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Formulation and Evaluation of in-situ Ophthalmic Gel of Ketorolac Tromethamine.

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ABSTRACT

Low bioavailability, frequent dosage, and rapid precorneal excretion are the drawbacks of conventional ketorolac tromethamine eye drops. These drawbacks can be overcome by in-situ ophthalmic gels, which extend ocular residence and offer prolonged drug release. Using poloxamer 188 and poloxamer 407 as thermos-responsive gelling agents, the current study sought to create and assess a sustained release in-situ ocular gel containing ketorolac tromethamine. Using varying concentration of poloxamer 188 and poloxamer 407 integrated as a gelling agent, several formulations were created. Clarity, pH, gelling capacity, and in-vitro drug release were assessed for the produced gels. To ensure gelation at ocular physiological temperature, the optimized formulation including poloxamer 407 and poloxamer showed a sol-to-gel transition at approximately 34.7°C. For long-term precorneal retention, the gel displayed pseudoplastic flow with sufficient viscosity. According to in-vitro release experiments, ketorolac tromethamine exhibits a sustained release that can last for up to 12 hours. The work shows that ketorolac tromethamine can be safely and effectively delivered using in-situ gels based on poloxamers 188 and 407. These formulations are a possible substitute for traditional eye drops in the treatment of ocular inflammation and pain because they can increase ocular bioavailability, decrease dose frequency, and improve patient compliance

Keywords: Ketorolac tromethamine, In-situ gel, Sustained release, Ophthalmic delivery

INTRODUCTION

The extremely protective barriers of the eye make delivering medications to the eye one of the most difficult problems in pharmaceutics. Drug absorption is restricted by blinking, tear turnover, nasolacrimal drainage, and the stratified corneal epithelium; intraocular tissues normally receive less than 5% of an administered dose[1,2]. Despite being the most often used dosage forms because of their ease of use and patient comfort, eye drops and suspensions are rapidly drained from the ocular surface, resulting in only temporary therapeutic levels and requiring repeated administration[3,4]. Although the duration of residency can be prolonged by ophthalmic ointments, patient comfort and compliance are frequently jeopardized by their greasiness and blurring abilities[5].

Novel ocular drug delivery methods have been studied in order to overcome these constraints; in-situ gelling formulations have gained a lot of interest[6]. These systems prolong precorneal residence and allow for continuous drug release by instilling liquid drops into the conjunctival sac and undergoing a sol-to-gel transition that is driven by physiological inputs like pH, temperature, or ionic strength[7,8]. Several polymers are utilized as ion-activated gelling agents, including gellan gum, alginate, and xanthan gum[9], Carbopol offers pH-responsive gelation[10], and poloxamer is well-known for its thermos-responsive qualities, with a gelation temperature that is near physiological ocular surface temperature[11] Ketorolac tromethamine (KT) is a derivative of pyrrolizine carboxylic acid with strong analgesic and anti-inflammatory properties, that is categorized as a non-steroidal anti-inflammatory medication (NSAID)[12]. Clinically, it is used to treat ocular discomfort, seasonal allergic conjunctivitis, and post-operative ocular inflammation[13]. Conventional KT eye drops, on the other hand, need frequent administration and result in poor patient compliance because to their weak corneal penetration and fast clearance[14,15]. Advanced delivery techniques as in-situ gelling platforms, mucoadhesive systems,

Therefore, creating KT as an in-situ ocular gel is a sensible way to get rid of the drawbacks of traditional dosing forms. These systems can prolong drug release, increase bioavailability, decrease dosage frequency, and ultimately improve patient compliance in Ophthalmic drug delivery system.

2. MATERIAL AND METHOD

2.1 Materials

Ketorolac tromethamine (API) was obtained as a gift sample from torrent research centre, village Bhat, Gandhinagar, Gujrat, India. Poloxamer 407 and Poloxamer 188 were obtained as gratis samples from Astron Research Limited in Ahmedabad, Gujarat, India and used as a polymer or gelling agent. Benzalkonium chloride was utilized as a preservative.

2.2 Determination of Drug-Polymer Interaction

2.2.1 Differential scanning calorimetry (DSC) study

A Differential Scanning Calorimetry study was conducted on a DSC-60 (Shimadzu, Japan) instrument to investigate the thermal behaviour of a drug, as well as two polymers named Poloxamer 407 and Poloxamer 188, and their physical mixtures with KT. The samples were prepared by weighing each component separately into aluminium pans, which were then covered with aluminium lids and hermetically sealed using a pan press. The sealed aluminium pans containing the samples were then inserted into the DSC-60 calorimeter, and the temperature of the pan gradually increased from 25ºC to 300ºC at a rate of 10 ºC/min, while nitrogen was purged at a flow rate of 45 mL/min throughout the experiment. The DSC-60 instrument measured the heat flow that occurred in the samples as the temperature changed, providing insights into their thermal properties such as melting or crystallization points, glass transitions, and other thermal events(18).

2.2.2 Fourier transform infrared spectroscopy (FT-IR) study

The FT-IR spectra of Drug (KT) and both the polymers Poloxamer 407 and Poloxamer 188 individually as well as their physical mixture, were recorded using an FT-IR spectrometer (F-8400, Shimadzu, Japan). Enough of each sample (10 mg) was placed to form a thin film covering the diamond window. The FT-IR spectra were recorded at a resolution of 2 cm-1, with an average of 120 scans. This process allowed for the measurement of the absorption of infrared radiation by the samples, providing insights into their chemical composition and functional groups present.

