

STATISTICALLY OPTIMIZATION AND FORMULATION DEVELOPMENT OF BROMOFENAC SODIUM OPHTHALMIC DRUG DELIVERY SYSTEM

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Abstract

The purpose of this work was to develop and optimise the Bromofenac sodium temperature sensitive ocular in-situ gel using a 3^2 complete factorial design. Two factors were evaluated at three levels each, and experimental trials were carried out using various combinations and central point values. As independent variables, the concentrations of gelling agent (X_1) and viscosity enhancer (X_2) were chosen. To improve the response data, dependant factors such as gelling capacity (Y_1), viscosity (Y_2), and 100 percent drug release (Y_3) were used. The Design Expert software was used to do analysis of variance (ANOVA), 3D surface plots, counter plots, optimization, and desirability. The comparative investigations used a commercially available medication (Megabrom) with a better formulation (F5). All of the formulations were clear, transparent, and yellow. When compared to the ocular pH of 7.4, the pH of the formulations ranges from 7.01 to 7.34, which is an acceptable range. All of the formulations had a gelation temperature of 37°C-43.5°C, and the drug content ranged from 95.13 to 98.55 percent. The pseudo plastic behaviour is observed in all formulations (shear thinning systems). The improved recipe had a higher desirability concern (1), indicating that it was a good formulation. The model's predictability and validity were demonstrated when the experimental values matched the expected values.

Keywords: Optimization, gelling agent, viscosity, megabrom, pH

Introduction

Artificial Neural Networks (ANN) is an abstract Bromofenac sodium is a non-steroidal anti-inflammatory medicine (NSAID) that is commonly used to treat severe inflammations and disorders of the ocular posterior segment, including retinal and choroidal neurovascular insertion and cystoids macular oedema. It was used 4-5 times a day as prescribed by the doctor after cataract surgery. In the present study ocular in-situ gels are mainly

prepared to overcome the problems exhibited by conventional eye drops. Generally only 5% of the installed dose was absorbed remaining was drained out by the tear fluid. The bromfenac sodium is being delivered more effectively using chondroitin sulphate-chitosan nanoparticles, a new innovative nanocarrier (Abdullah *et al.*, 2016), develop a sustained release microspheric in-situ gel for bromofenac sodium (BNa) to be administered

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via the ocular route (Yang *et al.*, 2014), Investigate the toxicity of commercial non-steroid anti-inflammatory drug (NSAID) eye solutions against corneal epithelial cells (Lee *et al.*, 2015), efficacy and safety of long-term therapy of patients with vernal kerato conjunctivitis (VKC) with bromofenac sodium eye drops in conjunction with corticosteroids and anti-allergic eye drops. In the United States (Uchio *et al.*, 2007; Ahuja *et al.*, 2008), five novel ophthalmic NSAID medicines have been approved for commercial use, prevention and treatment of CME after cataract surgery with bromofenac 0.07% or 0.09% (Cho and Madu, 2009), therapeutic use of NSAIDs for retinal illnesses, with a focus on potential future uses decrease of exudation secondary to age-related macular degeneration or diabetic maculopathy (Russo *et al.*, 2013), effectiveness of bromofenac sodium ophthalmic solution in patients with dry eye disease uncontrolled by artificial tears monotherapy (ATs) (Fujishima *et al.*, 2015), determine the best medicinal strategy for avoiding cystoid macular edema (CME) following cataract surgery. In the developed world, cystoid macular edema, in its different forms, is one of the primary causes of central vision loss (Cho and Madu, 2009; Cho *et al.*, 2009), diabetic cataract pathophysiology, clinical investigations studying the link between diabetes and cataract development (Kim and Jampel, 2016), and current diabetic cataract treatment (Pollreis and Schmidt-Erfurth, 2010), Using a crossover design (Mehlich and Fulmer, 1997), bromfenac sodium (10 mg or 50 mg) was given in single and repeated doses. Naproxen sodium (550 mg loading/ 275 mg repeat doses) was given to 54 women at random, for pain alleviation from primary dysmenorrhea. In a double-masked, parallel-group, multicenter, inpatient study (Johnson *et al.*, 1997), In patients with pain from abdominal gynecologic surgery, bromfenac was compared to an acetaminophen/oxycodone combination and ibuprofen. To overcome this problem we are preparing in-situ gels which undergo a sol-gel transition in the eye reported recently (Ellah *et al.*, 2018; Rajput and Butani, 2019; Agrawal *et al.*, 2020; Göttel *et al.*, 2020; Wei *et al.*, 2020;) and other drugs and deliveries on eye are reported (Kumar *et al.*, 1994; Pijls *et al.*, 2005; Liu *et al.*, 2006; Ma *et al.*, 2008; Mansour *et al.*, 2008; Gupta *et al.*, 2009; Almeida *et al.*, 2013; Sheppard, 2016; Okur *et al.*, 2019). The design of experiments (DOE) is a statistical technique for quickly optimising (Ramarao and Chowdary, 2011; Rao and Chowdary, 2015) system performance given known input variables (Teja and Damodharan, 2018). It begins with a screening experimental design test plan that includes all known parameters that may affect the system's

