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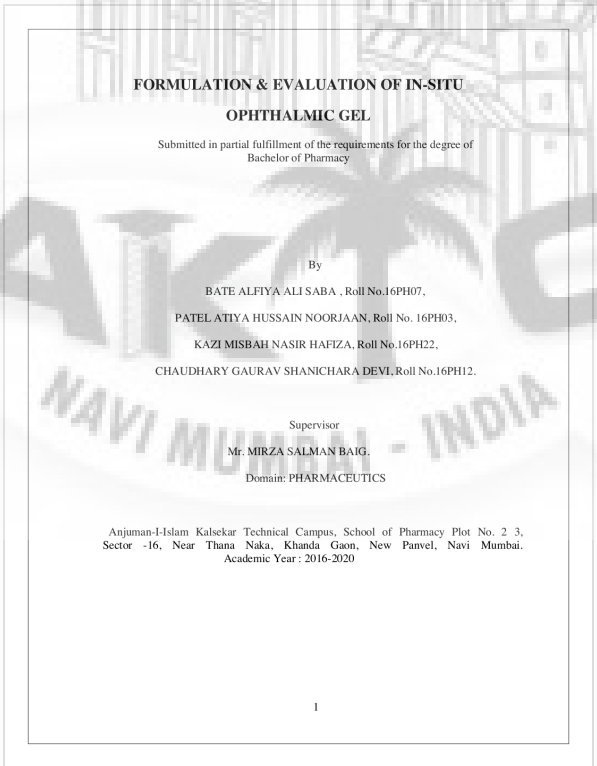

FORMULATION & EVALUATION OF IN-SITU

OPHTHALMIC GEL

Submitted in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy

By

BATE ALFIYA ALI SABA , Roll No.16PH07,

PATEL ATIYA HUSSAIN NOORJAAN, Roll No. 16PH03,

KAZI MISBAH NASIR HAFIZA, Roll No.16PH22,

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1

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Academic Year : 2016-2020

CERTIFICATE

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(Pharmaceutics domain)

This is to certify that the project entitled "**FORMULATION AND EVALUATION OF IN-SITU OPHTHALMIC GEL**" is a bonafide work of **BATE ALFIYA ALI SABA (Roll No.:16PH07)** submitted for the appreciation of the degree of Bachelor of Pharmacy in Pharmaceutics domain.

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Approval for Bachelor of Pharmacy

This project entitled "FORMULATION & EVALUATION OF IN-SITU OPHTHALMIC GEL" by BATE ALFIYA ALI SABA is approved for the degree of Bachelor of Pharmacy in Pharmaceutics domain

Examiners

1. .....

2. .....

Supervisors

1. .....

2. .....

DECLARATION

I state that this written submission reflects my ideas in my own terms, and where certain ideas or terms have been included; the original references have been properly cited and referenced. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand any type of viol.

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I would also like to extend my sincere thanks to all the faculty and non-teachers and friends for their cooperation.

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ABSTRACT

The delivery of drug to eye suffer major challenges like less absorption & bioavailability because of drainage of the drug solution from the ocular tissue etc. In this study in-situ gel was developed to overcome this problem. In-situ gel which is considered to be in the form of a solution at room temperature which then gets transformed into a gel when it is inserted in the eye by the effect of the physiological conditions like ionic strength, pH & the temperature. In present study the gelling property due to body temperature was exploited. Various concentration of poloxamer 188 and poloxamer 407 mixture were prepared and evaluated. Its effect on gelling temperature was studied. Gelling at body temperature was observed for a few formulations. Further, effect of ratio of poloxamer 188 and poloxamer 407 was studied on gelling temperature. Evaluation for the viscosity, pH, and clarity was performed for optimum formulation. In situ gel is promising ophthalmic drug delivery dosage form.

LIST OF TABLES

LIST OF FIGURES

CONTENTS

1- INTRODUCTION

Eye is the most sensitive yet the most complex part of the human body. It is basically divided into 2 halves the anterior and the posterior part. The prominent disease conditions of the eye like glaucoma, conjunctivitis & cataract affect the anterior section of the eye, whereas disease like diabetic-retinopathy known to affect the posterior segment.[1] Ocular tissue restrict the entry of drug molecules at site of action [1] for conventional ophthalmic delivery[2].

Ophthalmic dosage forms have turned out to be of the utmost importance and ones that are extensively and broadly evolved areas in the front edge of the industry for a long period now. Eye being most indisputably approachable area for the topical instillation of medicine. Ideally drug delivery should be sustained for ophthalmic medicine. It should release and maintain the contact to the anterior section of eyes through long time. Thus, this remains the reason for scientists to be interested in this dosage form.

