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"DESIGN, DEVELOPMENT AND CHARACTERIZATION OF NOVEL IN SITU GEL FOR OCULAR DRUG DELIVERY''

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ABSTRACT

In situ gels have been considered as promising drug delivery system for Ketorolac Tromethamine, since they have been shown to sustain the drug release up to 7 hours. The main objective of this study was to prepare and characterize in situ gel of Ketorolac Tromethanine. Gels were prepared using Sodium Alginate as the Ion Sensitive polymer and HPMC K4M, as viscosity Enhancer using the Ion Gelation method. Central composite experimental design was employed for the optimization of the effect of independent variables on the response (Viscosity, and % drug diffusion). Gels were evaluated for clarity, appearance, Gelling Capacity, and their performance in vitro and ex vivo using Franz diffusion cell. According to the findings of this research, an in situ gel of Ketorolac Tromathamine could be considered as a conceivable drug delivery system for treatment of post-surgical swelling.

1. INTRODUCTION

Conventional ophthalmic formulations like solution, suspension, and ointment have many disadvantages such as, high variability in efficiency, blurred vision and increased pre-corneal elimination results into poor bioavailability of drug in the ocular cavity . The bioavailability of ophthalmic drugs is, however, very poor due to efficient protective mechanisms of the eye. The formulation scientist faces a significant challenge in circumventing (bypassing) the protective barriers of the eye without causing permanent tissue damage. Blinking, baseline and reflex lachrymation, and drainage rapidly remove foreign substances, including drugs, from the eye's surface. Tears wash the surface of the eye permanently and have anti-infective properties due to the lysozyme and immunoglobulin's. Finally, the nasolacrimal pathways drain the

lachrymal fluid. All of these protective mechanisms are to blame for the rapid and widespread Precorneal loss of topically applied drugs on eye. The primary objective of diagnostic system strategy is to obtain the optimal concentration of a drug at the binding site for the appropriate duration.

Lacrimal fluids are mixed with the drug during eye drop administration. As a result, the drug's contact time with ocular tissue is extremely short. Half of the drugs are then drained through the upper canaliculus and the other half via the lower canaliculus. The drug penetrates the corneal epithelium via the Trans cellular or Para cellular pathway. Transcellular routes are appropriate for lipophilic drugs, while Para cellular routes are appropriate for hydrophilic drugs. Tran's corneal penetration is hampered due to drug binding to corneal tissues. So because cornea behaves as a drug reservoir, the drug is slowly released into the aqueous humour, accompanied by distribution to intra - ocular tissues as well as eventually elimination via the aqueous humour[16].

Over the last two decades, the researchers have worked to develop a novel approach that can avoid the obstacles subsidized by conventional ocular formulations. Formation of in-situ gel unquestionably most important benefit of this exercise. Early in 1980, the concept of in situ gel was introduced. Because of the viscous gels, it reduces drainage and increases contact time [21]. Cross linking occurs during gelation and can be accomplished through covalent and non-covalent bonding. In-situ gels are introduced into the conjunctival sac as a solution that undergoes phase transition due to changes in temperature, ion concentration, or pH. In response to environmental changes, in-situ hydrogel formation after instillation into a cul-de-sac produces viscoelastic gels [22 The ion sensitive polymer is used in this method. In the presence of ions such as Na++, K+, Ca++, and Mg, ion sensitive polymers may undergo phase change. Ion-sensitive polysaccharides include some polysaccharides. NSAIDs one of the mostly prescribed classes of pain and inflammations medications. They are responsible for about 5-10% of all medications take each year. In the practice setting, the prevalence of N.S.A.I.D. use in patients over the age of 65 is as high as 96 %.

2. MATERIALS AND METHODS

2.1. Drugs and chemicals

Ketorolac Tromethamine was gifted by Aarti Chemicals Mumbai, India. . Dialysis membrane (12,000–14,000 M W.) was purchased from HiMedia Laboratories Pvt. Ltd. Mumbai, India. HPMC K4M was obtained from Loba Chemie Pvt. Ltd, Mumbai, India. All other chemicals and reagents of analytical grade were used.

2.2. Experimental Design

DESIGN EXPERT software has been used for statistical experimental study for optimization as well as detection of effects of independent variable on responses, 32 (3 level 2 factor) surface response methodology independent variables were selected as sodium alginate concentration (X1) and concentration of HPMC K4M (X2), which varied at three levels: low (-1), medium (0), and high (+1). (Y2). Table 1 shows the statistical design for the selected dependent and independent variables:

Table 1: Stastical design for the selected dependent and independent variable

Independent variable	Low level(-1)	Medium level(0)	High level(+1)
X1= Concentration of sodium alginate	0.5	1	1.5
X2= Conc. of HPMC K4M	0.25	0.5	0.75

2.3. Development Of Formulations:

Ion sensitive in situ ocular gel of Ketorolac Tromethamine formulation development

- The polymeric solution was made by dispersing the required amount of sodium alginate as the main polymer as well as HPMC-K4M as the co-polymer in water with a magnetic stirrer until the polymers completely dissolved.
- An aqueous solution of Ketorolac Tromethamine was continuously stirred into polymeric solution.
- Buffering and osmolality agents, as well as benzalkonium chloride, were added to the resulting solution. 0.1 N Na0H/0.1 N HCl was used to adjust the pH of the solution to 7.4[4]

Table 2: Formulation Table of Insitu Gel

Sr. no	Name of Ingredients	F1.	F2.	F3.	F4.	F5.	F6.	F7.	F8.	F9.
1	Ketorolac Tromethamine	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
2	Sodium Alginate.	0.5	0.5	0.5	1.0	1.0	1.0	1.5	1.5	1.5
3	HPMCK_4M	0.25	0.5	0.75	0.25	0.5	0.75	0.25	0.5	0.75
4	Sodium Chloride	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
5	Deionized water q.s.to	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml

2.4 Evaluation Of Gel:

2.4.1Determination of visual appearance and clarity:

sssss

2.4.2. pH Determination:

The formulations evaluated for pH by using digital pH meter, which was pre calibrated using standard pH 4 and 7 buffers

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2.4.3. Determination of gelling capacity:

Based on formulation behaviours such as gelation & erosion time of formed gel owing to environmental changes, gelling capacity was calculated [15].

+- Gelled after few minutes and dissolves rapidly (with in mins),
++- Gelled after few minutes and remains intact for few hours,
+++- Gelled immediately and remains intact for extended period of time

2.4.4. Viscosity of formulation:

The viscosity was measured at 50 rpm using a Brookfield viscometer to spindle number 7. The viscosity of the gel solution was first measured, and then the solution was allowed to gellify by increasing the concentration of sodium alginate in the solution using a water bath. The observation of viscosity before and after Gelling

2.4.5 In vitro drug release studies:

In vitro diffusion study with dialysis membrane: Diffusion studies were carried out using a Franz diffusion cell that was made locally. The dialysis membrane was placed in the space between the donor and receptor compartments. The gel formulation was applied in a homogeneous manner to the membrane and clamped together. The receptor compartment was filled with phosphate buffer saline, pH 7.4, and kept at 37°C by continuous stirring at 50 rpm with a magnetic bead. At predetermined intervals, one milliliter of sample was removed and replaced with an equal volume of buffer. The samples were analyzed using a spectrophotometer after appropriate dilution at a maximum of 296. By plotting the amount of drug permeated versus square time, the release rate was calculated.

