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Formulation and Development of Environmentally Responsive Ophthalmic *In-Situ* Gel For Brimonidine Tartrate

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ABSTRACT

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. Brimonidine tartrate is an antiglaucomic agent which shows rapid precorneal exclusion and reduced ocular bioavailability when given in form of conventional ophthalmic formulations. The poor bioavailability and therapeutic response exhibited by conventional ophthalmic solutions may be overcome by the use of in-situ gel forming ophthalmic systems that are instilled as drops into the eye and undergo a sol–gel transition in the cul-de-sac. In the present study, environmentally responsive ophthalmic drug delivery system composed of two gelling polymers with different phase transition mechanisms was developed. Combination of polyacrylic acid (carbopol 934P) and xanthan gum was investigated as ophthalmic vehicle. Different ratios of these polymers were used to prepare environmentally responsive ophthalmic drug delivery system by simple mixing procedure. Developed formulation was assessed for various evaluation parameters such as appearance/clarity, pH, gelation, drug content, rheological measurement, in-vitro release, and sterility testing and stability study. Prepared formulation showed agreeable appearance/clarity, acceptable pH and good gelation property. In-vitro studies demonstrated adequate drug content, desired rheological behaviour and reasonable in-vitro drug release property. Formulation was stable over one month period. In conclusion, the optimum concentration of polymers results in minimized drug loss and sustained drug release. On the basis of these findings, prepared in-situ gel may be considered as a viable alternative to conventional brimonidine tartrate eye drops.

Keywords: carbopol 934P, xanthan gum, brimonidine tartrate, antiglaucomic

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INTRODUCTION

There are several possible routes of drug delivery into the ocular tissues. The selection of the route of administration depends primarily on the target tissue. Traditionally subconjunctival injections have been used to deliver drugs at increased levels to the urea. Currently this mode of drug delivery has gained new momentum for various reasons. The progress in materials sciences and pharmaceutical formulation have provided new exciting possibilities to develop controlled release formulations to deliver drugs to the posterior segment and to guide the healing process after surgery.

The major problems in conventional liquid ophthalmic formulations are washing out of drug from the pre-corneal area immediately upon instillation because of constant lachrymal secretion, nasolacrimal drainage and short precorneal residence time of the solution. To increase precorneal residence time and ocular bioavailability, different ophthalmic delivery system such as viscous solutions, ointments, gels, suspensions or polymeric inserts are used. But because of blurred vision (e.g. ointments) or lack of patient compliance (e.g. inserts), these formulations have not been widely accepted. This problem can be overcome by using *in-situ* gel forming ocular drug delivery system, prepared from polymer, exhibit sol-to-gel phase transition due to a change in a specific physico-chemical parameter (pH, temperature, ion-sensitive). This new concept of producing a gel *in-situ* was suggested first time in the early 1980s. Gelation occurs via the cross linking of polymer chain that can be achieved covalent bond formation (chemical cross linking) or non-covalent bond formation (physical cross linking). The rate of *in-situ* gel formation is important because between instillation in eye & before a strong gel is formed; the solution or weak gel is produced by the fluid mechanism of eye. They are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form viscoelastic gel and this provides a response to environmental changes. Three methods have been employed to cause phase transition in the eye surface. These are change in pH, change in temperature and ion activation.

MATERIALS AND METHOD

Preformulation testing is the first step in rational development of dosage forms of a drug substance. Preformulation study is the process of optimizing the delivery of drug through determination of physicochemical properties of the new compound that could affect drug performance and development of an efficacious, stable and safe dosage form.

Determination of melting point

Melting point of brimonidine tartrate was determined by capillary method.

Compatibility studies

FTIR spectroscopy was carried out to check the compatibility between drug and polymers. The FTIR spectra of drug with polymers were compared with the standard FTIR spectrum of the pure drug.

Selection of vehicle

The solubility of brimonidine tartrate was tested in distilled water. Solution of brimonidine tartrate in the above vehicle was prepared to test its solubility at the dosage level desired (0.15% w/v).

