RESEARCH ARTICLE

Development and Evaluation of a Nanogel Formulation of Oxaprozin

Bhardwaj S[1*], Kalra N[1], Khan W[2]

[1]*Lords University, Alwar, Rajasthan, India.*
[2]*Global Pharmacovigilance, Evolet Healthcare Pvt. Ltd., Gurugram, Haryana, India.*

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ABSTRACT
The proposed work was aimed to Development and evaluation of a nanotechnology based formulation of oxaprozin. The preformulation studies for the chosen medication Oxaprozin include IR spectroscopy, melting point determination, and physical appearance analysis as methods of identification. It can be inferred from the Eudragit S-100 DSC overlay thermogram of the physical mixture and the pure drug demonstrates that the drug and excipients do not interact. According to Oxaprozin's UV spectra, the drug exhibits absorbances, with the highest absorbance occurring at 285 nm when the solution is made in methanol. Homogenicity, particle size, pH, drug content, in vitro drug release, skin irritation test, spreadability, extrudability, and viscosity were all optimized in the formulation of the nanogel. The drug content (±SD 98.9 ± 0.02), in vitro drug release (%), and spreadability (g.cm/s) of the optimized F7 formulation are 95.85 ± 0.0658 and 6.5 ± 0.3, respectively. 281 ± 0.5 is the extrudability (g). The viscosity of in cp at 50 (rpm) 9857 were found.
Keywords: Oxaprozin, Nanogel, Eudragit S-100, Spreadability and hydrogel.
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INTRODUCTION

Nanotechnology defined by scale includes fields of science such as surface scienceenergy storage, engineering, microfabrication, the related research and applications span from extensions of traditional device physics to molecular self-assembly.[1] Although many osteoarthritis treatment guidelines have historically not included topical NSAIDs, new guidelines and Their use as a practical substitute for conventional oral formulations is now supported by recent evidence-based medicine. Especially for older patients and those who are more likely to experience gastrointestinal and cardiovascular adverse events from oral NSAIDs.[2] Additionally, a recent analysis of published research on topical treatments for osteoarthritis came to the conclusion that topical NSAIDs are both safe and effective. Although few studies have directly compared the effectiveness of topical and oral NSAIDs, the evidence currently available indicates that they are equally effective. Considering the indication range[3], the proven use as an oral therapy, and being one of the key drugs of its category with potential for other dosage forms, the objective of this research work is to develop a nanotechnology-based topical product of Oxaprozin for osteoarthritis and evaluate the stability, safety, and efficacy of the product.[4]

MATERIALS AND METHODS

The drug Oxaprozin was purchased from Simson Pharma Limited, Mumbai, Eudragit S-100 procured from Evonik Industries and Carbopol 940 from Amexin Pharma, Mumbai. Preformulation studies for the selected drug Oxaprozin include test for identification by examination of physical appearance, melting point determination, and IR spectroscopy, solubility studies and calibration curve. The drug Oxaprozin were visually inspected for physical state, colour and odour. Solubility of the drug Oxaprozin was checked in different solvents (distilled water, methyl alcohol, ethyl alcohol, ethyl acetate and acetone, etc). This was verified by dissolving a predetermined volume of drug in a predetermined volume of solvents. Spectrophotometric analysis was used to determine the amount of drug dissolved. Oxaprozin's melting point was determined using the capillary method. A tiny sample was taken in the capillary tube after it was closed on one side with a flame.[5] After that, the tube was put in a melting point apparatus, and the temperature was recorded. Three readings were taken and averaged. About 1.5 grams of powdered medication was precisely weighed in a porcelein dish that had been previously dried at 105°C in a hot air oven to a constant weight before being weighed in order to assess drying loss. The percentage of drying loss relative to the air-dried substance was computed based on the weight difference.[6]

Determination of λ_{max}

The UV spectrum of Oxaprozin was analyzed spectrophotometrically by using spectrophotometer (UV-1800 Shimadzu). To create the stock solution of 1000 µg/ml, 100 mg of the medication was precisely weighed, dissolved in an adequate amount of phosphate buffer (pH 6.8), and 100 milliliters was the final volume. Phosphate buffer was used to increase the volume to 100 ml after 1 ml of the stock solution was removed to obtain a solution of 10 µg/ml..[7] The resulting solution was scanned between 200 and 400 nm, and the spectrum was recorded in order to find the maximum wavelength, or λ max.