2.4.6. Optimization of batch:

The data obtained from gelation temperature, mucoadhesive strength and % CDR were used to find the optimized batch. This optimized batch was further subjected to ex vivo drug release and release kinetics, IR, characterisation.

2.4.7. Fourier Transformation Infrared Spectroscopy (FTIR):

The structural features of pure drug and optimized formula were estimated by FTIR. The spectra were recorded for using Bruker ATR-IR spectrophotometer. The sample is directly placed on clean ATR crystal and hold in probe. The sample were scanned over the range of 4000-450cm-1 [20].

2.4.8. Differential scanning Calorimetry (DSC):

The thermal stability of pure drug and optimized formula were determined by DSC. The DSC thermograms were recorded by using. Differential scanning Calorimeter (Universal V4.5A TA Instrument ((SDT Q600 V20.9 Build 20)). Sample were placed in aluminium pan and heated in the range 0-350 ^{0}C at the rate of 1^{0}C/min. in Nitrogen atmosphere [21].

2.4.9.Ex vivo permeation studies using sheep cornea:

Ex vivo drug permeation testing was performed on the best formulations. A fresh ocular cornea was extracted from the ocular cavity of a sheep obtained from a nearby slaughterhouse. The mucosa was frozen and stored in saline water. It was inserted between the donor and receptor compartments, and the same procedure was carried out.

2.4.10. Drug release kinetics:

Mechanism of release from in situ gel was understood by fitting the diffusion data of optimized formulations in model dependent kinetics. Based on the slope and the regression coefficient values (r^2) obtained from the above models, the mechanism of release was determined.

2. 4.11 Comparison of Optimized Formulation with marketed formulation:

The optimized formulation was compared to the marketed formulation of eye drop ACULAR (0.4 percent) by using the Franz diffusion cell apparatus to introduce drug release. As a media, simulated tear fluid with a pH of 7.4 was used.

2.5 RESULT AND DISCUSSION

Table 1: Appearance, pH, Gelation Temperature, Gelation Time and Gelling Capacity of formulations.

Sr.no	Formulation	Appearance	pH	Gelling capacity
1	F1	Transparent and Clear	6.92	++
2	F2	Transparent and Clear	7.2	++
3	F3	Transparent and Clear	7.1	++
4	F4	Transparent and Clear	7.21	++
5	F5	Transparent and Clear	7.32	++
6	F6	Transparent and Clear	7.13	++
7	F7	Cloudy and opaque	7.3	++
8	F8	Cloudy and opaque	7.2	++
9	F9	Cloudy and opaque	7.21	++

2.5.1. Determination of visual appearance and clarity:

The preparations were visually examined for visual appearance and clarity against a white and black background to check the presence of any Particulates. It was graded as follows: turbid, +; clear, ++; and very clear (glassy), +++.

In F1 to F9 Batches shows clear and transparent solution .Sodium Alginate and HPMCK4M are water soluble polymers and it gives clear solutions they are soluble in water.

2.5.2. Determination pH of gel:

The ophthalmic preparation pH mostly near to the ocular pH i.e.7.4 which does not gave irritation to the eye. The formulation adjusted pH by 0.1NaOH Solution, pH of batches of F1 to F9 shows 6.92 to 7.3

2.5.3. Gelling Capacity:

+- Gelled in a few minutes and dissolves quickly (within minutes),

++- Gelled in a few minutes and remains intact for a few hours,

+++- Immediately gelled and remained intact for an extended period of time.

By visually inspecting a drop of formulation in a vial containing 2 ml of freshly prepared simulated tear fluid, the gelling capacity of the prepared formulation was determined. It was timed to see how long it took for it to gel. Gelation capacity is beneficial in ensuring that the formulation remains intact gel at the specified time. Gelation occurs immediately and lasts for a few hours. (++) Batches F1 to F9 show that the gelation is still present after a few hours. As the concentration of the gelling agent increases It achieves maximum gelation in a matter of hours. The sodium alginate concentration ranges from 0.5 to 1 Percent.

Table 2: Viscosity, Drug content, and %CDR of formulations.

Sr.no	Formulation	Viscosity	Drug content	%CDR After 7 hrs
1	F1	63.63	93.3	64.17
2	F2	110.83	94.5	64.25
3	F3	168.49	92.6	65.56
4	F4	169.45	95.5	66.26
5	F5	172.3	96.2	69.76
6	F6	176.3	96.28	69.60
7	F7	178.6	97.28	70.41
8	F8	182.2	97.28	73.74
9	F9	189.52	97.40	72.13

2.4.5Viscosity determination:

The viscosity measurements were performed with a Brookfield viscometer model LVDV-E model. Viscosity was ascertained by spinning the spindle No. 7 at 50 rpm for 10 minutes before gelling and comparing the viscosity pre and post gelling. F1 to F9 rheological evaluation . In the eye, the formulation exhibited Newtonian flow before gelling and pseudoplastic flow after gelling. Following gelling, the viscosity increased. Furthermore, the gel formed in situ should retain its integrity for an extended period of time without dissolving or eroding. The concentration of HPMC K4M ranges from 0.25 to 0.375 percent. According to statistical data, design model, and ANOVA, both HPMCK4M and Sodium Alginate concentrations increase viscosity [2]

