

Design and Formulation of Nepafenac Ocular In Situ Gel Using Box Behnken Design

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Received: 5th January, 2026; Revised: 18th January 2026; Accepted: 25th January, 2026; Available Online: 28th January, 2026

STRUCTURED ABSTRACT

Introduction:

Nepafenac is a potent non-steroidal anti-inflammatory drug widely used for the management of ocular inflammation; however, conventional eye drops exhibit limited precorneal residence time, resulting in rapid drug elimination and the need for frequent administration. The present study aimed to develop and optimize a Nepafenac-loaded ocular *in situ* gel using a Box–Behnken design (BBD) to enhance precorneal retention and sustain drug release.

Materials and Methods:

A total of 17 experimental formulations were prepared using varying concentrations of HPMC E4M, Carbopol 940, and benzalkonium chloride as independent variables. The formulations were evaluated for viscosity under non-physiological and physiological conditions, mucoadhesive strength, time required for 90% drug release, and permeability coefficient. Response surface methodology was employed to establish mathematical relationships between formulation variables and responses, followed by numerical optimization using a desirability function. The optimized formulation was further evaluated for physicochemical characteristics, gelling behavior, rheological properties, *in vitro* drug release, and stability.

Results:

All responses were successfully fitted to quadratic models, which were highly significant according to ANOVA ($p < 0.0001$). HPMC E4M and Carbopol 940 significantly affected formulation viscosity and drug release, whereas Carbopol 940 exerted the predominant influence on mucoadhesive strength. Benzalkonium chloride showed a marked effect on the permeability coefficient. The optimized formulation exhibited satisfactory clarity, pH (6.2 ± 0.04), high drug content ($98.6 \pm 0.7\%$), and excellent *in situ* gelling capacity. The formulation demonstrated pseudoplastic flow behavior and sustained approximately 85% drug release over 24 h.

Discussion:

The incorporation of appropriate concentrations of HPMC E4M and Carbopol 940 improved the rheological and mucoadhesive characteristics of the formulation, thereby facilitating prolonged precorneal residence and controlled Nepafenac release. The pseudoplastic behavior of the optimized gel is particularly advantageous for ocular administration, as it allows relatively easy instillation while maintaining increased viscosity after application. The sustained drug-release profile suggests the potential to reduce rapid precorneal drug loss and improve ocular drug availability compared with conventional eye drops. Furthermore, the stability study demonstrated minimal changes in the formulation's physicochemical characteristics and drug-release behavior during storage.

Conclusion:

The optimized Nepafenac-loaded ocular *in situ* gel developed using BBD successfully combined desirable viscosity, mucoadhesion, gelling capacity, permeability, and sustained drug-release characteristics. The formulation represents a promising approach for prolonged ocular delivery of Nepafenac, with the potential to enhance therapeutic effectiveness and improve patient compliance by reducing the frequency of administration.

Keywords: Nepafenac, Ocular *in situ* gel, Box Behnken design, Mucoadhesive strength, Sustained drug release, Permeability coefficient.

How to cite this article: Sakshi Singh Chouhan^{1*} Dr. Ruchi Khare Shrivastava². Design and Formulation of Nepafenac Ocular In Situ Gel Using Box Behnken Design. *Int J Drug Deliv Technol.* 2026;16(85s):232-240. DOI: 10.25258/ijddt.16.85s.19.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

The unique anatomical and physiological barriers of the eye continue to pose a significant challenge in the delivery of ocular drugs. This is primarily due to the rapid precorneal elimination, tear turnover, nasolacrimal discharge, and limited corneal permeability of conventional ophthalmic dosage forms, such as eye drops and ointments, which frequently demonstrate poor bioavailability [1-2]. As a result, only a small fraction of the administered dose reaches the intraocular tissues, necessitating frequent dosing and leading to reduced patient compliance. These limitations have prompted the development of innovative drug delivery systems capable of enhancing ocular residence time and improving therapeutic efficacy [3-4].