[*]*Author for Correspondence: smriti.bhanu30@gmail.com*

Table 1: Oxaprozin Nanogel Composition of Batch-A.

Comosition	F1	F2	F3
Oxaprozin (g)	50	50	50
Eudragit S-100 (g)	0.15	0.20	0.25
Tween-80 (ml)	0.1	0.3	0.5
Glycerol (ml)	05	10	15
Carbopol (g)	0.5	0.1	0.3
Water (ml)	70	30	50
Triethanolamine (ml)	02	03	04

Table 2: Oxaprozin Nanogel Composition of Batch-B.

Comosition	F4	F5	F6
Oxaprozin (g)	50	50	50
Eudragit S-100 (g)	0.15	0.15	0.15
Tween-80 (ml)	0.10	0.10	0.10
Glycerol (ml)	05	05	05
Carbopol (g)	0.1	0.1	0.1
Water (ml)	30	30	30
Triethanolamine (ml)	02	02	02

Table 3: Standard CC of Oxaprozin in Phosphate buffer pH 6.8.

Sr. No.	Concentration (µg/ml)	Absorbance			Average Absorbance
		1	2	3	
1	10	0.125	0.121	0.130	0.125
2	20	0.292	0.287	0.292	0.292
3	30	0.399	0.393	0.402	0.399
4	40	0.574	0.569	0.579	0.574
5	50	0.771	0.768	0.776	0.771
6	60	0.918	0.915	0.921	0.918

Correlation Co-efficient (R^2) = 0.9947

Absorbance (y) = 0.159_x conc - 0.0445

Table 4: Solubility data of Oxaprozin (Drug).

Medium	Solubility (mg/50ml)
Distilled Water	102
Acetone	216
Ethyl Acetate	189
Ethanol	231
Methanol	237

Compatibilitystudies

Compatibility the drug Oxaprozin and the selected polymers checked by FTIR analysis and DSC studies.

FT-IRSpectroscopy

The drug Oxaprozin's compatibility with the chosen polymers was determined using FT-IR spectroscopy. Oxaprozin's pure FT-IR spectra were obtained independently. Shimadzu FT-IR was used to scan additional drug and polymer mixtures in the same ratio.

Differential Scanning Calorimetry Studies

Using the Perkin Elmer Instrument Pyris-1, DSC analyses of pure drugs and physical mixtures with Eudragit S-100 were conducted to verify the interactions between the excipients and the drugs.[8]

Particle Size Measurement

Malvonizer equipment and the sieve analysis method were used to analyze the particle size.

Preparation of Oxaprozin Nanogel

While stirring, a precisely weighed amount of the drug, the polymer Eudragit S-100, and the stabilizer Tween-80 are dissolved in glycerol. Water was used to dissolve carbopol-940 and heated while being stirred continuously to create the aqueous phase.[3] The Ultra Sonic Bath Sonicator is used to These drug-containing phases should be sonicated. To produce an emulsion, the drug phase is progressively added to the aqueous phase during homogenization. The homogenizer produced an O/W emulsion by converting the emulsion into nanodroplets.[9,10] Homogenization was maintained for an hour. Triethanolamine was added and the nanogel was constantly agitated to form the gel. F1, F2, and F3 batches were prepared with varying com positions at the maximum rpm of 8000. In contrast, the prototype Batches-B formulations F4, F5, and F6 and Batch-C formulations F7, F8, and F9 were prepared using a homogenizer at varying rpms of 5000, 6000, and 7000, respectively. as displayed in tables 5.3 to 5.5.

Centrifugation Speed in RPM Changed for the Batch-C

Evaluation Parameters

Appearance

The color, clarity, and particle presence of the prepared gel bases were visually assessed.

Homogeneity

Following their setting all of the developed gels in the container were visually Inspected to ensure they were homogeneous. Their appearance and the existence of any aggregates were examined.