1. **Graph of viscosity before and after Gelation**

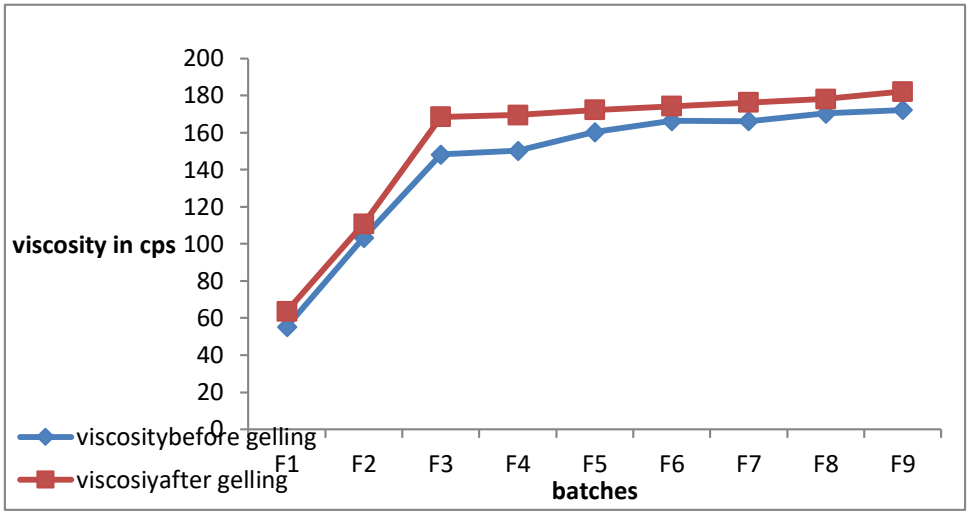


Figure 1: Graph of viscosity before and after Gelation

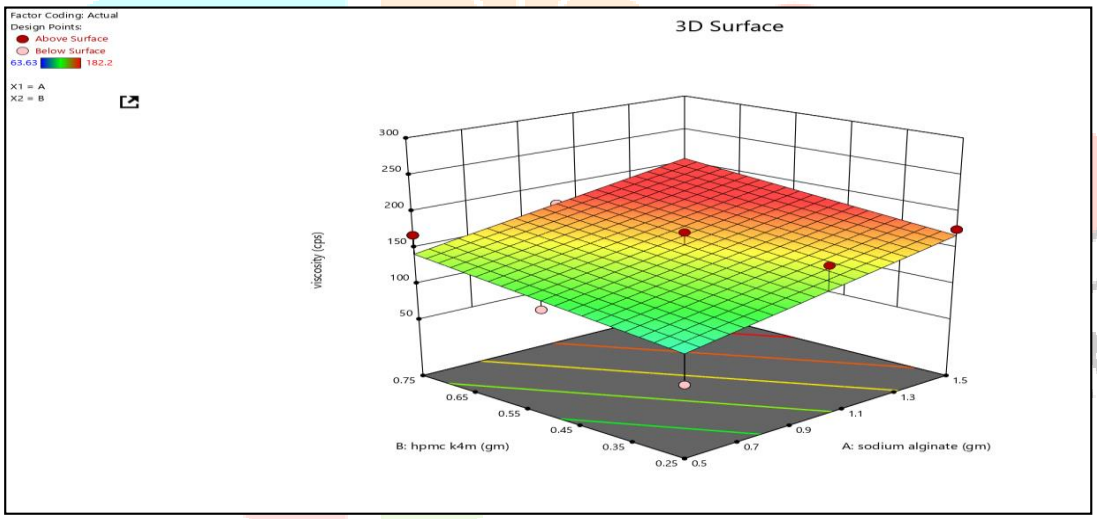


Figure2: 3D Surface Graph of Viscosity

Viscosity Actual = -48.78+166.21*A+18.935*B -25.24AB Equation No. (1)

2.4.6 Drug content:

A spectrophotometer was used to determine the amount of Ketorolac Tromethamine in each batch. The UV absorbance of the sample was measured at a wavelength of 296 nm. It specifies the amount of medication contained in the formulation. The optimum drug content of a given formulation was discovered to be between 93.3 and 97.28 percent in batches F1 to F9.

2.4.7 .In vitro permeation study:

In -vitro drug release study of F 1 to F 9 in situ gel batches were carried out. From above observation it was found that Ketorolac Tromethamine released from the gel by diffusion mechanism. It was also observed that gel shows controlled release activity. Sodium Alginate and HPMC K4M gel was used as a vehicle for Ketorolac Tromethamine, which is provides proper residence time for the drug which adheres to the eye. The percentage drug release after 7 hrs. of gels was (F1-64.17,F2-64.25,F365.56-,F4-66.26, F5-69.76, F6-69.60, F7-70.41, F8-73.74, F9-72.13). When the concentration of HPMCK4M and Sodium Alginate increase i.e.0.25 & 0.75w/w%and0.5&1%w/w respectively with appropriate concentration of Sodium Alginate then there is decrease in release from the formulations. From observations it is concludes , for the ion sensitive in situ ocular gel, HPMC K4M should be in lower range with appropriate conc. of sodium alginate retard as HPMCK4M concentration increases. According to statistical data, design model, and ANOVA, as the concentration of HPMCK4M and Sodium Alginate rises, so does the release.

Sonjoy Mandal et al. discovered that the percentage release of the drug from of the developed formulationsF1(93.86 percent),F2(92.78 percent),F3(89.97 percent),F4(82.80 percent),F5(80.49 percent),andF6(78.71 percent)a shown. This could explain why the developed formulations have higher concentrations of Sodium alginate and HPMC K4M. By observing the drug release profile.as determined by release data. Following the same pattern as described in the literature

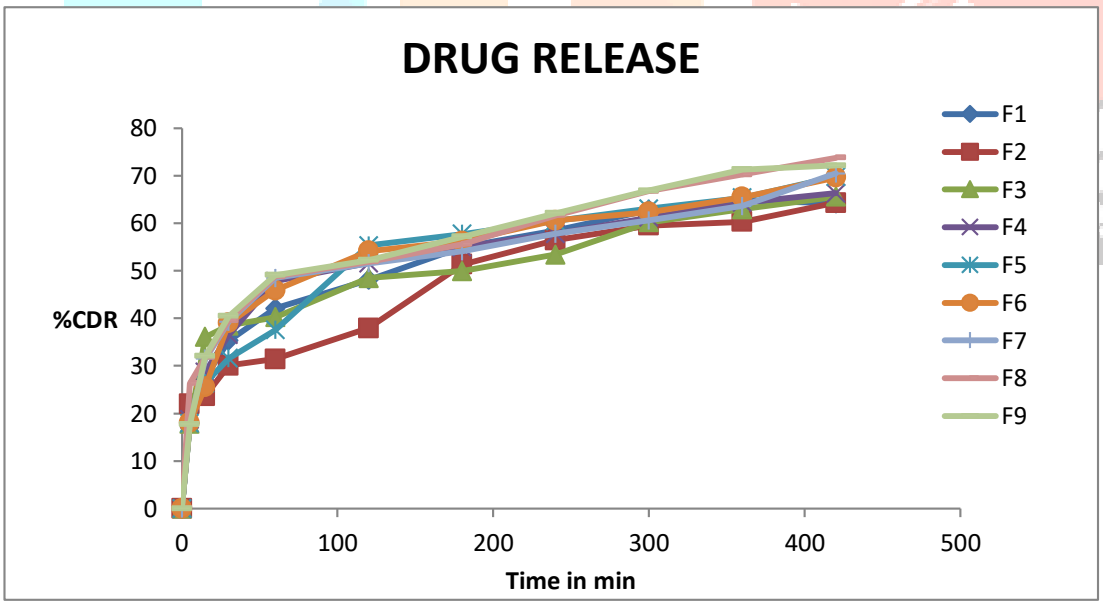


Figure 3: Graph of In -vitro drug release study

Drug release:

Equation:

