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DESIGN CHARACTERIZATION AND FORMULATION OF *IN-SITU* GELLING OPHTHALMIC DRUG DELIVERY SYSTEM CONTAINING PLANT DERIVED PHENOLS

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Keywords:

Catechin *in-situ* gel, Ion activated natural polymers, Rheological study, *In-vitro* diffusion study, Antioxidant activity, Draize test

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ABSTRACT: The objective of the present investigation was to formulate and evaluate ion-activated *in-situ* gel using the herbal drug catechin, a potential natural antioxidant for the treatment of glaucoma by lowering oxidative stress. A total of eight formulations were prepared and evaluated for parameters, namely physical appearance, gelling capacity, pH measurement, rheological studies, the effect of sterilization, drug content, *in-vitro* diffusion study, isotonicity evaluation, ocular irritancy studies, and stability test. Pre-formulation studies confirmed that the drug and polymer are compatible with each other. The XSG-2 formulation showed a maximum percentage drug release of 95.45%, which was considered as an optimized formulation and showed 5-6 folds increase in viscosity after gelation, which indicated good residence time further formulations were found to be non-irritating with no ocular toxicity and good stability. The current study results conclude that the developed catech in loaded ophthalmic in situ gel can be considered a better alternative approach to the conventional eye drop with an increase in precorneal residence time, reduced frequency of dosage, and patient compliance for the management of glaucoma.

INTRODUCTION: Designing ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist because of the critical and pharmaco-kinetically specific environment that exists in eye [1]. Conventional pharmaceutical formulations such as solutions, suspensions have many constraints like rapid precorneal elimination, drainage by gravity, normal tear turnover, frequent installation, enzymatic metabolism, nasolacrimal drainage, conjunctival absorption, absence of controlled release, and bioadhesive properties [2]. The residence time of most conventional ocular solutions is 5-25 min, and only 5% of the topically applied drug is absorbed 2 and reaches the deeper tissues so.

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It is necessary to develop a novel safe and patient complaint formulation and drug delivery devices, which may surpass these barriers and maintain drug levels in tissues. Due to the drawbacks with this route, new approaches have been investigated by means of the polymeric drug delivery system based on the concept of in situ gel formation, which exhibits reversible phase transitions (sol-gel) and pseudoplastic behavior, which is aimed at longer precorneal residence time, improved ocular bioavailability and patient acceptability [3].

In the present investigation, an attempt has been made to formulate and evaluate in situ gelling ophthalmic drug delivery system comprising of plant phenol catechin, using natural polymers like xanthan gum, sodium alginate, and gellan gum. In this system, gelling of polymer is triggered by ionic interaction of the polymer and divalent ions of the tear fluid, forming a viscoelasticge l.1. Plants are considered chemical factories as they contain numerous chemical compounds like alkaloids, glycosides, saponins, resins, flavonoids, and

polyphenols that have many therapeutic effects. Due to toxicity, side effects, and various interaction of synthetic drugs today, there is growing interest in phytoconstituents of plant-based medicine. Some advantages of extracts derived from plants contain more than one active component that acts as a synergist between different phytoconstituents which can be an important part of their overall therapeutic effect.

It is evident that, use of extracts derived from *Punica granatum* [4], *Moringa olifera* [5], *Camellasinensis*, *Coleus forskohli* [6], *Garcinia cola*, *Ocimum santum*, *Ginko biloba* [7,] *etc*. containing natural antioxidants such as polyphenols, punicalagin, elagic acid, gallic acid, catechin, ellagitanins, epigallocatechin [8], quercitin, forskolin, flavonoid, *etc*. has created much interest, which may be helpful in treatment of glaucoma [9].

Oxidative stress can cause chronic changes in the aqueous and vitreous humor, which may induce alterations in the trabecular meshwork and optic nerve head, which affects the regulation of extracellular matrix structure and alteration of flow of aqueous humor [9]. The only form of therapy to counteract the reduction of oxidative stress is by use of natural antioxidants such as catech in; hence there is a need to explore the full potential of catech in for the treatment of glaucoma, thereby reducing side effects.

MATERIALS AND METHODS:

Materials: Catechin and gallic acid procured from Yucca Enterprises Pvt Ltd., Mumbai, Xanthan gum (Lucid Colloids Ltd., Mumbai), Sodium alginate (Micro labs., Bangalore), Gellan gum (Life Expressions., Bangalore).