2.3 Preparation of in-situ gel formulations

To prepare solutions of Poloxamer 407 and Poloxamer 188 (% w/v) of different concentrations using different amounts of Poloxamer 407 and Poloxamer 188 were dissolved in cold deionized water, which had been equilibrated at 4-8ºC prior to use. The solutions were stirred for 2 hours, during which 5 mg/ml of KT was added to the preparation. The solution was then kept in a refrigerator for at least 24 hours to ensure complete dissolution. This process allowed for the creation of solutions with varying ratios of Poloxamer 407 and Poloxamer 188, which could be used to investigate the effect of polymer concentration on the properties of the resulting formulation. The use of cold deionized water and refrigeration during preparation helped to ensure the stability and homogeneity of the resulting solutions(18).

2.4 Determination of physical properties of in-situ gels

Before conducting any characterization studies, all preparations were visually inspected to assess their clarity, both before and after gelation. The gelation temperature and time of each preparation were then determined. Firstly, the sample was heated from 4ºC to 50ºC at a rate of 1ºC/min, while the solution was continuously stirred. The temperature at which the sample began to form a gel was recorded as the gelation temperature. The sample was then allowed to cool to 25ºC, and the time taken for the gel to form was recorded as the gelation time. This process allowed for the determination of the gelation temperature and time for each preparation, which are important parameters that can influence the properties and performance of the resulting gel.

2.4.1 Determination of gelation time and temperature

To determine the gelation temperature or sol-gel transition temperature (Tsol-gel), the tube inversion method was used. The test solution was placed in a test tube, which was then immersed in a water bath maintained at a temperature of 37ºC for 5 minutes. The temperature at which the test solution transformed into a gel state was noted as the gelation temperature. This was determined by tilting the test tube up to 90 degrees and observing if the gel ceased to flow, with no change in the meniscus. The temperature at which this occurred was recorded as the gelation temperature.

2.4.2 Determination of viscosity

The viscosity of various formulations prepared using Poloxamer 407 and Poloxamer 188 was measured using a Brookfield viscometer (Brookfield Engineering LABS. Inc., Middleboro, MA, USA). A spindle type 6 was used at shear rate of 100 RPM at 4ºC, with the spindle rate matching the working range of the torque. To ensure consistency among different

preparations, 25 ml of each sample was placed in a glass tube, and the rotational speed was kept constant for at least 60 seconds before a reading was taken. The measurements were carried out in triplicate, and the mean values ± standard deviation (SD) were calculated.

2.4.3 In-vitro release study

To evaluate the drug release profile, 1 ml of the formulation equivalent to 5 mg/ml of Ketorolac tromethamine was transferred to the donor compartment of a Franz-diffusion cell and covered with parafilm. The receptor chamber, which had a volume of 20 ml, was filled with artificial tear fluid at pH 7.4 and constantly stirred with a small magnetic bar. A dialysis membrane with a molecular weight cut-off of 12,000-14,000 Da was used to separate the donor and receptor compartments. The membrane was pre-soaked in the receptor medium overnight prior to the experiment. The temperature was set at 37±0.5ºC. Each ml sample was withdrawn at pre-determined time points over a period of up to 12 hrs, and an equal volume of the receptor medium was added to the receptor compartment after each withdrawal. The experiments were carried out in triplicate, and the samples containing Ketorolac tromethamine were analyzed by the UV-Visible spectroscopy method(19).

2.4.5 Sterility study

Sterilization of pharmaceutical products is done to eliminate living harmful microorganisms as the in-situ gel is intended to instil into eyes. The purpose of sterility tests is to identify the presence of living microorganisms in pharmaceutical products. The test was conducted in a controlled environment to prevent any accidental contamination of the product. The measures taken to prevent contamination microorganisms in the test. The procedure for conducting a sterility test as per the USP guidelines. To test for sterility, the alternative thioglycolate medium and soyabean casein digest medium are used for detecting the presence of aerobic bacteria and fungi. In each test, three sterile test tubes are used, labelled as negative control, test, and positive control. To test for aerobic bacteria, 20 ml each of sterile alternative thioglycolate is transferred to 3 tubes aseptically. The tube labelled as positive control is inoculated with viable aerobic microorganism Bacillus subtitles aseptically. 2.5 ml of the ophthalmic preparation is added to the tube labelled as test. Then all three tubes are incubated at 30-35˚C for not less than 7 days.

2.4.6 Short term accelerated stability study

The term "stability" refers to the ability of a product to maintain its properties and characteristics within specified limits throughout its storage and use period, known as its shelf life. Stability testing is carried out to ensure that drug products remain suitable for use until their expiration dates. Short term accelerated stability study was performed on sterilized, packaged formulations. It is period for which sample was analyzed for visual appearance, gelling capacity, viscosity, pH, drug content, and in-vitro drug release. This testing is essential to ensure that the product remains safe, effective, and of high quality throughout its shelf life(20).

2.4.7 Statistical analysis

Collected data was analyzed using statistical analysis techniques such as analysis of variance (ANOVA) to assess the significance of the factors and their interactions. This helps to understand the relationship between the factors and the response variable and draw conclusions based on the experimental results.

