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FORMULATION AND EVALUATION OF LEVOFLOXACIN OPHTALMIC *INSITU* GEL

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ABSTRACT
The present study focuses on the formulation and evaluation of Levofloxacin ophthalmic in situ gel for the effective treatment of ocular infections. Conventional eye drops show poor bioavailability due to rapid tear drainage and short pre corneal residence time. To overcome these limitations, an in-situ gelling system was developed to enhance ocular retention and provide sustained drug release. The Formulation was prepared using thermo sensitive and or pH-sensitive polymers polymers that exhibit sol-to- gel phase transitions due to change in specific physicochemical parameter such as (pH, temperature), in their environment, the cul-de-sac in this case such as carbopol 934. The prepared formulations were evaluated for clarity, pH, viscosity, drug content, gelation capacity, in vitro drug release, sterility, Rheological, Isotonicity test, Microbial Assay and stability test was performed. All formulations were found to be clear, with pH within the acceptable ocular range and uniform drug content. Viscosity studies confirmed sol-to-gel transition under physiological conditions. In vitro drug release studies demonstrated sustained release of Levo-0floxacin over an extended period compared to conventional ophthalmic solutions. The optimized formulation showed appropriate gelation behavior, prolonged drug release, and satisfactory stability. The study concludes that levofloxacin ophthalmic in situ gel is a promising alternative to conventional eye drops, offering improved bioavailability, reduced dosing frequency, and enhanced patient compliance in the management of bacterial eye infections.

KEYWORDS: Opthalmic, insitu gel, L.ofloxacin.

INTRODUCTION
The poor bioavailability and therapeutic response exhibited by conventional ophthalmic solutions due to rapid pre corneal elimination of the drug may be overcome by the use of *in situ* gel-forming systems that are instilled as drops into the eye and undergo a sol–gel transition in the *cul-de-sac.*

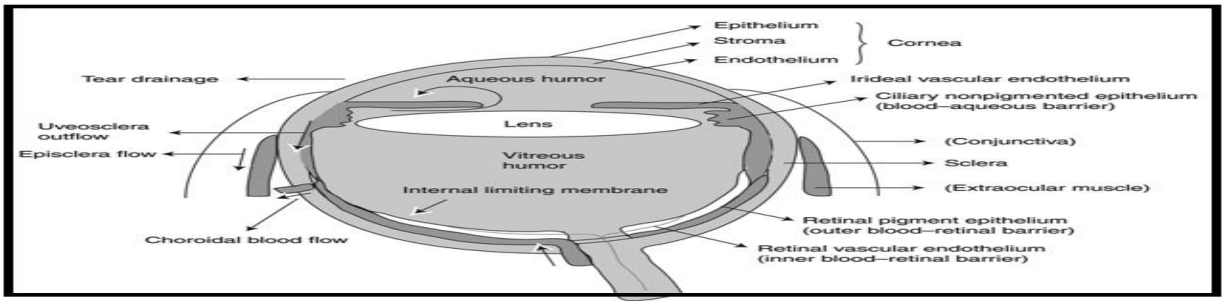


Fig no: 1.

➢ **ANATOMY AND PHYSIOLOGY OF EYE**
- SCLERA
- CHOROID LAYER
- RETINA

***In-situ* gelling system**

In situ-forming hydrogels are liquid upon instillation and undergo phase transition in the ocular *cul-de-sac* to form visco-elastic gel and this provides a response to environmental changes.

ISGS three tiggeredmethods
- Change in pH
- Change in temperature
- Ion activation

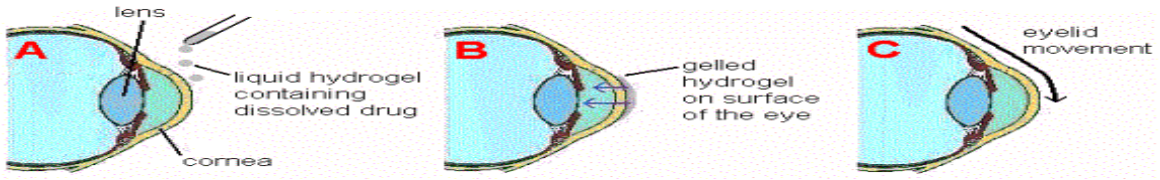


Fig no: 2.