Methods:

Preparation of Standard Calibration Curve of Drug Catechin Using Folinciocalteu Reagent: Pure drug catech in was accurately weighed and dissolved in distilled water to obtain a stock solution of concentration 100 µg/ml further aliquots of different concentration were taken, folin reagent and sodium carbonate solution added for the development of blue color and volume was made up with distilled water to get final concentration in the range of 2-18 µg/ml. Samples were measured in the UV Visible range at 760 nm against blank solution [10].

Drug-Polymer Compatibility Study: Physical mixture of catech in with sodium alginate, gellan gum, and xanthan gum were characterized by IR spectral studies of samples taken using Fourier Transform Infrared Spectroscopy (FT-IR) Thermo, USA Model-Nicolet IR 200. The mixture was prepared in the ratio of 1:1 in ambered colored glass bottles. Compatibility testing was carried out as per ICH guidelines at 40 ºC and 75% RH for a period of 28 d to detect any possible interaction in the mixture [11].

Preparation of Catechin *in-situ* Gelling System: The main prerequisites of an in situ gel are gelling capacity and viscosity. The formulation should be a free-flowing low viscous liquid that undergoes a phase transition from sol to gel, which should be strong enough to withstand shear forces in culdesac, providing longer residence time.

TABLE 1: FORMULATION DESIGN OF *IN-SITU* GELLING SYSTEM

Ingredients (%w/v)	XSG-1	XSG-2	XSG-3	XSG-4	XSG-5	XSG-6	XSG-7	XSG-8
Catechin	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Xanthan gum	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Sodium Alginate	0.1	0.2	0.4	0.8	0.2	0.2	0.2	0.2
Gellan gum	0.3	0.3	0.3	0.3	0.4	0.6	0.8	1
Potassium Chloride	0.19	0.19	0.19	0.19	0.19	0.19	0.19	0.19
Benzalkonium chloride	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Distilled water q/s	100	100	100	100	100	100	100	100

XSG-1 TO XSG-8 is formulation code (Xanthan gum sodium alginate gellan gum 1 to 8).

Polymer dispersion is prepared first in distilled water. The gum derivatives were allowed to swell overnight then, an aqueous solution of catech in was prepared. Agents for adjustment of tonicity and preservatives were added. The solution was added to the polymeric dispersion and mixed properly. pH was adjusted to 7.4 with 0.1N NaOH/HCl, and volume was made up with distilled water which was kept on a magnetic stirrer to obtain a homogenized mixture [12].

Characterization of Catechin *In-situ* Gel:

Physical Appearance: Formulations were examined for clarity under fluorescent light alternatively against white and black backgrounds for any particulate matter, homogeneity, or phase separation

pH: Ophthalmic formulations should have a pH range between 5 and 7.4 to maintain their stability, and at the same time, there would be no irritation to the patient's eye on administration. The pH of the ophthalmic formulation was determined using a digital pH meter [13].

Drug Content Estimation: Accurately 1ml of the formulation was taken and diluted with 0.5 ml folin reagent, 1.5 ml of 10% sodium carbonate solution, and volume was made up to 10 ml with distilled water to make a final concentration of 10 µg/ml. The sample was analyzed by UV/Visible spectrophotometer. The drug content was measured at 760 nm 15 against the blank solution, which contained sodium carbonate solution and folin reagent.

***In-vitro* Gelation Study:** Gelling strength of formulations was determined by placing 100 µl of polymeric solution in vials containing 2 ml of freshly prepared simulated tear fluid. Phase transition of solution to stiff viscous gel was observed [14]. The *in-vitro* gelling capacity was graded in three categories on the basis of gelation time and period for which formed gel remains. (+)– Gels after few minutes and dissolves quickly (++)– Gels immediately and remains for <4 to 5 h (+++)- Gels immediately and remains for > 8 h.

Rheology Analysis: Viscosity of instilled formulation is an important factor in determining the residence time of the drug in the eye. It was determined using Anton Paar DV-2P Brookfield viscometer. Formulations were mixed with the tear fluid having pH 7.4 in the ratio of 1:3 and placed in the small volume adapter, and analyzed using different spindles. The angular velocity of the spindle was increased from 0.3 to 200 rpm, and the viscosities of the gel were measured with the time gap of 3 min, and the viscosities were recorded [16].