Actual =58.99 + 7.26667 *A + 4.62 *B …… Equation No.2

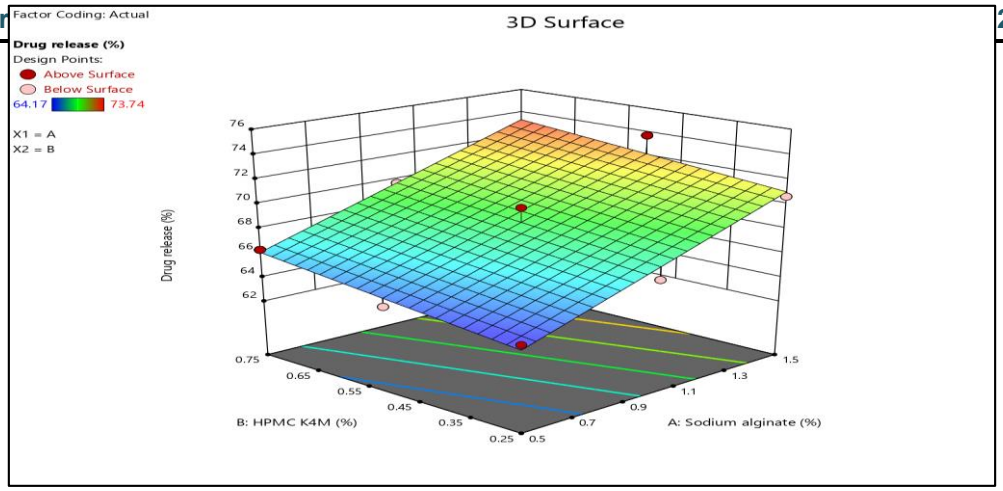


Figure 4: 3D Surface graph of Drug Release

2.5. OPTIMIZATION:

2.5.1. Fit Summary

I. Response 1: Viscosity

Table 6 : Fit Summary

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.0437		0.5302	0.0351	
2FI	0.0569		0.7455	0.3906	Suggested
Quadratic	0.2484		0.8324	0.2365	
Cubic	0.0942		0.9955	0.8985	Aliased

II. Response Drug release

Table 7: Fit Summary

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	0.0004		0.8983	0.8374	Suggested
2FI	0.7897		0.8799	0.7020	
Quadratic	0.5878		0.8596	0.3815	
Cubic	0.3072		0.9602	0.0942	Aliased

2.5.2 ANOVA for 2FI model

I. Response 1: Viscosity

Table 8: ANOVA for 2FI model Viscosity

Factor	Source	Sum of Squares	df	Mean Square	F-value	p-value	
	Model	11085.78	3	3695.26	8.81	0.0193	significant
	A-Sodium alginate	6386.34	1	6386.34	15.23	0.0114	
	B-HPMC K4M	2151.21	1	2151.21	5.13	0.0729	
	AB	2548.23	1	2548.23	6.08	0.0569	
	Residual	2096.41	5	419.28			
	Cor Total	13182.19	8				

coding has been coded.

Type III - Partial sum of squares

The model's F-value of 8.81 indicates that it is significant. An F-value this large could occur due to noise only 1.93 percent of the time. Model terms are significant.

if the P-value is less than 0.0500. A is a significant model term in this case. Values greater than 0.1000 indicate that the model terms are unimportant. Model reduction may improve your model if it contains a large number of insignificant model terms (excluding those required to support hierarchy).