3. RESULT AND DISCUSSION

3.1 Evaluation of drug -polymer interactions

The thermal behaviour of Ketorolac tromethamine (KT), poloxamer 407 and their physical mixture was analysed and presented in figure 1. The thermogram for KT showed one endothermic peak at 169.92ºC, indicating the melting of the KT salt. Similarly, Poloxamer 407 displayed an endothermic peak at 58 ºC, which is consistent with its melting point. The thermogram for Poloxamer 188 exhibited an endothermic peak at 60.62 ºC.

The thermal behaviour of Ketorolac tromethamine (KT), poloxamer 188, and their physical mixture (1:1 w/w) was analysed. Physical mixture of KT and poloxamer 407 was analysed, two endothermic peaks were observed at 56.1ºC and 165.8ºC, corresponding to the melting points of the polymer and the drug, respectively. The single peak for the drug showed a slight shift to a lower temperature, indicating a weak interaction between the drug and poloxamer 407, possibly due to electrostatic interaction between the two components

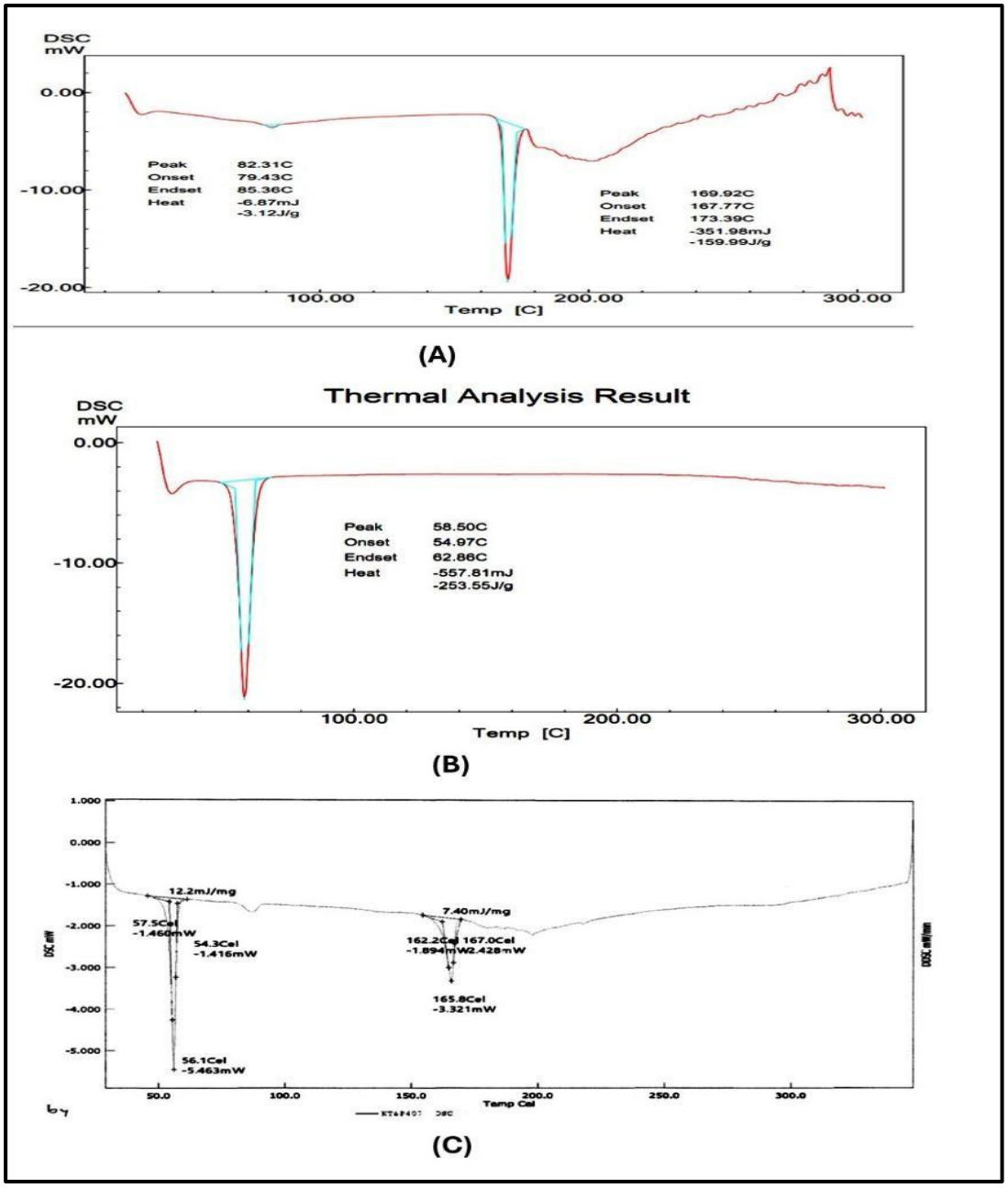


Figure 1: DSC of (A) Ketorolac tromethamine (B)poloxamer 407 (C) physical mixture Ketorolac tromethamine and poloxamer 407(1:1 w/w)

Similarly, the physical mixture of KT and poloxamer 188 showed two endothermic peaks at 165.1ºC and 54.6ºC, corresponding to the melting points of the polymer and the drug, respectively. This indicates a weak interaction between the drug and poloxamer 188, potentially due to electrostatic interactions between the drug and the polymer. Interestingly, the DSC thermogram of P407-KT and P188-KT showed no difference. The DSC thermogram for KT, P188, and their physical mixture exhibited the same thermal behaviour as those obtained with P407-KT.

