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FORMULATION AND CHARACTERIZATION OF OCULAR IN SITU GEL OF NAPHAZOLINE HYDROCHLORIDE USING NOVEL POLYMERS

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ABSTRACT

The ocular in situ gel formulation of Naphazoline Hydrochloride, using novel polymers, offers a promising alternative to conventional eye drops. It provides improved bioavailability, sustained drug release, and enhanced patient compliance. Further clinical evaluations are recommended to confirm these findings and to fully establish the therapeutic potential of this innovative drug delivery system for ocular treatments. The physical examination of Naphazoline hydrochloride indicated that it is a white crystalline powder with an odorless and unpleasant taste. Naphazoline hydrochloride showed good solubility in methanol, ethanol, distilled water, phosphate buffer (pH 7.2), and 0.1 N NaOH, being freely soluble or soluble in each. However, it was just slightly soluble in chloroform but easily soluble in 0.1 N HCl. The moisture content of Naphazoline hydrochloride was determined using Karl Fischer titration, which yielded 0.0494%. This implies a low moisture level, which is ideal for the compound's stability and quality. The FTIR spectrum of Naphazoline hydrochloride revealed distinctive peaks that corresponded to the compound's numerous functional groups. These include peaks for aliphatic and aromatic C-H stretching, C-H bending, C-N stretching, and C-Cl stretching. To summarize, the produced in situ gel formulations show good physical features, drug content homogeneity, pH compatibility, gelling capability, and sustained drug release characteristics. These findings set the groundwork for future preclinical and clinical research, with the potential to translate into therapeutic applications for a variety of medical diseases.

Index Terms **-** Naphazoline Hydrochloride, Situ Gel, Novel Polymers, Oculer Drug Delivery System.

INTRODUCTION

The most frequent technique of ocular [medicine] delivery is topical application of ophthalmic dose formulation drops into the lower cul-de-sac. Eye drops exit fast owing to eye blinking reflux, and the precorneal area returns to maintain a resident volume of around 7µl. The accessible concentration of medication in precorneal fluid acts as a driving factor for passive drug transport across the cornea.[1] However, the epithelium is the primary rate-limiting barrier for hydrophilic medicines, whereas the stroma is the rate-limiting step for the majority of lipophilic medications. The eye is the fundamental organ for seeing. Each of the two eyes is placed in the orbit, occupying approximately one-fifth of the orbital volume.[2] The remaining area is occupied by the extraocular muscles, fascia, fat, blood vessels, nerves, and lacrimal gland. The eye is an embryological outgrowth of the central nervous system. It has numerous anatomical and physiological similarities with the brain. Both are protected by bony walls, have robust fibrous coverings, and provide a dual blood supply to the retina's important nerve layer.[3] The eye and brain contain interior chambers that are perfused by fluids of similar composition and pressure. Given that the retina and optic nerve are brain outgrowths, it is not unexpected that identical disease processes affect the eye and central nervous system. The clinician should continuously remind oneself or herself of the different illness disorders that might impact both the eye and the central nervous system. Molecules up to 20,000 Da can pass through the conjunctiva, whereas molecules up to 5,000 Da can pass through the cornea. The human conjuctiva is 2-30 times more permeable to medicines than the cornea, resulting in drug loss. Precorneal tear film refers to a thin fluid coating that covers the exposed area of the eye.[4] The film thickness ranges from 3 to 10 mm, depending on the measuring technique, with a resident volume of around 10 µl. The osmolality of tear fluid in normal eyes ranges between 310 and 350 m Osm/kg, which is maintained by monovalent and divalent inorganic ions such as Na+, K+, Cl-, HCO3-, and proteins. The average pH of normal tears is around 7.4. Diurnal cycles cause the pH of tears to vary from acid to alkaline during the day. Bicarbonate ions, proteins, and mucin all contribute to the tears' buffer capacity.[6,7]

In Situ Gels :