Stability testing in different pH vehicles

Brimonidine tartrate stability was tested in STF (pH 7.4) and pH 5.0 solution (prepared by adjusting pH of distilled water with 0.5 N HCl). 0.15% w/v solution of brimonidine tartrate was prepared in both vehicles. 1 mL samples were withdrawn at 0, 1, 4, 8 and 24 h from both solutions. Samples were diluted to 100 mL with STF and analyzed by UV-visible spectrophotometer at 256 nm.

Standard calibration curve of brimonidine tartrate

Calibration curve of brimonidine tartrate was taken in STF pH 7.4. Stock solution of drug was prepared by dissolving 50 mg of drug in STF and making volume upto 50 mL with STF. 5 mL of stock solution was taken and diluted upto 50 mL with STF. Solutions of 3, 6, 9, 12, 15 and 18 µg/mL were prepared by diluting respectively 1.5,3, 4.5, 6, 7.5 and 9 mL of above solution to 50 mL with STF. Absorbance of all the solutions was measured by UV-visible spectrophotometer at 256 nm. Calibration curve was prepared by plotting concentration (µg/mL) on X-axis and absorbance on Y-axis.

Preliminary experiments

Selection of concentration of carbopol and xanthan gum

Based on literature review it is observed that carbopol 934P is used in the concentration range 0.1-0.5% w/v for ophthalmic *in-situ* gel. In IIG database upper concentration limit for xanthan gum is specified as 0.6% w/v for ophthalmic use.

Preparation of preliminary batches

Selection of carbopol concentration

Carbopol 934P solutions of concentration 0.1 – 0.5% w/v were prepared by dispersing required amount of carbopol 934P in distilled water. pH was adjusted to 5.0 using 0.5 M NaOH and allowed to hydrate overnight. *In-situ* gelling capacity of each solution was checked to select the concentrations suitable for *in-situ* gel preparation.

Selection of xanthan gum concentration

Xanthan gum solutions of concentration 0.1 – 0.6% w/v were prepared in distilled water and evaluated for pourability on an arbitrary scale. Xanthan gum was combined in different concentration ranging from 0.1-0.5% w/v with 0.3% w/v carbopol 934P solution. *In-vitro* gelling capacity of formulations was determined.

Method of environmentally responsive ophthalmic *in-situ* gel preparation

The formulations were prepared by using carbopol 934P and xanthan gum in different concentration. All glass wares were soaked overnight in hot cleaning solution, rinsed with distilled water, drained and placed in dust free environment. They were sterilized in hot air oven at 160°C for 1 h. Closures were cleaned by washing with a detergent rinsing with purified water and placed in benzalkonium chloride solution (0.02% w/v) and were subjected to saturated steam at 115–116°C for 30 min. Solution 1 was prepared by dispersing appropriate quantities of carbopol 934P in 30 mL of distilled water. Solution 2 was prepared by dispersing required quantities of xanthan gum in distilled water. In case of solution 3, brimonidine tartrate, benzalkonium chloride and disodium edetate were dissolved in 10 mL of distilled water. Solution 1 and 2 were mixed together; after uniform mixing, solution 3 was added and final volume was made to 100 mL by adding remaining quantity of distilled water and pH was adjusted to 5.0 by drop wise addition of 0.5 M NaOH solution. Glycerol was added in required amount to maintain isotonicity of the formulation. Finally, the resultant solution was subjected to terminal sterilization by autoclaving at 121ºC and 15 psi for 20 min.

Prepared formulations were stored in refrigerator at 15 – 25oC until further use.

Composition of *in-situ* gel formulations

Based on preliminary experiments conducted final formulations were prepared using different concentration of carbopol 934P (0.3, 0.4 and 0.5% w/v) and xanthan gum(0.2, 0.3 and 0.4% w/v)

Effect of autoclaving sterilization

To study the effect of autoclaving sterilization on physicochemical properties of brimonidine tartrate *in-situ* gels, two representative formulations, formulation F1 and F9 were treated under the autoclaving sterilization conditions. Briefly, screw cap glass bottles containing 50 mL of *in-situ* gel were placed in an autoclave. They were exposed to steam at 121oC, under a pressure of about 15 psi, for 20 min. Then, they were evaluated for physicochemical properties i.e. appearance, % drug content, pH, viscosity and gelling capacity, and compared to those of them before being autoclaved.

