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Development and Characterization of In-Situ Gel Forming Ophthalmic Formulation of Carteolol

Vaishnavi Jadhav*, Nidhi Bais, Sachin Kumar Jain and Sudha Venugurlekar

Faculty of Pharmacy, Oriental University, Indore (M.P.) - India

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Abstract

Eye is the most vital organ of body. The usual ophthalmic dosage forms are account for 90% of currently accessible ophthalmic formulations. Th emajor trouble encountered is quick precornel drug loss. To improve oph thalmic drug bioavailability, there are considerable efforts directed towar ds newer drug delivery systems for ophthalmic administration. Newer research in ophthalmic drug delivery systems is directed towards an amalgamation of several drug delivery technologies, that includes to buid up systems whichis not only extend the contact time of the vehicle at the ocular surface, but which at the same time slow down the removal of the drug. Conventional delivery systems often result in poor bioavailability and therapeutic response because high tear fluids turn over and dynamics causerapidelimination of the drug from the eyes. So, to overcome bioavai lability problems, ophthalmic in situ gels were developed.

Key Words: Insitu gel, Novel ocular drug delivery system, insitu system, Ophthalmic administration.

Introduction

The eye, which is also known as the window to our soul, is one of the body's most sensitive and important organs. In terms of anatomical and physiological structure, the eye is a special organ. The eye is thought of as a unique organ that prevents the entry of any foreign chemicals.Drug delivery systems for the eyes have emerged as one of the most fascinating and difficult fields of pharmaceutical research. [2,4] The eye contains a number of intricate defence mechanisms that make it challenging to achieve an effective concentration of drug within the targeted region of the eye, making drug delivery to the ocular region particularly challenging.The therapeutic dose of the drug and the clinical evaluation of the drug are necessary for targeting drugs using an ocular drug delivery system. [1,5]

Overview of Glaucoma

A set of multifactorial optic neuropathies known as glaucoma are characterised by a severe loss of retinal ganglion cells and an atrophy of the optic nerve. A normal eye can only tolerate a gradual increase in intraocular pressure (IOP) when glaucoma is present. The mean IOP of 15.5 2.57 mmHg indicates that the human eye is in good health. [34,56] IOP of 20.5 mmHg or above can indicate glaucoma suspicion, and IOP of 24 mmHg or higher indicates glaucoma confirmation.

Open angle glaucoma: It is characterised by a partial or total obstruction of the trabecular meshwork, which prevents the outflow of aqueous humour and raises IOP, resulting in glaucoma. [45,61]

***Corresponding Author**

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Closed-angle glaucoma: In this kind, the iris-cornea angle becomes partially or totally closed, obstructing the flow of aqueous humour and raising IOP as a result.[12,16] There may or may not be a partial or total blockage of the trabecular meshwork.

Types of Preservatives

There are several preservatives, but only a few are used frequently in topical ophthalmic preparation. (Table-2) Preservatives typically work by one of two basic mechanisms: they are either detergents or act through oxidative processes. Detergents (or,more specifically surfactants) act by dissolving or disrupting lipids.[23,56]

Common Preservatives Used for Ophthalmic Solutions[24,14]

Compound class	Example
Quaternary ammoniums	Benzalkonium chloride (BAK), Polyquaternium-1
Mercurials	Thiomersal, Phenyl mercuric nitrate, Phenyl mercuric acetate
Alcohols	Chlorbutanol, Benzyl alcohol
Carboxylic acid	Sorbic acid
Phenols	Methyl/propyl paraben
Amidines	Chlorhexidine
Other	Disodium EDTA

Factors Affecting Preservative Activity:[22,25,15]

Concentration (Dilution or Loss)
pH (non-optimal range)
Temperature (Non optimal range)
Partitioning

Diagnosis and therapy of Glaucoma

IOP can be determined in a variety of ways, including the visual acuity test, gonioscopy, pupil dilation test, tonometry, ophthamoscopy, perimetry, and pachymetry, for the diagnosis of glaucoma. Early detection is key to treating glaucoma because it does not yet have serious side effects like visual loss. [12,16] Anti-glaucomtic medications, such as betablockers, prostaglandins, alpha-adrenergic agents, carbonic anhydrase inhibitors, and para sympathomimetics, are the mainstay of glaucoma treatment.