A gel is a soft, stable, or solid-like substance composed of at least two components, one of which is a liquid in significant quantity. Gels are a kind of materials that lies in between liquid and solid states. Gels blend solid's cohesive capabilities with fluid's diffusive transport features. It is made up of a three-dimensional, reliable, and secure component network. The polymer network in gels is generated by the crosslinking of polymer chains, which can be covalent (chemical cross-linking) or non-covalent (physical cross-linking). Gels are divided into two groups based on their properties.[8] Physical gels include weak bonds such as hydrogen, electrostatic, and Vander Waal bonds. The innovative drug delivery method employs a variety of techniques, including in situ gelling, the utilization of mucoadhesive polymers, polymer-coated nanoparticles, and liposome formulations. These delivery methods delay the clearance of the active component from the eye while simultaneously improving the drug molecule's corneal penetration.[9]

Classification of in situ gelling polymers :

Based on their origin, polymers can be classified or the mechanism of gelation. According to a source in situ, gelling systems are classified into two types.

Natural polymers : (e.g., Alginic acid, carrageenan, chitosan, guar gum, gellan gum, pectin, sodium hyaluronate, xanthan gum, xyloglucan, etc.).

Synthetic or semi-synthetic polymers : (e.g., CAP, HPMC, MC, PAA, PLGA,poloxamers).[10]

Sol-gel method :

The starting materials,'sol', are often inorganic metal salts or organic compounds such as metal alkoxides. The conventional'sol-gel' approach involves the precursor going through hydrolysis, polymerization, or condensation processes to generate a colloidal suspension or solution. Complete polymerization and consequent depletion of solvent leads conversion from'sol' (liquid phase) to 'gel' (solid phase).[11]

Approaches of in situ gels :

There are Three generally defined mechanisms used for triggering the in situ gel formation of biomaterial.

Physiological stimuli : (e.g., temperature and pH)

Physical stimuli : (e.g., solvent exchange or diffusion and swelling)

Chemical stimuli : (e.g., enzymatic, chemical and photo-initiated polymerization)

DRUG PROFILE

Naphazoline hydrochloride :

Brand Name :

Advanced Eye Relief Redness Instant Relief, Ak-con, Clear Eyes Complete, Clear Eyes Cooling Comfort.

Background :

Naphazoline is a rapid acting imidazoline sympathomimetic vasoconstrictorof ocular or nasal artierioles. It acts to decrease congestion and is found in many over the counter (OTC) eye drops and nasal preparations.

IUPAC Name :

2-(naphthalen-1-ylmethyl)-4,5-dihydro-1*H*-imidazole;hydrochloride.

Chemical formula:

$C_{14}H_{15}ClN_2$.

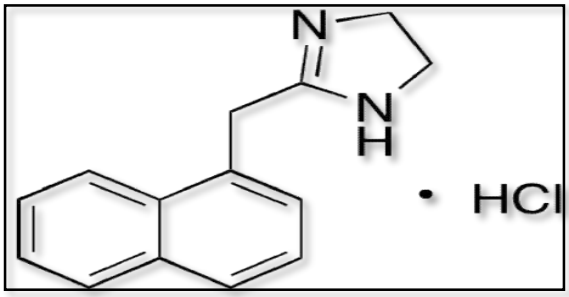

Figure 1: Structure of Naphazoline hydrochloride

Indication:

Naphazoline is indicated for use as OTC eyedrops for ocular vasoconstriction or as a nasal preparation for nasal congestion.

Pharmcodynamics:

Naphazoline is a sympathomimetic alpha adrenergic agonist that acts to vasoconstrict nasal or ocular arterioles, resulting in reduced congestion at the site of administration.

Mechanism of action

Naphazoline is a vasoconstrictor that functions by stimulating alpha adrenergic receptors in arterioles leading to decreased congestion at the site of administration. Naphazoline causes the release of norepinephrine in sympathetic nerves.

Absorption:

Absorption data for naphazoline are scarce but imidazoline compounds in general are weakly basic and lipophilic, with high bioavailability from the gastrointestinal tract.

Half life:

Half life has not been determined but effects last for 4 to 8 hours. Other imidazoline compounds have half lives varying from 2 to 12 hours.

Uses:

Naphazoline hydrochloride is a decongestant used to relieve redness, puffiness, and itchy/watering eyes due to colds, allergies, or eye irritations (smog, swimming, or wearing contact lenses).

Side effects: Chest pain, fast or uneven heart rate.