Effect of Sterilization on Viscosity of *in-situ* Gelling System: To check the rigors of sterilization effects on formulations, they were subjected to sterilization by the autoclaving process at 121 °C for a period of 15-20 min 13 and determination of viscosity was carried out using Brookfield viscometer.

***In-vitro* Drug Release Study of *In-situ* Gelling System:** The release studies of prepared formulations were carried out by using Franz Diffusion Cell across the dialysis membrane. The formulations were placed in the donor compartment with simulated tear fluid in the receptor compartment. Between donor and receptor dialysis membrane is placed, then the whole assembly is placed in a thermostatically controlled magnetic stirrer. The temperature of the medium was maintained at 37 ºC ± 0.5 ºC 14 3 ml of sample was withdrawn at a predetermined time interval of 1 h to 6 hr, and the same volume of fresh was replaced. To the samples, 0.5ml of folin reagent, 1.5 ml 10% w/v of a sodium carbonate solution was added, and volume was made up to 10 ml with distilled water. The samples were analyzed by UV/Visible spectrophotometer at 760 nm using a blank reagent.

Isotonicity Evaluation: Isotonicity is an important characteristic of ophthalmic preparations. Isotonicity has to be maintained to prevent tissue damage or irritation of the eye. Formulations were subjected to isotonicity testing to evaluate their isotonic, hypotonic and hypertonic nature. The formulations were mixed with one drop of blood and observed under microscope at 45 x magnification and compared with 0.9% sodium chloride and also standard marketed ciprofloxacin eye drop [17].

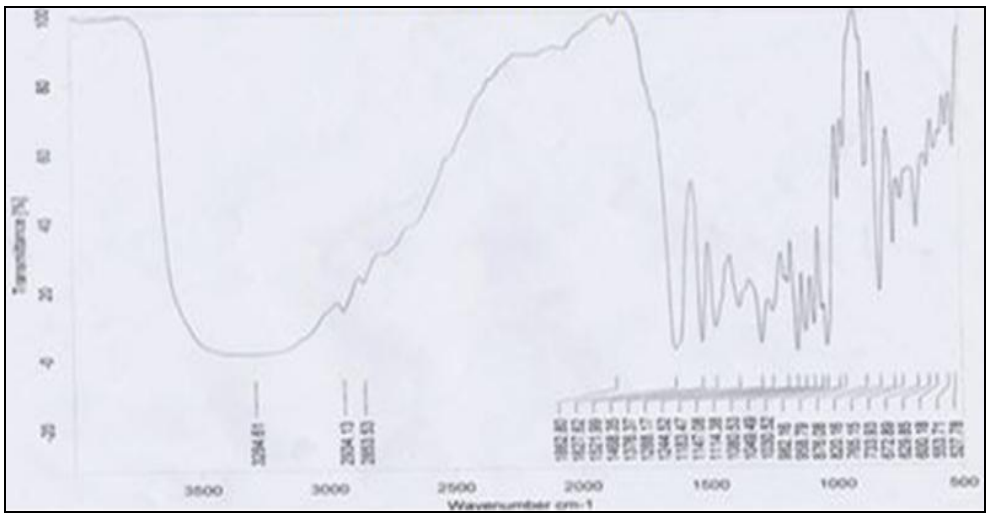
Ocular Irritancy Studies: The ocular irritancy study was carried out according to draize test protocol on New Zealand white albino rabbits, each weighing 2-3 kg. Animals were housed individually in a restraining box equipped with water and food in an environment maintained at a temperature of 23 ± 1 ºC and 45-65% RH. Cross-over study design was carried out, and scoring was done according to with Draize test protocol and OECD guidelines. 100µl of optimized formulation was instilled into the lower cul-de-sac to the right eye of the rabbit, and the left eye was considered as control. In order to prevent loss of drug, the lower eyelid was gently held together for 5-10 sec. The sterile formulation was instilled twice a day with a

3d washing period, and the rabbits were observed periodically for redness, excessive tearing, and inflammation of the eye after 1 h, 24 h, 48 h, and 1 week [17].

