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Temperature Triggered *In situ* Gelling System for Betaxolol in Glaucoma

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ABSTRACT

The aim of this research is to develop thermo sensitive drug vehicles for glaucoma therapy in *in-situ* form to overcome the problems of poor bioavailability, naso lachrymal drainage and rapid precorneal elimination exhibited by conventional eye drops. Thermo sensitive ophthalmic drop was prepared using cold method by mixing thermo sensitive polymer pluronic F-127, viscosifying agent HPMC-E 50 LV and antiglaucoma drug (betaxolol hydrochloride). Prepared *in situ* gels were evaluated for physical parameters like appearance, gelation temperature, pH, drug content, rheological properties, isotonicity, sterility test, in *vitro p*ermeation and *in-vivo* ocular irritation study. The drug released from selected batch provides sustained release of betaxolol over 7 hours period and showed excellent ocular tolerance. The overall results of this study supports that the Pluronic/HPMC based vehicle could be used for controlled drug release that exhibits a greater potential for glaucoma therapy.

INTRODUCTION

Betaxolol hydrochloride is a selective β_1 receptor blocker used in the treatment of hypertension and glaucoma. β-Blockers are commonly used for the treatment of open angle and closed angle glaucoma . It is available as 0.25 and 0.5% solutions. The ocular hypertensive effect caused by β -blockers is probably due to suppression of aqueous humour formation by blockage of the β-adreno receptors in the ciliary body. β-blockers decrease aqueous humour production by approximately one-third. To obtain the desired lowering in IOP, large quantity of conventional eye drops of betaxolol hydrochloride are used, and this usually leads to poor bioavailability, naso lachrymal drainage and rapid precorneal elimination (Martindale *et al.*, 2002; Betaxolol Hydrochloride drug profile 2009). This problem can be overcome by using *in situ* gel forming ophthalmic drug delivery systems prepared from polymers that exhibit reversible phase transitions (sol–gel) and pseudoplastic behavior to minimize interference with blinking (El.Kamel, 2002). Such a system can be formulated as a liquid dosage form suitable to be administered by instillation into the eye, which, on exposure to physiological conditions, changes to the gel phase, thus, increasing the precorneal residence time of the delivery system and enhancing ocular bioavailability. The objective of the present study was to develop an temperature triggered *in situ* gelling system of betaxolol hydrochloride a β-blockers used in the treatment of glaucoma (Sean CS ,2002] using pluronic F-127 as a polymer and HPMC E 50 LV as a viscosity enhancing agent, since high polymer concentration (25% poloxamer) which is not well tolerated by the eye. (DH Shastri et al,2010] Pluronic F-127 (Poloxamer 407, PF-127) is a thermo reversible gel. This characteristic has allowed PF-127 to be used as a carrier for most routes of administration including oral, topical, intranasal, vaginal, rectal, ocular and parenteral routes. PF-127 is of particular interest since concentrated solutions (>20% w/w) of the copolymer are transformed from low viscosity transparent solutions to solid gels on heating to body temperature. Furthermore, PF-127 has been reported to be the least toxic of commercially available copolymers (Escobar-Chávez1et al, 2006].

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The objective of the present work is to formulating temperature triggered *in situ* gelling system for betaxolol hydrochloride to overcome the problems of conventional eye drops , may enhance bioavailability of betaxolol hydrochloride and also provide sustained/controlled release by using a combination of pluronic F–127 biodegradable polymer and the viscosifying agent HPMC E 50 LV.

MATERIALS AND METHODS

Materials

Betaxolol hydrochloride sample was gifted from Medigraph Pharmaceuticals (P) Ltd. (Maharashtra), HPMC E50 LV was purchased from LOBA CHEMIE PVT.LTD (Mumbai), Pluronic F-127 from Sigma Aldrich Chemicals Pvt. Ltd, (Bangalore), and Sodium chloride, sodium bi carbonate, calcium chloride dihydrate and sodium hydroxide pellets were purchased from Karnataka fine chem. (Bangalore).