RESEARCH METHODOLOGY

Preformulation Research : A preformulation research is the initial stage in rationally developing a medicinal substance's dosage form. It is described as an examination of the physical and chemical characteristics of a drug ingredient both alone and in combination with excipients. The ultimate goal of preformulation testing is to provide information that will help the formulator build stable and bioavailable dosage forms that can be mass manufactured. Obviously, the sort of information needed depends on the dosage form that will be generated. Characterization of Naphazoline hydrochloride.

Physical Evaluation : It refers to the evaluation by sensory characters-taste, appearance, odor, feel of the drug etc.

Solubility: Solubility of the drug was determined by taking some quantity of drug (about 1-2 mg) in the test tube separately and added the 5 ml of the solvent (Water, ethanol,methanol, 0.1 N HCl, 0.1 N NaOH, 7.2 pH phosphate buffer and chloroform). Shake vigorously and kept for some time. Note the solubility of the drug in various solvents (at room temperature).

Melting Point: A small quantity of powder was placed into a fusion tube. That tube was placed in the melting point determining apparatus (Chemline) containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted.

Moisture Content Determination: Karl Fischer volumetry is used for samples with high water content, *i.e.* 1- 100 mg per sample. An iodine-containing solution serves as titrating agent. The water content of the sample is calculated using titration volume and titer of the titrating agent. Reagents conveniently contain all reactants (iodine, sulfur dioxide and a base) dissolved in a suitable alcohol in one solution, whereas two-component reagents contain all necessary reactants separated in two different solutions to enhance the rapidity of the Karl Fischer reaction and the titer stability of the titrating agent. Karl Fischer coulometry is a micro-method and is particularly suitable for samples with low water content, from 10 µgup to 10 mg. Here, the required iodine is generated electrochemically in the titration vesselby anodic oxidation from iodide contained in the coulometric reagents. The amount of consumed electric charge is used to calculate the consumption of iodine and therefore the amount of water in the sample.

Identification Test Using FTIR Spectroscopy : Infra- red spectrum is an important record which gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption band from which a wealth of information can be derived about the structure of an organic compound. The region from 0.8 µ to 2.5 µ is called Near Infra-red and that from 15 µ to 200 µ is called Far infra-red region. Identification of Naphazoline hydrochloride was done by FTIR Spectroscopy with respectto marker compound. Naphazoline hydrochloride was obtained as white crystalline powder.It was identified from the result of IR spectrum as per specification.

Determination of λ_{max} of Naphazoline Hydrochloride : The λ_{max} of Naphazoline hydrochloride was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer. Accurately weighed 10 mg of drugwas dissolved in 10 ml of 7.2 pH phosphate buffer solutions in 10 ml of volumetric flask. The resulted solution 1000µg/ml and from this solution 0.1 ml pipette out and transfer into 10 ml volumetric flask and volume make up with 7.2 pH phosphate buffer solution prepare suitable dilution to make it to a concentration of 10µg/ml for Naphazoline hydrochloride.The spectrum

of this solution was run in 200-400 nm range in U.V. spectrophotometer(Labindia-3000+).

Calibration curve of Naphazoline hydrochloride Preparation of standard stock solution: 10 mg of drug was weighed accurately and transferred to 10 ml volumetric flask, and the volume was adjusted to the mark with the 7.2 pH phosphate buffer to give a stock solutionof 1000 ppm or µg/ml.

Preparation of working standard solution : From stock solutions of Naphazoline hydrochloride 1 ml was taken and diluted up to 10 ml. from this solution 0.5, 1.0, 1.5, 2.0 and 2.5 ml solutions were transferred to 10ml volumetric flasks and make up the volume up to 10 ml with 7.2 pH phosphate buffer, gives standarddrug solution of 5, 10, 15, 20 and 25 µg/ml concentration.

Formulation Development of In-Situ Gel : The formulation development of an in-situ gel of Naphazoline hydrochloride holds significant importance and presents a compelling need for study.

Selection of Vehicle : The solubility of Naphazoline hydrochloride was tested in various buffers such as acetate buffer I.P. (pH 6.0 & 6.5), citrophosphate buffer B.P. (pH 6.0 and 6.2) and phosphate buffer USP (pH 7.2 and 7.4) in order to select a suitable vehicle. Solutions of Naphazoline hydrochloride in the above buffers were prepared to test its solubility at the dosage level desired.

