from one another. Moxifloxacin as well as mixture of polymer and drug.

Evaluation of Gels

Clarity

All gels were found to be translucent viscous. All gels were free from the presence of particles.

pH

The pH value of all developed formulations of gels (F1-F8) were in the range of 6.3 – 6.9.

Homogeneity

All fully formed (F1-F8) gels displayed excellent homogeneity and were lump-free. The prepared materials were considerably more transparent and clearer.

Spreadability

The spreadability rating shows that a tiny amount of shear can spread the gel with ease. Spreadability of gels in the range of 19.01-27.27g.cm/sec. Indicating the spreadability of HPMC K4M containing Moxifloxacin gel was good as compared to other gel.

Viscosity measurement

The viscosity was measured using a Brookfield viscometer using several Moxifloxacin gel preparation. Every system of prepared gels' rheological behavior was investigated. The proportion of the solid fraction, which creates the structure, to the liquid fraction determines the consistency of a gel system. The range of viscosity for variously designed gels was 8798 to 9890 centipoises.

Drug content

The percentage drug content 102.47 to 99.69% of all created gel formulations were discovered to fall within this range. It was determined that formulations' drug content percentages were satisfactory. Consequently, the techniques used to create gels were deemed appropriate.

Extrudability

When applying the gel and ensuring that the patient accepts it, the extrusion of the gel from the tube is crucial. A sufficient consistency is necessary in order to extrude the gel from the tube since high consistency gels may not do so, whilst low viscosity gels may flow easily. It was discovered that HPMC gel compositions have good extrudability. Although the extrudability of other gels were satisfactory.

Skin Irritation

Patients accept lack of skin irritation in gel formulation. A test for skin irritation was run, but no skin reddening occurred. It was discovered that none of the gel formulations caused irritation. Thus, observations suggest that these gels are suitable for topical use.

DISCUSSION

The prepared 8 *In-situ* gel physical and chemical parameters were assessed for formulations, and they were found to be within limits (As per USP).

In-Vitro Drug Diffusion Studies

Purified water was used as the dissolution medium for the in-vitro drug release investigations, and the findings were tabulated as well as graphically depicted by placing Time (hrs)

Table 6 In-vitro drug release of Moxifloxacin

Time (hrs)	Cumulative % Drug released							
	F1	F2	F3	F4	F5	F6	F7	F8
1	22.45	16.45	20.72	21.22	19.78	20.71	23.82	16.88
2	29.50	23.44	27.66	31.62	26.48	27.07	37.76	29.54
3	36.87	35.52	32.53	38.41	32.71	34.89	52.61	44.31
4	42.53	44.32	38.62	50.15	43.66	46.76	65.81	58.74
6	52.65	53.28	45.56	59.70	51.68	55.42	80.32	73.64
8	59.32	60.52	52.94	65.52	59.78	62.89	81.22	82.41
10	73.52	72.56	64.29	78.07	72.08	75.76	90.18	91.38
12	81.56	82.40	73.68	97.09	79.42	84.82	91.62	96.61

Table 7 Data on the kinetics of in vitro drug release for formulation F4

Zero order		First order	Higuchi's data		Korsemayer- peppas data	
Time (h)	Cum% of a drug release	Time (h) versus cumulative remaining medication dosage	length of time	Cum% of a drug release	Log time	total cumulative medication release
1	21.22	1.91324	1	21.22	0	1.31344
2	31.62	1.85125	1.42344	31.62	0.31236	1.49765
3	38.41	1.80322	1.74335	38.41	0.48901	1.58433
4	50.15	1.71733	2	50.15	0.61225	1.70883
6	59.70	1.62788	2.45667	59.70	0.78901	1.77890
8	65.52	1.56223	2.83563	65.52	0.91223	1.81225
10	78.07	1.37921	3.17247	78.07	1	1.89886
12	97.09	0.60322	3.4755	97.09	1.08076	1.99876