RESULTS AND DISCUSSION

Identification of drug

Determination of melting point

Melting point of brimonidine tartrate was found to be in the range of 207-208ºC as reported in literature (207.5oC), thus indicating purity of the drug sample. Any impurity, if present, will cause variation in the melting point of a given drug substance.

Compatibility studies

The interaction of drug with excipients in the formulation was studied by FTIR spectroscopy. The IR spectra have been depicted in Figure 8 and 9. The characteristics peaks of pure brimonidine tartrate were found for –NH stretching at 3208.98 cm-1, –CN stretching at 1299.82 cm-1, carboxylate ions at 1592.33 cm-1, –C=O stretching at 1650.78 cm-1. Similar peaks were identified in the spectrum of physical mixture with minor differences in frequencies. Hence, it can be said that the drug had no interaction with excipients of formulation.

Selection of vehicle

Buffer play important role in stability of formulation by resisting pH change. Even though no buffer system was utilized in formulations because buffer system contains salt, which is incompatible with carbopol 934P. Decrease in viscosity with increasing concentration of NaCl as a salt. (Lubrizol, Pharmaceutical Bulletin 6, Thickening Properties). So distilled water was used throughout the experiment. Drug is freely soluble in distilled water. The solubility of BRT is found be pH dependent, with solubility higher on acidic side and decreasing as pH is increased. From the pKa value of 7.22, it is evident that drug is weakly basic in nature. It exists in predominately in ionized form at lower pH, hence a higher solubility of free base. As the pH is increased, solubility was found to decrease. The solubility in triple distilled water was found to be 29.85 mg/mL.

Stability testing in different pH vehicles

Results of stability testing at different pH. It is obvious that there was only minor difference in amount of drug in both pH solution at 0 h and 24 h. It indicates that drug was stable at both formulation pH (pH 5.0) and physiological pH of eye (pH 7.4).

Standard calibration curve of brimonidine tartrate

the absorbance of brimonidine tartrate standard solutions containing 0-18 µg/mL of drug in STF pH 7.4. Figure 12 shows a representative standard calibration curve with slope, regression coefficient, and intercept of 0.0516, 0.999, and 0.0008 respectively. The curve was found to be linear in the range of 0-18 µg/mL at λmax 256 nm. The calculations of the drug content, *in-vitro* release were based on this calibration curve.

Preliminary experiments

Selection of carbopol concentration

The two main prerequisites of an *in-situ* gelling system are viscosity and gelling capacity (speed and extent of gelation). Gelling capacity of different concentration of carbopol solutions. is shown in Table 1. Depending on gelling capacity carbopol solutions of 0.3, 0.4 and 0.5% w/v were selected for further studies.

Table 1: Gelling capacity of carbopol solutions

Solution	Carbopol 934P (% w/v)	Gelling capacity
1	0.1	-
2	0.2	-
3	0.3	+
4	0.4	+
5	0.5	++

- = no gelation

+ = gels after 1 to 2 minutes and dissolve within 1 h

++ = gels after 1 to 2 minutes and remains for 1 to 2 h

Selection of xanthan gum concentration

Xanthan gum was incorporated in the formulation as viscosity enhancer. Viscosity of xanthan gum solutions was checked in terms of pourability. Solutions of 0.1, 0.2 and 0.3% w/v were found to be easily pourable, 0.4 and 0.5% w/v moderately pourable, and 0.6% w/v difficult to pour. Due to high viscosity that leads to difficulty in pourability and compromises patient compliance, 0.6% w/v xanthan gum was not selected for preparation of *in-situ* gel. Gelling capacity of combination of different concentration of xanthan gum with 0.3% w/v carbopol is depicted in Table 2.