3.2 Fourier transform infrared spectroscopy (FT-IR) study

The FT-IR spectra of KT, KT-P407 PM and KT-P188 PM are shown in Figure 2, with characteristic peaks at around 3000 cm-1 and around 1100 cm-1(22) as shown in Table 1:The spectrum of KT showed major peaks at 3449 cm-1 (NH stretching vibration), 1775 cm-1 (C=O stretch of diaryl ketone), 1468 cm-1 (C-C aromatic stretching), 2144 cm-1 (C-H - Bending vibration) and 3088 cm-1 (O-H-Carboxylic acid)(21

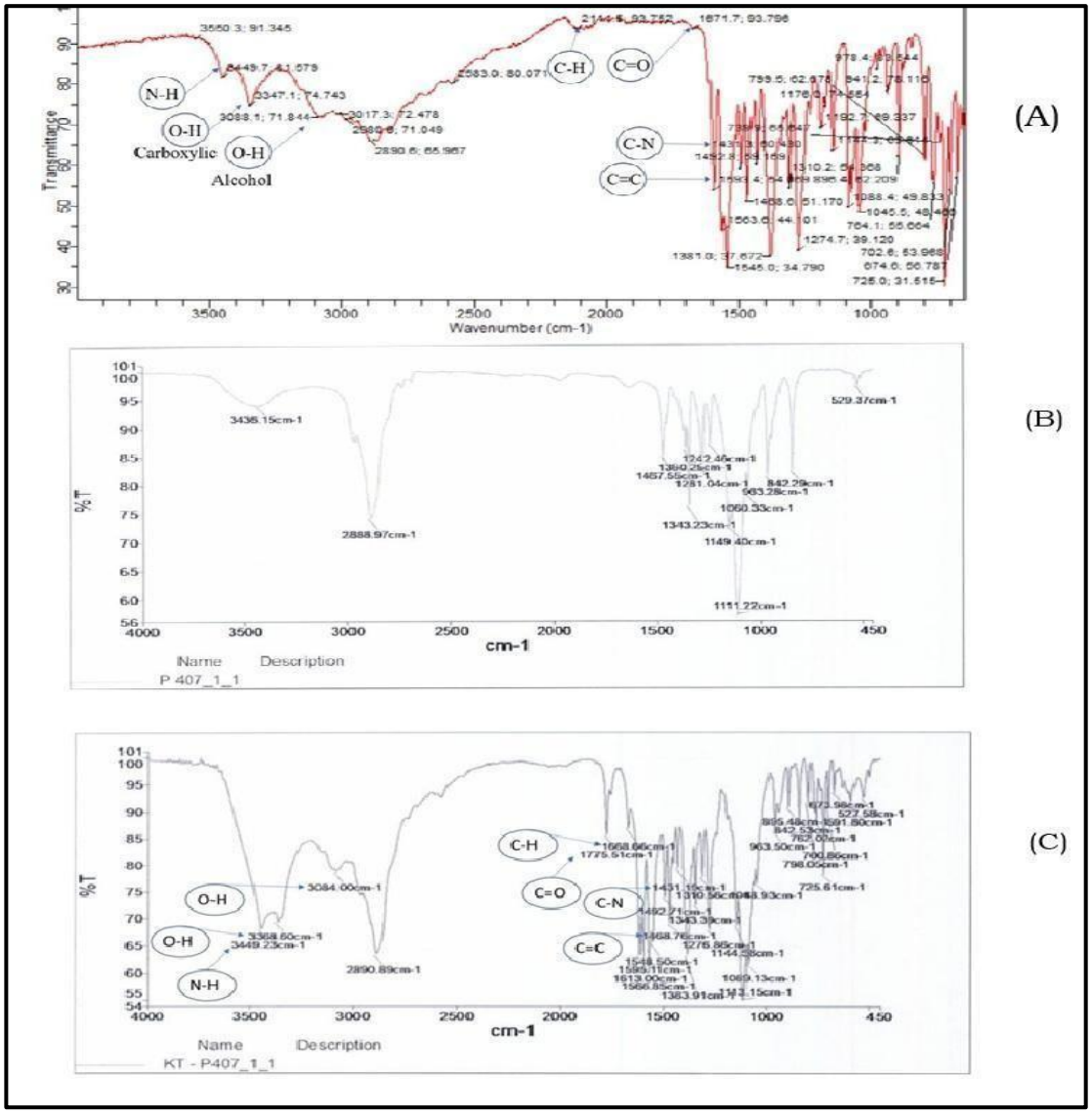


Figure 2: FTIR of spectra of (a) pure drug Ketorolac tromethamine (b) KT-P407 PM (c) KT-P188 PM

Table 1: Comparative FTIR Interpretation

Sr.No.	Functional group	Peak Value (cm^{-1})		
		KT	KT-P407 PM	KT-P188 PM
1	N-H - Stretching vibration	3449	3449	3449
2	C-N - Bending vibration	1431	1431	1430.95
3	O-H - Carboxylic acid	3088	3080	2889.43

The FT-IR spectrum for the physical mixture of KT and P188 as well as KT and P407 (figure 2) did not show any shifts in the peaks of both the drug and the polymer but the intensity of the peak slightly decreased which may be due to the dilution of the drug with the polymer compared with KT alone. Thus, it can be concluded that based on FT-IR spectra there is no interaction between the drug and polymer in the physical mixture.