Methods

Fourier Transform-Infra Red Spectroscopy Studies (FT-IR)

The compatibility between the drug and Pluronic F-127 was studied on FT-IR (Bruker optics, Tensor 27) spectroscopy. Spectra of pure Betaxolol hydrochloride, pure Pluronic F-127, pure HPMC E50 LV and physical mixture of Betaxolol hydrochloride with Pluronic F-127, HPMC E50 LV were compared at 400 to 4000cm-1 is shown in Fig. (1, 2, 3).

Sample preparation

Temperature triggered Pluronic F–127 and HPMC based in situ gelling system

The formulations were prepared using cold method. Drug and isotonicity adjusting agent was dissolved in distilled de-ionized water and kept in refrigerator. After cooling, required quantity of PF-127 was added and kept at 4°C with periodical stirring to ensure complete dissolution. Solution of PF-127 in the concentrations of 15, 18 and 20% were prepared. Formulation containing PF-127 and viscosity enhancing agent were also prepared. HPMC E 50 LV was used as a viscosity enhancing agent. In this case, required amount of viscosity enhancing agent was dissolved in hot water (80-90˚C) with continuous stirring for complete dissolution of HPMC E 50 LV. The drug and isotonicity adjusting agents were then added. The resulting polymeric solutions were kept in refrigerator. After cooling, the required amount of PF-127 were added in HPMC solutions and kept in refrigerator at 4°C for complete dissolution of PF-127. The pH of all the formulations was measured and found in the range of 6.5-7.2. The concentration of isotonicity adjusting agents that rendered the formulation isotonic with eye fluid was calculated by sodium chloride equivalent method. Benzalkonium chloride (BKC) (0.01%) was added as a preservative. In order to identify the composition suitable for use as *in situ* gelling, aqueous solutions of PF-127 and HPMC with different concentration and grades were prepared and evaluated for gelling capacity and transparency at physiological conditions. The formulations were then subjected to terminal sterilization by autoclaving at 121°C and 15 psig for 20 min. (Somnath Sakore et al 2010](El.Kamel.A.H 2002] The table 1 shows the composition of all the twelve formulations.

Evaluation of prepared *in situ* gelling system

Clarity and pH

The general appearance of the formulation was observed which included color and clarity of solution. The pH of the prepared formulations was checked by using pocket pen pH meter.

Drug content estimation

Drug content estimation was done by pipette out 0.1 ml (0.25 mg) of 0.25% sample solution diluted to 10ml with simulated tear fluid (Sodium chloride 0.670 g, 0.200 g sodium bicarbonate and 0.008 g calcium chloride 2H2O was dissolved in distilled water and diluted to 100.0 ml] in 10ml volumetric flask. The absorbance of the resulting sample solution was measured at 222.5 nm .The results are as shown in table 2.

Gelling temperature determination

Measurement of the GT 10 ml of sample solution and a magnetic bar were put in a transparent vial that was placed in a low temperature water bath. A thermometer with accuracy of 0.1˚C was immersed in the sample solution. The solution was heated at the rate of 1˚C/min with continuous agitation (100 rpm). The temperature was determined as GT, at which the magnetic bar stopped due to gelation. Each sample was measured in triplicate. The results are as shown in table 2. (Tong-Ying Jiang et al 2009]

Drug content estimation

The drug content was estimated by pipetted out 0.1 ml (»0.25 mg) of 0.25% sample solution and diluted to 10 ml with simulated tear fluid in 10 ml volumetric flask. The absorbance of the resulting sample solution was measured at 222.5 nm. The results are as shown in table 2.