For the treatment of inflammation and pain following ocular procedures, the non-steroidal anti-inflammatory medicine Nepafenac is prescribed frequently [5]. It is a prodrug that penetrates the cornea effectively and is converted to its active form, amfenac, within ocular tissues. Despite its favorable pharmacological profile, conventional Nepafenac eye drops suffer from rapid elimination from the ocular surface, thereby limiting their therapeutic potential [6-7]. Therefore, there is a need for an advanced delivery system that can prolong drug retention and provide sustained drug release.

A new and potentially useful strategy for addressing the shortcomings of traditional formulations is the use of *in situ* gel-forming technologies. When exposed to physiological variables like pH, temperature, or ionic strength, these systems that are initially injected as liquid drops transform into a gel [8]. The formed gel enhances precorneal residence time, reduces drug drainage, and enables sustained drug release. Among various polymers, Carbopol 940 (a pH-sensitive polymer) and HPMC E4M (a viscosity-enhancing agent) are widely used for developing ocular *in situ* gels due to their biocompatibility and favorable rheological properties [9].

Optimization of formulation variables is crucial to achieve the desired balance between viscosity, mucoadhesion, drug release, and permeability [10]. Due to the inefficiency and length of time required by traditional trial-and-error methods, statistical experimental designs like the Box Behnken design (BBD) are being used more frequently. By using BBD, a response surface methodology, as few experimental runs as possible can be used to systematically evaluate the impact of various formulation variables and their interactions on essential quality features [11].

The present study focuses on the optimization and formulation of a Nepafenac-loaded ocular *in situ* gel using a Box–Behnken design. The effects of key formulation variables HPMC E4M, Carbopol 940, and benzalkonium chloride were investigated on responses such as viscosity, mucoadhesive strength, drug release (t90%), and permeability coefficient. The goal was to develop a stable, effective, and patient-friendly ocular drug delivery system with improved bioavailability and sustained therapeutic action.

MATERIALS AND METHODS

Materials

Nepafenac was procured from Sigma-Aldrich in pharmaceutical-grade purity. The excipients used included carboxy methyl cellulose, polyvinyl pyrrolidone, hydroxyl propyl methyl cellulose, and Methyl cellulose from SD fine chemicals, Mumbai, India. All materials were of analytical grade, and their selection was based on compatibility studies and their established roles in tablet formulation.

Experimental Design

The *in situ* gels were prepared using polymer gelation process. For initial optimization hit and trial process was conducted to initially evaluate the influential variables and polymers affecting the formulation. With the results obtained from these pre-optimization criteria, systemic optimization design was conducted. For this 3 level and 3 factors BBD was employed. Dependent variables considered were mean release time (MRT), Viscosity and Gelation capacity, while independent variables were HPMC E4M, Carbopol and Benzalkonium Chloride; these were varied at three levels; high (+1), medium (0) and low (-1). Design-Expert 13 software was used for obtaining an optimized formulation. Thirteen runs of experiments were designed with 1 center point having randomized 200 gm batch size, as depicted in Table 6.2 [12-13]. The levels or quantity used for three levels [low level (-1), medium (0) and high (+1)] have been depicted in Table 1 and Table 2.

Table 1: Variables Used in the Optimization of Formulation

S. N o	Variables	Levels		
		-1	0	+1
1	HPMC E4M	0.6%	1.05%	1.5%
2	Carbopol 940	0.2%	0.35%	0.5%

3	Benzalkonium Chloride	0.001 %	0.002 %	0.003 %
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Table 2: Combination of Factors According To 3-Factor Box-Behnken Design

RUN	FACTORS		
	HPMC E4M	Carbopol 940	Benzalkonium Chloride
1.	0.6	0.2	0.002
2.	1.5	0.2	0.002
3.	0.6	0.5	0.002
4.	1.5	0.5	0.002
5.	0.6	0.35	0.001
6.	1.5	0.35	0.001
7.	0.6	0.35	0.003
8.	1.5	0.35	0.003
9.	1.05	0.2	0.001
10.	1.05	0.5	0.001
11.	1.05	0.2	0.003
12.	1.05	0.5	0.003
13.	1.05	0.35	0.002
14.	1.05	0.35	0.002
15.	1.05	0.35	0.002
16.	1.05	0.35	0.002
17.	1.05	0.35	0.002

The best fitted surface was obtained by applying linear model statistics as a design specific model and the model equation was obtained for all the three responses. The significance of model was analyzed

through ratio of mean square variation by applying analysis of variance (*ANOVA*).