The recent trends in ophthalmic drug delivery
- Mucoadhesive dosage forms:
- Phase Transition systems: *in-situ* gelling
- Ocular Inserts or films: SODI, NODS, Lacrisert, BODI, Dry drops and gelfoams, minidiscs
- Collagen shields
- Drug presoaked hydrogel type contact lens and pledgets
- Ocular Iontophoresis (Pulsatile drug delivery)
- Chemical delivery systems vesicular systems: Microspheres, microparticles, Nanoparticles, liposomes, niosomes, and PEGylation, dendrimers

➢ **AIM AND OBJECTIVE**
- The main aim of study was to prepare and evaluate Levofloxacin *in situ* gel
- Objectives of *in situ* gel is improves the therapeutic profile and safety, reducing dosing frequency and dose quantity, enhancing drug bioavailability and minimizing the occurrence of extra pyramidal side effects.

➢ **Plan of Work**
- Literature survey.
- Preparation of calibration curve of Levofloxacin hemihydrates.
- Drug -Excipients compatibility studies by using FTIR studies.
- To prepare ophthalmic *in situ* gel by using pH sensitive polymer.

➢ **Evaluation of *in situ* gel**
- **Clarity:** Ophthalmic solutions must be free from visible foreign particles and are examined against black and white backgrounds under good light to ensure clarity. If any particulate matter is observed, the formulation fails the test.

- **pH:** Ophthalmic preparations should have a pH close to tear fluid (≈7.4) for comfort and compatibility. The pH is optimized using suitable buffers to ensure drug stability throughout shelf life.

- **Drug content:** The drug content was determined by taking1mlof the formulation and diluting it to 100ml with distilled water. Aliquot of 5ml was withdrawn and further diluted to 25ml with distilled water. Levofloxacin concentration was determined at 290nm by using UV-V spectrophotometer.

- **Gelling capacity:** The gelling capacity of the prepared formulation was determined by placinga drop of the formulation in a vial containing 2ml of freshly prepared simulated tear fluid and visually observed. The time taken for its gelling was noted.

- **Rheological Studies:** The developed formulation was poured into the small sample adaptor of the Brookfield Synchrolectric viscometer and the angular velocity increased gradually from 10 to 100 rpm. The hierarchy of the angular velocity was reversed. The average of the two readings was used to calculate the viscosity. The formulation was then poured into an ointment jar and the pH raisedto 7.4 by adding 0.5M NaOH.

- **Isotonicity test:** Isotonicity is important characteristic of the ophthalmic in situ gel preparations. Isotonicity has to be maintained to prevent tissue damage or irritation of eye. Formulations were subjected to isotonicity testing, since they exhibited good release characteristics and gelling capacity and the required viscosity. Formulations were mixed with few drops of blood and observed under microscope at 45X magnification and compared with standard marketed ophthalmic formulation containing ciprofloxacin. Figure.9.7 depicts the isotonic nature of Standard ciprofloxacin and F1toF5 respectively. The shape of blood cell was compared with standard marketed ophthalmic formulation containing ciprofloxacin.

- **Sterility test:** The formulation showed no turbidity in Fluid Thioglycollate Medium after 14 days of incubation, indicating absence of microbial growth. Hence, the prepared ophthalmic in situ gel passed the sterility test and was found to be sterile.
- **Eye irritation test:** Acute ocular tolerance studies

were done by slight modification of the Draize procedure. Six rabbits were used and they were kept in restraining boxes in a normal upright posture. The right eye of all animals received 100 L of formulation every 30 minutes for 6 hours. The left eye remained untreated and served as acontrol. Aftereach instillation, amacroscopic evaluation was done to disclose possible lacrimation, blinking frequency, edema, conjunctival congestion, swelling, and corneal opacification. At 3 h, 6.5 h, and 24 h after the first instillation, a microscopic evaluation using a slit lamp was done to study possible damage in the conjunctiva, cornea, and iris. These results were used to determine the irritant indices according to a scale of predetermined scores.

- **Microbial Assay:** This was determined by the agar diffusion test employing "cup plate technique". Sterile solutions of Ciprofloxacin hydrochloride (marketed eye drops used as standard solution) and the different formulation(test solutions) these solutions were poured in to cups bored into sterile nutrient agar previously seeded with test organisms (Pseudomonas aeruginosa). After allowing diffusion of the solutions for 2 hours, the agar plates were incubated at 37ºC for 24hrs. The zone of inhibition (ZOI) measured around each cup was compared with that of control. The entire operation except the incubation was carried out in a laminar airflow unit.