The primarily reason for the development of this drug form is to increase the bioavailability and reduce the frequency of application. It is often to associated with the need to treat ophthalmic disease. In order to achieve this newer drug form have been developed, like so called in situ gel.

Topical ophthalmic drug form:

1. **Liquid ophthalmic drug forms:**

   Eye drops can be emulsion, solution, or suspension

2. **Semi solid ophthalmic drug forms:**

   Eye ointment: After applying to the eye they decompose to smaller droplets and have few disadvantages like they cause blurring vision and irritating effect.

One of the key drawbacks in the delivery of ocular drugs is to achieve & maintain optimum concentration of drug at the target site of action [1]. Several conventional ophthalmic dosage forms were investigated to increase residence time of drugs in eye following topical innstillation[1].

The residence time has been increased at cornea with those formulations.[1] However, they were not fully embraced due to blurred vision problem after applying ointments.[1]

Designing a new approach to delivering safely eye drugs requires innovative strategies [1] Developed to enhance eye delivery system. Over the past few years, the ophthalmic in-situ gel has been exploited to solve the problem.[1]

1.1 IN-SITU GEL[1]

In-situ means on spot. In such system exist in the form of the solution before administration in the body[3] but after administration, it convert to in-situ gel, because of stimulus like pH temperature etc. Then drug-release occur slowly [4].

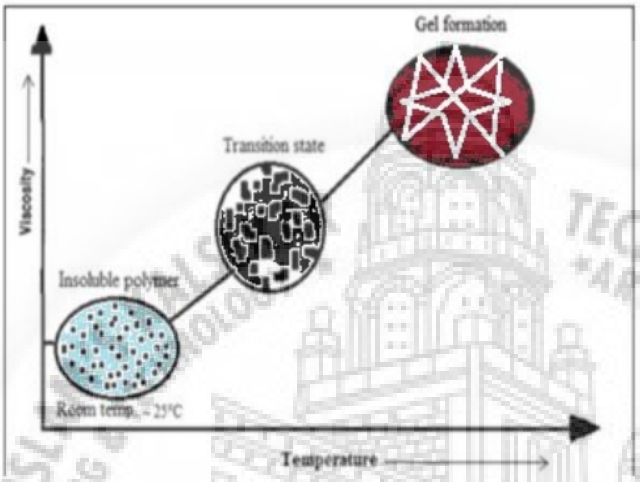

Figure 1. Effect of temperature on viscosity of gel

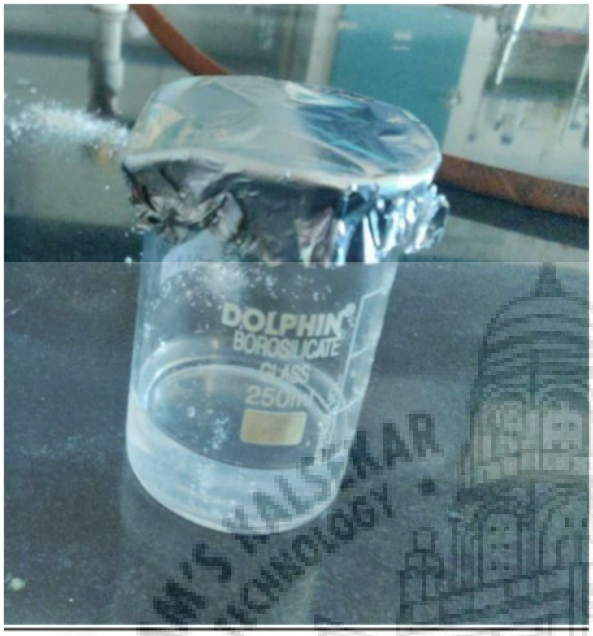

Figure 2. In-situ gel at room temperature.

Figure 3. in situ gel at body temperature.

1.2 ADVANTAGES OF IN-SITU FORMING GEL

The advantage of in-situ gel is that, it don't need frequent instillation of drug as the release of drug is prolonged.

- Compared with ointment it causes less blurred vision.
- High bioavailability because of high precorneal time of residence and low naso-lachrymal drainage.
- It is more secure than injection which is insoluble or soluble.

1.3 MECHANISM OF ACTION OF IN-SITU FORMING GELS:

1.Temperature directed in-situ gel

Polymeric solution remain liquid sol at room temperature (upto 30 degress celsius) but formation of gel occur at physiological body temperature (30-38 degrees celsius)[3]. The phase-transition temperature must be higher than the room temperature (i.e. 27 degrees celsius) for an optimal temperature induced in situ gelling system.