Measurement of particle size of formulation

The Malvern Mastersizer 2000 MS was used to calculate the mean size of the chosen nanogels. The average size of the particles was noted.

pH measurement

The glass electrode and the reference electrode were fully submerged in the gel system to cover them in order to perform the pH measurement using a calibrated digital type pH meter.

Drug content

Oxaprozin was extracted using 50 milliliters of phosphate buffer 6.8 from 1 gram of gel formulation, and the resulting mixture was passed through a membrane filter with a 0.45 µm pore size in order to estimate the drug in the gel.[11] Two milliliters were pipetted out of this to make ten milliliters. Using spectrophotometry, the sample's absorbance at 285 nm was ascertained.

***In vitro* Release studies**

The Franz Diffusion Cell apparatus, which consists of a cylindrical glass tube that has been opened on both ends, was used to measure the drug release from the formulation. Following a 24-hour soak in the medium, 1 gm of gel (10 mg of Oxaprozin) was evenly applied to the cellophane membrane's surface and fastened to one end of the tube. The whole thing was fastened so that the lower end of the gel-containing tube just touched (1-2 mm deep) the surface of the diffusion medium, which is 100 ml of pH 6.8 phosphate buffer in a 100 ml beaker.[12] The assembly was set up on a magnetic stirrer on a thermostatic hot plate and kept at 37°±2°. For 24 hours, the contents were agitated at 100 rpm using a magnetic bar, and 5 ml of samples were taken out at various points in time[13] After diluting the 5 ml with 10 ml

Table 5: Evaluation Parameters for Batch A.

S. No.	Evaluation parameters	F1	F2	F3
1	Appearance	Clear	Clear	Clear
2	Homogenicity	Homogeneous	Homogeneous	Homogeneous
3	Particle size (nm)	167	187	209
4	pH	6.9 ± 0.01	6.7 ± 0.01	6.3 ± 0.10
5	Drug content±SD	98.9 ± 0.02	96.8 ± 0.01	97.6 ± 0.03
6	*In vitro* drug release (%)	95.85 ± 0.0658	94.80 ± 0.825	92.98 ± 0.92
7	Skin irritation test	No irritation	No irritation	No irritation
8	Spreadability (g.cm/s)	6.3 ± 0.4	6.6 ± 0.7	6.1 ± 0.5
9	Extrudability (g)	281 ± 0.5	269 ± 0.5	257 ± 0.6
10	Viscosity in cp at 50 (rpm)	9577	8574	7986

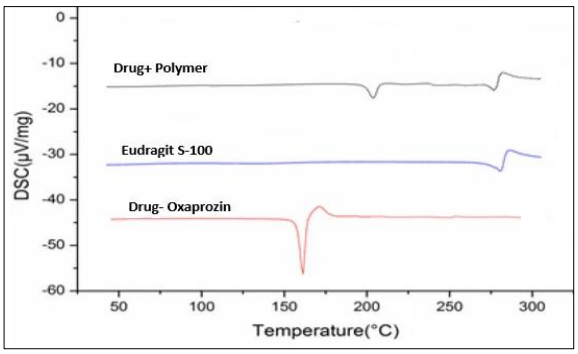


Figure 1: DSC graph of Oxaprozin

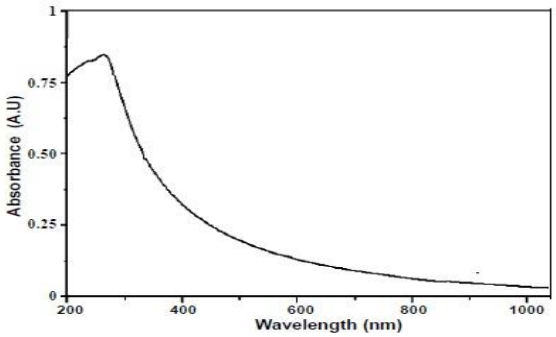


Figure 2: UV spectrum of Oxaprozin in 6.8 phosphate buffer.