Table 2: Gelling capacity of carbopol - xanthan gum combinations

Formulation	Carbopol 934P (% w/v)	Xanthan gum (% w/v)	Gelling capacity
1	0.3	0.1	+
2	0.3	0.2	++
3	0.3	0.3	++
4	0.3	0.4	+++
5	0.3	0.5	+++

+ = gels after 90 s and dissolve within 1 h

++ = gels within 60 – 90 s and remains for 2 to 3 h

+++ = gelation within 60 s and remains for upto 5 h

These results clearly indicates that incorporation of xanthan gum in carbopol 934P solution decreases gelation time and increases time for which gel remains. 0.1% w/v xanthan gum was not suitable for current purpose because it does not improve gelling capacity to required extent. 0.5% w/v xanthan gum in combination with 0.3% w/v carbopol had more viscosity and it was difficult to pour. Keeping these facts in mind xanthan gum concentrations of 0.2, 0.3 and 0.4% w/v were selected for further studies.

Effect of autoclaving sterilization

Table 3 shows various physicochemical properties of formulations F1 and F9 before and after autoclaving sterilization.

Table 3: Effect of autoclaving sterilization on *in-situ* gel formulations

Formulations		Appearance	Clarity	Gelling capacity	Viscosity	pH	%Drug content
F1	Before autoclaving	Light yellow	Slightly translucent	+	375	5.0	99.25
	After autoclaving	Light yellow	Slightly translucent	+	375	5.1	98.73
F9	Before autoclaving	Light yellow	Slightly translucent	+++	1100	5.0	99.38
	After autoclaving	Light yellow	Slightly translucent	+++	1050	5.3	98.47

+ = gelation in 60–90 s and the formed gels collapsed within 2-3 h.

+++ = gelation within 60 s and stable for about 7–8 h.

It was found that autoclaving sterilization could not alter appearance, clarity, gelling capacity, viscosity, pH and % drug content of test samples significantly as seen in Table 3. This finding suggested that sterilization by autoclaving was suitable method of sterilization for prepared *in-situ* gels.

Evaluation parameters

Test for appearance/clarity

When all the formulations were observed against black and white background for appearance/clarity, pale yellow color of formulations was observed. All formulations were slightly translucent in nature, odorless and free from foreign suspended particles. Terminal sterilization by autoclaving had no effect on the clarity. Translucent nature of all the formulations was attributed to carbopol 934P. Upon neutralization carbopol 934P forms clear gel and cause no vision problem.

Determination of pH

The tolerable pH of human eye: ophthalmic preparations requires strict to pH range, the tolerance pH for human eye is 5.0–9.0. The pH of the formulations was found to be satisfactory and was in the range of 4.8 - 5.3. The formulations were liquid at room temperature and at the pH formulated. Terminal sterilization by autoclaving had no effect on the pH.

Table 4: Physicochemical properties of brimonidine tartrate *in-situ* gel

Formulation	Clarity	pH	Gelling capacity	Viscosity at 20 rpm (cP)	Avg. % drug content±SD
1	Slightly translucent	5.1	+	375	98.65±0.78

2	Slightly translucent	5.3	++	600	99.81±0.79
3	Slightly translucent	4.8	+++	950	98.56±0.86
4	Slightly translucent	5.3	++	425	99.94±0.78
5	Slightly translucent	5.0	++	675	98.86±0.90
6	Slightly translucent	4.8	+++	1000	100.80±0.93
7	Slightly translucent	4.9	++	450	98.99±1.03
8	Slightly translucent	5.2	+++	725	98.95±0.79
9	Slightly translucent	5.3	+++	1050	99.34±0.91

± SD indicates standard deviation, n = 3

+ = gelation in 60–90 s and the formed gels collapsed within 2–3 h

++ = gelation within 60 s but failed to maintain gel structure for more than 5 h

+++ = gelation within 60 s and stable for about 7–8 h

Drug content

Table 4 shows the percent drug content for all formulations. The drug content was found to be in acceptable range for all the formulations. Percent drug content of formulations lies between 98 – 101% indicating uniform distribution of drug.