Rheological Studies

The viscosity measurements were done by using Brookfield DV-II+ viscometer using small sample adaptor SC4-18 spindle for 19.1˚C and LV2 spindle for 35.6 ˚C The developed formulations at 19.1˚C were poured into the adapter of the viscometer and the angular velocity was increased gradually from 10 to 100 rpm with a wait period of 6 seconds at each speed. The hierarchy of angular velocity was reversed (100 rpm to10rpm) with a similar wait of 6 seconds. The average of three readings was used to calculate the viscosity. By increasing the temperature to body temperature at 35.6 ˚C the formulations were made into gel form and viscosity was determined as specified above using LV-2 spindle. The results are shown in fig.4 and fig.5 respectively.

***In vitro* drug diffusion studies**

The *in vitro* diffusion was studied through cellophane membrane using a Franz diffusion apparatus. The diffusion medium used was freshly prepared Simulated Tear Fluid (STF). Cellophane membrane, previously soaked overnight in the diffusion medium (STF), was placed in between the donor and receptor compartment.1 ml volume of the formulation was accurately instilled into the donor compartment. 130ml of STF was placed in the receptor compartment. The whole assembly was placed on the thermostatically controlled magnetic stirrer. The temperature of the medium was maintained at 37°C ± 0.5°C. The magnetic bead was rotated such that it produced a vortex and touched the cellophane membrane. Aliquots, each 1 ml volume, were withdrawn at hourly intervals and replaced by an equal volume of the receptor medium. The aliquots were diluted with10ml of STF and analyzed by UV visible spectrophotometer at 222.5 nm (Sindhu A *et al* 2009]. The release profiles of the formulations were shown in Fig-6 and table 3.

Isotonicity evaluation

Isotonicity is important characteristic of the ophthalmic formulations which has to be maintained to prevent tissue damage or irritation of eye (Hiremath SSP *et al* 2008].

F6 was subjected to isotonicity testing, since it exhibited good release characteristics and gelling capacity and the required viscosity. Formulation (1 ml) was mixed with few drops (4 drops) of blood and observed under microscope at 45X magnification and the shape of the blood cell was compared with the standard marketed ophthalmic formulation containing betaxolol hydrochloride.

Test for Sterility

Tests for sterility were performed for aerobic, anaerobic bacteria and fungi by using alternative thioglycollate medium and soya bean casein digest medium (R.S.Goud *et al* 1999], (Pharmacopoeia of India,1996].

Sterility (negative control) test

Alternate thioglycollate media was incubated at 30-35ºC and soya bean casein digest medium at 20-25ºC for 7 days. No growth of organisms occurs.

Growth promotion (positive control) test

Here, the sterile media is inoculated with about 100 viable micro-organisms and incubated according to the conditions specified. The test media would be satisfactory, if clear evidence of growth appears in all media within 7 days. Ophthalmic preparations should be sterile and must be checked for the presence of any bacteria or fungi before it is used. Since the formulations is an ophthalmic preparation and the number of formulations in the batch is not more than 200, two containers were selected for sterility test according to IP procedure. In each test, three sterile test tubes were used in the study and are labeled as 'negative control', 'test' and 'positive control'.

Test for aerobic bacteria

Twenty ml each of sterile alternative thioglycollate was transferred to 3 tubes aseptically. The tube labeled as positive control was inoculated with viable aerobic microorganism *Bacillus subtilis* (ATCC No. 6633) aseptically. 2.5 ml of the ophthalmic preparation was added to the tube labeled as test. Then incubate all three tubes at 30-35ºC for 7 days.

Test for anaerobic bacteria

Twenty ml each of sterile alternative thioglycollate was transferred to 3 tubes aseptically. The tube labeled as positive control was inoculated with viable anaerobic microorganism *bacteriodes vulgatus* (ATCC NO. 8482) aseptically. 2.5 ml of the ophthalmic preparation was added to the tube labeled as test. Then incubate all three tubes at 30-35ºc for 7 days.