Methodology for formulations preparation:

- For the preparation of Pluronic F127 based ocular *in-situ* gel all the ingredients were sieved from sieve no 44.
- Then 0.1% of drug was prepared in acetate buffer 5.0 I.P.
- The solution was cooled in an ice bath and pluronic F127 was added slowly with continuous stirring.
- Then the resulting solution was kept in a refrigerator under 4^0C for 24h. This storage was help in dissolving the Pluronic F 127 completely.
- After 24h carbopol 934 and HPMC 15cps were added slowly along with other exepients with continuous stirring. The stirring should be continued to 2-3 hours for proper mixing and avoid slug formation.
- The resulting formulation kept on probe sonicator to remove air bubble. All formulations were stored in LDPE (Low Density Polyethelene) bottles for further use. All the containers stored in refrigerator.

Evaluations of Formulations

Appearance : Clarity is one of the most important characteristic features of ophthalmic preparations. All developed formulations were evaluated for clarity by visual observation against a black and white background.

Drug content: The assay of Naphazoline hydrochloride was performed by UV method. The calculation was based on calibration curve method using regression equation (Y=mx+c).

pH : pH is one of the most important parameter involved in the ophthalmic formulation. The two areas of critical importance are the effect of pH on solubility and stability. The pH of ophthalmic formulation should be such that the formulation will be stable at that pH and at the same time there would be no irritation to the patient upon administration of the formulation. Ophthalmic formulations should have pH range in between 5 to 7.4. The developed formulations were evaluated for pH by using calibrated digital pH meter For In situ gel pH 5.0 should be optimum because both the drug is stable at pH 3.5-5.0. Lowering the pH from 5.0 can causes irritation to eye and on raise the above 5 will result in gelation of formulation due to presence of carbopol.

In-situ gelling capacity: In situ gelling capacity determined by visual inspection. The formulation has been exposed to the physiological conditions of temperature and pH. Simulated tear fluid (STF) was prepared and warm up to 37^0C. Formulations were introduce into STF in a ratio of 1:2 Change in consistency of Formulations were visually inspected.

Viscosity study: At pH 5.0 and temperature less than 16ºC the developed formulations were in liquid state and show low viscosity. For viscosity studies the pH of formulations were raised from pH 5.0 to pH 7.4 and the temperature was raised to 37^0C. pH was raised to 7.4 by the additionof 0.5M NaOH. The resulting gel studied for viscosity on Brookfield Synchrolectric Viscometer using Spindle No.7 at 50 RPM for comparative study. The angular viscosity was measured by gradually increase the RPM from 10 to 70.

In-vitro drug diffusion study : The in vitro release of drugs from the formulations was studied through cellophane membrane. The dissolution medium used was artificial tear fluid freshly prepared (pH 7.4). Cellophane membrane, previously soaked overnight in the dissolution medium, was tied to one end of a specifically designed glass cylinder (open at both ends and of 5 cm diameter). A 1-ml volume of the formulation was accurately pipetted into this assembly. The cylinder was attached to the metallic driveshaft and suspended in 50 ml of dissolution medium maintained at 37±1°C so that the membrane just touched the receptor medium surface. The dissolution medium was stirred at 50 rpm using magnetic stirrer. Methodology Aliquots, each of 1-ml volume, were withdrawn at hourly intervals and replaced by an equal volumeof the receptor medium.

Stability studies : Optimized sterile formulation was subjected to stability testing. Sterile optimized ophthalmic formulation was filled in glass vials, closed with gray butyl rubber closures and sealed with an aluminium caps. The vials contain optimized formulation were kept in stability chamber, maintained at 40 ± 2°C and 75 ± 5% RH for one month. Samples were withdrawn weekly and estimated for drug content and In-situ gelling capacity.

RESULTS AND DISCUSSION

Results of characterization of Naphazoline hydrochlorid

Results of physical evaluation :

S. No.	Sensory characters	Physical evaluation of Naphazoline hydrochloride
1.	Colour	White crystalline powder
2.	Odor	Odorless
3.	Taste	Bitter

Table 1: Physical evaluation of drug.