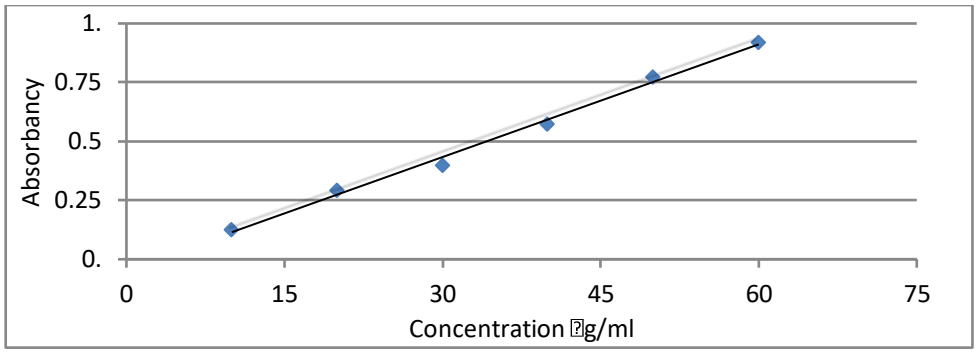
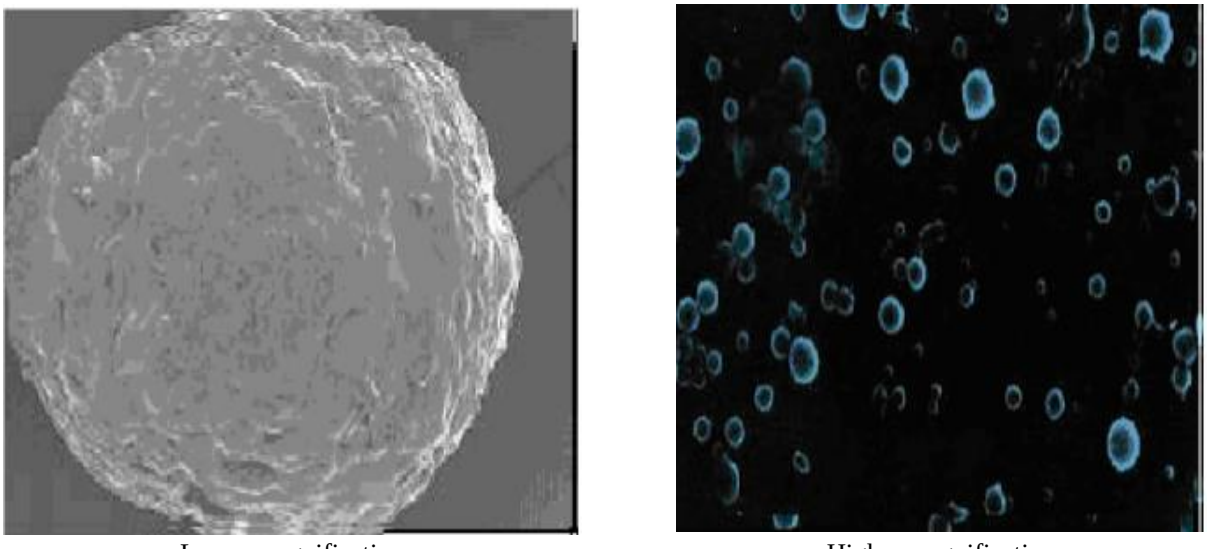


Figure 3: Drug calibration curve in Phosphate buffer pH6.8.



Lower magnification Higher magnification

Figure 4: Scanning electron microphotograph of Oxaprozin.

Table 6: Evaluation Parameters for Batch B.

S. No.	Evaluation parameters	F4	F5	F6
1	Appearance	Clear	Clear	Clear
2	Homogenicity	Homogeneous	Homogeneous	Homogeneous
3	Particle size (nm)	164	174	219
4	pH	6.9 ± 0.02	6.6 ± 0.02	6.4 ± 0.2
5	Drug content±SD	98.9 ± 0.02	97.5 ± 0.01	98.2 ± 0.01
6	*In vitro* drug release (%)	95.85 ± 0.0658	95.30 ± 0.826	94.75 ± 0.96
7	Skin irritation test	No irritation	No irritation	No irritation
8	Spreadability (g.cm/s)	6.5 ± 0.3	6.3 ± 0.7	6.2 ± 0.6
9	Extrudability (g)	281 ± 0.5	270 ± 0.4	262 ± 0.2
10	Viscosity in cp at 50 rpm	9857	9547	9891

Table 7 : *In-vitro* Drugrelease studies of formulation (F1-F3).