2. In situ gelling system[3] directed by ph .

Ph directed in-situ gel forming systems are solutions[3] that change into gel phase eg. when exposed to the ph of the lachrymal in the eye.

3. Ion-directed in-situ gelling[1].

Ion-directed in-situ gel forming systems creates a cross-connection with any the cations in the tear fluid (Ca2+,Na2 + etc.) to creates a gel on the eye surface, which results in increased corneal contact[1].

2- LITERATURE REVIEW

1.International Journal of Pharmaceutical (2020): Ocular route of drug administration is a quite common route of administration for eye diseases. A lot of eye solutions are available which assurance of greater uniformity of dosage and bioavailability. But conventional ophthalmic eye drops have one major drawback of short residence.

Therefore to overcome this disadvantage Yidan WEI, Conghao LI, Qiang ZHU, Sitrui MAO (2019)[5] has developed sustained ophthalmic drug delivery from in situ gel system triggered by temperature thermo sensitivity. The study was conducted on two polymers that are polaxamer 407 and methylcellulose and studied two different formulations that are thermo-sensitive. The rheological measurements were performed, resulting in the addition of HPMC in P407 solution and PEG MC solution gels showing adequate gelling temperature.[5] Such were further compared to corneal resin suspension of eye drops and showed higher AUC and MRT.[5]

2. Yanxia Cao a, Wenbin Shen, Yu Qineng Ping, Zhihong Ceng Liangli (Lucy).[6] A pharmaceutical university (China) has developed a 32-degree analysis based on thermo-sensitive polymer polymer (N-isopropylacrylamide) (PNIPAAm) which one is close to the human body surface temperature. They used a combination of the two polymers which demonstrated proper use in developing an effective in situ gel. Compared to other gels, the gel made was effective and CARBOPOL improved bioavailability and showed better properties. Water soluble drugs were used which did not show any cytotoxic reactions. Moreover, this review suggested that use and the ability of the thermo sensitive polymer or hydro gels in the preparation of a gel which showed therapeutic efficacy in several eye diseases such as glaucoma. In addition it showed less cytotoxicity and low risk.tage In-situ gel forming system was used.[6]

3.Hongyi Qi, Wenmen Chen, Chuny[7] formulated an in-situ thermo-sensitive gelling system and a muco adhesive ocular drug delivery system containing puerarin-based on analog poloxamer & carbapol[7]. The combination of this solution has been converted to form gel for a long period of time under physiological condition into ocular mucosal surface. Both studies in vitro and in vivo show an analog of P 407 / P188 and carbapol solution retain drug better than was the case for individual solutions. The mixture of liquid solution at room temperature creates gel power and prevents a rapid removal of the cornea. The combined system can therefore be used as an in situ ophthalmic gel to enhance the bioavailability[7].

4. Yumei Wu, Yuanyuan Liu[1], Xinyue li, Dereje Kebe[1], Bing Zhang,[1] Jin Ren, Jun lun, Jiawei li[1], Shouying Du[1], hindong liu[1] developed an ophthalmic drug delivery system in situ gel as it poses a major challenge to deliver the drug to the anterior and posterior segments due to various protective barriers and eye structure-related removal mechanisms[3]. The study was based on the mechanism of in situ gelling system that is thermo sensitive. The polymers used were poloxamer (pluronic), xyloglucan, chitosan in the development of this formulation.The incorporation of poloxamer along with sodium alginate showed no irritation to the mucosa of the eye[1].

5. Karim A Soliman et al. drug discov today. 2019 aug[4] a study was done in order to study the merits of in situ gel in accordance with its advantages that are easy instillation and

sustain release of drug in the eye[4]. In order to study the thermo sensitive effect the polymer used was poloxamer due to its thermo responsive behavior. Further studies like gelling temperature, drug release profile and mucoadhesive properties were done. It resulted that poloxamer were stable at steam sterilization and biocompatible with corneal tissues. Thus it was concluded that poloxamers 188 and poloxamer 407 can be mixed in different proportions to obtain the appropriate gelling temperature and can be helpful in transferring the drug in all portion of the human eye. Along with this, it was also stated that these two polymers could also be used along with other polymers to give an ease.[4]

6. Ananth Prabhu,Marina Koland[8] developed in situ[4] thermo gelling system of ofloxacin for controlled ocular delivery. From this research their aim is to prolong corneal residence time while controlling drug release.[4] From Poloxamer 407 they prepared in situ tell solution in which a temperature sensitive telling polymer and mucoadhesive polymers like HPMC and PVA .Drug is incorporated gels were prepared and evaluate for their pH, Gelation temperature and in vitro drug release studies[8]. They incorporate the drug in the formulation increased the gelling temperature while the addition of mucoadhesive polymer decreased the gelling temperature. Due to increase the concentration of bioadhesive polymers retarded the release of ofloxacin from Poloxamer solutions and API release was sustained after a period of 9 h. They found PVA has no significant effect on the gelation temperature and could not sustain the drug release for longer durations. From this research they concluded that developed system would be used in treatment of ocular infections with the combined advantage of ease of administration, increased bioavailability and prolonged retention time.[8]