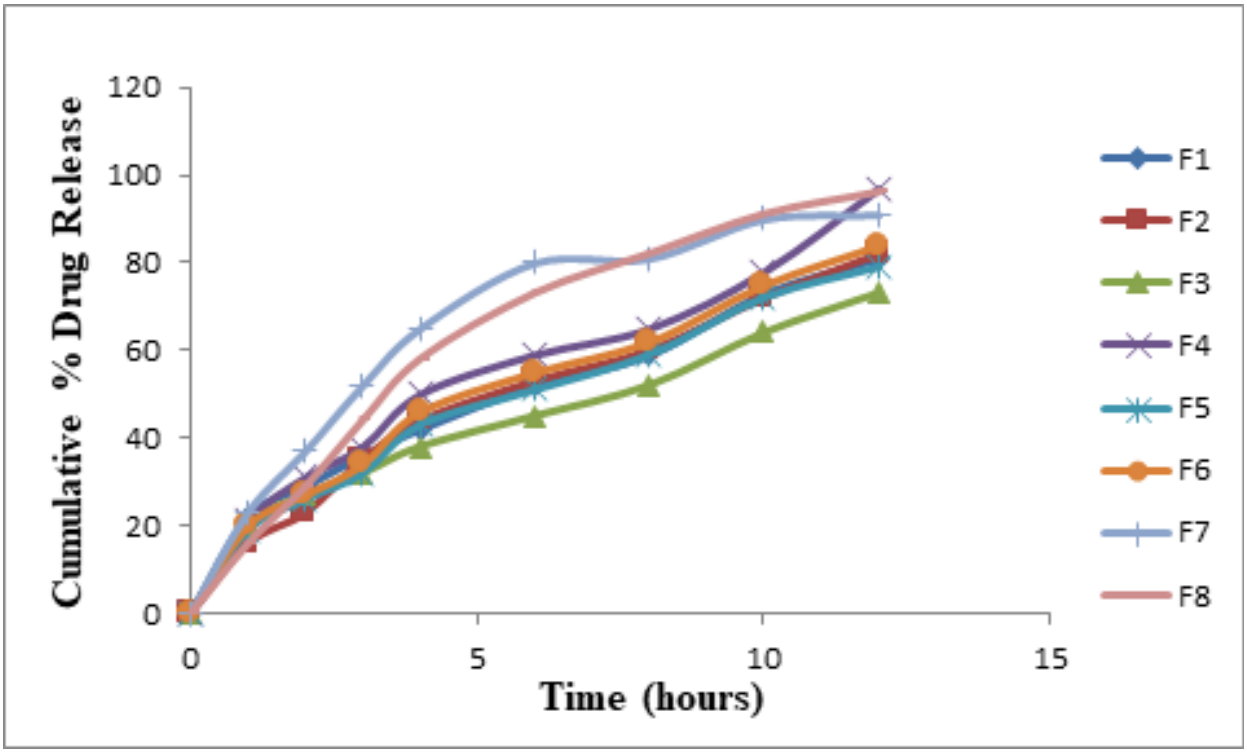

Figure 4 Comparative diffusion profile of F1 to F8 formulations

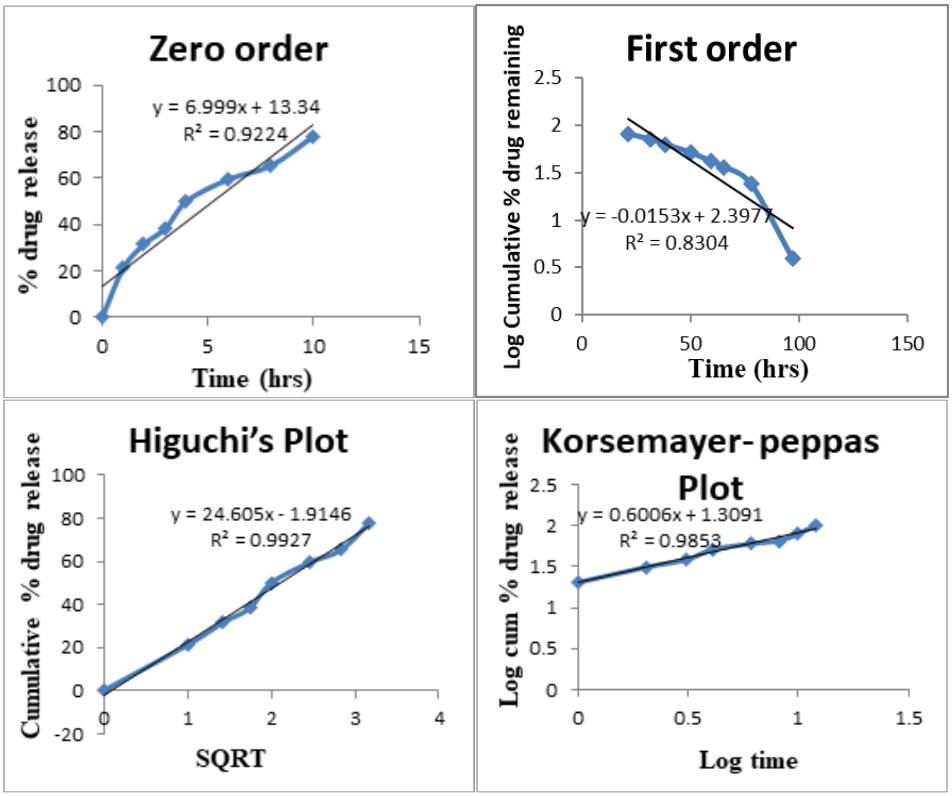

Figure 5 In vitro drug release kinetics of Moxifloxacin In-situ gel of F4 formulation