Topical ocular drug delivery and the constraints to ocular therapy [36,38]

For ailments of the eye, topical administration is usually preferred over systemic administration for obvious reasons:

- The systemic toxicity of many ophthalmic drugs,
- The rapid onset of action, and
- The smaller dose required compared to the systemic route. The topically applied ocular drugs have to reach inner parts of the eye to elicit responses.

Drug Profile

Carteolol

Carteolol is a non-selective beta blocker used to treat glaucoma. It has been found to act as a serotonin 5-HT_{1A} and 5-HT_{1B} receptor antagonist in addition to being a beta blocker. It is an optically active drug and generally formulated for topical ophthalmic use. It was patented in 1972 and approved for medical use in 1980.

Structure

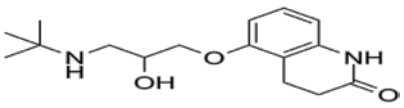

Figure 01: Structure of Cartolol

The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, bronchospasm, congestive heart failure and hypotension.Carteolol ophthalmic is used in the treatment of:Glaucoma, Open Angle,Intraocular Hypertension.The primary mechanism of the ocular hypotensive action of carteolol in reducing intraocular pressure is most likely a decrease in aqueous humor production. This process is initiated by the non-selective beta1 and beta2 adrenergic receptor blockade.

Experimental Details

A. Materials & Equipment's

Excipient Name	Company Name	Excipient Name	Company Name
Drug Carteolol	Sun pharma laboratories	Mechanical stirrer	Bombay India ltd.
Poly acrylic acid (Carbopol	Sun pharma laboratorie	Brookfield viscometer	A.R. and Companies

940)	s		
Hydroxy propyl methyl cellulose	Sun pharma laboratories	Electronic Balance	A&D Company, Japan
Tween 20	S.D. Fine chem Ltd	Magnetic Stirrer	MC Dalal & co
Benzalkonium chloride	Nice chemicals	UV Visible Spectrophotometer	UV Pharma spec 1700, Shimadzu
Di-sodium hydrogen phosphate	Nice chemicals	FTIR Spectrophotometer	FTIR, Shimadzu
Citric acid	Nice chemicals	Environmental chamber	Inlab equipment's (Madras pvt ltd)
Sodium chloride	Loba chemie		
Hydrochloric acid	Nice chemicals		
Sodium hydrogen carbonate	Merck		
Calcium chloride	Nice chemicals		
Sodium hydroxide	Nice chemicals		

C. PREFORMULATION study

Preformulation studies were commenced by characterisation of drug substance and excipients. carteololwas characterised for physicochemical properties as per compendial and non-compendial specifications including Melting point, Solubility, UV and IR.

D. calibration curve for Carteolol preparation of calibration medium

Simulated tear fluid or artificial tear fluid: - Sodium chloride -0.670g, sodium bi carbonate - 0.200g, calcium chloride - 0.008g is placed in 100ml volumetric flask and dissolved and make up to volume with distilled water.

Preparation of standard curve for Carteolol:- The standard stock solution of carteololis prepared by dissolving a known amount of drug in sodium hydroxide solution and dilution with simulated tear fluid. From the above stock solution, different concentrations of 5,10,15,20……50µg/ml is prepared in simulated tear fluid. The resulting solution is scanned in UV Spectrophotometer to find λ max and the absorbance is measured at λ max (229nm). The standard curve is plotted by taking concentration in X-axis and absorbance in Y-axis. The standard curve is used to estimate drug content and percentage drug release.

E. Formulation of pH triggered in situ gelling system of Carteolol

Optimum concentration of polymers Carbopol is a polyacrylic acid (PAA) polymer, which shows sol to gel transition in aqueous solution as the pH is raised above its pka of about 5.5.