2.5.3. Contour plot:

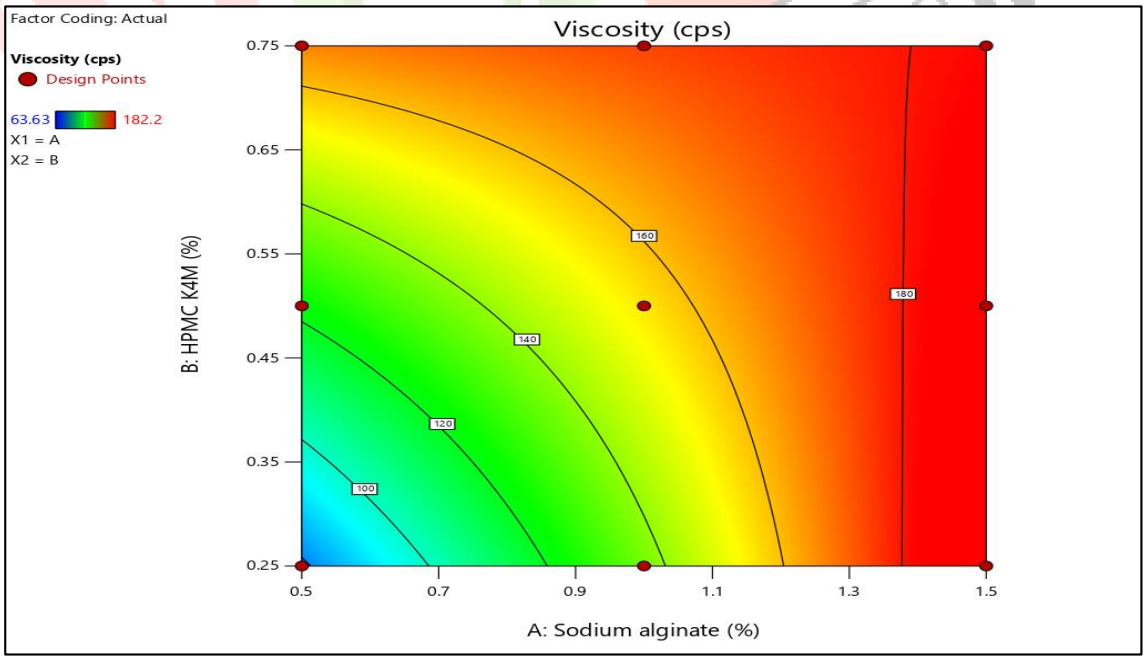


Figure 5: Contour plot of viscosity

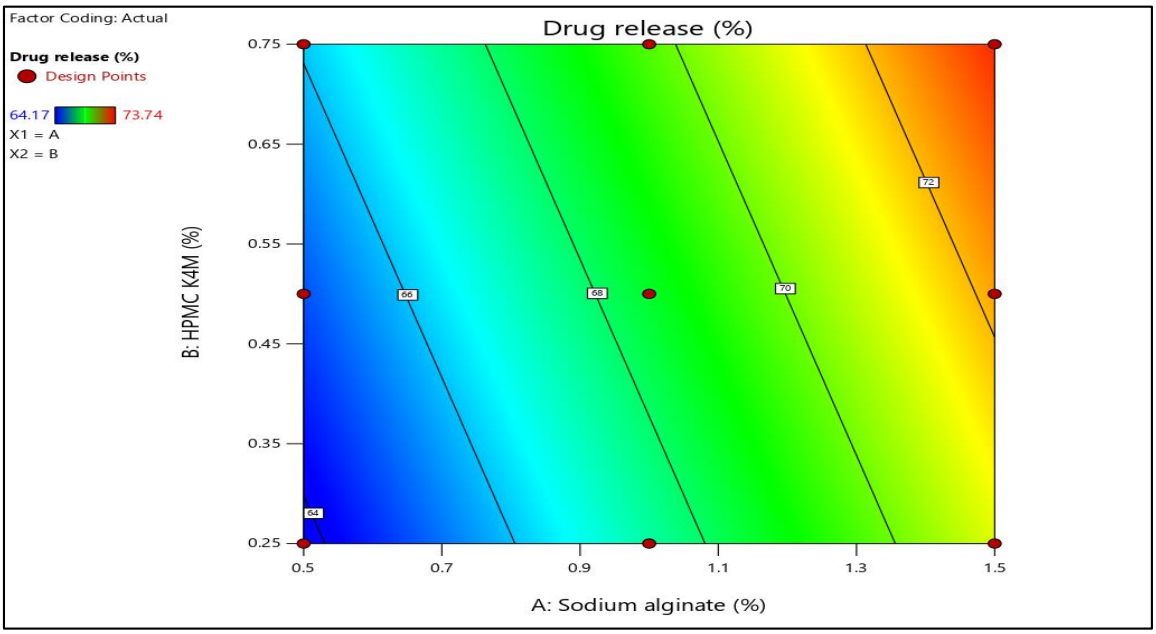


Figure 6: Contour plot of drug release

2.5.4 Optimization:

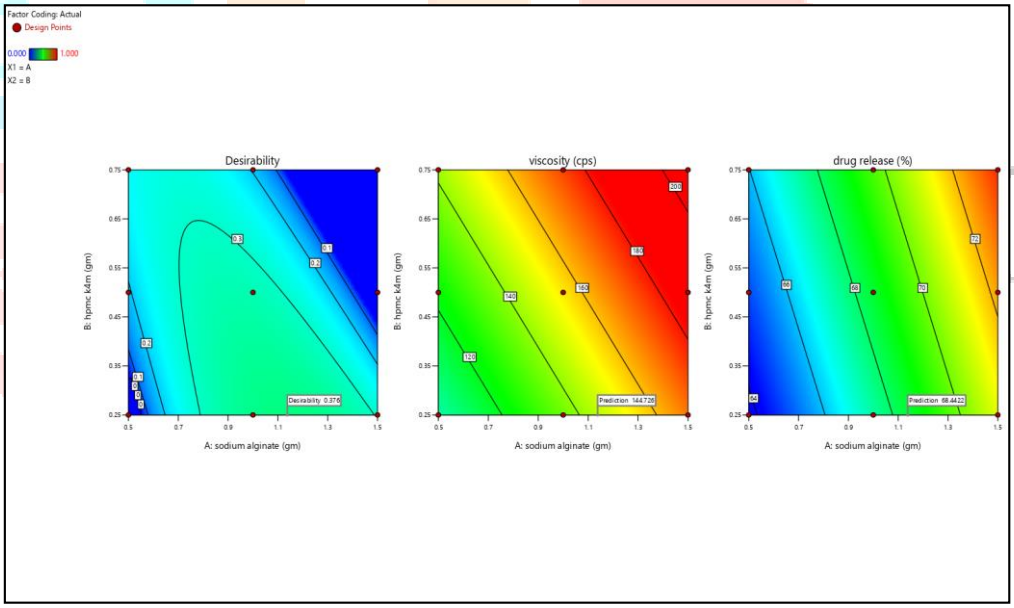


Figure 7: Graph of Design Point

2.5.2 Overlay plot:

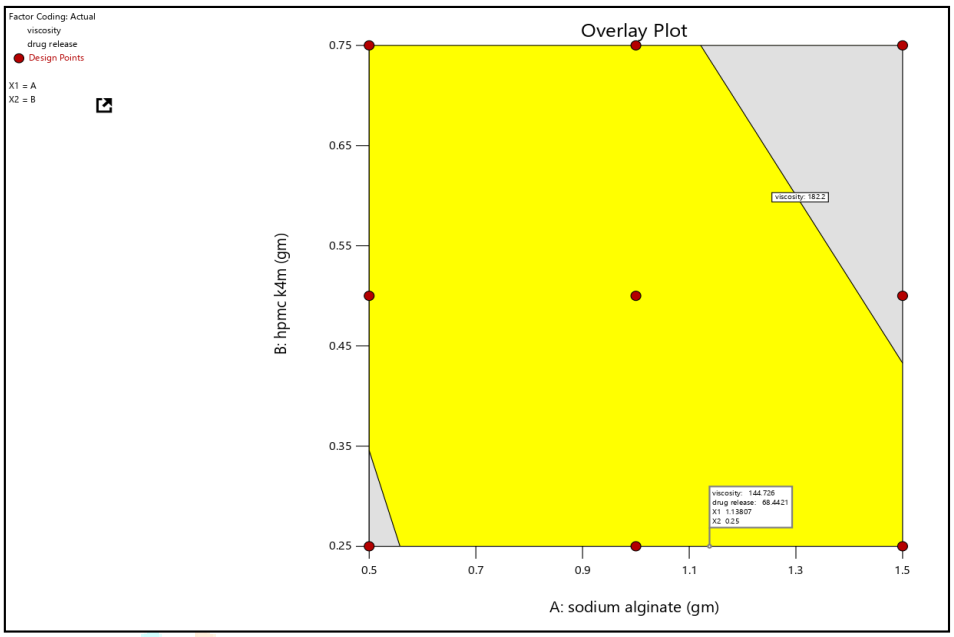


Figure 8: Overlay Plot

2.6. Characterization of optimized formulation:

2.6.1 Solutions:

Table 9: Solutions for characterization of optimized formulation

Number	sodium alginate	HPMC K4M	Viscosity Cps	Drug release%	Desirability	
1	1.138	0.250	144.726	68.442	0.376	Selected

2.6.2 FTIR STUDY

FTIR was used to estimate the structural features of both the pure drug and the optimised formula. The spectra were captured with a Bruker ATR-IR spectrophotometer. The sample is placed directly on a clean ATR crystal and held in the probe. The sample was scanned in the 4000-450cm-1 range.