7. Quantum Jiang, ping Zhang, Jing li[9] developed a thermo sensitive in situ forming ophthalmic gel constituted by P407 which includes simple methods for analysis and evaluation of P407 gel. In which result was poorly water soluble API improve the intensity of P407 and reduce solution dynamic rate and hence gelation temperature reduces while enhancing the corneal adhesion[9]. If HPMC is added it will strengths the gel because HPMC and P407 formed strong interactions in between.[9] All of these results give rise to instructions for developing and evaluating thermo sensitive in situ forming ophthalmic gel.[9]

8. Anuja T. Kadam[10], Rahul L[10]. Jadhav[10], Pradnya B. Salunke[10], [10]Satwashila S. Kadam[10].There is this Modified chitosan based moxifloxacin-HCl which was developed by using cold method. The polymer used is polaxomer 407 which is added in DW(distilled water) and the solution is kept for cooling. moxifloxacin-HCl and modified chitosan was prepared distintly in distilled water which was then added to the polymeric solution and continuously stirred. This Prepared formulation was tested for its drug content, rheological study, gelling capacity, in vitro drug release ,the content of phase change temperature ,release kinetics, antibacterial studies and statistical analysis was carried out[10]. This formulation of in situ gelling had the ideal combination of the polymer and modified chitosan as they were suitable appreciably and sustained the drug release in situ gel. This formulation of moxifloxacin- HCl comes out to be ideal drug delivery for the bacterial infections of the eye.[10]

10. Manas Bhowmika, Puja Kumari a, Gunjan Sarkar b,[11] Mrinal Kanti Bainb,[11] Biplab Bhowmick b,[11] Md. Masud Rahaman Mollick b,[11] Dibyendu Mondal b,[11] Dipanwita Maity b,[11]

Dipak Ranac,Debashis Bhattacharjee d,[11] Dipankar Chattopadhyay b[11] developed a novel formulation of in situ gel which is based upon poloxamer 407 (P407) for sustain reales ocular drug. For decreasing the P407 concentration without any compromise in gel capacity as well as enhancing the release time of drug guar gum and xanthan gum are added in the P407 solution for developing many formulations. When the concentration is 18% /above P407 forms gel and undergoes solution gel transition under body temperature.

If the xanthan gum and guar gum taken in a ratio of 3:7 in weight they convert the P407solution to solution under the body temperature at P407 concentration under 18%.[11] In vitro and in vivo studies shows that P407 with guar gum and xanthan gum when taken in combination they have greater ability to keep drug that than P407 alone[11].

Results suggested that the in situ gel formulation which contain P407 with xanthan gum and guar gum superior alternative drug than that of conventional ophthalmic drops[11].

11. Verma S et al [12] developed a new system which is in situ gel forming system. They developed formulation which undergoes phase transition in the eye to form gel result in improved visual bioavailability due to prolonging the precorneal contact time[13] . The work comprises of polymer or mixture of polymers which result in Solution gel transition due to physicochemical parameters i.e. temperature, ion exchange and pH of the body [13].

3 – AIM, OBJECTIVE AND PLAN OF WORK

Aim:

The research aimed at formulating, developing, and optimizing in situ gelling systems.

Objective:

• To investigate the gelation effects of polymer 188 and polymer 407, depending on the thermo-sensitive property. The effect of total polymer concentration on gelation properties to be investigated also to study the effect of polymer ratios on gelation.

• To test the viscosity of the two-polymer mixture.

• To examine whether the pH of the formulation is eye-fitting.

• To study the difference in formulation clarity

Plan of work:

- Selection of ingredients: Polymer selection was carried out based on literature survey. Two polymers P188 and P407 were selected
- Various gel formulations (A to H) were prepared, of variable polymer concentration but same ratio of both the polymers
- The formulations were evaluated for its gelling temperature
- Optimum formulation (H) was selected based on gelling at body temperature
- Various formulations prepared by changing ratio of polymers (P188 and P407) in optimum formulation
- Optimum formulation (H3) was selected for further analysis
- Viscosity, pH, and clarity testing was performed for H3 formulation

4- MATERIALS

4.1 REQUIREMENTS:

Apparatus: Magnetic stirrer, magnetic beads, beaker, vial, thermometer, viscometer (fungilab), tripod stand, burner, water bath.