Test for fungi

Twenty ml each of sterile soya bean-casein digest medium was transferred to 3 tubes aseptically. The tube labeled as positive control was inoculated with *candida albicans* (ATCC NO. 10231) aseptically. 2.5 ml of the ophthalmic preparation was added to the tube labeled as test. Then incubate all three tubes at 20-25ºc for 7 days.

Eye Irritation Studies

The ethical committee of the institution had permitted the ocular irritation studies. Four albino rabbits of both sexes weighing 2.0 to 2.5 kgs were used for the study. 0.25 µl of the selected formulation- F6 was instilled in the conjunctival sac of right eye of each rabbit and readings were observed at 1, 24 and 48 h.

Eye was evaluated for injuries to the cornea, conjunctiva and the iris were scored separately. In the above studies, the left eye was served as control (without drug-placebo) and the right eye was served as test (sterile formulation). The scoring was given according to Draize irritancy scale (Michael H *et al* 2003]. The total scores of four rabbits for 1st, 24th and 48th in each section are as per table-4

RESULTS AND DISCUSSION

***FT-IR* Studies**

FT-IR spectrum of pure drug and mixture of drug and polymer are shown in Fig. 1-3. The results revealed no considerable changes in the IR peaks of betaxolol hydrochloride when mixed with excipient compared to pure betaxolol hydrochloride. Hence, no specific interaction was observed between the drug and the polymers used in the formulations.

All the twelve formulations of betaxolol hydrochloride *in situ* gelling systems were prepared by using various concentrations of Pluronic/HPMC based vehicle in different ratio as per formula given in Table-1. All the formulations had fixed drug concentration of (0.25%w/v) betaxolol hydrochloride.

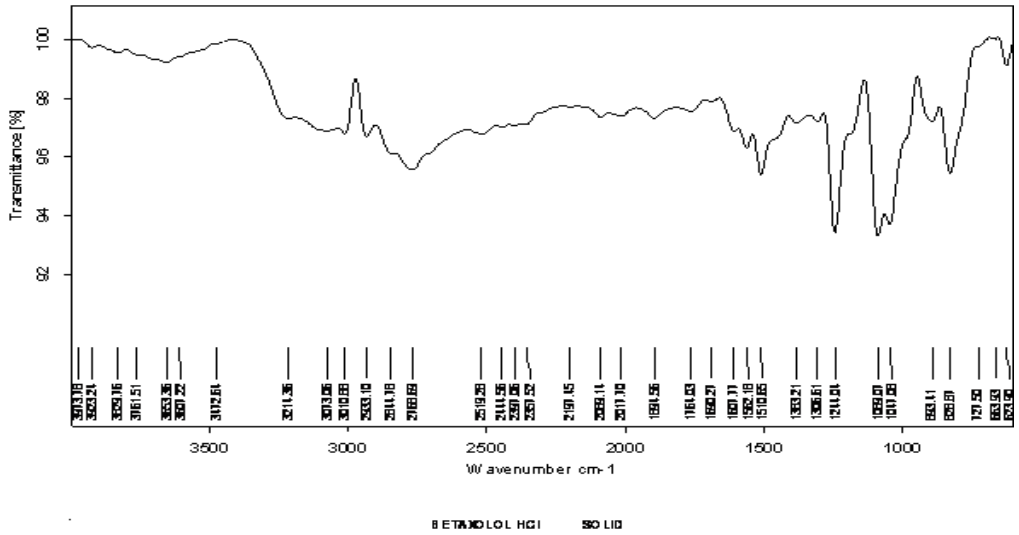

Fig. 1: *FT- IR* spectra of pure drug betaxolol hydrochloride.