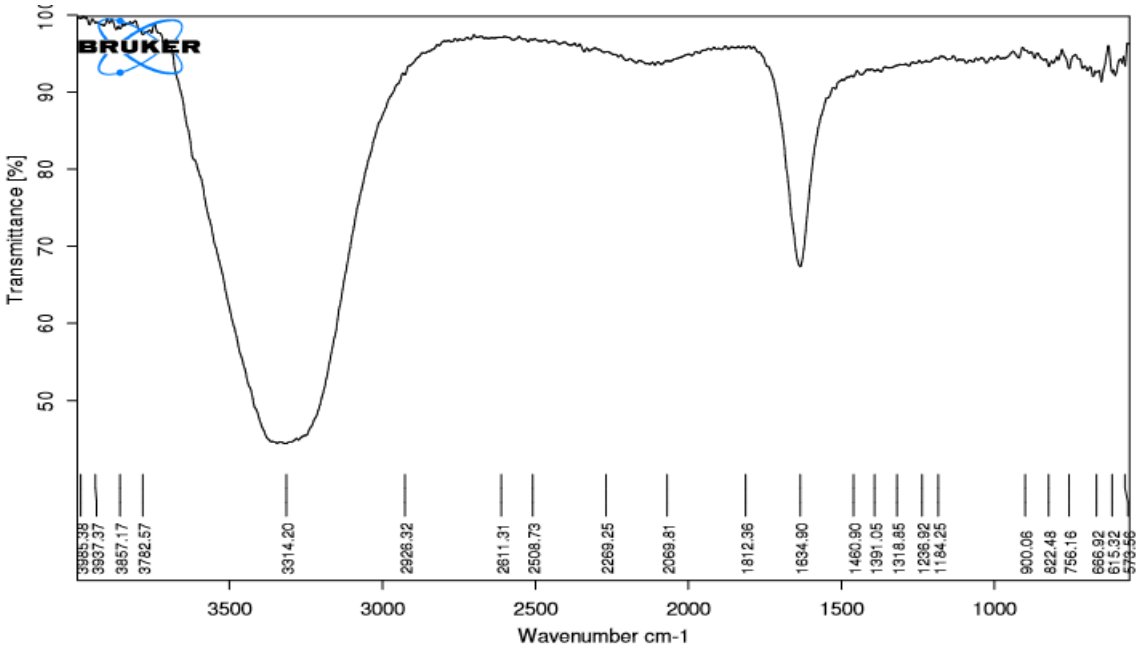


Figure 9: FTIR Spectra of Optimized Formulation

Table 10: FTIR Spectra of Optimized Formulation

Sr.No	Groups	Functional Group	Wave number cm-1
1	C= C Streching	Tri-substituted alkene	1634
2	N- H Streching	Amine	3314

2.6.3. DSC Study

DSC was used to analyze the heat stability of both the pure drug and the optimized formula. The DSC thermograms were captured using. Calorimeter with differential scanning (Universal V4.5A TA Instrument ((SDT Q600 V20.9 Build 20)). 4.09mg of sample were placed in an aluminium pan and heated in a nitrogen atmosphere at a rate of 10C/min in the range 0-3500Cat.

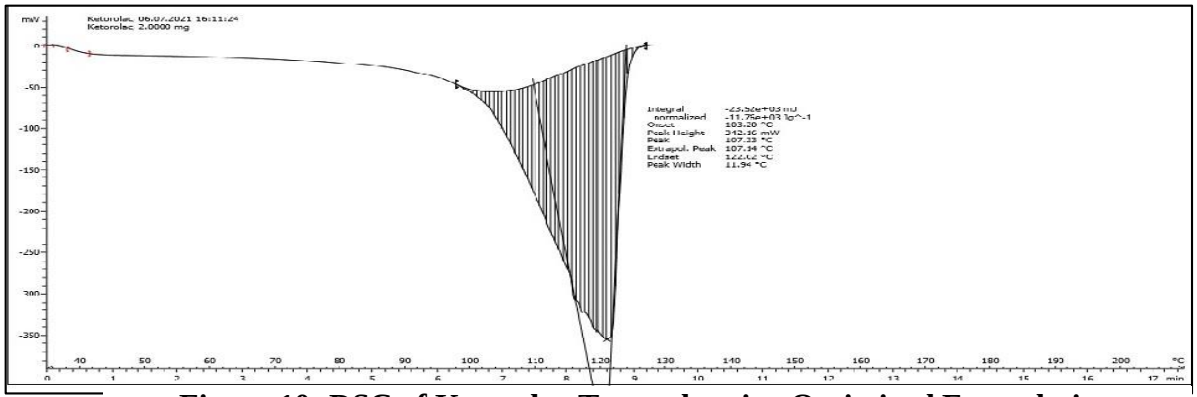


Figure 10: DSC of Ketorolac Tromethamine Optimized Formulation

Discussion:

It is a thermal analysis device that measures how the physical properties of a sample change over time and at different temperatures. In other words, the device is a thermal analysis device that calculates the temperature and heat flow associated with material transitions as a function of time and temperature.

2.6.4. OTHER STUDY:

Table11: Other Studies of optimized formulation

Tests	Results
clarity	++
Gelling capacity	++
PH	7.3
Drug Content	97.3

2.6.5. Viscosity study:

Table 12: Viscosity study of optimized formulation

Viscosity before gelling Cps	Viscosity after gelling Cps
148	164.72

2.6.6. In vitro drug release:

Table 13: In-Vitro drug Release of Optimized Batch

Time (min)	0	5	15	30	60	120	180	240	300	360	420
%CDR	0	17.9	26.36	31.56	37.52	55.32	57.71	60.47	63.02	65.36	68

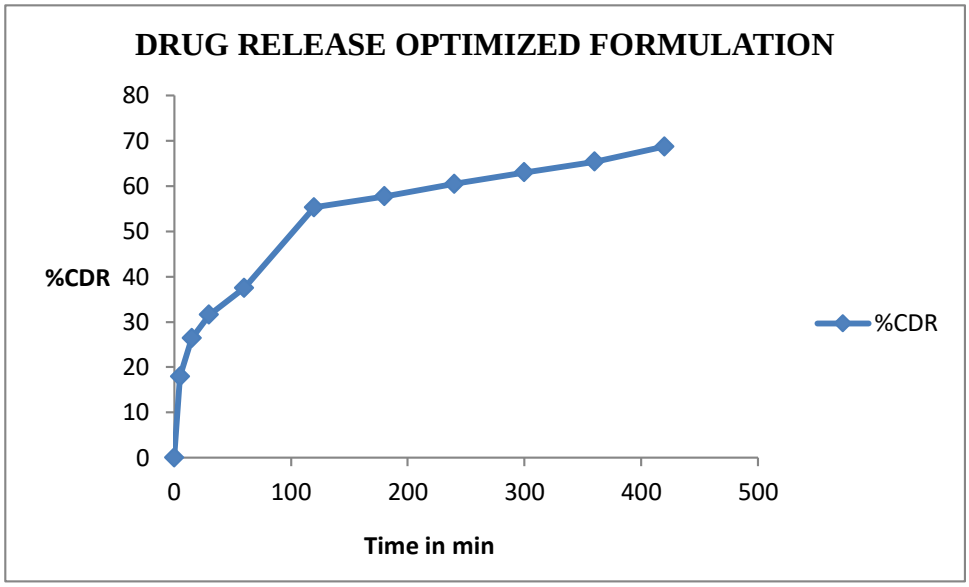


Figure11: Drug Release of Optimized Formulation

The optimized formulation shows 68% release at 7 hrs. This gives sustain release pattern.