Time (hr)	F1	F2	F3
0	0.0	0.0	0.0
1	0.21	0.15	0.31
2	0.53	0.49	0.36
3	1.49	1.72	1.26
4	6.42	8.17	6.46
5	19.72	22.26	20.85
6	25.82	28.74	26.12
7	31.29	36.76	33.32
8	42.64	46.29	43.16
9	53.32	56.61	54.88
10	61.79	64.69	62.55
11	69.21	73.57	71.21
12	79.32	85.35	81.53
13	88.52	91.67	89.23
14	93.01	93.12	90.24
15	95.85	94.80	92.98

of fresh phosphate buffer (pH 6.8), the sample was examined for oxaprozin at 285 nm using a UV-Vis spectrometer.

Skin irritation test

Human volunteers were used in the irritation test. Four volunteers were chosen for each gel, and 1.0 g of the prepared gel was applied to the back of the hand in a 2-square-inch area. The volunteers were checked for irritation or lesions.[14]

Spreadability

Mutimer's proposed apparatus determines spreadibility. A pulley at one end provides support for the wooden block that makes up this structure. This approach uses "Slip" and "Drag" to measure spreadibility. A ground glass slide is attached to this block. This ground slide, a 0.1 g sample of the nanogel under investigation is put. To remove air and create a consistent layer of nanogel between two slides, The gel is sandwiched between two slides and fixed using the beach formula, and a 1 kg weight is placed on top of two slides. This process is repeated for approximately five minutes. The excess gel is scraped off the edges.[15]

After that, the weight is pulled on the top plate. The time it takes the top slide to travel the distance is recorded with the aid of a string that is attached to the hook. Better spreadability is indicated by a shorter interval; spreadability was determined using the formula.[16]

S=M.L/T,

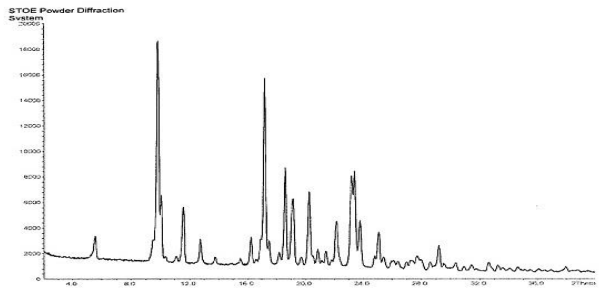


Figure 5: X-ray powder diffraction pattern of Oxaprozin in crystalline form.

Extrudability

Usually, an empirical measurement was performed of the force required to extrude the material from a tube. The procedure for estimating than that of the imposed shear in rheogram region that demonstrates plug flow and corresponds to a shear rate greater yield value. The percentage of nanogel and nanogel extruded from a lacquered thermoplastic collapsible tube after applying the weight in grams required to create a minimum 0.5-cm ribbon of nanogel in 10 seconds is the basis for the method used to evaluate the extrudability of the nanogel formulation. The extrudability of each formulation is evaluated three times, and the average result is shown.[17]

Extrudability = Applied weight to extrude the nanogel from tube (in gm)/ Area (in cm^2).

Rheological Studies

The Brookfield viscometer was employed in the research. The spindle was first dipped into the gel until its notch made contact with the gel's surface. In the study, 3 grams of gel I and gel II (room temperature and stability chamber) were used. Based on the gel's viscosity, spindles 61, 63, and 64 were chosen.[18] Viscosity was measured and dial readings were obtained at 50, 100, 150, and 250 rpm.