performance. When there are a lot of input variables or test factors, the main goal of the experiment is to reduce the number of them to a manageable quantity (Solaiman *et al.*, 2016; Ramarao *et al.*, 2017; Aydar., 2018; Ramarao *et al.*, 2018; Ramarao and Madhuri, 2022a; 2022b). The statistical design of experiments (DoE) is a strong tool for optimising processes that have been used throughout the API development process (Challa, 2018; Rao and Bhavyasri, 2018 Murali and Ramarao, 2022). The main aim of present study is preparation of twice-a-day formulation of bromofenac sodium thermo-sensitive ocular in-situ gel by using poloxamer as a thermo-sensitive polymer for ocular delivery, prolong contact and residence time with corneal tissue, sustain drug for a long time, increase bioavailability, design the study in 3^2 full factorial design, prepare the ocular in-situ gel according to the formula designed, evaluate prepared ocular in-situ gel and to optimize the formula, cross validate the experimental values with the predicted values for optimized formula, Comparison with marketed formulation. A 3^2 full factorial design was used for the development and optimization of the bromofenac sodium thermo sensitive ocular in-situ gel, two factors were evaluated each at three levels and experimental trials were performed using all the nine possible combinations and middle value was performed in quadruplicate. The concentration of gelling agent (X_1) and concentration of viscosity enhancer (X_2) were selected as independent variables. Gelling Capacity, viscosity, 100% drug release were selected as dependant variables to

Table 1. Experimental range and levels of the independent Variables in a 3^2 full factorial design

Run No.	Variable level in coded form	
	X_1	X_2
1	-1	-1
2	0	-1
3	+1	-1
4	-1	0
5	0	0
6	+1	0
7	-1	+1
8	0	+1
9	+1	+1
10	0	0
11	0	0
12	0	0
13	0	0
Coded values	Actual values	
	X_1 (amount of polymer in mg)	X_2 (stirring speed in RPM)
-1	10	1
0	15	1.75
+1	20	2.5

optimize the response data. The experimental design was used in the present study and is shown in Table 1.

Materials and Methods

Bromfenac sodium was purchased from Sigma Aldrich, USA, Poloxamer were purchased from Yarrow chemicals, Mumbai, HPMC E5 purchased from Yarrow chemicals, Mumbai, Sodium chloride purchased from Qualigens fine chemicals from Maharashtra, Sodium bi carbonate purchased from Qualigens fine chemicals, Maharashtra, Calcium chloride purchased from Qualigens fine chemicals, Maharashtra, Citric acid purchased from Qualigens fine chemicals, Maharashtra and Disodium hydrogen orthophosphate purchased from Qualigens fine chemicals, Maharashtra.