2.6.7. Release kinetic parameter:

Table14: Release kinetic parameter

Sr.NO	Release Kinetic Model	Correlation coefficient
1	Zero Order	**0.7477**
2	First Order	**0.8654**
3	Hixson Crowell	**0.8289**
4	Higuchi plot	**0.9363**
5	Korsmeyer-Peppas Model	**0.9947**

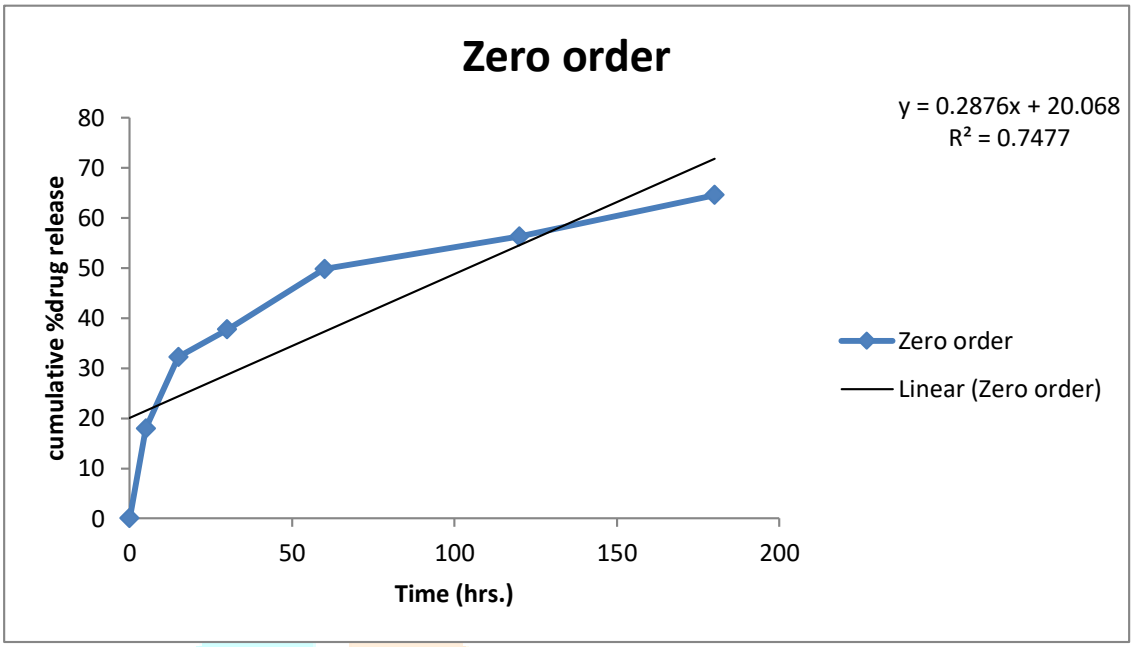
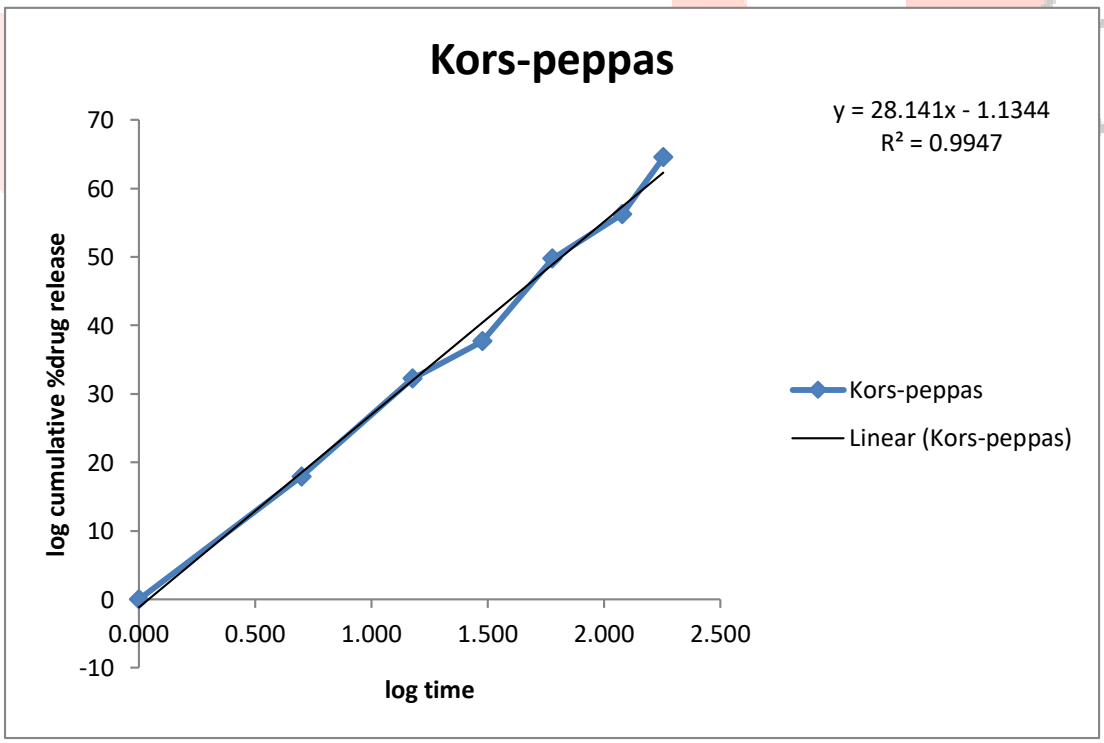


Figure12: Graph of Zero Model of Optimized Batch

Figure 13: Graph of kors-peppas Model of Optimized Batch



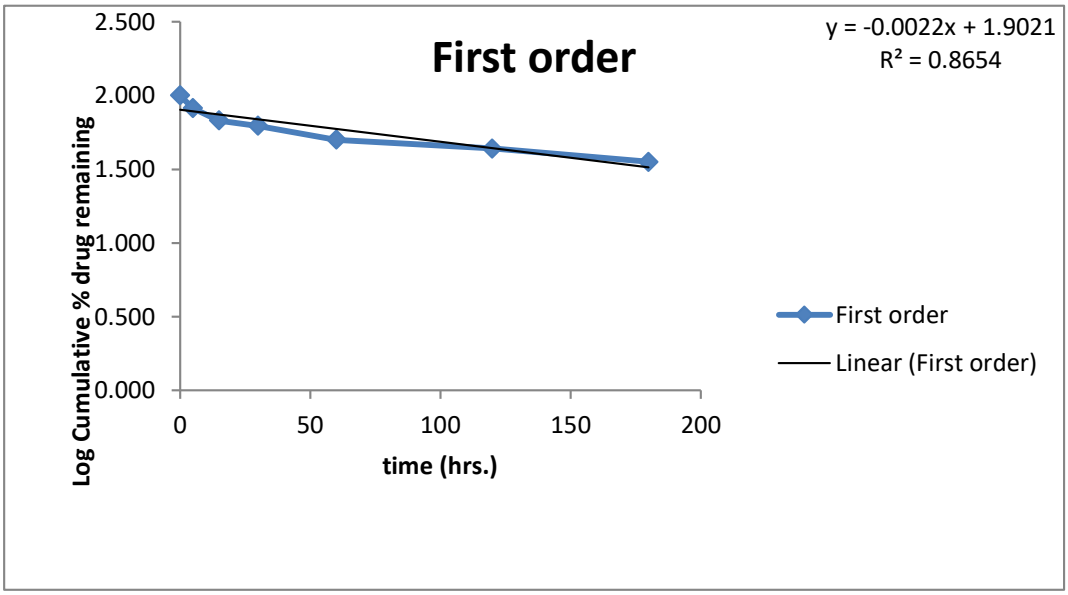


Figure14: Graph of First Model of Optimized Batch

The in-vitro drug release data of the final optimized batch was fitted into different kinetic models to determine the mechanism of drug release. The model that best fits the release data was evaluated by correlation coefficient (r2). The results obtained are shown in Table no.28.The optimized batch shows korsmeyer peppas model of release.