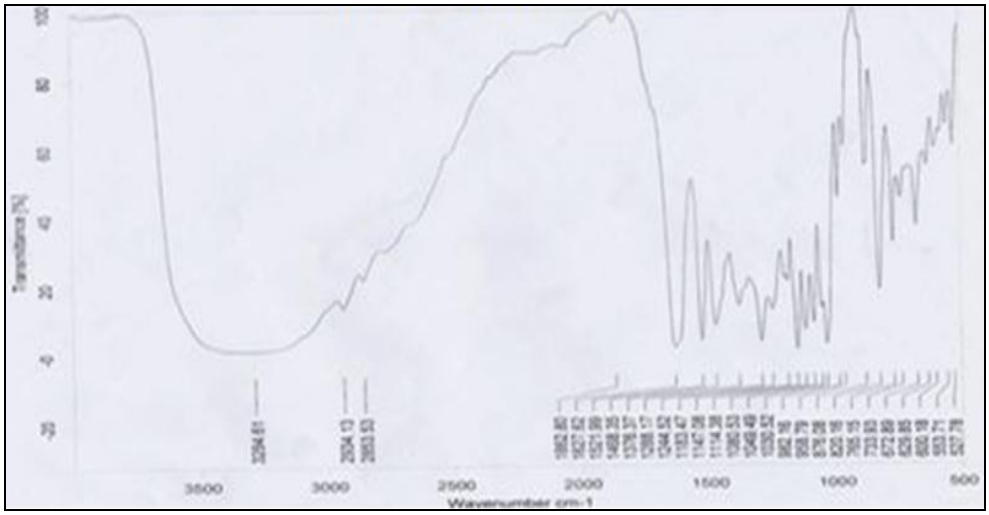
Stability Studies: The stability studies were carried out on the developed formulations as per the ICH guidelines. Formulations were stored in tightly closed amber colored glass vials sealed with aluminum foil at room temperature 25 ºC ± 2 ºC and 40 ºC ± 2 ºC, 75% RH Samples were evaluated on 1st, 3rd, 7th, 14th, 21st, and 28th day for clarity, pH, drug content, gelling capacity and viscosity [18].

Antioxidant Activity Studies: Metabolism of oxygen by cells generates potentially deleterious reactive oxygen species. It is a reaction of ferrous ion (Fe^{+2}) with 1, 10-phenanthroline.

Ferrous ion specifically forms red-orange tri-phenanthroline complex, which absorbs at 510 nm. To the series of volumetric flask 0.25 ml of 1Mm ferrous ammonium sulphate was added, 1.5 ml of different concentrations of drug solution ranging from 2-20 µg/ml drug solutions were added than 62.5 µl of 5 Mm hydrogen peroxide solution was added and incubated in the dark for 5 min in the incubator, next to the above dilution 1.5 ml of 1mm 1, 10 phenanthroline solution was added which resulted in the formation of complex red-orange color and was again incubated for 10 min. Absorbances were taken at 510 nm against blank distilled water using UV/Visible spectroscopy [19, 20,] and the percentage inhibitory effect was calculated and compared with standard Gallic acid.



FTIR SPECTRUM OF PURE DRUG



FTIR SPECTRUM OF CATECHINGALLAN GUM, XANTHAN GUM, ANS SODIUM ALGINATE

FIG. 1: FTIR SPECTRUM OF PURE DRUG CATECHIN AND PHYSICAL MIXTURE (CATECHIN, XANTHAN GUM, SODIUM ALGINATE AND GELLAN GUM

RESULTS: The linear regression analysis was done on absorbance data. Linear regression equation Absorbance = 0.051 × +0.029 (y = mx+c) was generated.

Compatibility study between drug and excipients was done by characterizing the physical mixture of drug and polymer by FTIR spectral analysis to access any chemical alteration of the drug characteristics through its functional groups' *in-situ* gels were formulated by ion activated method using different concentration of polymers.

The formulations were subjected to different evaluation parameters like pH, visual appearance, gel formation time, gel erosion time, drug content, rheology study, *in-vitro* drug release, isotonicity, and stability study.

An antioxidant study for pure drug catechin was carried out and found that IC_{50} values of catechin were found to compare with that of standard gallic acid, indicating potent antioxidant activity and good choice of herbal drug for the treatment of ocular diseases.