Results of solubility:

Solvents	Results of Solubility
Methanol	Freely soluble
Ethanol	Soluble
Chloroform	Slightly soluble
Distilled water	Freely soluble
7.2 pH phosphate buffer	Soluble
0.1 N HCl	Freely soluble
0.1 N NaOH	Soluble

Table 2: Solubility of Naphazoline hydrochloride.

It has been observed that Naphazoline hydrochloride was freely soluble in methanol, distilled water and 0.1 N HCl, soluble in ethanol, 7.2 pH phosphate buffer and 0.1 N NaOH, Slightly soluble in chloroform.

Results of melting point:

Melting point of Naphazoline hydrochloride was found to be 258-260°C.

S. No.	Melting Point of Naphazoline hydrochloride
1.	258-260°C

Table 3: Melting point of Naphazoline hydrochloride.

Results of moisture content determination:

S. No.	Drug	KF Factor	Amount of KF Reagent consumed	Moisture content
1.	Naphazoline hydrochloride	0.247	0.2ml	0.0494

Table 4: Moisture content determination.

Results of identification test using FTIR Spectroscopy :

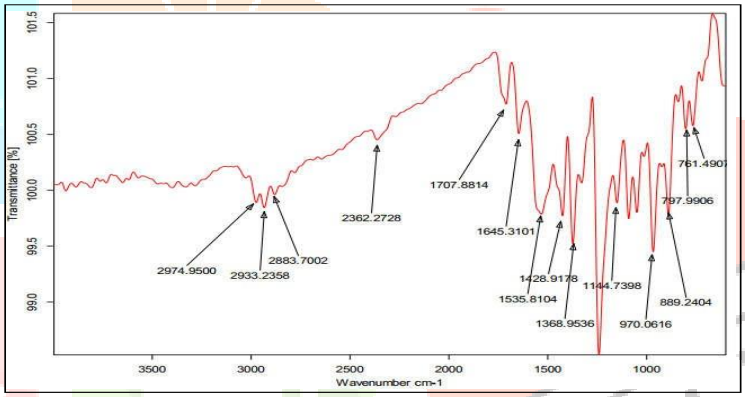

Figure 2 : FT-IR Spectrum (Naphazoline hydrochloride).

S. No.	Peak Position (cm^{-1})	Functional Group
1	2883.7002	Aliphatic C-H Stretching
2	2974.9500	Aromatic C-H Stretching
3	1645.3101	C-H Bending
4	1368.9536	C-N Stretching
5	797.9906	C-Cl Stretching

Table 5: Interpretation of Naphazoline hydrochloride.

Determination of λ max and Calibration curve of Naphazoline hydrochloride :

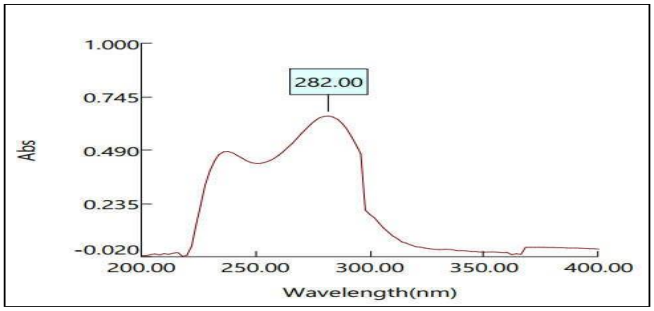

Figure 3 : Determination of λ_{max} of Naphazoline hydrochloride.

S. No.	Concentration (µg/ml)	Mean absorbance
1.	0	0
2.	5	0.345
3.	10	0.665
4.	15	0.965
5.	20	1.256
6.	25	1.499

Table 6: Readings for calibration curve of Naphazoline hydrochloride.