2.6.8. Ex-Vivo study:

Ex vivo release studies were performed on the formulations. The dissolution medium for these ex vivo release studies was simulated tear fluid (STF) with a pH of 7.4. Before beginning the release study, the goat cornea is dipped in STF[3].

Table15: Ex-Vivo study of optimized formulation

Time	%CDR
0	0
5	19.41176
15.	21.36471
30	23.95294
60	24.55294
120	26.55294
180	28.53882
240	36.56706
300	43.87765
360	47.54824
420	59.01176

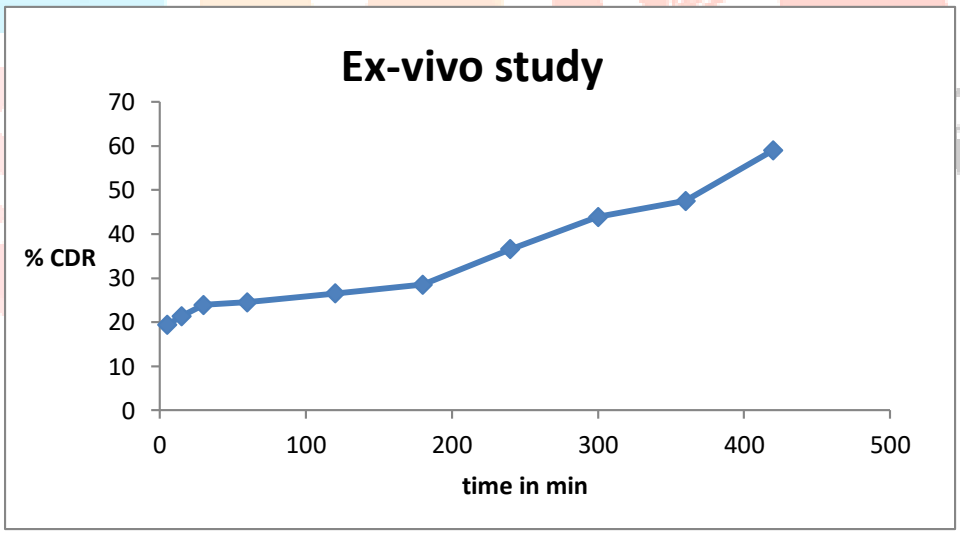


Figure 13: Graph of Ex- vivo study.

Discussion:

Ex vivo release studies were performed on the formulations. The dissolution medium for these ex vivo release studies was simulated tear fluid (STF) with a pH of 7.4. Ex vivo drug release data for formulas was obtained as follows. The plot of percent drug released as a function of time for formulation revealed that the formulation had a percent drug release after 7 hours. . Ex vivo drug release conditions may differ significantly from those encountered in the eye. The results, on the other hand, clearly show that the gels have the ability to sustain release, 7.5-10l is the normal resident volume of lachrymal fluid in the human eye. Sadhana R Shahi and colleagues The corneal goat membrane demonstrated slow drug release of Olopatadine HCl containing Sodium Alginate for up to 10 hours [3].

2.6.9. Comparison with marketed formulation

Table 16: Comparison with marketed formulation

	MARKETED FORMULATION	OPTIMIZED FORMULATION
Time	%CDR	%CDR
0	0	0
5	19.41176	17.94118
15	28.30588	32.24706
30	42.21176	37.68471
60	51.10588	49.76
120	61.32235	56.26118
180	80.48094	64.53647
240		64.74
300		66.32
360		67.3
420		68

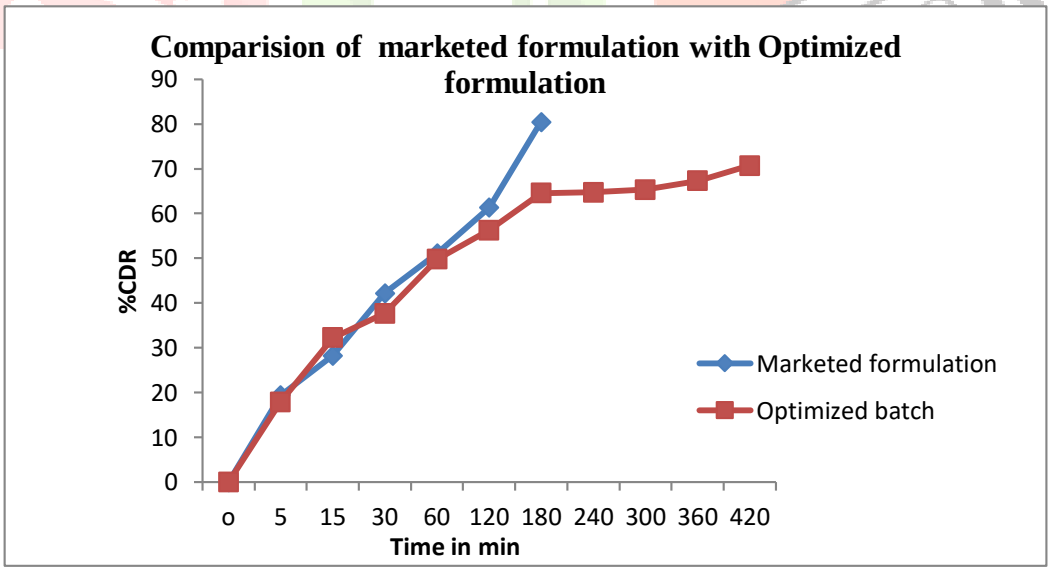


Figure15: Comparison of Optimized Formulation with marketed formulation.

Discussion:

In-vitro release studies were conducted using in-situ gels of optimized formulations and marketed products ACULAR (0.4 percent) of eye drops. The in-vitro release study was carried out using a modified dissolution testing apparatus. The release test was carried out with 100 ml of pH 7.4 buffer (simulated artificial tear fluid). At 3 hours, the ACULAR (0.4 percent) shows an 80 percent release. However, the Optimized Batch shows a 68 percent release after 7 hours.

When compared to the marketed formulation (ACULAR (0.4 percent), the optimized formulation has a longer duration of release.

Sonjoy Mandal et al. found that when the optimized formulation was compared to the Miliflox marketed formulation eye drops, the maximum release occurred after a few hours. However, the release of optimized batch demonstrates susustain release[2].

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