Gelation studies

The two main prerequisites of an *in-situ* gelling system are viscosity and gelling capacity (speed and extent of gelation). The formulation should have an optimum viscosity that will allow easy instillation into the eye as a liquid (drops), which would undergo a rapid sol-to-gel transition. Additionally, to facilitate sustained release of drug to the ocular tissue, the gel formed *in-situ* should preserve its integrity without dissolving or eroding for a prolonged period of time. Table 4 shows the gelling capacity of all formulations.

Viscosity

Table 4 also shows the viscosity (cP) of all the formulations at 20 rpm measured using RV 03 spindle. The viscosity measured at 20 rpm was used for purpose of comparative evaluation. Figure 14 show the effects of independent variables on viscosity of the formulations. Viscosity increased in proportion with viscofying agent (xanthan gum) at all three concentration of gelling agent (carbopol), i.e. gelling agent had a little effect on viscosity. At formulation pH (pH 5.0) carbopol 934P is unneutralized, and unneutralized carbopol solutions have very low viscosity. On the basis of gelling capacity and viscosity, formulations F3, F6, F8 and F9 showed optimum results within the desired range. Hence, these four formulations were subjected for further evaluation parameters.

Rheological studies

Table 5 shows the viscosity values obtained for formulations F3, F6, F8 and F9 using Brookfield

RVT viscometer at different angular velocity at physiological condition (pH 7.4). Formulations were shear thinning and an increase in shear stress was observed with increase in angular velocity (pseudoplastic rheology). The results obtained from the rheological study of prepared *in-situ* gelling systems F3, F6, F8 and F9 revealed that the viscosity decreases as the angular velocity increases.

Table 5: Rheological profile of *in-situ* gelling systems

Angular velocity (rpm)	Viscosity (cP)			
	3	**6**	**8**	**9**
1	21000	24000	29000	31000
5	10200	11600	14400	15000
10	7400	7700	8700	9000
20	4100	4550	5300	5650
50	2240	2340	2500	2560
100	1600	1650	1780	1840

***In-vitro* release studies**

The release profile of a drug predicts how a delivery system might function and gives valuable insight into its *in-vivo* behaviour. The four *in-situ* gelling formulations of brimonidine tartrate F3, F6, F8 and F9 were subjected to *in-vitro* release studies. These *in-vitro* release studies were carried out using STF of pH 7.4 as the dissolution medium. The drug release data obtained for formulations F3, F6, F8 and F9 is tabulated in Table 6. Figure 1 shows the plot of cumulative percent drug released as a function of time for formulation F3, F6, F8 and F9. All the four formulations showed an initial burst release. The prolonged release in the later stage can be attributed to the slow diffusion of the drug through polymer matrix. The initial burst release of the drug can be explained by the fact that, the *in-situ* gelling system is formulated in water and hence the polymer was completely hydrated. When they come in contact with STF, gelation occurs and a prehydrated matrix is formed in which hydration and water penetration no longer limit drug release, leading to an apparent diffusion-controlled release.

Table 6: *In-vitro* release profile of *in-situ* gels

Time (h)	Avg. % CPR±SD (n=3)			
	Formulations			
	3	**6**	**8**	**9**
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
0.5	25.77±0.38	20.71±0.53	19.65±0.50	15.80±0.42
1	41.78±0.50	37.30±0.27	38.31±0.47	27.43±0.73
2	53.13±0.32	49.79±0.57	50.05±0.96	38.22±0.53
3	65.64±0.45	61.10±0.42	61.33±1.15	47.08±1.15

4	78.94±1.06	73.93±0.49	75.07±1.31	60.16±0.83
5	90.03±1.13	85.07±1.20	86.81±0.91	68.44±0.77
6	98.92±0.97	93.45±0.91	95.13±0.27	77.74±0.82
7	99.08±0.91	99.15±1.13	99.69±0.15	85.55±0.62
8	99.14±0.84	99.18±1.12	99.82±0.10	94.89±0.48