TABLE 2: EVALUATION OF VARIOUS PHYSICOCHEMICAL PARAMETERS OF *IN-SITU* GEL

Formulation code	Visual appearance	pH (at 25ºC)	Gel formation time	Gel erosion time	Drug content (%)
XSG-1	Reddish-brown	7.27±0.02	+	++	99.41±0.0007
XSG-2	Reddish-brown	7.25±0.03	+++	+++	99.80±0.0030
XSG-3	Reddish-brown	7.22±0.03	+++	+++	92.74±0.0040
XSG-4	Reddish-brown	7.24±0.05	+++	+++	99.21±0.0047
XSG-5	Reddish-brown	6.88±0.06	+++	+++	97.64±0.0070
XSG-6	Reddish-brown	7.40±0.007	++	+++	96.73±0.0030
XSG-7	Reddish-brown	7.30±0.01	+++	+++	95.62±0.0020
XSG-8	Reddish-brown	7.36±0.04	+++	+++	91.89±0.0080

TABLE 3: VISCOSITY VALUES FOR *IN-SITU* FORMED GELS BEFORE AND AFTER STERILIZATION AND % VISCOSITY VARIATION

Formulation code	Viscosity value for *in-situ* formed gels(cps)		% Viscosity variation	
	Before sterilization[a]	After sterilization[b]		
	Before gelation	After gelation	Before gelation	After gelation
XSG-1	332.2[a] 347.8[b]	1475.2[a] 1512.8[b]	4.69%	2.54%
XSG-2	415.3[a] 410.8[b]	2163.1[a] 2148.6[b]	-1.08%	-0.67%
XSG-3	1641.2[a] 1630.6[b]	4036.2[a] 4022.8[b]	-0.64%	-0.33%
XSG-4	515.8[a] 523.1[b]	2803.2[a] 2761.3[b]	1.41%	-1.49%
XSG-5	2912.6[a] 2336.1[b]	6456.1[a] 6512.1[b]	0.80%	2.41%
XSG-6	4170.3[a] 4023.6[b]	14350[a] 14276[b]	-3.5%	-0.5%
XSG-7	8252.5[a] 9636.6[b]	18472[a] 18838[b]	16.77%	1.98%
XSG-8	6521.6[a] 7245.9[b]	10626[a] 11581[b]	11.10%	8.98%

TABLE 4: STABILITY STUDIES

Parameters	0 d	3 d	7 d	14 d	21 d	28 d
pH	7.25±0.002	7.24±0.001	7.25±0.003	7.20±0.001	7.30±0.005	7.32±0.004
Physical appearance	Reddish-brown solution	Reddish-brown solution	Reddish-brown solution	Reddish-brown solution	Reddish brown solution	Reddish brown solution
(%) Drug content	99.80±0.003	99.41±0.007	98.03±0.004	96.47±0.002	96.86±0.003	96.72±0.003
Gel formation time	Instantly	Instantly	Instantly	Instantly	Instantly	Instantly
Gel erosion time	More than 8 h	More than 8 h	More than 8 h	More than 8 h	More than 8 h	More than 8 h
Viscosity(sol) At 1.5rpm	415.3	433.6	489.5	528.6	610.9	633.1
Viscosity (gel) At 1.5rpm	2136.1	2189.2	2304.6	2436.9	2523.7	2613.8
%viscosity variation	0.00%(sol) 0.00%(gel)	4.40% (sol) 1.21%(gel)	7.89%(sol) 5.27%(gel)	9.98%(sol) 5.74%(gel)	8.56%(sol) 3.60%(gel)	3.36%(sol) 3.57%(gel)