It is noted that carbopol concentration 0.2% (W/V) had free flowing properties and this composition could not form gel at physiological condition. On the other hand,carbopol concentration above 0.5%(W/V) formed stiff gel even at pH 4.0.Based on the work of Helene hagerstrom, the carbopol concentration was fixed from 0.25 %(W/V) to 0.5 %(W/V). The HPMC of different grades in concentration fixed form 0.5 %(W/V) to 1.5 %(W/V) and the formulations made. Various in situ gelling system of carteolol is prepared by utilizing the phase transition properties of hydroxy propyl methyl cellulose, E15LV, E50LV, K4M grade and carbopol 940 in different ratios by using pH triggered in situ gelling system.

Selection of vehicle

The vehicle is selected based on the solubility and stability of the drug. The solubility of carteolol is starting from the pH 2.0 to pH 6.5 and maximum at pH6.2. The marketed formulation showed the pH 6.2.For these reasons the citro-phosphate buffer pH 6.0 is selected as vehicle for carteolol.

F. Preparation of pH-triggered in situ gelling system

Aqueous solutions of varying concentrations of Carbopol 940 and Hydroxy propyl methyl cellulose of different grades are prepared. The buffer salts are dissolved in specified quantity of purified water. To this methocel (E15LV, E50LV, K4M) is added and allowed to hydrate. Carbopol 940 is sprinkled over this solution and allowed to hydrate overnight. The solution is stirred with an overhead stirrer, Tween 20 added whilst stirring. carteololis dissolved in sodium hydroxide solution and pH is adjusted. Benzalkonium chloride (BKC) is then added and the solution is filtered. All the formulations are sterilized using autoclave at 121˚C and 15 p.s.i for 20 minutes.

Table no :01 composition of Carteolo in situ gel

S.No	Materials	Formulations					
		F-1	F-2	F-3	F-4	F-5	F-6
1.	Carteolol	50	50	50	50	50	50
1	Cabapol (0.2 %) Polyacrylic acid	0.50	0.50	0.50	0.50	0.50	0.50
2	HPMC (0.5-1.5%W/V)	0.7	0.5	0.8	1.1	1.4	1.0
3	Methanol	20	30	26	28	30	25
4	Tween 20	32	20	21	20	23	22
5	Sodium hydroxide	25	27	26	24	22	24
6	Bezalkonium chloride	0.01 %	0.01 %	0.01 %	0.01 %	0.01 %	0.01 %
7	Purified water	Up to 100	100	100	100	100	100

G. Evaluation of formulated in situ gelling system

The formulated carteololin situ gels is evaluated for clarity, pH measurement, gelling capacity, drug content measurement, rheological study, sterility test, in vitro release study, anti-microbial activity, eye irritation testing and stability testing. Determination of visual appearance, clarity and color. The visual appearance, clarity and color of the in-situ gel formulation is noted.

Determination of visual appearance, clarity and color

The visual appearance, clarity and color of the in-situ gel formulation is noted.

PH measurement

The pH of all the prepared in situ gelling system is measured by using pH meter. Drug content analysis Drug content of in situ gel is determined by taking 2ml of in situ gel containing a known amount of drug in a 100ml volumetric flask and diluted with simulated tear fluid of ph 7.4 to get the concentration of 10µg/ml.

Texture analysis

The consistency, firmness and cohesiveness of ins itu gel are assessed byusing texture profile analyz er which mainlyindicatedgel strength and easiness in administration invivo. Higher values of adhesi veness of gels are needed to maintain an intimate contact with mucus surface.

Gelling capacity

The prepared in situ gelling system is evaluated for gelling capacity in order to identify the composition suitable for use as in situ system. The in-situ gelling system is mixed with simulated tear fluid in the proportion of 25:7(application volume 25µl.normal volume of tear fluid in the eye is 7µl).