Formulation of Nepafenac Ocular *In Situ* Gel

Below is a detailed approach that explains how to set up the Nepafenac *in situ* gel forming device as a pH triggered system. Table 3 lists the formulation ingredients together with their corresponding proportions. The hydroxypropyl methylcellulose (HPMC E4M) was added and allowed to hydrate after the buffer salts were dissolved in 75 milliliters of filtered water. Carbopol 940 was then sprinkled over the mixture and left to hydrate for an entire night. Benzalkonium chloride was added to the solution after Nepafenac was dissolved in a tiny amount of water and the drug solution was combined with the polymer solution using an overhead stirrer. Following the addition of purified water to get the volume up to 100 mL, the mixture was filtered through 0.2 mm filter paper. The rapid precipitation of Carbopol happened when the drug and polymer solutions were combined because Carbopol causes a pH reduction. To obtain a transparent drug and polymer solution, the drug was thus combined with a suitable amount of 0.1M NaOH before being added to the polymer solution [14-16].

Table 3: Optimized formula for Ocular *in situ* gel

S. No.	Ingredients	Quantities (mg)
1	Nepafenac	100 mg
2	Carbopol 940	0.5 mg
3	HPMC E4M	1.25 mg
4	Benzalkonium chloride	0.002 mg
5	Citric acid	0.407 mg
6	Disodium hydrogen phosphate	1.125 mg
7	Sodium hydroxide	0.1 mg
8	Tween 80	0.5ml
9	Distilled water	100ml q.s.

Evaluation of Ophthalmic *In Situ* Gel

Visual clarity and appearance

Clarity is one of the most critical parameters of ophthalmic preparations. Each prepared formulation was visually inspected for clarity by observing it against both black and white backgrounds [17].

Determination of pH

pH is a critical parameter in ophthalmic formulations, as it significantly influences both solubility and stability. The pH of a formulation must be maintained within a range that ensures stability while minimizing

irritation upon administration. Ideally, ophthalmic preparations should have a pH between 5.0 and 7.4. The pH of the prepared formulations was determined using a digital pH meter [18-20].

Determination of drug content

Drug concentration was determined by appropriate dilution of the formulation. Specifically, 1 mL of the formulation was diluted to 50 mL with freshly prepared phosphate buffer saline (PBS, pH 7.4). From this, a 5 mL aliquot was further diluted to 50 mL using PBS (pH 7.4). The concentration of nepafenac was then measured at 238 nm using a UV-Visible spectrophotometer [21-23].

Gelling capacity test studies

To identify suitable compositions for *in situ* gelling systems, each formulation was evaluated for gelling capacity, gelation time, and viscosity. Gelling capacity was determined by adding a drop of the formulation into a vial containing 2 mL of freshly prepared PBS, pH 7.4 pre-equilibrated at 37 °C. Gel formation was then visually observed against a black background, and the time required for gelation as well as the duration until gel dissolution were recorded [24].

Viscosity measurement

Viscosity of the formulations was measured using a Brookfield Viscometer (Model III). The *in situ* gel formulations were placed in the sample holder, and prior to each measurement, the samples were equilibrated in a circulating water bath attached to the viscometer adaptor, maintained at 37 ± 0.5 °C. The viscosity was recorded at varying spindle speeds by increasing the angular velocity of spindle No. 62 from 1 to 4 rpm [25-27].