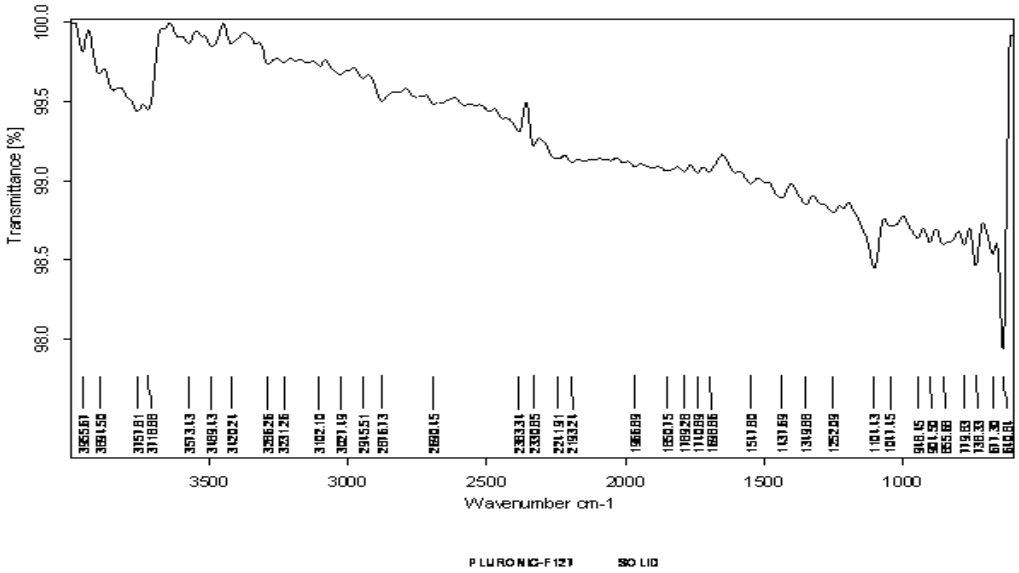

Fig. 2: *FT-IR* spectra of pure polymer Pluronic F-127.

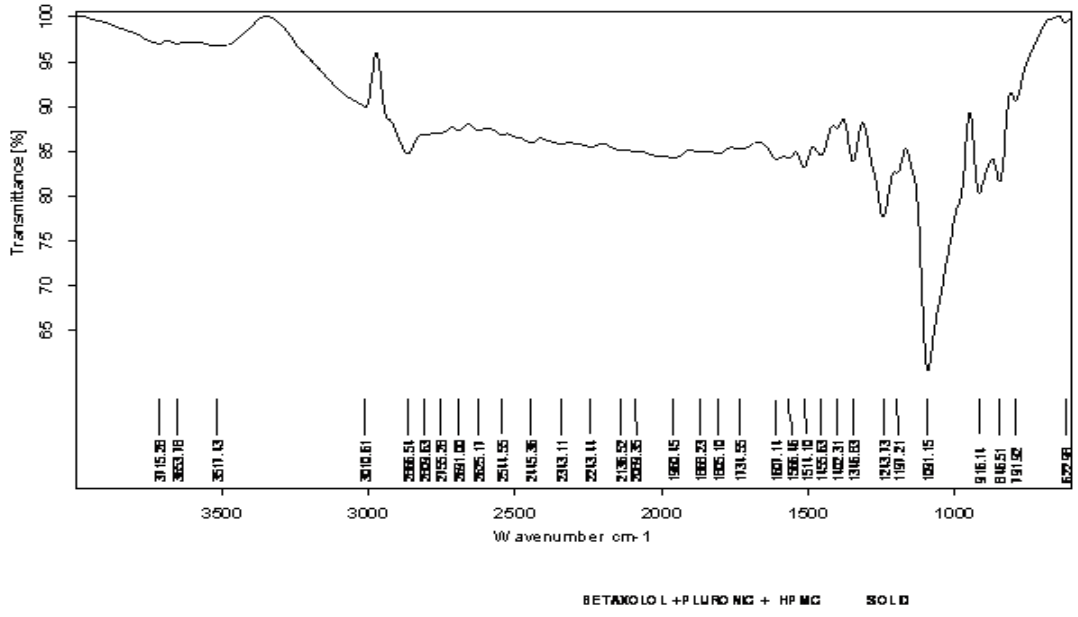

Fig. 3: ***FT****- IR* spectra of physical mixture of betaxolol hydrochloride and pluronic F-127 & HPMC E 50 LV.