1. **In vitro release studies**

This was in turn placed on an inverted USP basket kept inside a 250-ml beaker. Dissolution medium of 200ml of simulated tear fluid is added and stirred with a magnetic bead. Temperature of 37±1◦C is maintained throughout the study. The absorbance of the samples is measured at λ max (288nm) by UV-spectrophotometer using blank to calculate amount of drug release from in situ gel. The percentage of drug release is plotted against time to find the drug release pattern of all in situ gel preparation.

2. **Rheological studies**

The relationship between contact time and the rheology is easily understood for viscosity enhanced ophthalmic solutions. Viscosity determinations of the prepared formulations are carried out by Brookfield synchroelectric viscometer (LVDV Pro II), spindle S18(small sample adaptor) and the angular velocity increased from 0.01,0.1,0.5,1.0,5.0,10,20,50,75 to 100 and measurements are noted.

3. **Antimicrobial activity**

Antimicrobial efficiency studies are carried out to ascertain the biological activity of sol-to-gel systems against microorganisms. This is determined by agar diffusion test employing “cup plate technique”. Sterile solution of marketed carteolol eye drops is used as a standard. After allowing diffusion of solutions for two hours, the plates are incubated for 24h at 37°C.The zone of inhibition (ZOI)measured around each cup is compared with that of the standard.

4. **Sterility testing**

Sterility testing is carried out by incubating formulations for not less than 14 days at 30 to 35°c in case of fluid thioglycolate medium for bacteria and at 20 to 25◦c in case of soyabean-casein digest medium for fungi and observations made.Samples were removed periodically (1, 2 and 3 months) and examined for drug content and particle size.

5. **Ocular irritancy studies**

Ocular irritation studies are performed on male albino rabbits weighing 1- 2kg.The modified Draize technique is designed for the ocular irritation potential of the ophthalmic product.

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According to Draize test, the amount of substance applied to the eye is normally 100 µl placed to the lower cul-de-sac and observed at the time interval of 1hr,24hrs,48hrs,72hrs, and 1 week after administration. The rabbits observed periodically for redness, swelling and watering of the eyes.

10. Accelerated stability studies

The sol-to-gel systems are placed in amber-colored vials and sealed with aluminium foil for a short term accelerated stability study at 40◦±2◦c and 75±5% RH as per International Conference on Harmonization states guidelines. Samples are analysed every 15 days for appearance, pH, gelling studies and drug content.

11.FT-IR studies

The possibility of drug-excipient interactions is further investigated by FTIR. The FTIR graph of pure drug and combination of drug with excipient are recorded. The analysis is performed using KBR pellets.

RESULTS

A. PREFORMULATION STUDY

1.Melting Point: - An endothermic transition assignable to the melting of the compound was observed at a temperature of 249-250 ^{0}C which was observed for the drug as well as for drug excipient blend.

2. Solubility: -Carteolol (hydrochloride) is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide, which should be purged with an inert gas. The solubility of carteolol (hydrochloride) in these solvents is approximately 11, 16, and 14 mg/ml, respectively.

3.UV:- The developed method (UV-spectroscopy) was found to be simple, accurate, sensitive and reproducible can be used for routine quality control analysis of Carteolol Hydrochloride.

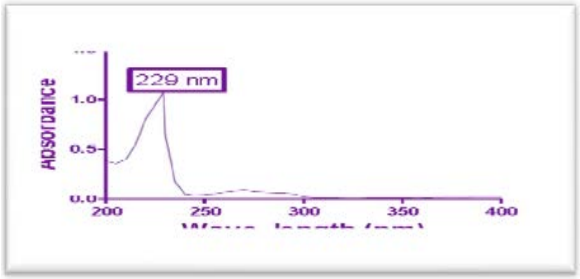

Figure 02:lambda max of Carteolol Hydrochloride.

4.IR:-The prominent peaks characteristic of functional groups like –F, - C=O, -NH stretching, -OH and aromatic substitution were retained at characteristic frequency values in pure drug as well as in excipient blend as indicated in Table 2 and Fig 03.