Stability batches evaluation

The optimized formulation was used for the stability tests. According to ICH guidelines, the samples were kept for three months at 40oC±2oC and 75%±5% relative humidity. Samples were taken out and examined for appearance, pH, particle size, drug content, spreadability, extrudability, and viscosity after one, two, and three months.[19]

RESULT AND DISCUSSION

Differential Scanning Calorimetry Studies

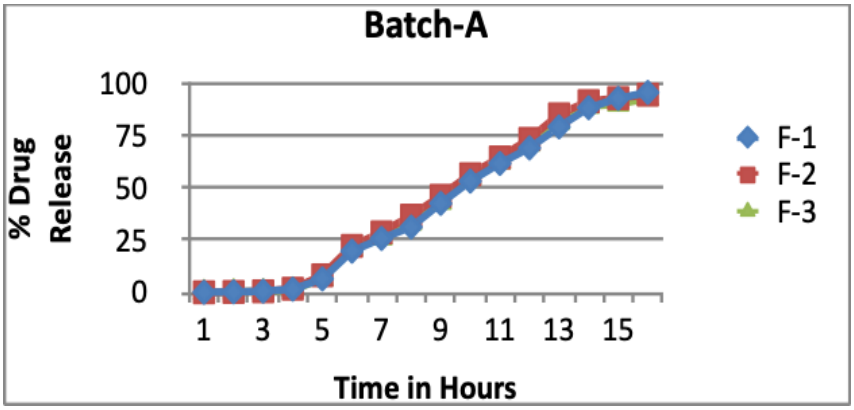


Figure 6: *In-vitro* Drugrelease (%) of formulation for Batch A.

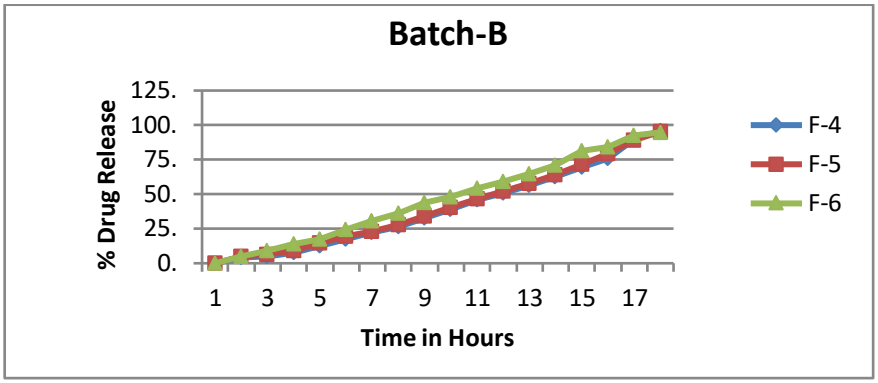


Figure 7: % Drug release of formulation for Batch B.

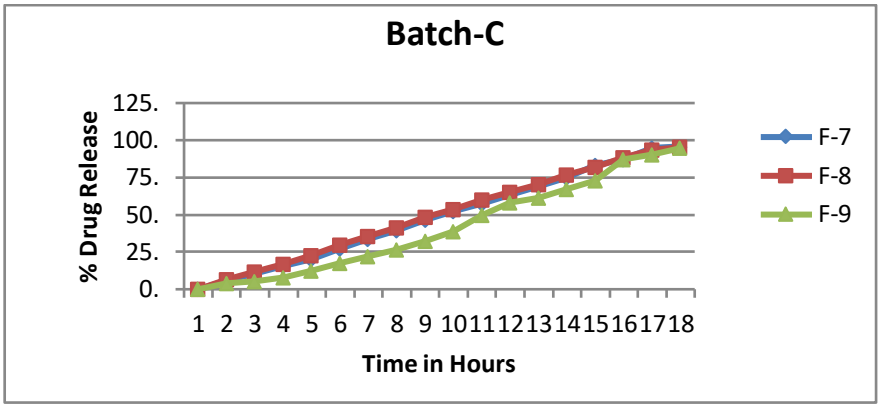


Figure 8: % Drug release of formulation for Batch C.

Figure 1 displays the Oxaprozin DSC thermogram. The drug's purity is indicated by a sharp endothermic peak at 164°C, which corresponds to the sample's melting point and matches that of oxaprozin, according to DSC studies. It can be inferred from the DSC overlay thermogram of the pure drug and the physical mixture using Eudragit S-100 that there is no interaction between the drug and the excipients.[20] Additionally, the drug and excipients did not form a complex because the endothermic peaks did not move.