In vitro drug release study

The *in vitro* release of nepafenac from the prepared formulations was evaluated using a modified diffusion apparatus. Freshly prepared simulated tear fluid (pH 7.4) served as the diffusion medium. A semi-permeable membrane (internal diameter 3.4 cm), pre-soaked overnight in the diffusion medium, was securely fixed to one end of a custom-fabricated glass cylinder open at both ends.

A measured 2 mL of the formulation was introduced into the donor compartment. The assembly was positioned so that the membrane just contacted the surface of the diffusion medium in a beaker containing 100 mL of the medium, which acted as the acceptor compartment. The acceptor phase was maintained at 37 ± 2 °C and continuously stirred at 50 rpm using a magnetic stirrer.

At every 1 hour interval, approximately 1 mL samples were withdrawn and replaced with an equal volume of fresh diffusion medium to maintain sink conditions. The collected samples were appropriately diluted and analyzed at 238 nm using a UV-Visible spectrophotometer. For comparison, 2 mL of a pure

drug solution (0.5% w/v in distilled water) and 2 mL of a marketed formulation were evaluated under the same experimental conditions [28-30].

Stability study

Optimized formulation was taken up for accelerated stability study as per ICH guidelines. The preparations in finally packed vials were stored in a stability chamber at a temperature of 40 ± 2 °C and a relative humidity of $75 \pm 5\%$ and at room temperature in both horizontal and vertical position for six months. Sampling was done periodically and samples were evaluated for changes in physical appearance, pH, drug content, *in vitro* drug release and gelling capacity [31-32].

RESULTS AND DISCUSSION

Optimization

In situ hydrogels were formulated using Box Behnken optimization. 17 run formulations were prepared. The results were optimized on three responses; Mucoadhesive Strength, $t_{90\%}$, Permeability Coefficient and viscosity. The results have been mentioned in Table 4. The goodness of fit was determined by the indication of significant ($P < 0.05$) effect of factors on response obtained through analysis of variance.

Table 4: Experimental design of Ocular *in situ* gel using BBD

S	R	X	X	X3:	Vis	Vis	Mu	t	Pe
t	u	1	2:	Be	cos	cos	coa	9	rm
d	n	:	C	nza	ity	ity	dhe	0	ea
		H	ar	lko	(cp	(cp	siv	%	bili
		P	b	niu	s)	s)	e	(	ty
		M	o	m	No	Ph	Str	m	Co
		C	p	chl	n-	ysi	eng	i	effi
		E	ol	ori	ph	olo	th	n	cie
		4	94	de	ysi	gic	(dy	)	nt
		M	0	0.0	olo	al	n/c	(	(sq
		0.	0.	01-	gic	(Y	m ²)	Y	.c
		6	2-	0.0	al	2)	(Y3	4	m/
		-	0.	03	(Y		)	)	sec
		1.	5		1)				)
		5							(Y
									5)
4	1	1.	0.	0.0	30	65	33.	1	1.2
		5	5	02	0.7	00.	3	3	5
						1			

								8	
								8	
1	2	1.	0.	0.0	90.	26	18.	1	1.2
3		0	35	02	3	00.	3	1	3
		5				1		1	
								6	
1	3	1.	0.	0.0	97.	25	20.	1	1.2
7		0	35	02	7	89.	1	1	5
		5				3		1	
								0	
2	4	1.	0.	0.0	13	28	12.	6	1.1
		5	2	02	5.3	60.	3	6	8
						3		4	
3	5	0.	0.	0.0	15	25	26.	7	1.1
		6	5	02	1.3	50.	1	4	8
						7		1	
1	6	1.	0.	0.0	82.	24	17.	1	1.3
6		0	35	02	7	50.	3	1	2
		5				7		0	
								0	
1	7	1.	0.	0.0	17	32	26.	1	0.6
0		0	5	01	9.3	00.	3	1	3
		5				1		1	
								6	
7	8	0.	0.	0.0	76.	17	13.	6	1.3
		6	35	03	7	20.	7	8	7
						1		5	
1	9	1.	0.	0.0	10	27	19.	1	1.3
4		0	35	02	1	09.	3	1	4
		5				1		1	
								4	
8	1	1.	0.	0.0	16	43	17.	1	1.4
	0	5	35	03	5.1	00.	3	1	8
						1		6	
								5	