- ***Invitro* drug release studies:** The *in-vitro* release of Levofloxacin from the prepared formulations was studied through dialysis membrane using dissolution testing apparatus10. The dissolution medium used was artificial tear fluid freshly prepared of pH 7.4.buffer dialysis membrane previously soaked over night in the dissolution medium was tied to one end of a specifically designed glass cylinder(open at bothendsof5cmdiameter)a2 ml volume of the formulation was accurately pipette in to this assembly. The cylinder was attached to the metallic drive shaft and suspended in 100 mlof dissolution medium maintained at 37±1^{o}c so that the membrane just touched the receptor medium surface. The shaft was rotated at 50-rpm aliquots each of 1 ml volume, was with dra wnat hourly intervals and replaced by an equal volumes of the receptor medium. The aliquots were diluted with receptor medium and absorbance was measured at 290nm.

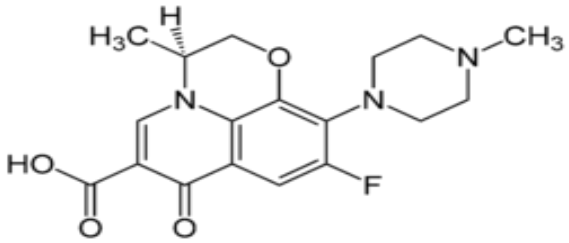
- **Drug Profile**

LEVOFLOXACIN[40]

Levofloxacin is a synthetic chemotherapeutic antibiotic of the fluoroquinolone drug class.

Chemical name :(S)-9fluoro-2, 3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4benzoxazine-6-carboxylicacid hemihydrates

- **Chemical structure**



- **PHARMACOKINETIC PARAMETERS**

Bioavailability: 99%
Protein binding: 28 to 38%
Metabolism: renal
Half life: 6 to 8hours
Molecular Formula: $C_{18}H_{20}F N_3O_4 \cdot ½H_20$
Molecular Weight: 370.38.
Colour: yellowish white to yellow powder.
Appearance: Transparent
Solubility: Sparingly soluble in water.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Levofloxacin is a broad spectrumantibiotic that is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase iv, which is an enzyme necessary to separate replicated DNA, thereby inhibiting cell division.

ADVERSE REACTIONS

- Irreversible peripheral neuropathy
- Acute liver failure or serious liver injury (Hepatitis)

CONTRAINDICATIONS

Pediatric use is contraincated due to the risk of serious, life-threatening and permanent injury to the pediatric patient. It is not use.

MATERIALS AND METHODS

S.No	Ingredients	F-1	F-2	F-3	F-4	F-5
1.	Drug	500mg	500mg	500mg	500mg	500mg
2.	Carbopol 940	0.3gm	0.3gm	0.3gm	0.3gm	0.3gm

3.	Hydroxy propyl methyl cellulose	0.5g	1gm	1.5gm	2gm	2.5gm
4.	Citric acid IP	0.407gm	0.407gm	0.407gm	0.407gm	0.407gm
5.	Disodium hydrogen phosphate IP	1.125gm	1.125gm	1.125gm	1.125gm	1.125gm
6.	Benzalkonium chloride (BKC)	0.02ml	0.02ml	0.02ml	0.02 ml	0.02ml
7.	Purified water	100ml	100ml	100ml	100ml	100ml

MATERIALS AND METHODS

Preparation of Levofloxacin *In situ* gel

pH Tiggered System

Step 1: Buffer salts were dissolved in 75ml of purified water, methocel E-50lv was added and allowed to hydrate, carbopol was sprinkled over this solution and allowed to hydrate overnight.

Step 2: The solution was stirred with an overhead stirrer, Levofloxacin was dissolved in small quantity of water, benzylkonium chloride (BKC) was added to this solution, the drug solution was added to the polymer solution was obtained.

Step 3: Purified water was then added to make up the volume to 100ml of this solution was filtered through 0-2mm filter paper. The drug was incorporated in a sufficient quantity of 0.5M NaoH and then added to the polymer solution to get a clear solution of drug and polymer.