Method of Preparation

In the present work in-situ gels were prepared by cooling technique (Venkatesh *et al.*, 2020). By using different concentrations of polymer and viscosity enhancers in-situ gels were prepared as per the composition is shown in Table 1. The Distilled water 70 ml was taken and accurately weighed citric acid and disodium hydrogen phosphate were dissolved in it. To this solution, HPMC E5 was added and it was dissolved to form a clear solution without any lumps. Required quantities of poloxamer 188 were taken and then sprinkled into the above solution and they were kept overnight for swelling in the refrigerator. After that, the polymer solution was taken into a beaker with continuous stirring (magnetic stirrer) until a uniform solution was obtained. Accurately weighed bromofenac (90 mg) was taken and dissolved in 5 ml of distilled water. The drug solution was then added to the polymeric solution under constant stirring on a magnetic stirrer until a uniform solution was obtained. Then it was made up to the final volume 100 mL. The generated formulations were autoclaved for 20 min at 121°C and 15 psi for terminal sterilization.

Clarity

All the in-situ gels were visually inspected for colour and clarity.

Determination of pH

One of the most crucial aspects of the formulation process is pH. The effects of pH on solubility and stability are two areas of essential importance. The pH of an ophthalmic formulation

should be such that the formulation remains stable at that pH while also causing minimal irritation to the patient when it is administered. A pH meter was used to assess the pH of the produced mixtures.

Gelling Capacity

Two drops of formulation were placed in a test tube containing two mL of freshly produced artificial tear fluid (ATF) solution to measure gelling capability. Time required for gelation and time taken for formed gel to dissolve was recorded and temperature was maintained at 37°C.

Gelation Temperature

The sample solution of one mL was taken in to a beaker containing two mL of tear fluid. The solution was heated at a rate of 2°C/min with continuous stirring. The temperature at which the gel was formed was noted.

Composition of the Drug

To achieve dosage uniformity, the active component must be distributed uniformly. One mL of the formulation was dilute to 100 mL with distilled water to ascertain the drug concentration. The concentration of bromfenac sodium was then measured using a UV-Vis spectrophotometer at 230 nm.

Drug release *in vitro*

In vitro release of in-situ gel was studied using the Franz diffusion cell. In the donor compartment, one ml of formulation was inserted, and in the receptor compartment, newly made artificial tear fluid was placed. A dialysis membrane was inserted between the donor and receptor compartments and soaked in medium overnight. The entire apparatus was placed on a magnetic stirrer with a thermostat. The medium was kept at a constant temperature of 37°C±0.5°C. Every 1 h until 6 h, and then every 2 h until 12 h, an aliquot of one ml of sample was withdrawn at predefined time intervals. The equal volume of fresh medium was used to replace it. The withdrawn samples were diluted and analyzed by UV-Visible spectrophotometer at 230 nm using blank. The same procedure was triplicate and recordings are noted.

Rheological Studies

The viscosity was determined by using cone and plate viscometer. Formulation, 1 ml was taken and placed in a plate then cone was adjusted to the position. Then it was adjusted to zero reading. The viscosity of formulations was determined at different angular velocities from 10 to 100 rpm and 100 to 10 rpm. Then one drop of formulation was

placed in ATF then the viscosity of formulations was determined from 10 to 100 rpm and 100 to 10 rpm. Then the recordings are noted.

Drug-Polymer Compatibility Studies (FTIR)

FTIR spectroscopy was used to investigate drug-polymer interactions. Pure drug, pure polymers, and a physical combination of drug and polymers had their spectra recorded. FTIR-BRUKER was used to obtain the spectra of the sample. The KBr disc method was employed in this experiment. To achieve consistent mixing, the sample was combined with KBr and triturated in a mortar and pestle. This slurry was squeezed into discs for 3 min using a hydraulic press at 7 tonnes of pressure. The pellet was positioned in the direction of light, and the spectra were recorded in the 4,000-500 cm^{-1} region.