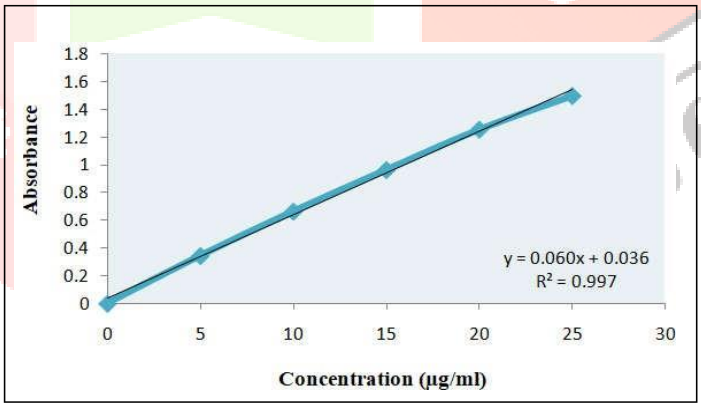

Figure 4 : Calibration curve of Naphazoline hydrochloride at 282 nm.

Results of evaluation parameter of in situ gel :

Clarity test :

The clarity test results for the in situ gel formulations indicate that the majority of theformulations (F1 to F7) exhibit clarity, suggesting good transparency and lack of visible particulates or turbidity. However, formulations F8 and F9 appear turbid, indicating the presence of suspended particles or aggregates that affect the visual clarity of the gel.

Formulation code	Clarity
F1	Clear
F2	Clear
F3	Clear
F4	Clear
F5	Clear
F6	Clear
F7	Clear
F8	Turbid
F9	Turbid

Table 7: Clarity test of in situ gel formulations

The turbidity observed in formulations F8 and F9 could be attributed to various factors suchas improper dispersion of components, phase separation, or the formation of aggregates during gel preparation. It's essential to investigate the root cause of turbidity in these formulations to ensure their suitability for intended applications.The clarity test highlights the importance of visual inspection in assessing the physical appearance and quality of in situ gel formulations, with clear formulations typically indicating proper formulation and good stability. Further characterization and optimization may be necessary for turbid formulations to improve their clarity and ensure their efficacy and safety.

Drug Content :

Evaluation of drug content is a critical parameter in assessing the quality and performanceof in situ gels. The drug content evaluation aims to determine the amount of active pharmaceutical ingredient (API) present in the gel formulation. The drug content of both the drug in formulations was determined by UV method. The drug content of formulation F1 toF9 was found between 95.52±0.36 to 98.95±0.47%. The maximum Drug Content was foundin formulation F6 (98.95±0.47).

Formulation	Drug Content (%)*
F1	96.45±0.25
F2	97.65±0.32
F3	98.85±0.47
F4	96.52±0.69
F5	95.74±0.85
F6	98.95±0.47

F7	97.74±0.32
F8	96.65±0.25
F9	95.52±0.36

Table 8: Drug content analysis

***Average of three determinations (n=3)**

The drug content directly influences the drug release profile and therapeutic effectiveness of the in situ gel. If the drug content deviates significantly from the target value, it may affectthe release kinetics and result in suboptimal drug delivery. Therefore, it is essential to maintain consistent drug content to ensure if the drug content deviates from the desired target, further formulation optimization may be required.

pH Determination :

The pH determination results provide insight into the acidity or alkalinity of the formulations, which is crucial for ensuring stability, compatibility, and effectiveness of the products. In this study, formulations F1, F3, F4, and F5 have pH values close to the target pH of 5.0 ± 0.1, indicating that they are within the acceptable range for pharmaceutical preparations.

Formulation	pH Determination	Adjust to
F1	4.8	5.0 ±0.1
F2	4.3	5.0 ±0.1
F3	4.7	5.0 ±0.1
F4	4.9	5.0 ±0.1
F5	4.8	5.0 ±0.1
F6	4.5	5.0 ±0.1
F7	4.7	5.0 ±0.1
F8	4.3	5.0 ±0.1
F9	4.5	5.0 ±0.1

Table 9: pH Determination

However, formulations F2, F6, F7, F8, and F9 deviate slightly from the target pH, with values ranging from 4.3 to 4.9. It's essential to adjust the pH of these formulations to bring them closer to the desired target pH range. pH adjustment may involve the addition of acidic or alkaline substances to achieve the specified pH range, ensuring consistency and standardization across different batches. Maintaining proper pH levels is critical for ensuring the stability and efficacy of the formulations, as pH can influence factors such as drug solubility, chemical stability, and biological activity. Therefore, careful pH adjustment and monitoring are necessary steps in the formulation process to optimize the performance and quality of the products.