With an increase in concentration of carbopol, the drug release rates were found to decrease gradually. It is obvious from drug release data shown in Table 6 that as the concentration of carbopol increases in formulations F3, F6 and F9 at fixed concentration of xanthan gum initial burst release was decreased. This may be due to increase in viscosity imparted by increasing concentration of carbopol. It was found that most of drug was released at 6 h in case of formulation F3 and at 7 h in case of formulations F6 and F8. In case of formulation F9 drug release was extended for 8 h. 94.89% drug released at the end of 8 h. This clearly indicates that formulation F9 showed better sustained effect than other three formulations.

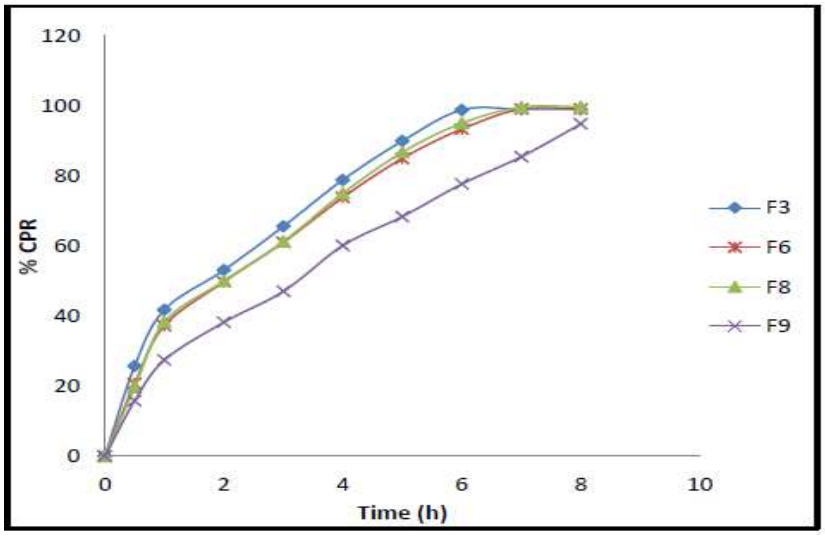

Figure 1: Comparative *in-vitro* release profile

On the basis of gelation properties, viscosity, percentage drug content, *in-vitro* release studies; the optimum *in-situ* gelling formulation of and carbopol and xanthan gum combination F9 was selected and subjected for further studies. The results obtained of *in-vitro* release studies of formulation F9 were attempted to fit into various mathematical models as follows:

1. Cumulative percent drug released Vs. Time (Zero order rate kinetics)
2. Log Cumulative percent drug retained Vs. Time (First order rate kinetics)
3. Cumulative percent released Vs. √T [Higuchi's classical diffusion equation (Higuchi matrix)]
4. Log of cumulative percent drug released Vs. Log Time (Peppas exponential equation)
5. (Percentage Retained)1/3 Vs. Time (Hixson-Crowell erosion equation) Plots of zero order, first

order, Higuchi matrix, Peppas and Hixson-Crowell are depicted in The regression coefficient (r) and 'n' values of zero order, first order, Higuchi matrix, Peppas and Hixson-Crowell are tabulated in Table 8 for formulation F9. From the table, it is clear that the drug was released in a controlled manner over a period of time and followed Korsmeyer-Peppas model. 'n' value for Korsmeyer-Peppas model was 0.61, which is indicative of non-Fickian diffusion (anomalous transport).