Comparative Studies

Bromfenac (Megabrom) was taken from the market and drug release experiments were done on it before being compared to the optimised formulation.

Data Analysis

For statistical analysis and optimization, the responses Y_1 (gelling capacity), Y_2 (percent gelation temperature), and Y_3 (percent drug release) were used. The design expert software was used to fit the responses from the nine runs to linear, interactive, and quadratic models at the same time. Based on the coefficient of determination (R^2) and predicted residual sum of squares (PRESS) values, the software will pick and offer the highest order polynomial model as a suitable model (Pathan *et al.*, 2013; Ramarao and Madhuri, 2022).

Discussion and Conclusion

Clarity

The clarity of all of the formulations discovered was satisfactory. The mixtures were clear, translucent, and yellow in appearance.

pH

All of the formulas have a pH range of 7.06 to 7.34. Because the pH is within an acceptable range, it is possible to assume that the formulation will not cause irritation when administered. Table 2. Displays the outcome.

Gelling Capacity

The formulations' gelling capacity was determined to be between 4 h and 10 h. Viscosity and gelling capacity are the two most important requirements for a gelling system (speed and extent of gelation). The formulation should have a viscosity that allows for simple instillation into the eye as a liquid (drops), followed by a quick sol to gel transition due to temperature changes. Furthermore, the in-situ formed gel must maintain its integrity for an extended period of time in order to permit sustained drug release to the ocular region. On contact with ATF, all of the formulations gelled instantly (in less than a minute). When the formulations were added to the ATF, they created a translucent matrix, according to ocular inspection. It's possible that the gelation is caused by a temperature change. Table 2. Summarises the findings.

Gelation Temperature

It is observed that the gelation temperature of the formulations are in the range of 34°C-43.5°C.

Table 2. Physical Characteristic of prepared formulations

Formulation	Clarity	pH	Gelling capacity (h)	Gelling temperature (°C)	Drug Content (%)
F1	Clear, transparent, yellow	7.14	4.30	43.5	98.55
F2	Clear, transparent, yellow	7.29	3.55	42.5	98.00
F3	Clear, transparent, yellow	7.34	5.25	41.5	98.55
F4	Clear, transparent, yellow	7.32	6.23	37.0	99.80
F5	Clear, transparent, yellow	7.34	7.23	37.0	95.13
F6	Clear, transparent, yellow	7.12	6.27	36.5	98.28
F7	Clear, transparent, yellow	7.16	10.21	34.0	95.59
F8	Clear, transparent, yellow	7.06	10.22	33.5	95.56
F9	Clear, transparent, yellow	7.18	10.00	34.0	95.66
F10	Clear, transparent, yellow	7.18	7.29	37.5	95.14
F11	Clear, transparent, yellow	7.09	7.42	37.0	95.14
F12	Clear, transparent, yellow	7.32	7.30	36.5	95.14
F13	Clear, transparent, yellow	7.27	7.15	37.0	95.13