3.4 Preliminary formulation and Evaluation of trial batches

Table 2: Composition of In-situ gelling system of developed formulation

Sr. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7
1	Ketorolac tromethamine (mg/ml)	5	5	5	5	5	5	5
2	Poloxamer 407 (%w/v)	15	20	23	25	15	20	23
3	Poloxamer 188 (%w/v)	5	5	5	5	10	10	10
4	Benzalk onium chloride	0.01	0.01	0.01	0.01	0.01	0.01	0.01
5	Deionize d water (ml)	100	100	100	100	100	100	100

The in-situ gel formulations were prepared using different combinations of Poloxamer 407 and Poloxamer 188 as shown in table 2. The primary batches from F1 to F7 were visually observed to be clear, colorless, and transparent. Clarity is an important characteristic for ophthalmic formulations since non-transparent formulations can cause blurred vision and may not be acceptable to patients(23).

The pH of the P407/P188 in-situ gel formulations was determined using a pre-calibrated pH-meter. All the formulations were found to have a neutral pH ranging from 6.8 to 7.2.

The gelation time of the prepared P407/P188 in-situ gel formulations was measured, and the results are presented in. At a constant Poloxamer 188 concentration, the gelation time of the formulations decreased as the concentration of Poloxamer 407 increased(24). Batches F4 and F7 give gelation at 37ºC temperature for 5 min. other formulations batches F1, F2, F3, F5 and F6 do not give gelation at 37ºC temperature for 5 min.

3.4 32 Full factorial design

3.4.1 Experimental run for 32 full factorial design

32 full factorial design was implemented to examine the effects of two independent factors on a dependent factor. In this design, there are three levels for each of the two factors, resulting in a total of nine treatment combinations (32 = 9). The two factors are X1 and X2. Each factor has three levels: low (coded as -1), medium (coded as 0), and high (coded as +1). The design matrix for the 32 full factorial designs are shown in table 3 as follows

Table 3: Experimental run for 3^2 full factorial design

Batch Code	Coded value		Decoded value	
	(Poloxamer 407) X1	(Poloxamer 188) X2	(Poloxamer P407) X1	(Poloxamer 188) X2
B1	-1	-1	20	8
B2	0	-1	22.5	8
B3	+1	-1	25	8

B4	-1	0	20	10
B5	0	0	22.5	10
B6	+1	0	25	10

B7	-1	+1	20	12
B8	0	+1	22.5	12
B9	+1	+1	25	12

Each row in the design matrix represents a unique combination of factor levels. The advantage of 32 full factorial design is that it allows to simultaneously examine the main effects of each factor and their interactions. By systematically varying the levels of both factors, they can assess the individual effects of Factor X1 and Factor X2, as well as their combined effects. The experiments are conducted, and the response variable data is collected, statistical analysis techniques such as analysis of variance (ANOVA) can be applied to assess the significance of the factors and their interactions. This helps to understand the relationship between the factors and the response variable and draw conclusions based on the experimental results.

3.5 Evaluation of primary design batches

Ideal gelation time is generally short (but not too fast) to allow administration and quick in-situ gelling. After getting data of evaluation parameters that gelation time is ranging from 3.5 min to 20 min. Visual Observation as shown in table 4 states that all batches are Clear, colourless, transparent shows good appearance and may have patient acceptability. pH ranges 6.8–7.0, which is close to physiological pH means it is suitable for ocular formulations (non-irritant). Drug Release (12 hr) shows variation from 34.28% to 67.49%.

Table 4 : Evaluation of design batches

Batch code	**Gelation time at 37°C (min)**	**Visual observation**	**pH**	**Cumulative % drug release for 12 hr)**
B1	9.5	Clear, colourless and transparent	7	67.49
B2	5.3	Clear, colourless and transparent	6.8	43.66
B3	4.2	Clear, colourless and transparent	7	34.28
B4	12	Clear, colourless and transparent	7	46.79
B5	4.4	Clear, colourless and transparent	6.9	43.87
B6	3.5	Clear, colourless and transparent	7	38.22
B7	20	Clear, colourless and transparent	7	56.91
B8	13	Clear, colourless and transparent	6.8	57.32
B9	12.5	Clear, colourless and transparent	6.9	61.37

3.6 Regression analysis

3.6.1 Regression analysis of Response Y1

Based on data received quadratic model was selected in design expert to evaluate the effect of X1 and X2 on dependent variable Y1 showing equation,

$Y1 = 4.82 - 3.55X1 + 4.42X2 – 0.5500X1X2 + 2.72X12 + 4.12X$

Effect of X_1 and X_2 on Y_1

From the quadratic model equation as shown above, it can be concluded that as factor X_1 i.e., as poloxamer 407 increases, gelation time decreases but as factor X_2 i.e., poloxamer 188 increases, gelation time increases. Poly-nominal term of X_1X_2 ($ß_{12}$) was found in significant as their p-value was more than 0.05. The result of ANOVA suggests that F - Value of Y_1 was found to be 51.34 and it was concluded that given model is significant. R^2 value is 0.9884, which explains that about 98.84% of variability is expressed by this model. The effect of X_1 and X_2 on Y_1 was expressed in 3D surface response plot and counter plot