UV Spectroscopy

After examining Oxaprozin's UV spectra, it was discovered that the drug exhibits absorbances, with the highest absorbance occurring at 285 nm[21] when a solution is made in methanol. Thus, 285 nm was regarded as the λmax. Figure 2 displays Oxaprozin's UV spectra.

Effect of change in pH on λ_{max}

To see how pH affected λmax, the drug's λmax was measured by varying the pH of its solution. Oxaprozin's λmax did not significantly alter at different pH values. Therefore, a calibration plot can be made with distilled water[22] and used for quantitative evaluation; however, phosphate buffer pH 7.4 is the medium of evaluation of release.

Calibration curve of Oxaprozin

Figure 3 displays the Oxaprozin calibration curve in phosphate buffer 6.8, while Table 3 displays the observation values. In the concentration range of 4–24 µg/ml at 285 nm, the absorbance vs. concentration graph was found to be linear. It was discovered that the calibration curve's R2 was 0.9974. It was determined from the FTIR

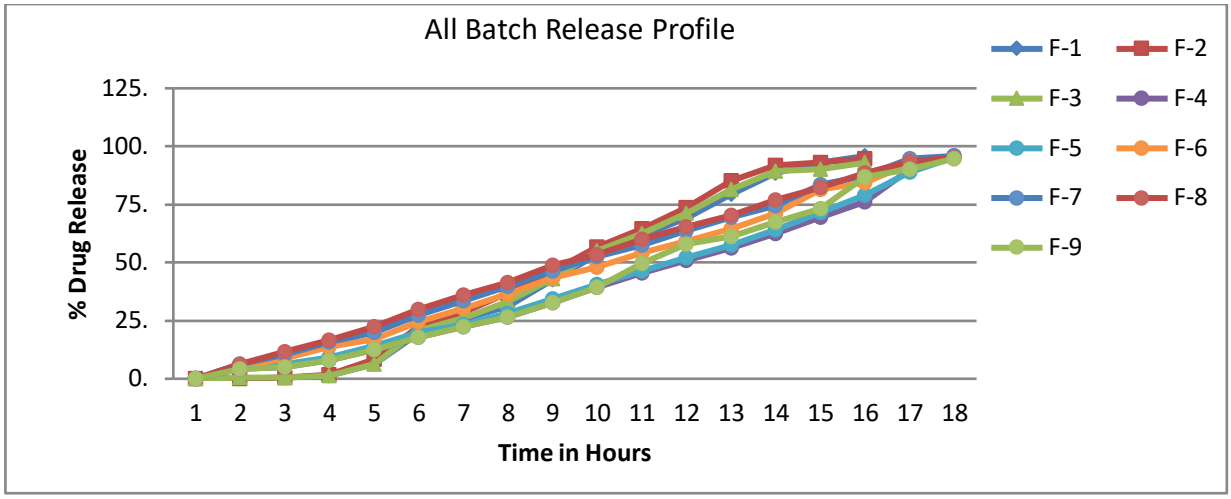


Figure 9: *In-vitro* drug Diffusion release of formulation (F1-F9)