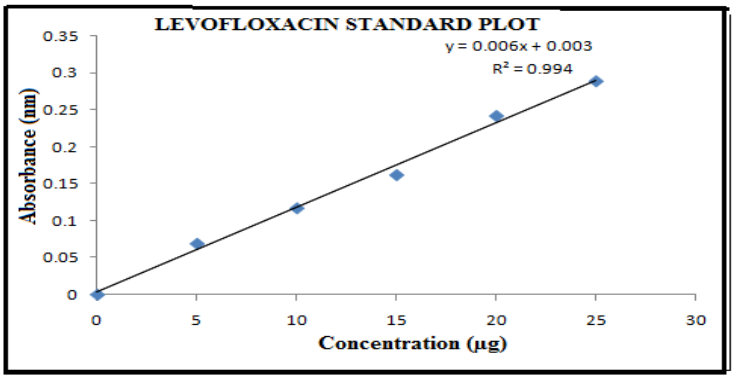
EXPERIMENTAL WORK

PREFORMULATION STUDIES

Organoleptic properties

Colour: yellowish white to yellow powder.
Appearance: Transparant
Solubility: Soluble in water

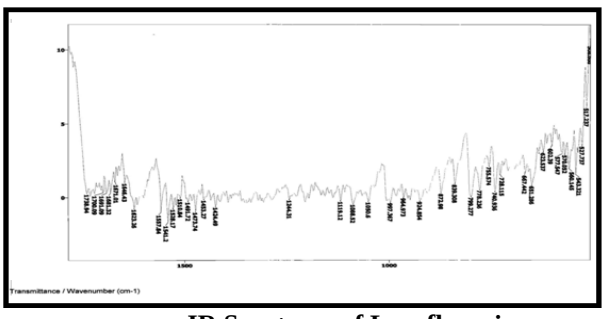
Calibration curve of Levofloxacin



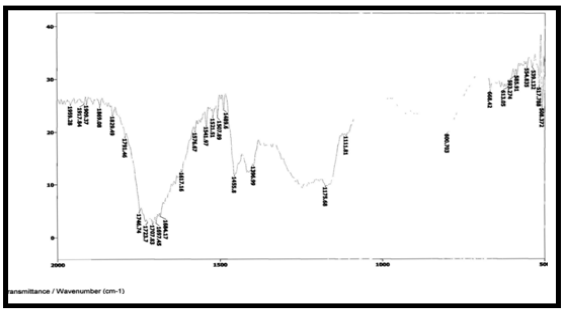
Concentration (µm)	Absorbance (nm)
0	0
5	0.069
10	0.117
15	0.162
20	0.242
25	0.289

Compatibility studies

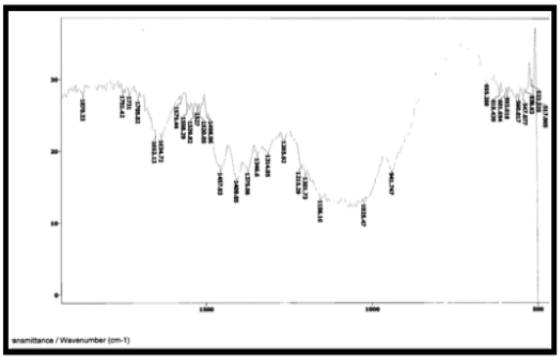
Fouriertrans formin frared spectroscopy



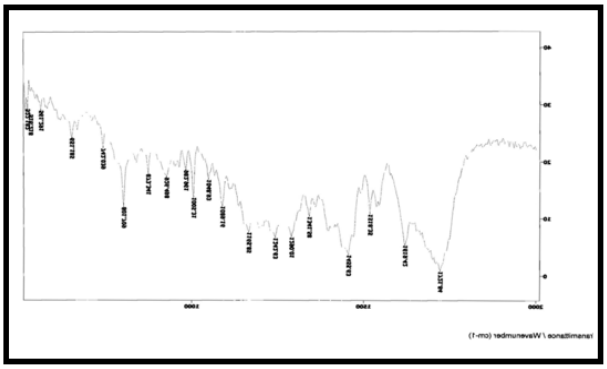
IR Spectrum of Levofloxacin



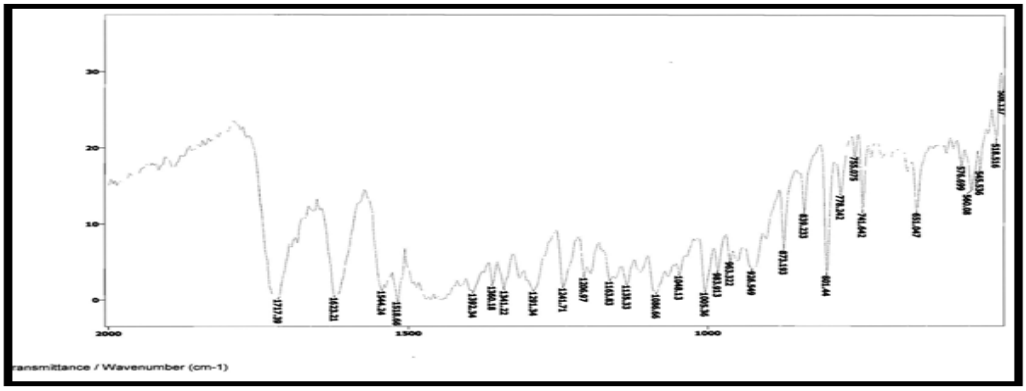
IR spectrum of carbopol-940



IR Spectrum of HPMC E50



Spectrum of Levofloxacin and carbopol-940



IR Spectrum of levofloxacin and HPMC E 50.