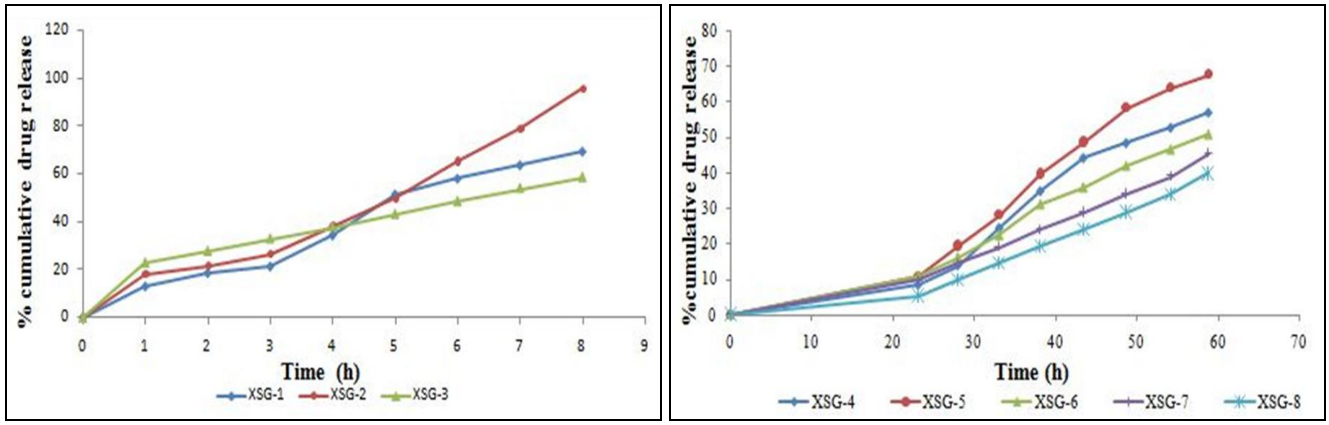
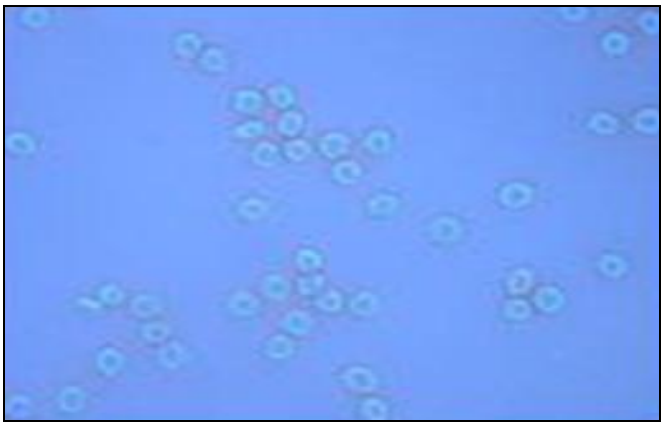
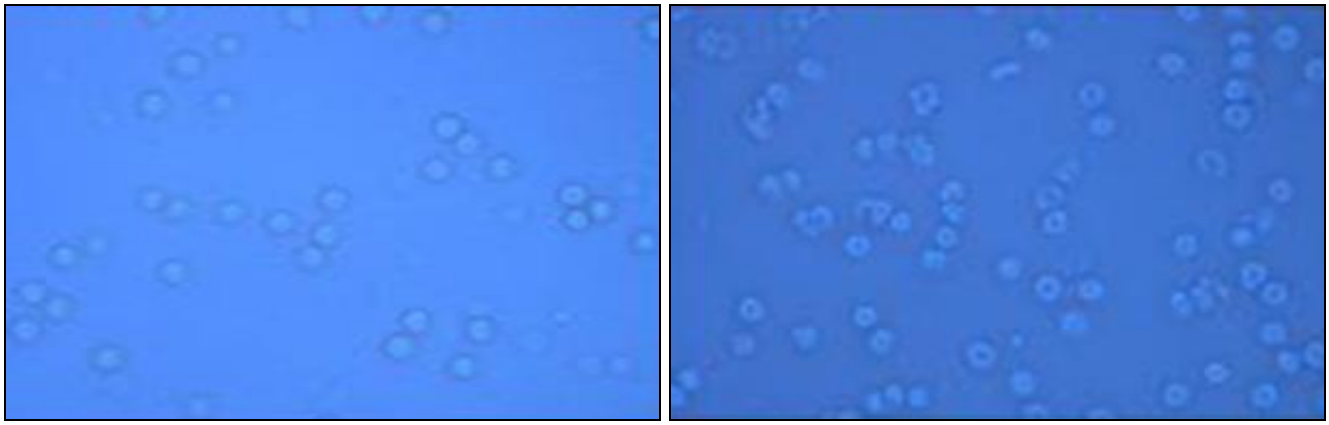