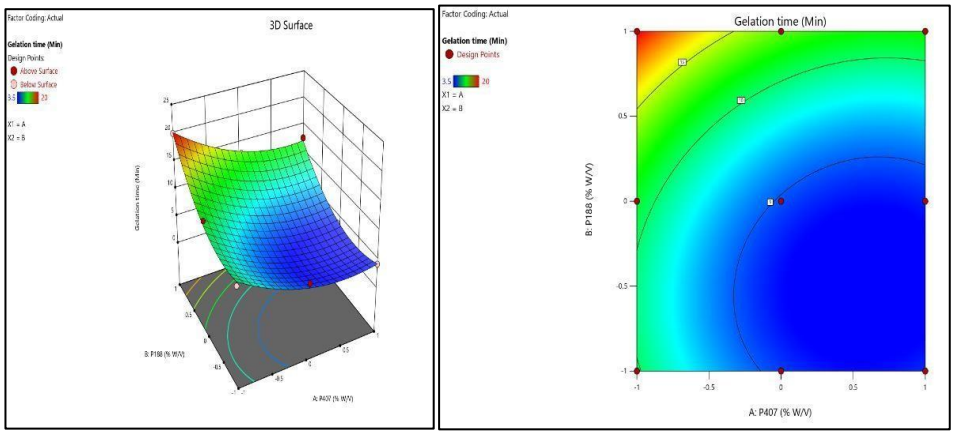


Figure 3: (A) 3D response surface plot (B) Counter plot of gelation time (Y1)

Regression analysis of Response Y2

Based on data received quadratic model was selected in design expert to evaluate the effect of X_1 and X_2 on dependent variable Y_1 showing equation,

$Y2 = 41.32 - 6.17X1 + 5.03X2 + 9.42X1X2 + 2.61X_1^2 + 10.45X^2$

Effect of X_1 and X_2 on Y_2

From the quadratic model equation as shown in table21, it can be concluded that as factorX_1 i.e., as poloxamer 407decreases % drug release increase. On other hand, factor X_2 i.e., as poloxamer 188 increase % drug release increase. Polynomial term of X_1^1($ß_{11}$) was found in significant their p-value was more than 0.05. The result of ANOVA suggests that F - Value of $Y_2$was 15.79 and it was concluded that given model is significant.

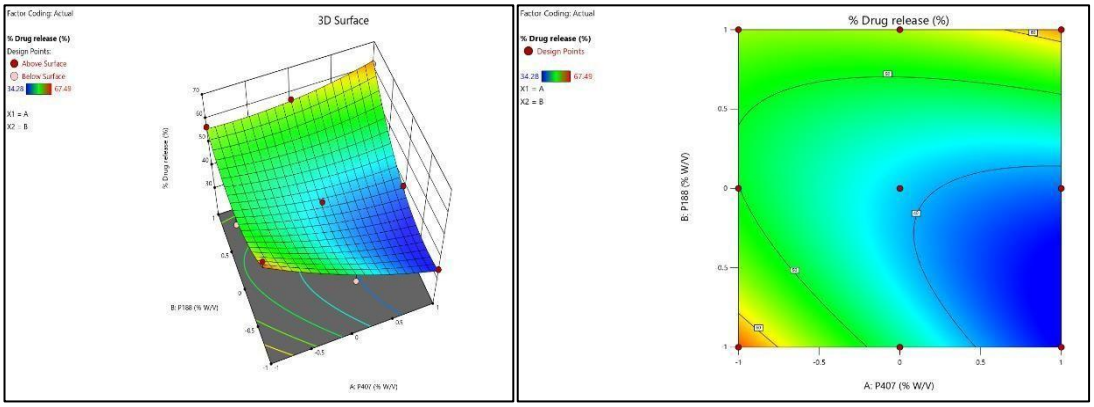


Figure 4: (A) 3D response surface plot (B) Counter plot of % Drug Release (Y2)

Formulation Optimization

Optimization of formulation was done by Design Expert Software 13. To optimize formulation following constraints were used

Table 5: Constrain values to optimize formulation

Responses	Constrains		
	Minimum	Maximum	Goal
Poloxamer 407	-1	1	Maximum
Poloxamer 188	-1	1	Target
Gelation time	3.5	20	Minimum
% Drug release	34.28	67.49	Minimum