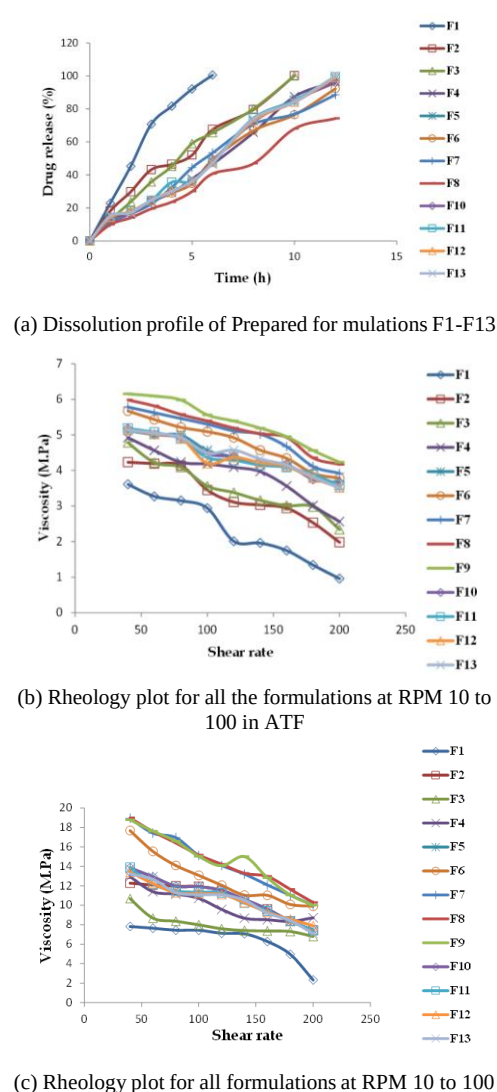


Figure 1. (a) Dissolution profile, (b) Rheology ATF, (c) Rheology all formulations

But a gelation temperature range 37°C-37.5°C is preferred for the formulations to be installed into the eye to avoid damage to the eye. The results are shown in Table 2.

Drug Content

For all formulations, the drug content was confirmed to be within permissible limits. Table 2. shows the result of percent drug content in all the 13 formulations is in the range of 95.13%-99.88%, indicating uniform distribution of drug.

In vitro Drug Release

For all formulations, *in vitro* release kinetics was performed using artificial tear fluid (ATF)

as the diffusion medium. Among all formulations, it was discovered that medication release from F5, F10, F11, F12, and F13 had a stronger sustaining impact. Figure 1(a) depicted the cumulative drug discharges.

Rheological Studies

The formulations displayed pseudo plastic rheology, or shear thinning, in which the viscosity of the formulation decreased when the shear rate was increased. The viscosity of the formulation was related to the amount of polymers in it. The viscosity rise as the poloxamer and HPMC E5 concentrations were increased. Were increased. Figures 1(b) and 1(c) depicts a plot of shear rate vs viscosity.

Data Analysis

Two factors, the amount of gelling agent (X_1) and the amount of viscosity enhancer (X_2), were tested separately at three levels of low, medium, and high in this 3^2 -factorial design of experiment. Three responses were chosen for statistical optimization and fitted to linear, interactive, and quadratic models utilizing this data: gelling capacity (Y_1), gelation temperature (Y_2), and 100 percent drug release (Y_3). The comparative R^2 , adjusted R^2 , predicted R^2 , PRESS, s.d., F-values, and p-values were calculated using the Design Expert and are provided in Tables 4 and 5. Based on the coefficient of determination and PRESS values, an appropriate polynomial model for describing the data was chosen. Responses Y_1 and Y_2 used a linear model, while Y_3 and Y_4 used a quadratic model. As a result of their better R^2 and F-values and lower PRESS and p-values, these models were chosen for further optimization. Tables 3 and 4 show the ANOVA findings for all formulations. These parameters were utilised to create the response's independent variables (Ramaraao and Chowdary, 2011). The replies Y_1 , Y_2 , and Y_3 had F-values of 71.75, 231.97, and 36.18, respectively, indicating that the models were significant. The importance of the models was indicated by Prob <0.05 values for all replies. Using the response surface technique, the following regression equations were found.

$$Y_1 = 7.11 + 0.15 X_1 + 2.91 X_2 \quad (1)$$

$$Y_2 = 37.02 + 0.42 X_1 - 4.33 X_2 + 0.50 X_1 X_2 - 0.062 X_1^2 + 1.19 X_2^2 \quad (2)$$

$$Y_3 = 98.19 - 4.70 X_1 - 12.14 X_2 - 5.74 X_1 X_2 - 1.70 X_1^2 - 8.94 X_2^2 \quad (3)$$

Where X_1 and X_2 are the coded values for the test variables of gelling agent and viscosity enhancer amounts, respectively. Table 3 shows