In-Situ gelling capacity :

The evaluation parameter of in-situ gelling capacity is crucial when assessing ocular in situ gels. The in-situ gelling capacity refers to the ability of the gel to undergo a phase transition from a liquid to a gel state upon instillation into the eye. he in-situ gelling capacity is determined by visually observing the gel formation immediately or shortly after the gel is instilled onto the ocular surface. The gel should exhibit a rapid and uniform transition froma liquid to a gel state, forming a cohesive and transparent gel.

In situ gelling capacity determined by visual inspection. The formulation has been exposed to the physiological conditions of temperature and pH. Simulated tear fluid (STF) was prepared and warm up to 37^0C. Solution was introduced into STF in a ratio of 1:2 Changes in consistency of solution visually inspected. Formulation F7, F8 and F9 show poor gelling capacity in simulated physiological conditions of pH and temperature because of comparatively less concentration of pluronic F127, F4. F5 and F6 formulation show better gelling capacity.

Viscosity study :

The viscosity of in situ formulations is a crucial parameter that can affect various aspects of the formulation, including ease of administration, spreading, and drug release. From the comparative data provided, it's evident that the viscosity varies among the formulations, which can be attributed to differences in the percentage of Pluronic F127 used.For formulations with the same percentage of Pluronic F127, such as F1, F4, and F7, the viscosity varies slightly, suggesting that other factors may also influence viscosity, such as formulation composition and interactions between ingredients. Upon gelation, there is a notable increase in viscosity for all formulations. This increase is expected as the gelation process transforms the liquid formulations into semisolid or gel-like structures, leading to higher viscosity values. Formulations with higher percentages of Pluronic F127 generally exhibit higher viscosities, both before and after gelation. This trend is consistent with the known thickening and gelling properties of Pluronic F127.

Formulation code	% of Pluronic F 127	Viscosity of solution (in cps)	Viscosity after galation
F1	10	685	2715
F2	12	715	2845
F3	14	785	2918
F4	10	679	2465
F5	12	725	2685
F6	14	796	2745
F7	10	655	2654
F8	12	683	2965
F9	14	715	3165

Table 10 : Comparative viscosity* of In situ formulation

On the basis of results of drug content, pH, Viscosity the formulation F6 select as optimized formulation.

In- vitro drug release study of optimized formulation :

The evaluation parameter of in vitro drug release is an important aspect of assessing the performance of ocular in situ gelsIn vitro drug release is typically conducted using a suitable dissolution apparatus or diffusion cell setup that simulates the physiological conditions of the eye. The test conditions should mimic relevant parameters such as temperature, pH, and stirring rate. The rate of drug release from the gel is an important parameter to evaluate.

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative % Drug Release	Log Cumulative % Drug Release	Cumulativ e % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	19.98	1.301	80.02	1.903
1	1	0	33.65	1.527	66.35	1.822
1.5	1.225	0.176	49.95	1.699	50.05	1.699
2	1.414	0.301	56.65	1.753	43.35	1.637
2.5	1.581	0.398	69.85	1.844	30.15	1.479
3	1.732	0.477	76.65	1.885	23.35	1.368
4	2	0.602	88.78	1.948	11.22	1.050
5	2.236	0.699	97.74	1.990	2.26	0.354

Table 11: In vitro drug release profile of Naphazoline hydrochloride from in situ Formulation F6.

Release kinetics of drugs loaded optimized formulation F-6

Zero order release kinetics of optimized formulation

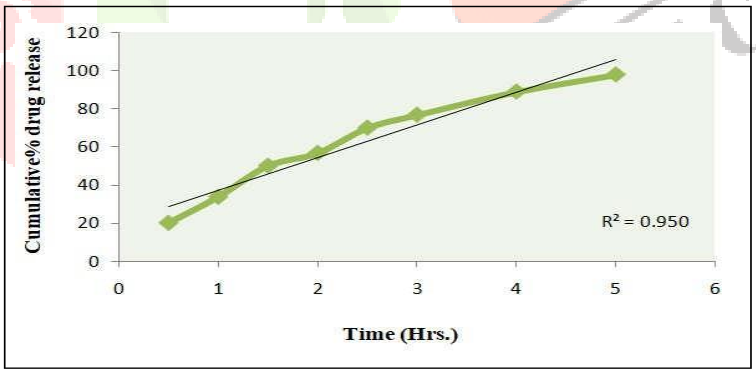

Figure 5 : zero order release kinetics.