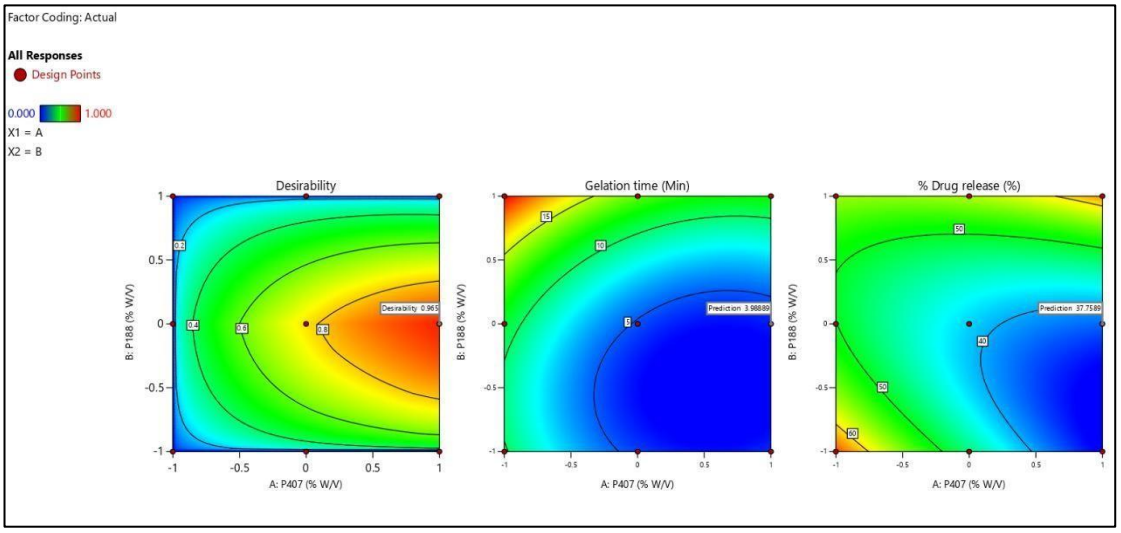


Figure 5: Optimization of desirability function by Design-Expert 13

The optimum formulation was selected based on the criteria of minimum, target and maximum values of response variables as observed in table 5. An overall desirability function dependent on all the investigated formulation variables was used to predict the ranges of variables where the optimum formulation might occur.

The desirable ranges are from zero to one (least to most desirable, respectively). The optimized batch constrains value is given in Table 6. From the figure 25, it could be concluded that suggested batch with X_1 =1 and X_2 =0 was selected as optimized batch which has desirability of 0.965

Table 6: Optimized formulation composition

Sr. No.	Ingredients	Qty
1	Ketorolac tromethamine (mg/ml)	5
2	Poloxamer 407 (%w/v)	25
3	Poloxamer 188 (%w/v)	10
4	Benzalkonium chloride	0.01
5	Deionized water (ml)	100

Evaluation of optimized *in-situ* gel formulation

Test for Clarity and pH

The *in-situ* gel formulations were prepared using different combinations of Poloxamer 407 and Poloxamer 188 and visually observed to be clear, colorless, and transparent. pH of the Poloxamer 407/Poloxamer 188 *in-situ* gel formulations were found to have a neutral pH ranging from 6.8 to 7.

Gelation study

Gelation capacity of prepared *in-situ* was performed using tube inversion method. Gelation time for optimized formulation found was 3.5 minutes.

Viscosity of prepared In-situ Gel

At ambient temperature, every gel formulation had a distinctive pseudoplastic (shear thinning) flow behavior. For all formulations studied, the viscosity rose significantly ($P < 0.001$) as the concentration of Poloxamer 407 and Poloxamer 188 increased. This could be explained by the fact that any small increase in shear rate causes the polymer chains to align parallel to one another along their axes in the direction of flow, which lowers the material's internal resistance and viscosity[25]. Viscosity of optimized formulation found 220 cps at 100 RPM before gelation and 352 cps at 100 RPM after gelation. These findings are consistent with those of Ricci et al., who found that Poloxamer 407 gels were pseudoplastic and that, as a result, their viscosity decreased under shear deformation[26].

In-vitro drug release study

In-vitro drug release data is shown in Table no.5. As the Poloxamer 407/Poloxamer 188 ratio increased, the release rate of KT reduced, indicating that Poloxamer 188 and Poloxamer 407 delayed the drug's breakdown in a concentration-dependent way. Optimized formulation showed 38.22% of drug release after 12 hours, but it also showed a sustained drug release when compared to the KT solution. The release data indicates that Poloxamer 407 molecules use hydrogen bonds to form tight gel structures in aqueous solution. Additionally, because KT is soluble in water, it interacts with poloxamer, delaying the pattern of drug release.

Various *in-situ* gel formulations were compared for % drug release profiles. Suspension of pure drug of Ketorolac tromethamine was prepared in water and another same product was marketed eye drop. These two samples were compared with *in-situ* ophthalmic gel of Ketorolac tromethamine. Consequently, suspension of pure drug of Ketorolac tromethamine was 94.36 % drug release and another same marketed Ketorolac tromethamine eye drop was 68.73 % drug release in only 6 hr. While *in-situ* ophthalmic gel of ketorolac tromethamine was 38.22 % drug release in 12 hr. it was concluded that optimized *in-situ* ophthalmic gel formulation of Ketorolac tromethamine using polymer Poloxamer 407 and Poloxamer 188 provide sustained release of drug