Table 3. Model comparison of different responses

Response	Model	R ²	Adjusted R ²	Predicted R ²	PRESS	s.d	F Value	P Value	Remarks
Y ₁	Linear	0.9410	0.9279	0.8755	6.76	0.60	71.75	<0.0001	Suggested
	Interactive	0.9457	0.9253	0.8063	10.51	0.61	0.69	0.4295	
	Quadratic	0.9549	0.9172	0.6571	18.61	0.64	0.61	0.5743	
Y ₂	Linear	0.9522	0.9416	0.8925	12.83	0.80	89.64	<0.0001	-
	Interactive	0.9606	0.9458	0.8241	21.01	0.71	1.70	0.2287	
	Quadratic	0.9949	0.9906	0.9683	3.79	0.32	19.98	0.0022	
Y ₃	Linear	0.6894	0.6204	0.3444	966.63	7.13	9.99	0.0052	-
	Interactive	0.7790	0.6961	0.2737	1070.81	6.38	3.24	0.1095	-
	Quadratic	0.9679	0.9411	0.7348	390.96	2.81	17.64	0.0031	suggested

Table 4. Analysis of variance of responses Y₁, Y₂ and Y₃

ANOVAs for response Y ₁							Remarks
Response	Source	SS	D.F	MS	F	P	
Y ₁	Model	51.06	2	25.53	71.75	<0.0001	Significance
	X ₁	0.13	1	0.13	0.37	0.5575	
	X ₂	50.93	1	50.93	143.14	<0.0001	
	Residual	3.20	9	0.36	66	0.0028	
ANOVAs for response Y ₂							Remarks
Y ₂	Model	118.80	5	23.76	231.97	<0.0001	Significance
	X ₁	1.04	1	1.04	10.17	0.0189	
	X ₂	112.67	1	112.67	1099.93	<0.0001	
	X ₁ X ₂	1.00	1	1.00	9.76	0.0205	
	X ₁₂	0.010	1	0.10	0.16	0.7606	
	X ₂₂	3.76	1	3.76	36.71	0.0009	
Y ₃	Residual	0.61	6				Significance
	Model	1427.02	5	285.40	36.18	0.0002	
	X ₁	132.45	1	132.45	16.79	0.0064	
	X ₂	884.03	1	884.03	112.07	<0.0001	
	X ₁ X ₂	132.02	1	132.02	16.74	0.0064	
	X ₁₂	7.67	1	7.67	0.97	0.3621	
Y ₃	X ₂₂	212.95	1	212.95	27.06	0.0020	Significance
	Residual	47.33	6	7.89			

a full description of the findings of multiple regression analysis of dependent variables for all responses. All of the selected independent variables, such as the amount of gelling agent (X₁) and the amount of viscosity enhancer (X₂), have very significant main effects ($p < 0.05$). All responses had additive and antagonistic effects with increasing the quantity of gelling agent (X₁) and viscosity enhancer (X₂), showing enhanced responses with increasing the amount of gelling agent and viscosity enhancer, respectively. The variance of inflation factor (VIF) evaluates how much the absence of orthogonality in the design inflated the variance of a given model coefficient. All of the models' VIF values were found to be closer to 1, indicating good coefficient estimation. The contour plots are used to assess the relationship between two independent parameters, the amount of gelling agent (X₁) and the amount of viscosity enhancer (X₂), and their impact on dependent factors, such as the responses Y₁, Y₂, and Y₃. To determine the effect on response variables, response surface plots were also created.