3.6 Stability Study of optimized formulation (F7):

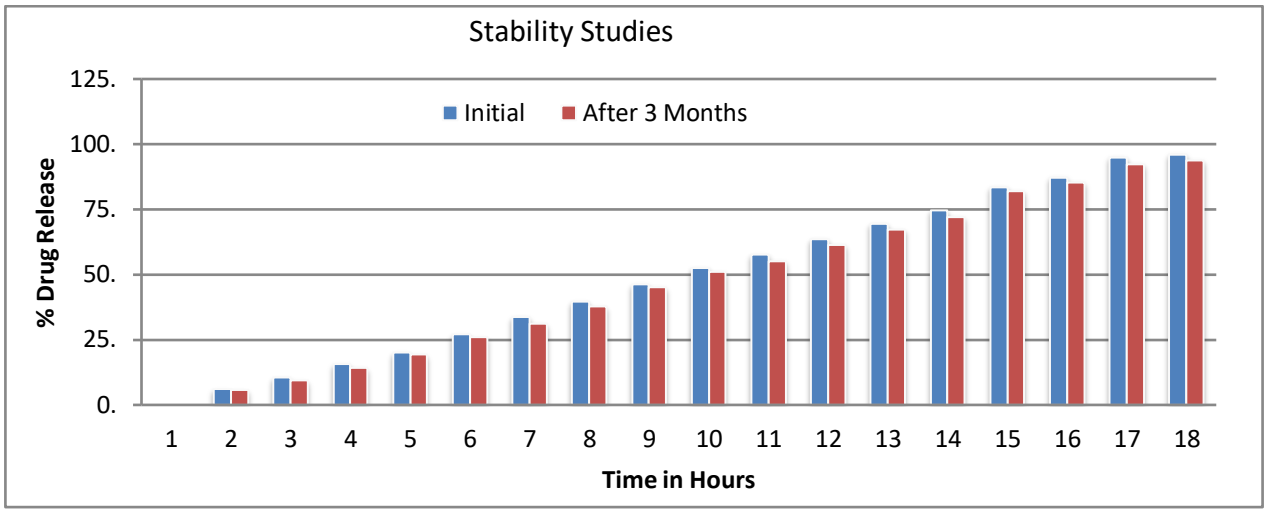


Figure 10: Comparative study of drug release after 3 month

Table 8: *In-vitro* Drugrelease studies of formulation (F4-F6):

Time (hr)	F-4	F-5	F-6
0	0	0	0
1	4.19	5.22	4.95
2	5.19	6.31	8.92
3	8.04	9.16	13.76
4	12.49	14.34	17.18
5	17.72	19.81	24.39
6	22.35	23.09	30.33
7	26.49	28.04	36.27
8	32.57	34.33	43.64
9	39.16	40.49	48.16
10	45.63	46.45	54.38
11	51.08	52.24	59.15
12	56.31	57.58	64.59
13	62.34	64.23	71.09
14	69.73	71.54	81.32
15	76.15	79.01	84.28
16	90.03	89.12	92.65
17	95.85	95.30	94.75

analysis and physical observations above that there was no discernible drug-excipient interaction. The FTIR study's findings indicated that the drug's melting peak remained unchanged.[23] Thus, we can say that the drug and other excipients work well together.

CONCLUSION

Preparation of Oxaprozin Nanogel prepared at different concentration of excipients for batch A, batch B and Batch C and Homogenicity, particle size, pH, drug content, in vitro drug release, skin irritation test, spreadability, extrudability, and viscosity were all optimized in the formulation of the nanogel. The drug content (±SD 98.9 ± 0.02), in vitro drug release (%), and spreadability (g.cm/s) of the optimized F7 formulation are 95.85 ± 0.0658 and 6.5 ± 0.3, respectively. 281 ± 0.5 is the extrudability (g).

Viscosity was measured in cp at 50 (rpm) 9857. An inflection point in the release profiles suggested that gel had formed on the diffusion membrane in the diffusion cell's donor compartment. Drug release slowed as the

Table 9: *In-vitro* Drugrelease studies of formulation (F7-F9):

Time (hr)	F-7	F-8	F-9
0	0	0	0
1	6.11	6.32	4.19
2	10.42	11.63	5.19
3	15.74	16.74	8.04
4	20.13	22.56	12.49
5	27.25	29.81	17.72
6	33.74	35.88	22.35
7	39.76	41.34	26.49
8	46.29	48.73	32.57
9	52.61	53.37	39.16
10	57.69	59.88	49.63
11	63.57	65.43	58.08
12	69.35	70.55	61.31
13	74.67	76.76	67.34
14	83.53	82.34	73.14
15	87.24	88.45	86.97
16	94.85	93.57	90.22
17	95.89	95.3	94.75

Table

Time (hr)	Inital	After 3 month
0	0	0
1	6.11	5.72
2	10.42	9.37
3	15.74	14.23
4	20.13	19.22
5	27.25	26.16
6	33.74	31.14
7	39.76	37.63
8	46.29	45.03
9	52.61	51.04
10	57.69	55.21
11	63.57	61.45
12	69.35	67.2
13	74.67	72.11
14	83.53	81.98
15	87.24	85.14
16	94.85	92.37
17	95.89	93.62

formulation changed into the gel phase during gel formation.

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