TABLE 02: REPORTED AND OBSERVED IR FREQUENCY OF MOXIFLOXACIN HYDROCHLORIDE AND ITS COMBINED BLEND

Functional group	Reported frequency (in cm-1)	Observed frequency in pure frug (in cm-1)	Observed frequency in combined blend (in cm-1)
-F	1091	1091	1090
-C=O	1698	1698	1698
-NH stretching	3467	3466	3465
O-H	3527	3525	3527
Aromatic substitution	788	788	785

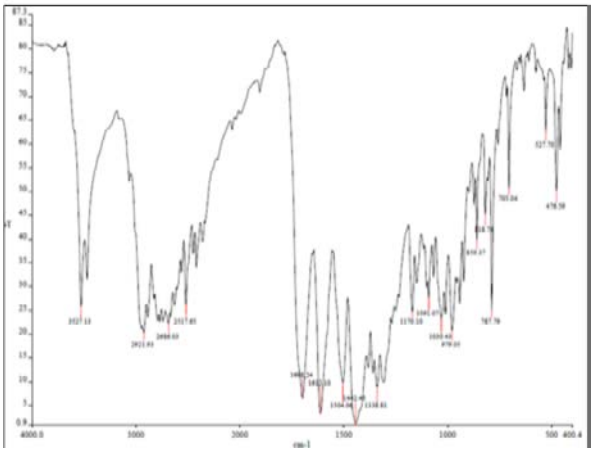

FIG. 03: IR SPECTRUM OF CARTEOLOL

B. CALIBRATION CURVE OF CARTEOLOL

Calibration curve of carteololwas done in simulated tear fluid pH-7.4. carteololshows λmax of 229 nm in simulated tear fluid pH7.4.The correlation coefficient was 0.99929866.Hence, carteolol obeys the beer's law within the concentration range of 5 to 50µg/ml. Calibration plots of carteololin simulated tear fluid was showed in table 03 and fig.17.The maximum absorbance showed in fig.17.

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TABLE 03: CALIBRATION PLOTS OF CARTEOLOL IN SIMULATED TEAR FLUID

Sr.No.	Con (µg/ml)	eat229nm±standarddeviation
1	2	0.226±0.0026
2	4	0.386±0.00360
3	6	0.581±0.00556
4	8	0.768±0.00503
5	10	0.958±0.0036
6	12	1.165±0.0020
7	14	1.326±0.00305
8	16	1.555±0.00360
9	18	1.745±0.0055
10	20	1.931±0.002636

Figure 04:Standard Calibration curve

C.RESULTS

Table no 04: PHYSICAL PROPERTIES

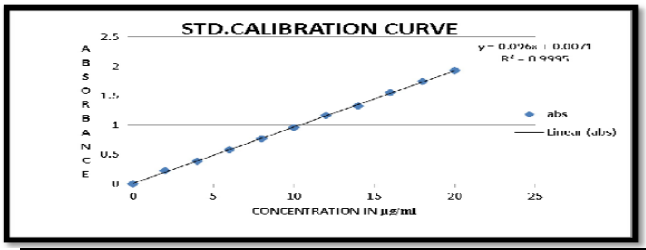
	F-1	F-2	F-3	F-4	F-5	F-6
Visual Appearance	Gel like	Gel like	Gel like	Gel like	Gel like	Gel like
Clarity	Clear	Clear	Unclear	Clear	Clear	Unclear
Color	Whitist	Whitist	Whitist	Whitist	Whitist	Whitist
pH Measurement	7.3	7.5	7.3	7.4	7.5	7.4
Texture Analysis	Gel Like	Gel Like	Gel Like	Gel Like	Gel Like	Gel Like

Gelling capacity:

The viscosity and gelling capacity plays important role for in situ gelling system. The formulation should have an optimum viscosity for easy instillation into the eye as a liquid which undergo sol-to-gel transition. The gelling capacity of various formulation given in table no.4 F-4 and F-6 showed better gelling capacity. The other formulations were not having desirable gelling capacity.