Materials: Polaxamer (P407 and P188) provided by Glenmark Pharmaceuticals Limited.

4.3 POLYMER PROFILE[1]

A. *Poloxamer 188*[14]

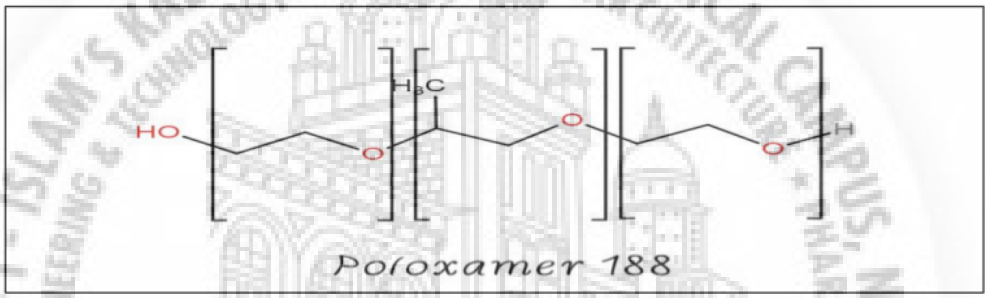

Figure 4 Structure of poloxamer 188.

- **Molecular formula**- $C_8H_8O_3$ [15]
- **Molecular weight** : 162.23gmol^{-1} [15]
- **Appearance** : waxy powder, almost white or white[15]
- **Melting point**:- 52-57 degrees Celsius[15]
- **Description**- poloxamer 188 (P188) is a non-ionic block linear copolymer that exhibit rheological, anti-thrombotic, anti-inflammatory activities [14]. P188 is a polymer which qualifies and enhance great variety of functional application. Composed of two hydrophilic side chain attached to a hydrophobic center core its average molecular weight is 8400 Dalton[14]. P188 could be enhanced absorption, solubility and bioavailability of poorly soluble formulation[14]. P188 serve in form of plasticizing agent a solubilizer and emulsifying supporter both in liquid and solid dispersion[14].

• **Incompatibility**: Depending on the relative concentration example: poloxamer 188 is unsuitable with parabens and phenols.

B. Poloxamer 407 [14]

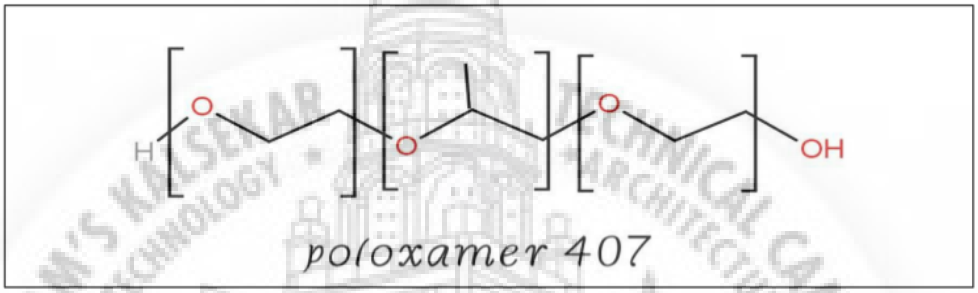

Figure 5 structure of poloxamer 407.

• **Molecular formula** : $C_5H_{10}O_2$[16]

• **Molecular weight** : 102.13g/mol[16]

• **Appearance** : waxy powder, almost white or white[16]

• **Melting point**- 52-57 degrees Celsius[16].

• **Description**- Poloxamer 407 (P407) is a hydrophilic nonionic surfactant of a additional common category of copolymer called as poloxamer.[14] P407, structurally it is triblock copolymer which contain hydrophobic block of polypropylene glycol in the center which is bound to two polyethylene glycol of hydrophilic block[14]P407 formulation give rise to increase in the solubility of API those are not soluble in water and it will prolonged the release form for numerous galvanic application for example - oral, topical, nasal, rectal, ophthalmic, injectable preparation etc but when it is use alone it did not show clearly any appropriate advantage[14]. When the other excipients are combined with poloxamer 407 such as mucoadhesive or Poloxamer 188 polymer advanced the P407 activity by enhancing bioadhesive property or by solution gel transition temperature[14].