Table 7: *In-vitro* drug release profile of formulation F9

Time (h)	Root Time	Log Time	% CPR	Log % CPR	Log % Drug retained	(% Drug retained)$^{1/3}$
0.0	0.00	-	0.00	-	2.00	4.64
0.5	0.71	-0.30	15.80	1.20	2.00	4.65
1.0	1.00	0.00	27.43	1.44	2.00	4.64
2.0	1.41	0.30	38.22	1.58	1.99	4.64
3.0	1.73	0.48	47.08	1.67	1.99	4.63
4.0	2.00	0.60	60.16	1.78	1.98	4.63
5.0	2.24	0.70	68.44	1.84	1.98	4.63
6.0	2.45	0.78	77.74	1.89	1.97	4.63
7.0	2.65	0.85	85.55	1.93	1.97	4.63
8.0	2.83	0.90	94.89	1.98	1.96	4.63

Table 8: Model fitting for the release profile of formulation F9

Formulation	Zero order	First order	Higuchi matrix	Korsmeyer-Peppas		Hixon-Crowell	Best fit model
	r	r	r	r	n	r	
F9	0.9725	0.9152	0.9864	0.9891	0.61	0.9757	Korsmeyer-Peppas

Sterility testing

The sterility testing of ophthalmic drug delivery system was performed for aerobic bacteria and fungi by using alternative thioglycollate medium and soyabean casein digest medium as per the IP Procedure. The positive control (growth promotion) and negative control (sterility) tests were also carried out in parallel with the test on the preparations being examined.

Test for aerobic bacteria: Here *Bacillus subtilis* was used as a test organism; all the three tubes were examined during and after the incubation period for macroscopic evidence of microbial growth. there was no evidence of growth found in the 'negative control' and 'test' tubes and there was macroscopic evidence of microbial growth in 'positive control' test tube. The results suggest that, the ophthalmic formulation tested for aerobic bacteria was passed the test for sterility.

Test for fungi: Here *Candida albicans* was used as a test organisms, all the three tubes were examined during and after the incubation period for macroscopic evidence of microbial growth. there was no evidence of growth found in 'negative control' and 'test' tubes and there was a clear

macroscopic evidence of microbial growth in 'positive control' test tube. The results indicate that, the ophthalmic formulation tested for fungi passed the test for sterility.

The overall results of the sterility test showed that, the ophthalmic formulation prepared passed the sterility test and hence it was sterile preparation.

Stability study

The stability study was carried out on optimized formulation (F9) at 30 ± 2°C and 60 ± 5% RH over the period of 30 days.

Table 9: Effect of stability testing on various parameters of formulation F9

Sr. No.	Parameters	Storage period at 30 ± 2°C and 60 ± 5 % RH	
		0 day	30 days
1	Clarity	Slightly translucent	Slightly translucent
2	pH	5.3	5.2
3	Drug content (%)	99.90	98.99
4	Viscosity (cP)	1050	1000
5	Gelling capacity	+++	+++
6	Drug release after 8 h (%)	94.89	96.73

The formulation retained the clarity. No remarkable change was observed in drug content, pH, gelling capacity. There was small decrease in viscosity, which led to slightly higher drug release after 8 h, but changes were insignificant (Table 9). Negligible difference was observed in results obtained during optimization and those after the stability study. Thus the optimized formulation retained the good stability at accelerated conditions of temperature and humidity.

CONCLUSION

In the present study, environmentally responsive brimonidine tartrate ophthalmic *in-situ* gels were prepared using two polymers with different phase transition mechanism. Carbopol 934P (pH sensitive polymer) and xanthan gum (ion sensitive polymer and viscosity enhancer) were combined in different concentrations. FTIR studies revealed compatibility of drug with formulation excipients. Autoclaving sterilization could not alter appearance, clarity, gelling capacity, viscosity, pH and % drug content of formulation significantly. Optimum formulation F9 (0.5% w/v carbopol 934P and 0.4% w/v xanthan gum) was satisfactory in terms of clarity/appearance, viscosity, gelling capacity, pH, drug content, and rheological properties. It afforded sustained drug delivery over an 8 h period. It was sterile and stable over one month period of stability testing. Prepared *in-situ* gel of brimonidine tartrate prevents precorneal drug loss and extends drug release for longer period of time. So it is considered as a viable alternative to conventional brimonidine tartrate eye drops.

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