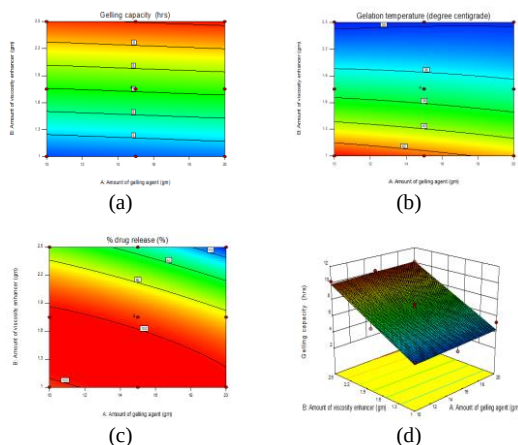
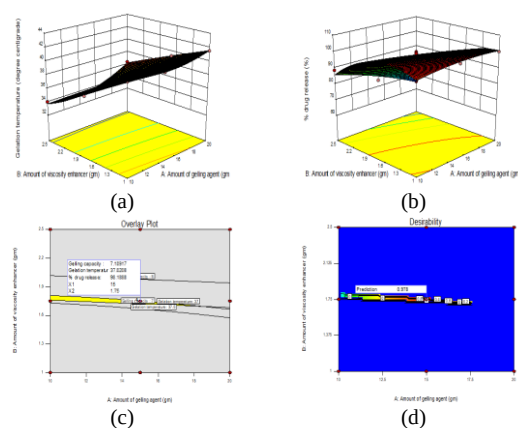
The independent factors X₁ and X₂ have a cumulative effect on Y₁ answers. The independent component X₁ has an additive influence on Y₂ responses, while X₂ has an antagonistic effect. The independent factors X₁ and X₂ have an antagonistic effect on Y₃ responses. These findings imply that the amount of gelling agent and viscosity enhancer used has a direct impact on the reaction. Figures 2 and 3 show contour plots and 3D Surface plots, respectively.

Optimization

In this experimental design optimization is done both by numerically and graphically. In numerical optimization the desired character for the response was selected, automatically software will choose the solutions with desired characters and limits. Among different solutions, it also suggests the solution with desirability near to 1. Graphically optimization was done by desirability plot and overlay plot which contains optimal values of independent variables. Higher the desirability the

Table 5. Experimental and predicted results of optimized formula

Response	Predicted value	Observed value	% predicted error
Y ₁	7.109	7.23	1.6
Y ₂	37.02	37	0.054
Y ₃	98.18	98.70	0.526

**Figure 2. (a) Contour plot for gelling capacity (Y₁), (b) Contour plot for gelling temperature (Y₂), (c) Contour plot for cumulative percent drug release (Y₃), (d) Response surface plot for gelling capacity (Y₁)****Figure 3. (a) Response surface plot for gelation temperature (Y₂), (b) Response surface plot for cumulative percent drug release (Y₃), (c) Overlay plot, (d) Desirability plot**

more suitable is the formulation. The desirability plot and overlay plot with optimized formula are shown in Figure 4. The optimal formula contains X₁

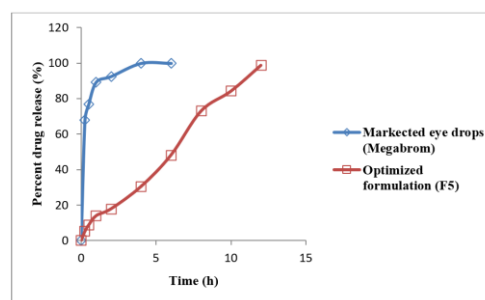
(amount of gelling agent) as 15 gms and X₂ (amount of viscosity enhancer) as 1.75 gms.

Cross-Validation of Model

The model theoretically predicts an optimum formula as shown in the overlay graphic. The optimal formulation used a non-Fickian mechanism with zero order release. The prediction error was measured by comparing the observed responses to the anticipated replies, and it was less than 5.0 percent (Table 5) (Rao and Chowdary, 2015; Ramarao and Chowdary, 2015). Lower relative error levels suggested that the experimental and anticipated values were in close agreement. This established the model's predictability and validity, as well as the impacts of the amount of gelling agent and viscosity enhancer on responses (Durakovic, 2017; Fukuda *et al.*, 2018).