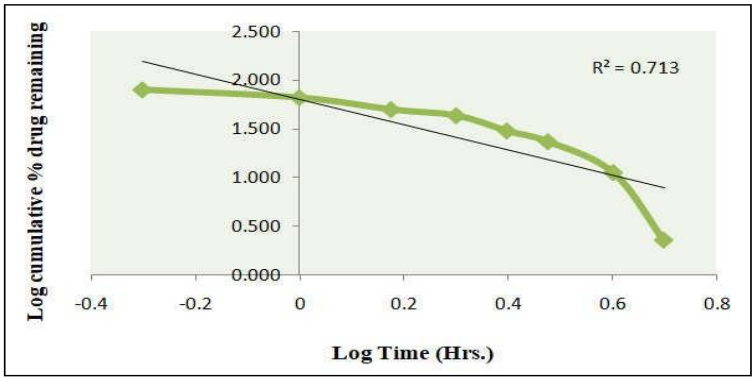

Figure 6 : First order release kinetics.

Drug	Zero order	First order
Naphazoline hydrochloride	$R^2 = 0.950$	$R^2 = 0.713$

Table 12 : Comparative study of regression coefficient for selection of optimizeFormulation F6.

The In vitro drug release data of the optimized formulation was subjected to goodness of fittest by linear regression analysis according to zero order and first order kinetic equation in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of Zero order was maximum hence indicating drug release from formulations was found to follow Zero order release kinetics.

Stability studies :

Stability studies are essential to assess the long-term stability and shelf-life of ocular in situ gels. These studies provide valuable information about the physical, chemical, and microbiological stability of the gel formulation over time. Chemical stability assessment focuses on evaluating the stability of the active pharmaceutical ingredient (API) within the gel formulation. The concentration of the API should remain within acceptable limits throughout the shelf-life of the gel. Analytical techniques spectroscopic methods are used to determine the degradation or loss of the API.

F. code	Parameter Evaluated (40 ± 2°C, 75 ± 5 % RH)					
	7 days		15 days		30 days	
	Drug content	*In-situ* gelling capacity	Drug content	*In-situ* gelling capacity	Drug content	In-situ gelling capacity
F6	98.95	++	98.45	++	97.25	++

Table 13 : Stability data sheet.

Figure 8.7 : Graph of stability data.

CONCLUSION

The physical evaluation of Naphazoline hydrochloride revealed that it exists as a white crystalline powder with an odorless characteristic and a bitter taste. In terms of solubility, Naphazoline hydrochloride demonstrated good solubility in methanol, ethanol, distilled water, phosphate buffer (pH 7.2), and 0.1 N NaOH, being freely soluble or soluble in these solvents. However, it exhibited only slight solubility in chloroform and was freely soluble in 0.1 N HCl. The melting point of Naphazoline hydrochloride was found to be in the range of 258-260°C. The moisture content determination of Naphazoline hydrochloride using Karl Fischer titration revealed a moisture content of 0.0494%. The clarity test conducted on the in situ gel formulations revealed that formulations F1 to F7 exhibited clear appearance, indicating good transparency. However, formulations F8 and F9 were found to be turbid, which could be attributed to the presence of particulate matter or phase separation. pH determination of the formulations revealed values close to the target pH of 5.0 ± 0.1 after adjustment. This is crucial for ensuring compatibility with physiological conditions and minimizing irritation upon application. The in vitro drug release study of the optimized formulation F6 demonstrated sustained drug release over time, with cumulative percentages increasing progressively. This sustained release profile suggests the potential of formulation F6 for achieving prolonged therapeutic effects with reduced dosing frequency. In conclusion the developed in situ gel formulations demonstrate promising physical properties, drug content uniformity, pH suitability, gelling capacity, and sustained drug release characteristics. These findings lay the foundation for further preclinical and clinical studies, with the potential for translation into therapeutic applications for various medical conditions.

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