Preliminary Evaluation Studies of *In-Situ* Gel Formulations.

TESTS	F-1	F-2	F-3	F-4	F-5
Visual appearance	Transparent	Transparent	Transparent	Transparent	Transparent
Clarity	clear	Clear	Clear	Clear	Clear
pH	6.7	6.6	6.9	6.7	6.8
Drug content (%)	97±0.42	98±0.54	100±0.64	99±0.45	96±0.76

GELLING CAPACITY

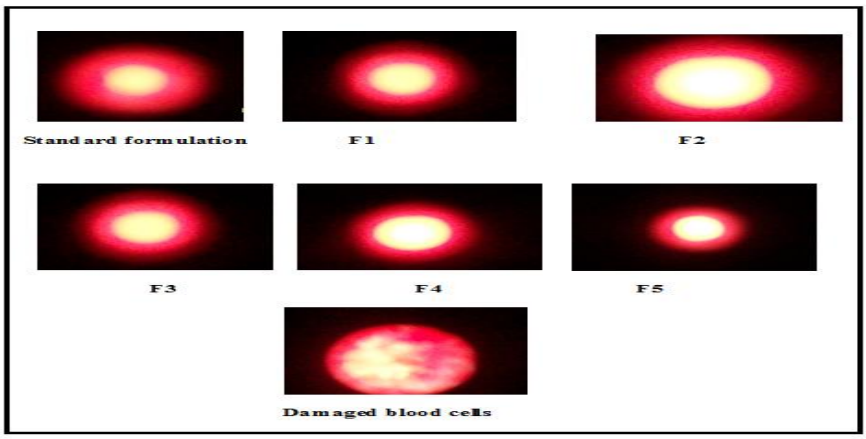
FORMULATION	GELLING CAPACITY
F-1	+
F-2	++
F-3	+++
F-4	+++
F-5	+++
+: Gels after few minutes. ++: Gelation immediate remains for few hours. +++: Gelation immediate remains, for extended period.	

RHEOLOGICAL STUDIES

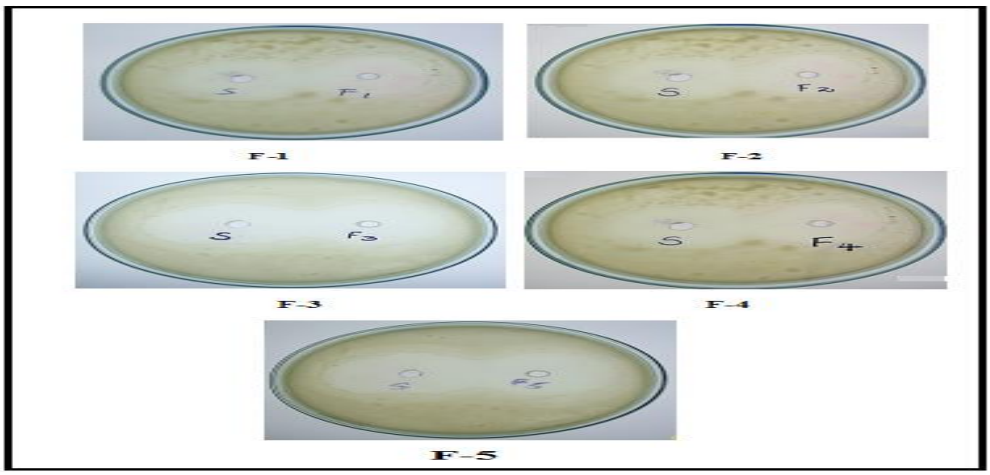
ANGULAR VELOCITY (rpm)	VISCOSITIES(cps)				
	F1	F2	F3	F4	F5
10	30	40	40	50	70
30	50	50	50	60	90
50	65	70	75	70	110
70	75	80	80	80	150
90	80	85	90	90	190
100	90	90	100	110	250