In vitro drug release: The formulated gels F2, F4, F5 prolonged the release of drug for 10-12 hr whereas F1, F3, F6 release drug quickly within 6-8 hr. Comparatively, the release rates of F3 and F6 were faster than their former formulations.

Table no: 05In Vitro drug release



S.No	Time	% Drug release
F-1	6-8 hr	20%
F-2	10-12 hr	40%
F-3	6-8hr	50%
F-4	10-12hr	70%
F-5	10-12hr	80%
F-6	6-8hr	100%

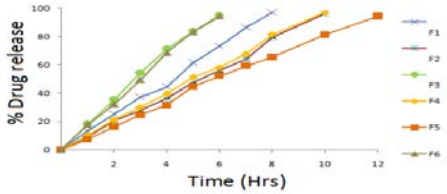


Figure 05: In vitro drug release from the hydrogel

RHEOLOGICAL STUDIED

Table 06: RHEOLOGICAL STUDIED Figure 06: Rheological study

Formulation	Viscosity	Speed
F-1	50	0.01
F-2	100	0.1
F-3	200	5.0
F-4	400	20
F-5	600	50
F-6	800	100

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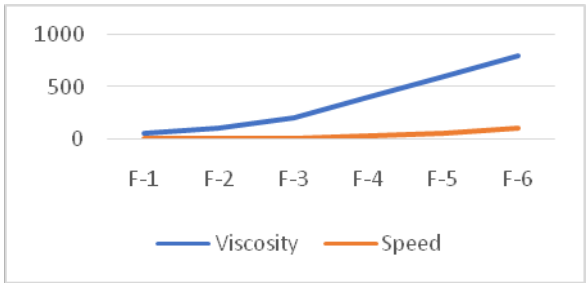
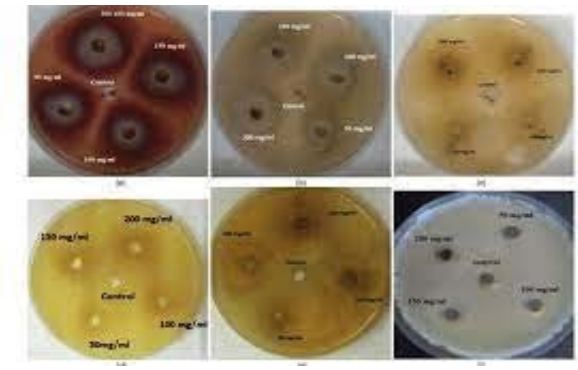


ANTI-MICROBIAL STUDY



Here antimicrobial study were performed between 6 samples the sample F-6 shown good activity as compare to others.

Figure 07: Anti-microbial stud

STERILITY STUDY

Table 07: Sterility study

Formulation	Drug content	Particle size
Thioglycolate medium		
F-1	20gm	12-17
F-2	25gm	18-20
F-3	22gm	21-24
F-4	21gm	26-28
F-5	20gm	30-32
F-6	18gm	34-38
Soyabean-casein digest medium		
F-1	22gm	12-13
F-2	26gm	14-20
F-3	22gm	20-26
F-4	27gm	23-29
F-5	15gm	31-35
F-6	14gm	38-40