FIG. 2: COMPARATIVE *IN-VITRO* DIFFUSION PROFILE OF THE FOLLOWING FORMULATION



NORMAL BLOOD CELLS



BLOOD CELL WITH STANDARD CIPROFLOXACIN EYE DROP

BLOOD CELLS WITH XSG-2 FORMULATION

FIG. 3: ISOTONICITY STUDY

DISCUSSION: The only form of therapy to counteract the reduction of oxidative stress is by use of antioxidants; there is a need to explore the full potential of natural antioxidants like polyphenols. Plants are considered to be chemical factories as they contain numerous chemical compounds. Due to the toxicity, side effects, and various interactions of synthetic drugs today, there is a growing interest in phytoconstituents of plant-based medicine. Extracts derived from the plants contain more than one active component that acts as a synergist between different phytoconstituents which can be important part for overall therapeutic effect. The etiology of most ocular disease involves free radical-mediated oxidative damage. Catech in has an important role as an antioxidant where oxidative stress is implicated in a number of vision pathologies. Catechins loaded in situ gel were formulated by ion gelation method using polymers which achieved desired rheological behavior. Based on the solubility of the drug, distilled water was selected as a vehicle in the formulation.

FTIR studies revealed that there were no signs of interaction peaks that indicated compatibility between drug and polymers. All the formulations prepared were clear without any turbidity, suspended particles, or impurities. The pH of the formulations was between 6.8 to 7.4, which is an acceptable range for ophthalmic preparations. The gelling capability of the formulations was examined by mixing the solution with simulated tear fluid which gelled instantaneously and extended more than 8h preserving its integrity which was suitable for our study. Rheological studies play an important role in the optimization of the formulation.

Viscosity determines the residence time of the drug. The formulations' viscosity at different angular velocities exhibited pseudoplastic flow patterns that allowed easy instillation as a liquid, which undergoes a rapid sol-gel transition due to the ionic interaction with the tear fluid. Formulation XSG-2 showed 4-6 folds increase in viscosity while others showed 1-2 folds increase in viscosity. All the formulations were subjected to sterilization by means of autoclaving at 121° C for 20 min to check the rigors of sterilization effects on a formulation. Formulations XSG-2, XSG-3, XSG-4, XSG-5, and XSG-6 exhibited no significant change in viscosity after sterilization, indicating good physical stability. XSG-7 and XSG-8 variation in viscosity were probably due to the less polymer interaction, which showed loss in physical stability upon sterilization. *In-vitro* drug release showed maximum release up to 8h exhibiting therapeutic efficacy.

Significant increases in rate of drug release were observed with decrease in polymer concentration. Among the prepared formulations XSG-4, XSG-3, XSG-1, XSG-5 and XSG-2 showed cumulative drug release of 56.93%, 58.68%, 63.43%, 67.59% and 95.45% at 8 h, respectively exhibited sustained release of drug due to the effect of polymers where as it was not seen with XSG-6, XSG-7 and XSG-8 since these exhibited constant drug release. The formulation XSG-2 containing 0.2% xantham gum and sodium alginate and 0.3% gellan gum showed maximum drug release of 95.45% in 8 h which may be due to the formation of hydrogen bonds between drug and polymer which have helped to sustain rate release of drug thus was considered as an optimized formulation is tonicity studies revealed that formulations were isotonic with that of blood cells it was observed that blood cells maintained its integrity and there was no lysis. Ocular toxicity studies were carried out as per draize test protocol which revealed no abnormal clinical signs for cornea, conjunctiva, and iris, indicating formulation to be nonirritant for ocular administration.

Stability studies for optimized formulation showed no significant changes in viscosity, gelling ability, pH, and drug content, indicating a stable formulation. Antioxidant activity of drug catechin found that IC_{50} value of standard gallic acid was found to be 12.10 µg/ml and that of catechin was found to be 15.11µg/ml indicating potent antioxidant activity and a choice of herbal drug for the treatment of ocular diseases.

CONCLUSION: Catechin, a polyphenol used in the treatment of intraocular pressure-related glaucoma were successfully formulated as an ion-activated in situ gelling system comprising of natural polymers. XSG-2 was reported as an optimized formulation which showed 95.45% drug release at the end of 8 h. All the formulations showed decrease in viscosity with increase in shear rate; thus, exhibited optimum viscosity and pseudo plastic behavior indicating good residence time.

It was concluded that there was no significant change in viscosity after sterilization retaining its physical stability. Formulation was nonirritant for ocular administration. Further studies showed that catechin had a potent antioxidant property. The sustained period of drug release may be due to the slow diffusion of the drug from a combined effect of polymers, which is due to the formation of hydrogen bonds between the drug and polymers, thus helped in sustain the release of a drug and a viable alternative to conventional eye drop.

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CONFLICTS OF INTEREST: None

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