STERILITYTESTS

ISOTONICITY TEST

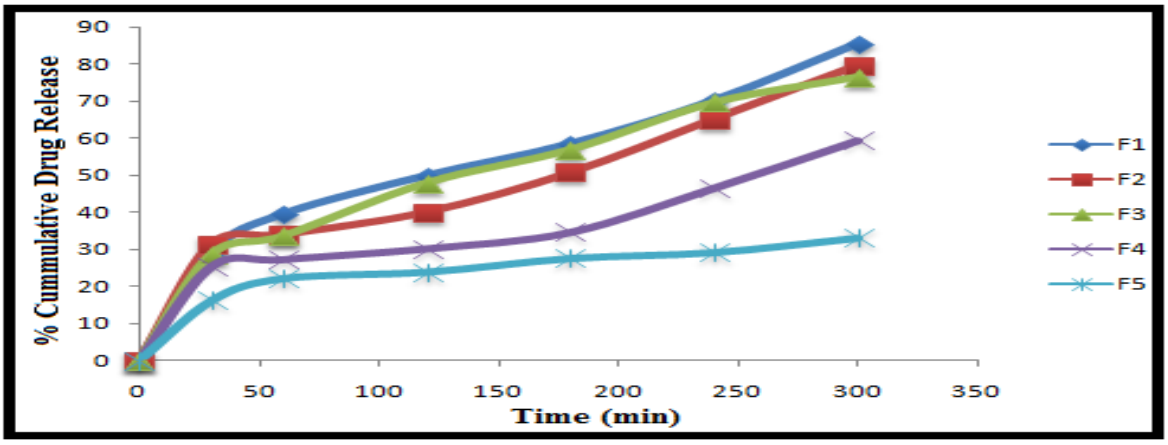


ANTIMICROBIAL EFFICACY STUDIES



***In vitro* drug release studies**

S.NO	TIME	%CUMMULATIVE DRUG RELEASE				
		F-1	F2	F-3	F-4	F-5
1	0	0	0	0	0	0
2	30	29.20±0.10	31.34±0.11	28.57±0.1	25.32±0.12	16.48±0.15
3	60	39.47±0.12	33.91±0.09	33.54±0.1	27.24±0.10	22.18±0.08
4	120	49.82±0.1	39.99±0.1	47.83±0.1	30.18±0.10	23.93±0.1
5	180	58.36±0.1	50.63±0.1	56.77±0.11	34.59±0.11	27.62±0.1
6	240	70.05±0.1	65.10±0.1	69.45±0.1	46.55±0.11	29.23±0.11
7	300	85.31±0.1	79.50±0.1	76.30±0.1	59.39±0.10	33.13±0.1



***In-vitro* diffusion Profiles of Levofloxacin.**

Rabbit conjuctival observation

Redness	Normal rating	Rating for formulation
		F-3
Vessels normal	0 none	0
Vessels definitely injected above Normal	1 slight	0
More diffuse, deeper crimson red with individual vessels not easily discemible	2 moderate	0
Diffuse beefy red	3 severe	0

Ocular irritation studies

opacity	Normal rating for opacity	Rating for formulation	Area of cornea involved	Normal rating for opacity	Rating for formulation
		F-3			F-3
No opacity	0 None	0	25% or less(not 0)	1	0
Diffuse area, details of iris clearly visible	1 Slight	0	25% to 50%	2	0
Easily visible translucent areas, details of iris slightly obscure	2 Mild	0	50% to 75%	3	0
Opalescent areas, no details of iris	3 Moderate	0	Greater than 75%	4	0
Opaque, iris invisible	4severe	0	_	_	0

SUMMARY AND CONCLUSION

- Ophthalmic drug delivery is one of the most interesting and Challenging endeavors facing the pharmaceutical scientists. Although very few ophthalmic formulations containing bio adhesive or penetration enhancer are commercially available in the market, research in this area has provided a new impetus and dynamism, as never before, for the development of modified or novel ophthalmic formulations.
- A major problem in ocular therapeutics is the attainment of optimal drug concentration at the site of action, which is compromised mainly due to precorneal loss resulting in only a small fraction of the drug being ocularly absorbed. The effective dose administered may be altered by increasing the retention time of medication into the eye by using *in*

situ gel forming systems.

- The developed formulations are viable alternative to conventional eye drops by virtue of its stability to enhance bioavailability through its longer precorneal residence time and ability to sustain drug release. Also important is the ease of administration afforded and decreased frequency of administration resulting in better patient acceptance.

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