Table 8 Kinetic values obtained from in-vitro released data of Formulation F1-F8

Code	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	N
F1	0.974	0.983	0.996	0.991	0.519
F2	0.978	0.993	0.993	0.987	0.669
F3	0.974	0.977	0.994	0.992	0.492
F4	0.978	0.990	0.989	0.994	0.578
F5	0.978	0.992	0.996	0.989	0.582
F6	0.978	0.992	0.994	0.987	0.594
F7	0.966	0.970	0.993	0.989	0.660
F8	0.984	0.992	0.986	0.992	0.806

on the X-axis and Cumulative percentage drug release on the Y-axis.

In **formulation F1** the Moxifloxacin *In-situ* gel were prepared with 2mg of drug and 500mg of Sodium Alginate and 500mg of HPMC K15M, they shown drug release of 81.56% in water at end of 12th hour.

In **formulation F2** the Moxifloxacin *In-situ* gel were prepared with 2mg of drug and 1000mg of Sodium Alginate and 1000mg of HPMC K15M, they shown drug release of 82.40% in water at end of 12th hour.

In **formulation F4** the Moxifloxacin *In-situ* gel were prepared with 2mg of drug and 1000mg of Sodium Alginate and 500mg of HPMC K15M, they shown drug release of 97.09% in water at end of 12th hour.

To compare the dissolving profiles of the best formulation F4, various model-dependent techniques (Zero order, First order, Higuchi, and Korsemayer-Peppas plots) were used. According to the output of these models, the formulation F4 follow Peppas is the model that fits data the best. This is a result of a previously established fact based on the fitted R2 value. Formulation F4 has a Korsemayer-Peppas release exponent (n) value of

Table 9 (40°C ± 2°C / 75% ± 5% RH) In-vitro drug release profile of F4 during stability tests

Time (hours)	Cumulative % drug release (X± S.D)*			
	Initial	1month (25^{0}C- 60%RH)	2 month (40^{0}C-70%RH)	3 month (60^{0}C-80%RH)
0	0	0	0	0
1	21.22	20.61	21.58	21.92
2	31.62	29.28	32.38	30.42
3	38.41	37.34	38.89	36.45
4	50.15	49.89	52.28	48.88
6	59.70	59.66	61.62	59.72
8	65.52	66.22	65.89	64.81
10	78.07	79.68	78.71	76.98
12	97.09	98.42	97.88	96.41

0.578, which is more than 0.45 and indicates non-fickian diffusion.

STABILITY DATA

Stability Studies of Physical and Chemical Parameters

The chosen formulation The F4 formulation was kept in storage for three months at 40°C ± 2°C / 75% ± 5% RH. Following storage, samples were examined for 1, 2and 3 months.

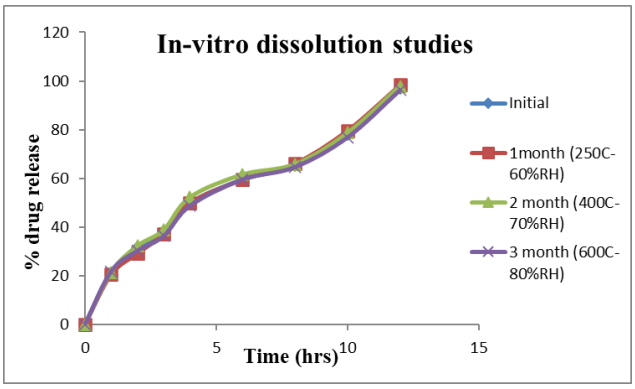

Figure 6 (40°C ± 2°C / 75% ± 5% RH) In-vitro drug release profile of F4 during stability

CONCLUSION

The current analysis leads to the conclusion that designing and creating oral in-situ gels of Moxifloxacin requires careful selection of polymers and medication. According to IR and UV investigations, the polymer chosen, sodium alginate and HPMC, were discovered to be compatible with the medication Moxifloxacin. It was discovered that the two polymers' different concentrations had an impact on the gel's viscosity, flowability, or drug release. Gel formulations demonstrated good durability or uniformity. But, a gel formula, that exhibited a highest percentage for drug release and favourable rheological characteristics, ended up being the formula of choice. Better and quicker patient improvement is given by Formulation F4. There is room for additional pharmacokinetic research because the outcomes of the studies that have already been done are encouraging. When compared to other formulations, the F4 formulation is the most optimal. Based on in vitro release investigations, the formulations of the Moxifloxacin gels used in this inquiry were found to be satisfactory, according to the thesis's results. With this prolonged drug delivery system, the medicine's bioavailability can also be increased, benefiting patient efficacy, compliance, and therapeutic usefulness.

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