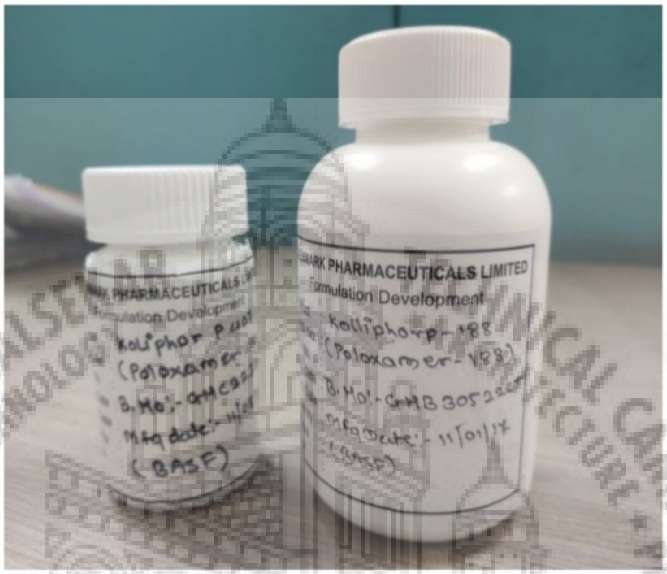

Figure 6 Storage of polymers

5- METHODS

5.1 METHOD OF PREPARATION OF IN-SITU GEL

The polymeric solution was fabricated by scattering required quantity of poloxamer 407 and 188 in distilled water at room temperature i.e. 37°C.

After preparing this solution magnetic bead were added to the vial containing solution and then was kept on the magnetic stirrer. The speed of the magnetic stirrer was set at 200- 250 rpm. The prepared solution was mixed until the poloxamers were completely dispersed i.e. for about 30 to 45 minutes.

After completely dispersing the polymer in the vial it was kept for 24 hours for hydration and then used for the further evaluation. To recognize the constitution which is acceptable for the in situ gel forming system, different concentrations and ratios of both the poloxamer were prepared then it was used for the further evaluation.

Figure 7. Preparation of In-situ gel.

5.2 GELLING CAPACITY:

APPARATUS: Test tube, vials, water bath, thermometer, stirrer.

PROCEDURE: 1mlof prepared gel was inserted in water bath was gradually increased to physiological temperature from room temperature.

The temperature at beginning was recorded and after each 2 degrees Celsius the vials were tilted at an angle of 90 degrees.

The formulation in the vials where visually evaluated and the gelling capacity was recorded at 37 degrees Celsius.

5.3 VISCOSITY TEST:

Brookfield viscometer was used to calculate the viscosity of the formulations. The prepared in situ gel sample was put in the test tube and analyzed at room temperature (37 degrees C physiological temperature).

The bar spindles were used in increasing viscosity to estimate the viscosity of the formulation. The spindles used were in size 1-4.

Measurements were done by varying rotation of spindle from 100-200 rpm.

5.4 pH:

The pH of formulation must be such that the formulation should be steady at the pH and should not irritate the eye at the same time[4].

Range of ophthalmic formulation must be 5-7.

The formulated gels were measured with the use of automated ph meter.

Make: Hanna instruments.

5.5 VISUAL APPEARANCE AND CLARITY

The haziness which occurred after mixing with magnetic stirrer was evaluated in this test. Result was evaluated by standing over night.

6- RESULT AND DISCUSSION

6.1. GELLING TEMPERATURE

Different concentration formulations were prepared as shown in Table 1. The gelling temperature evaluation were performed for various formulations and results are shown in Table 2 and figure 8. Formulation containing 44% w/v polymers found to have good gelling temperature.

Table 1. Composition of the various formulations

SR NO	FORMULATION	TOTAL POLYMER CONCENTRATION (W/V)	RATIO OF POLYMERS
			[poloxamer 188] : [poloxamer 407]
1.	A	16%	1:1
2.	B	20%	1:1
3.	C	24%	1:1
4.	D	28%	1:1
5.	E	32%	1:1
6.	F	36%	1:1
7.	G	40%	1:1
8.	H	44%	1:1

As shown in table 1, various formulations of different concentrations was prepared. Further the gel formation was evaluated at temperature starting from 25 degrees Celsius to 60 degrees Celsius based on the change in the consistency of the formulation. Table 2 shows gelling temperature for various formulations.

Table 2. Gelling temperature of various formulations.