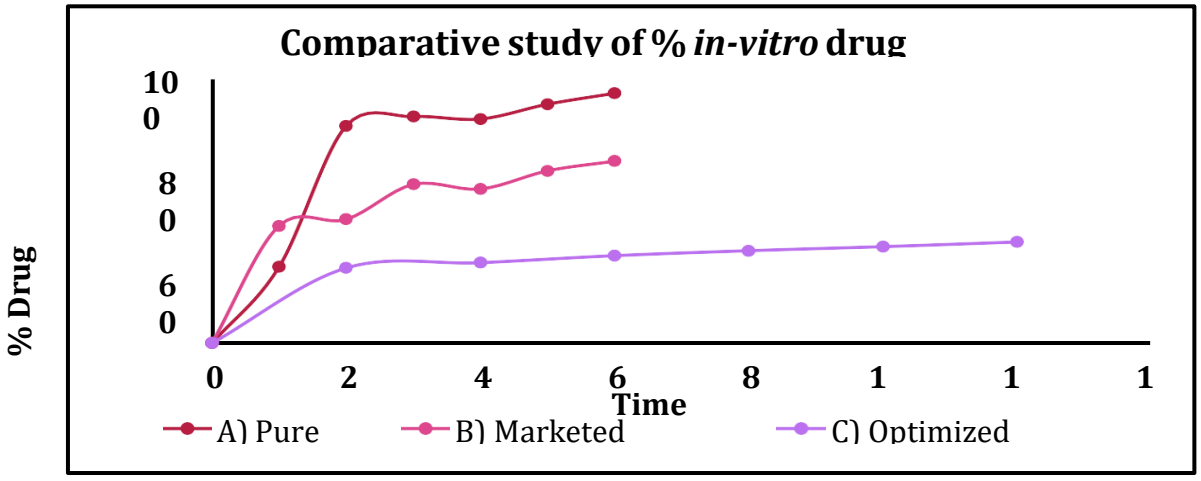


Figure 6: Comparative study of % *in-vitro* drug release of pure drug and different formulation

3.8.4 Sterility study

As shown in figure 7 sterility test was performed for sample and positive and negative control. Results from sterility test are shown in table no. 7. No microorganism growth found in test tube containing sample test tube proving sterility of prepared Ketorolac tromethamine *in-situ* gel

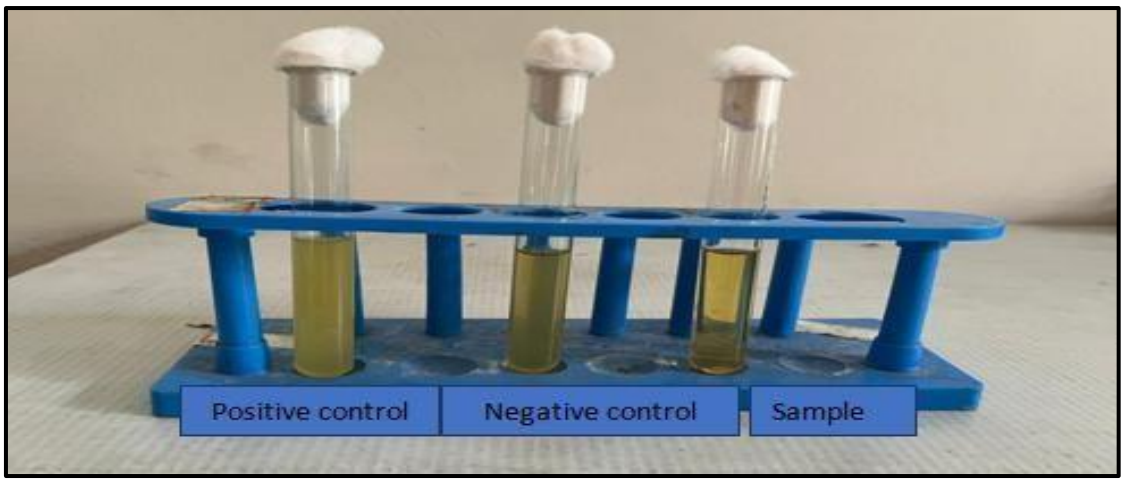


Figure 7: Sterility test

Table 7: Observation table of sterility test

Sr. No.	Test tube containing media	Growth of bacteria or fungi	Result
1	Positive control	Present	Sterile
2	Sample	Absent	
3	Negative control	Absent	

3.8.4 Accelerated stability study

Stability testing was carried out to ensure that drug products remain suitable for use until their expiry dates. Stability study was carried out as per ICH Q1A (R2) guidelines. Short term accelerated stability study is performed on sterilized, packaged formulations at 40 ± 2°C and 75 ± 5% Relative Humidity (RH) for 45 days. Samples were than taken for analysis of various parameters like pH, appearance of gel, gelation time and *in-vitro* release of drug and observed data are mentioned in table 8.

Table 8: Stability study

Sr. No.	Evaluation parameters	Before stability	After stability
1	Appearance	Clear, colourless and transparent	Clear, colourless and transparent
2	pH	7	6.8
3	Gelation time (at 37ºC)	3.5	3
4	*In-vitro* drug release for 12 hr.	38.22 %	36.32 %

4.CONCLUSION

Selection of two hydrophilic polymers, poloxamer 407 and poloxamer 188 for sustained delivery of ketorolac tromethamine (KT) to the eye. Poloxamer 407 acts as a thermos-responsive and poloxamer 188 acts as a modified the temperature of poloxamer 407. Drug-polymer interaction studies were conducted using DSC and FT-IR. DSC and FT-IR analyses indicated possible electrostatic interactions between the drug and polymers. Viscosity was checked by Brookfield Viscometer. The

gels containing Poloxamer 407 and Poloxamer 188 show pseudoplastic behaviour at different concentrations. The gelation temperature (Tsol-gel) was constant at 37ºC gelation time was measured using tube inversion method for 5 min. In-vitro release experiments showed that the in-situ gels effectively prolonged and controlled KT release, approximately 40 % of KT released within 12 hours. In-vitro permeation study shows that the prepared in-situ gels sustained drug release pattern when compared with KT solution. Suspension of pure drug in water and this suspension was approximately 100 % drug release, and the same marketed Ketorolac tromethamine eye drop was approximately 70 % drug release in 6 hr. While in-situ gel Ketorolac tromethamine was approximately 40 % drug released in 12 hrs. So finally, it can be concluded that Ketorolac tromethamine loaded thermos-responsive in- situ gel formulations are sustained release for 12 hrs.

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