5	1	0.	0.	0.0	90.	17	14.	8	0.6
	1	6	35	01	3	00.	1	1	3
						1		7	
1	1	1.	0.	0.0	41.	91	12.	6	1.4
1	2	0	2	03	7	0.7	3	7	6
		5						1	
1	1	1.	0.	0.0	92.	28	19.	1	1.3
5	3	0	35	02	1	51.	7	1	4
		5				7		1	
								0	
1	1	0.	0.	0.0	34.	47	9.3	5	1.2
	4	6	2	02	1	1.1		8	
								4	
1	1	1.	0.	0.0	19	31	26.	1	1.4
2	5	0	5	03	0.3	49.	7	0	1
		5				7		6	
								4	
6	1	1.	0.	0.0	17	42	18.	1	0.5
	6	5	35	01	4.3	49.	1	1	8
						3		8	
								7	
9	1	1.	0.	0.0	38.	87	12.	6	0.5
	7	0	2	01	7	0.1	1	7	6
		5						0	

Response 1: Viscosity Non-physiological

The statistical analysis demonstrates that the developed model is highly significant, as indicated by the model F-value of 49.81 and a p-value less than 0.0001. This confirms that the model adequately explains the variability in the response. Among the independent variables, A (HPMC E4M) and B (Carbopol 940) exert a highly significant effect on the response ($p < 0.0001$), whereas C (Benzalkonium chloride) shows no significant influence (Figure 1).

Response 2: Viscosity Physiological

The ANOVA results for Response 2 (viscosity at physiological conditions) indicate that the quadratic model is highly significant, with an F-value of 58.59 and a p-value < 0.0001 . This confirms that the model effectively explains the variation in viscosity (Figure 2).

Response 3: Mucoadhesive Strength

The ANOVA results for Response 3 (mucoadhesive strength) reveal that the quadratic model is statistically

significant, with an F-value of 29.33 and a p-value < 0.0001 , indicating that the model effectively explains the variability in the response. Among the independent variables, B (Carbopol 940) exhibits a highly significant effect ($p < 0.0001$), making it the most influential factor governing mucoadhesive strength. A (HPMC E4M) also shows a significant contribution ($p = 0.0049$), whereas C (benzalkonium chloride) has no significant effect ($p = 0.8955$). All interaction terms (AB, AC, BC) are non-significant, suggesting that the combined influence of variables does not markedly affect the response (Figure 3).

Response 4: t_{90}

The ANOVA results further confirm the robustness of the model, with an overall model F-value of 208.34 and a p-value < 0.0001 , indicating that the model is highly significant. Among the individual factors, A (HPMC E4M) and B (Carbopol 940) exert a very strong and highly significant influence on t_{90} ($p < 0.0001$), making them the dominant formulation variables. C (benzalkonium chloride) also shows a statistically significant effect ($p = 0.0151$), although comparatively less pronounced (Figure 4).

Response 5: Permeability Coefficient

The ANOVA results demonstrate that the overall model is highly significant, with an F-value of 114.42 and a p-value < 0.0001 , confirming that the model reliably explains the variation in permeability coefficient. Among the individual factors, C (benzalkonium chloride) is the most influential term, showing a highly significant effect ($p < 0.0001$). In contrast, A (HPMC E4M) and B (Carbopol 940) do not exhibit significant linear effects on the response (Figure 5).