Figure:08 sterility study data

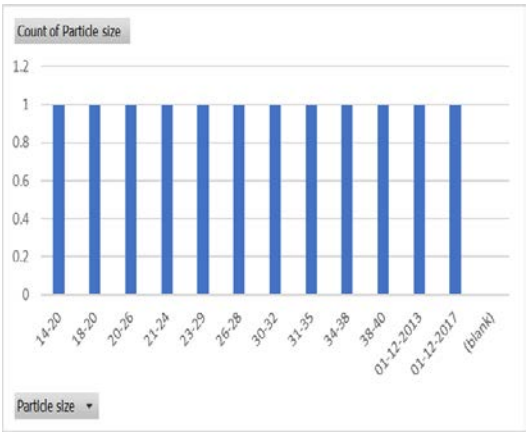


Table:08OCCULAR IRRITANCYACCELERATED STABILITY STUDIES

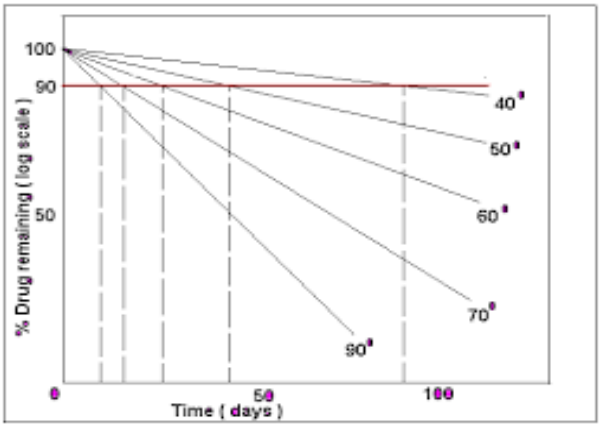


Figure:09 accelerated stability study

Formulation	Male albino rabbit	Time interval
F-1	Swelling	1hr,24hr,48hr,72hr and 1week
F-2	Redness	1hr,24hr,48hr,72hr and 1week
F-3	Watering of eye	1hr,24hr,48hr,72hr and 1week
F-4	Swelling	1hr,24hr,48hr,72hr and 1week
F-5	Watering of eye	1hr,24hr,48hr,72hr and 1week
F-6	Watering of eye	1hr,24hr,48hr,72hr and 1week

FT-IR STUDIES

FT-IR spectrum of pure drug and mixture of drug and polymers and given in fig no. From this study it was observed that there were no significant changes between the spectrum of pure drug and the mixture. It showed that there were no specific interactions between the drug and excipients used in the formulations.

Table 17:FT-IR data

S.no	IR -interpretation
F-1	4000-3000
F-2	3000-2000
F-3	2000-1500
F-4	1500-1000
F-5	1000-500
F-6	500-200

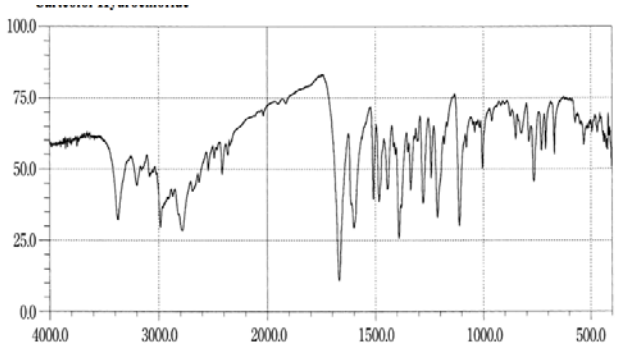


Figure 10:FT-IR Data

SUMMARY AND CONCLUSION

The purpose of this research was to develop a novel ophthalmic in situ drug delivery system of carteolol to improve its poor ocular bioavailability. The ocular in situ gel of carteolol was prepared by using carbopol 940 and HPMC by pH-triggered in situ gelling technique. The broad-spectrum antibacterial agent used in the treatment of ocular infections like conjunctivitis was successfully formulated in situ gelling system using 0.5%W/V of carteolol.The better gelling capacity was obtained by optimized concentrations of carbopol 940 and HPMC when these two vehicles were combined, the gel strength and gelling capacity under physiological conditions were appropriate. The formulations showed better gelling capacity which can be easily instil as a drop. In order to achieve high stability all, the formulations sterilized by autoclave at 121c and 15 p.s.i for 20 minutes.The test for anti-microbial efficacy proved the formulation to be therapeutically efficacious. Stability studies indicated that the drug retention capacity of in situ gelling system was not changed significantly. The methodology adopted for the in-situ gelling system is cost effective. The in-situ gelling formulation evaluated here has potential in ophthalmic use, for reason that it is more readily administered and hence the pH-triggered in situ gelling considered to be promising for prolonging the ocular residence time without causing irritation to eyes and a viable alternative to marketed eye drops.

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