SR NO	FORMULATION	GELLING TEMPERATURE (°C)
1.	A	60
2.	B	57
3.	C	54
4.	D	51
5.	E	48
6.	F	45
7.	G	40
8.	H	38

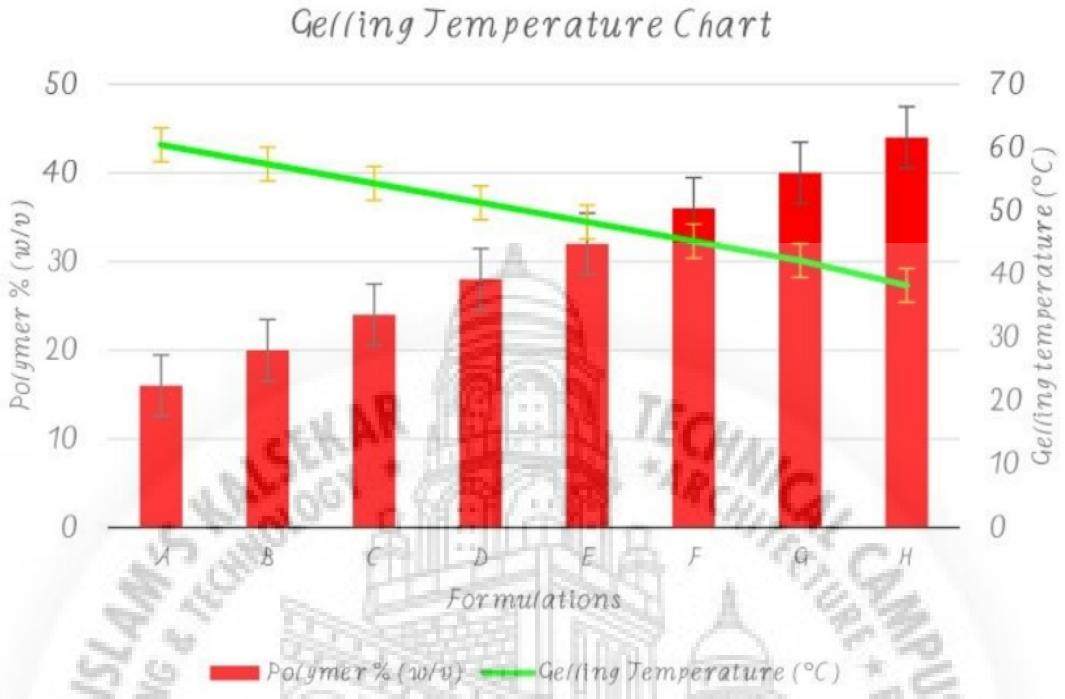

Figure 8. Gelling temperature chart of various formulations

Figure 8 shows the effect of polymer concentration on gelling temperature. Gelling temperature reduces when polymer concentration increases.

Formulation H3 (44%, 1:1) was found to posses optimum gelling temperature i.e. 38 °C which is awfully close to physiological temperature. Hence, formulation H was selected for further investigations. To further validate the appropriate gelling temperature formulation H of different ratios were prepared.

Table 3. Showing composition of various H (44%) formulations bases on ratio of polymers.

SR NO	FORMULATION	TOTAL POLYMER CONCENTRATION (W/V)	RATIO OF POLYMERS
			[poloxamer 188] : [poloxamer 407]
1.	H1	44%	3:1
2.	H2	44%	2:1
3.	H3	44%	1:1
4.	H4	44%	1:2
5.	H5	44%	1:3

According to Table 3 t the formulations H (44%) of various polymer ratios were prepared and investigated to check the optimum ratio for gelling temperature at 38 °C

Table 4. showing the variation in gelling temperature for various ratios of H (44%)

SR NO	FORMULATION	RATIO OF POLYMERS [poloxamer 188] : [poloxamer 407]	GELLING TEMPERATURE (°C)
1.	H1	3:1	48
2.	H2	2:1	44
3.	H3	1:1	38
4.	H4	1:2	32
5.	H5	1:3	27

Based on the investigation formulation H3 (44%, 1:1) was found to be optimum formulation with gelling temperature 38°C as shown in Table 4.

Figure 9. Gel formation of H3

6.2 VISCOSITY TEST

Further, the optimum formulation H3 (44%, 1:1) of in-situ gel was evaluated to obtain accurate viscosity. It was evaluated with the help of Brookfield viscometer by changing the different spindles and speed

Table 5. Shows viscosity of optimum formulation H3 (44%, 1:1) at different speed.

SR NO.	FORMULATION	SPEED(RPM)	SPINDLE	RESULT (cp)
1.	H3	50	L1	29.0
2.	H3	60	L1	29.3
3.	H3	100	L1	29.5

The formulation H3 was observed to show almost constant viscosity at different speed i.e. 29 c.p. Hence, optimum viscosity for absolute flow of gel was obtained. This can help in overcoming the drawbacks of conventional formulations like less contact time.

Figure 10. Brookfield viscometer

6.3. pH TEST:

The determination of pH of the formulation is of utmost importance because it gives us knowledge about the acidity/alkalinity of the solution which should be suitable and safe for the eye because eye is a sensitive organ. The pH obtained for formulation H3 was 7.16 which is compatible with the pH of the eye. Thus, it shall not cause irritation to the ocular tissue.