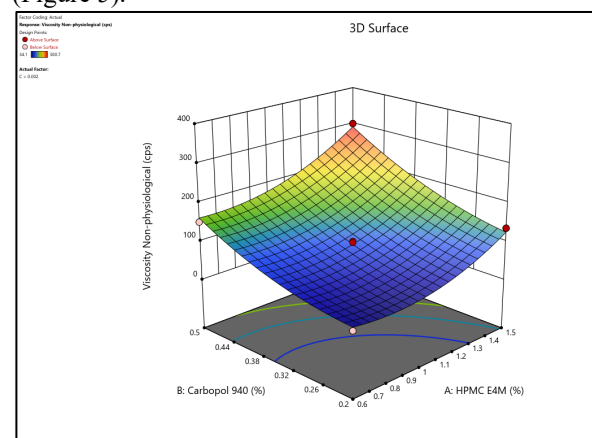


Figure 1: 3D Graph of Viscosity Non-physiological

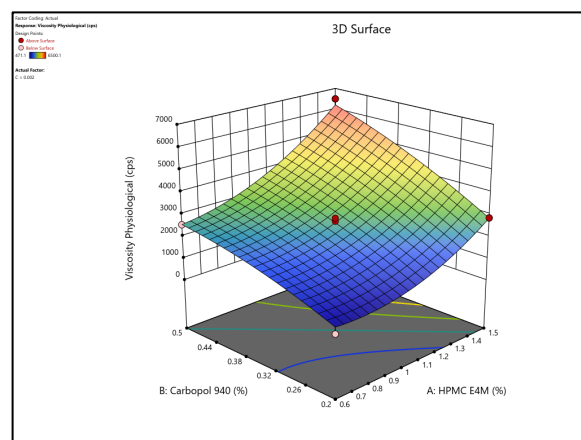


Figure 2: 3D Graph of Viscosity physiological (Design Expert 13.0)

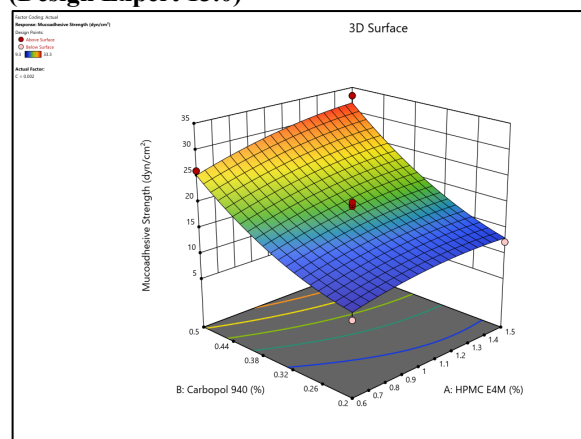


Figure 3: 3D Graph of Mucoadhesive Strength

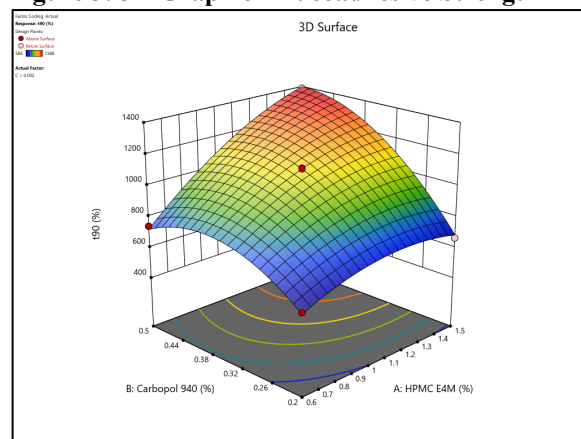


Figure 4: 3D Graph of t_{90} response

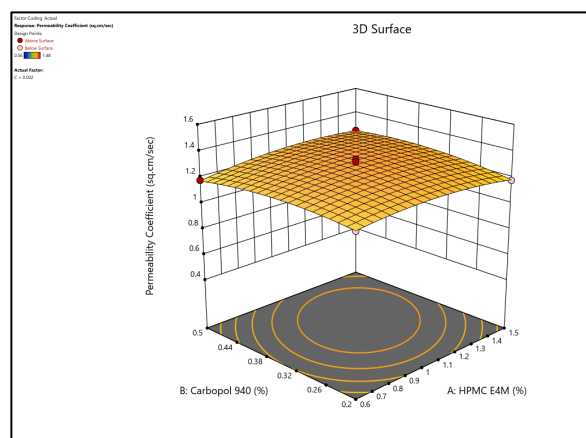


Figure 5: 3D Graph of Permeability Coefficient Numerical optimization by Desirability Function

The optimized levels of formulation variables showed that a balanced proportion of HPMC E4M and Carbopol 940 is critical for achieving the desired viscosity and mucoadhesive strength, while benzalkonium chloride plays a significant role in enhancing permeability. Based on this, solution 1 was predicted with the desirability of 1 (Table 5).