Comparison with Marketed Formulation

The marketed formulation released the whole drug within 6 h but the optimised released the complete drug within 12 h. The results are shown in Figure 4.

**Figure 4. Comparison of cumulative percentage drug release of optimised (F5) with marketed formulation**

Drug-polymer Compatibility Studies (FT-IR)

The results of FTIR spectrum were shown in Figure 5. The 3,500-3,300 cm⁻¹ due to 1° amines Stretching, 600-500 cm⁻¹ due to Br Stretching, 3,000-3,050 cm⁻¹ Aromatic C-H Stretching, 1,650-1,950 cm⁻¹ due to C = O Stretching, based on characteristic peaks observed to conform pure drug structure. None of the changes in the position of the peak were seen when the physical mixture and drug polymer were mixed. In the formulation mixture all the characteristic peaks of drug and polymers are retained showing no significant interaction between them. In the present work bromofenac ocular in-situ gels were prepared by cooling technique and statistically optimized by 3² full factorial designs. The FTIR study shows that, there are no interactions

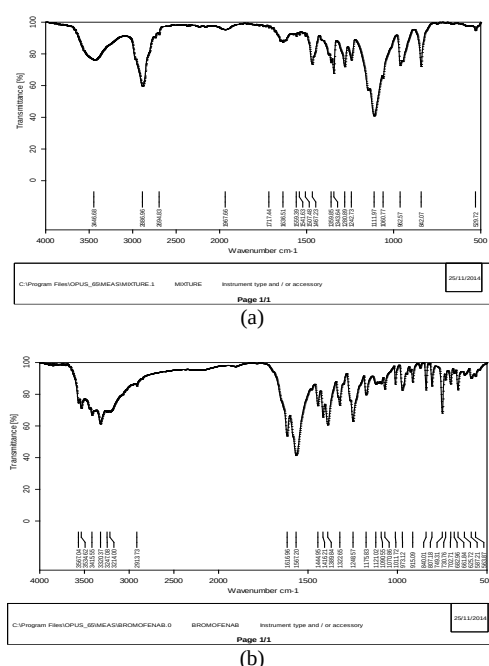


Figure 5. FT-IR spectra of (a) Bromfenac sodium, (b) Physical mixture

between drug and polymer. The gelling capacity of the formulations was found to be between 4-10 h. The formulas were all clear, transparent, and yellow in colour. When compared to the ocular pH of 7.4, the pH of the formulations ranges from 7.01 to 7.34, which is an acceptable range. All of the formulations had a gelation temperature of 37°C-43.5°C, and the drug content ranged from 95.13% to 98.55%. All the formulations follow pseudo plastic behavior (shear thinning systems). A shear thinning ophthalmic system does not cause any inconvenience to the patient. When the amount of gelling agent and viscosity enhancer was increased, the formulations' *in-vitro* drug release was reduced. All the effects of factors and responses of parameters are shown by contour plots and response surface plots. X_1 and X_2 15 g and 1.75 g respectively is optimized from the overlay plot. The optimized formula is cross validated using experimental values and % relative error calculated was less than 5%. This shows the correctness of the values, or the accuracy of the design. Optimized formulation was compared with a marketed formulation and it was found that *in-situ* gel sustained the drug for 12 h and exhibited better release than the marketed formulation which sustained the release is only for 6 h. Optimized formulation followed zero order and non Fickian mechanism. Thus the objective of this research project undertaken was achieved. Twice-a-day formulation of ocular *in-situ* gel of bromfenac

sodium was developed and it could give sustained release for a long time. All the evaluated parameters are suitable to the physiological conditions of the eye. Contribution of this research project: This research project succeeded in developing techniques suitable for the preparation of thermo sensitive ocular *in-situ* gel. It has also helped in establishing factorial experimentation which may be utilized for optimizing the design of a formulation (Srikanth *et al.*, 2012).

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