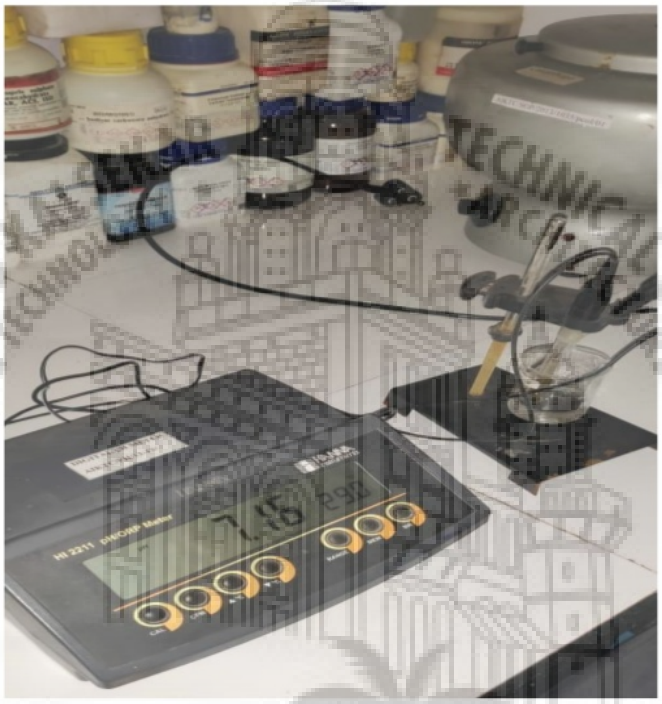

Figure 11 Automated pH meter showing pH of H3.

6.4. CLEARITY TEST

For any formulation to be instilled into the eye it is very important to be contamination free so that, it does not damage the ocular tissue. The formulation H3 (44%, 1:1) was found to be clear. A clear solution was observed after keeping the formulation over night and observed against contrast background.

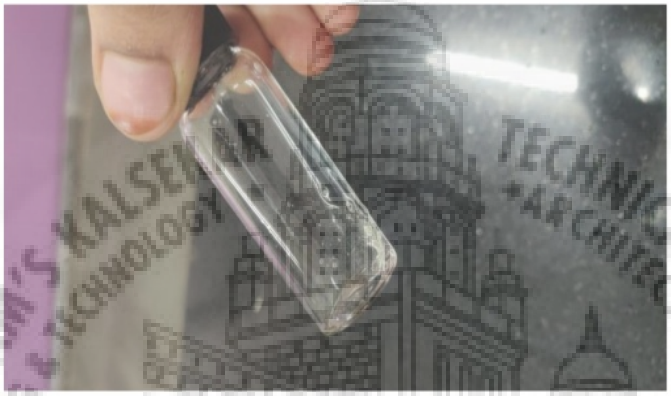

Figure 12 Clear H3 formulation.

7- CONCLUSION

Poloxamer 188 and Poloxamer 407 based ophthalmic formulation was developed. In current investigation it was found that the formulation remains in a liquid state at 25 °C while at the physiological temperature, i.e. 37 °C, the liquid becomes a gel.

The optimum H3 formulation was free flowing at room-temperature but formed gel at the physiological temperature hence it is expected to increase the ophthalmic residence-time and hence bioavailability of the medicine. This is expected to reduce the frequency of application of dosage form.

The pH data ensures that it is sufficient for the continuing release of drugs for legitimate drug treatment for eye-related disorders. It is well known that the combination of two polymers in the same formulation exhibits greater compliance and therapeutic effectiveness.[17]

Poloxomer based in situ gel forming formulations are very well exploited in the market. A lot of work has been done on its effect on the anterior parts of the eye but, the effects on the posterior part remains limited. In future in situ forming gels can be combined along with other technologies to have more effect on the posterior parts.

In current investigation the in situ gels are only formulated without drug but in future it could be formulated with one or more than one API. The ophthalmic in situ gel could be a better alternative to the conventional eye drops.

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APPENDIX

TABLE OF ABBREVIATIONS

SR NO.	ABBREVIATIONS	FULL FORMS
1	P118	POLOXAMER 188
2	P407	POLOXAMER 407
3	API	ACTIVE PHARMACEUTICAL INGRIDIENT
4	AUC	AREA UNDER THE CURVE
5	MRT	MEAN RESIDENCE TIME
6	PVA	POLY (VINYL ALCOHOL)
7	c.p.	CENTIPOISE
8	RPM	ROTATIONS PER MINUTE

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