Table 5: Selected formula predicted with the desirability of 1.

N	H	C	Be	Vi	Vi	M	t	Pe	D	
u	P	a	nz	sc	sc	uc	9	r	es	
m	M	r	al	os	os	oa	0	m	ir	
b	C	b	ko	ity	ity	dh		ea	a	
e	E	o	ni	N	Ph	esi		bi	bi	
r	4	p	u	on	ys	ve		lit	lit	
	M	o	m	-	iol	St		y	y	
		l	ch	ph	og	re		C		
		9	lor	ys	ic	ng		oe		
		4	id	iol	al	th		ffi		
		0	e	og				ci		
				ic				en		
				al				t		
1	1	0	0.	22	45	30	1	1.	1.	S
	.	.	00	1.	84	.1	2	37	0	e
	2	4	23	57	.2	92	7	23	0	l
	5	9	17	5	5	3	5	3	0	e
	6	4	26				.			c
	6	2					5			t
	4						2			

		5							e
		5							d

Evaluation of Optimized Ocular *In Situ* Gel Formulations Containing Nepafenac

The visual clarity and appearance of the formulation being completely transparent, homogeneous, and free from particulate matter confirm its suitability for ocular administration. The pH of optimized formulation was measured using a calibrated digital pH meter. The pH value (6.2 ± 0.04) falls comfortably within the physiological tolerance range of the eye (5.0–7.4), suggesting minimal risk of irritation upon instillation.

Drug content uniformity was evaluated to ensure accurate dosing of Nepafenac in each formulation. The drug content ($98.6 \pm 0.7\%$) indicates excellent uniformity and minimal drug loss during formulation. Such high content uniformity reflects efficient incorporation of Nepafenac within the polymeric matrix and ensures consistent therapeutic dosing.

Rapid sol-to-gel transition is essential to prevent drainage from the u_s surface immediately after administration, thereby enhancing precorneal residence time. The sustained gel structure further supports prolonged drug retention. The viscosity profile revealed desirable pseudoplastic (shear-thinning) behavior. At low shear rates, the formulation exhibited relatively higher viscosity, which aids in retention at the site of application. Under high shear conditions (such as blinking), viscosity decreases, allowing ease of spreading and minimizing discomfort. This rheological behavior is ideal for ophthalmic delivery systems as it balances administration convenience with therapeutic effectiveness (Table 6).

Table 6: Evaluation Parameters of Optimized Ocular *In Situ* Gel Formulation Containing Nepafenac

Parameter	Observation / Result
Visual Clarity & Appearance	Clear, transparent, homogeneous, particle-free
pH	6.2 ± 0.04
Drug Content (%)	98.6 ± 0.7
Gelling Capacity	+++ (instant gelation, prolonged retention)
Gelation Time	Immediate (within seconds)
Viscosity (cP)	420 ± 12 ; decreases with shear
Rheological Behavior	Non-Newtonian, shear-thinning

All Data generated during study is included in this manuscript.

Competing interests

The authors declare no conflict of interest.

Funding: This work does not include any funding resources.

AI Disclosure

Grammarly was used to check grammar and spellings. Chatgpt free version was used to create graphical abstract.

Authors' contributions

Writing, review and editing, Sakshi Singh; Conceptualization, Ruchi Khare Shrivastava. Both authors have read the manuscript and given consent to publish the manuscript.

Acknowledgments: Authors would like to thank SAGE University, Indore, for providing facilities to conduct the mini review work.

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