Table. 1: Formulation chart of temperature triggered *in situ* gelling systems of Betoxolol HCL.

Ingredients	Ingredient concentration(% w/v)											
	F1	F2	F3	F4	F 5	F6	F7	F8	F9	F10	F11	F12
Betoxolol HCL	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Pluronic F-127	15	18	20	15	15	15	18	18	18	20	20	20
HPMC E 50 LV	-	-	-	0.5	0.75	1.0	0.5	0.75	1.0	0.5	0.75	1.0
Sodium chloride	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Benzalkonium chloride(%V/V)	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Dil.water upto (ml)	100	100	100	100	100	100	100	100	100	100	100	100

Table. 2: Evaluation of ophthalmic temperature triggered *in situ* gelling systems of betaxolol hydrochloride.

Formulation Code	Drug Content (%)	Visual appearance	Clarity	Gelling capacity	Gelation temp.(˚C)	pH
F1	97.23±1.78	Transparent	Clear	+++	32.8±0.4	6.78
F2	97.56±1.45	Transparent	Clear	+++	30.7±0.71	6.77
F3	98.45±2.78	Transparent	Clear	+++	29.1±0.23	6.83
F4	98.12±1.23	Transparent	Clear	+++	37.9±0.49	7.06
F5	98.96±1.45	Transparent	Clear	+++	36.3±0.45	6.92
F6	98.76±1.65	Transparent	Clear	+++	36.6±0.26	6.75
F7	99.34±1.43	Transparent	Clear	+++	36.6±0.32	6.84
F8	99.89±1.54	Transparent	Clear	+++	35.5±0.27	7.3
F9	100.56±1.01	Transparent	Clear	+++	34.8±0.45	7.01
F10	100.67±1.23	Transparent	Clear	+++	27.5±0.53	6.82
F11	101.24±1.67	Transparent	Clear	+++	26.7±0.19	7.15
F12	99.87±2.78	Transparent	Clear	+++	25.6±0.43	6.83

General Appearance and pH

The formulations were transparent and the clarity was found to be satisfactory. Terminal sterilization by autoclaving had no effect on the formulations. The pH of all the formulations was within the acceptable range i.e., between 6.77-7.3and hence would not cause any irritation upon administration which is desirable for the ophthalmic formulations.

Drug Content Estimation

The drug content of all the formulations was in the range of 97.23to 101.24 indicating the greater uniformity of the dosage in the formulations. The evaluation results are mentioned in Table **2**.

Gelling Capacity

The two main prerequisites of gelling system are viscosity and gelling capacity. The formulations should have an optimum viscosity for easy instillation into the eye as a liquid which undergo sol-to-gel transition. Except for the formulations F1 & F2 all the formulations gelled instantaneously with a translucent matrix by increasing the body temperature. In F4 & F7 gel was remain for very few hours. In case of F10, F11 and F12 very thick stiff gel by increasing the temperature . but in case of F6, F8 & F9 the optimum gelation was observed when the temperature increased to body temperature due to the optimum concentration of pluronic F-127 & HPMC E 50 LV. The grading for gelling capacity is shown in Table **2**.

Rheological Studies

The pseudo plastic character of precorneal tear film should be disturbed less by the administration of ophthalmic products. The ocular shear rate is about 0.03 s-1 during interblinking periods and 4250 – 28500 s-1 during blinking. So, the viscoelastic fluids having high viscosity under low shear rates and low viscosity under high shear rates, which is called as pseudo plastic fluid, is often preferred (Mohanambal E *et al* 2011]. The viscosity of the formulations F1 –F12 ranged from 100- 420 cps at 19.1˚C is shown in Fig. (**4**).

All the formulations exhibited pseudo-plastic rheology in solution form, i.e., an decrease in the viscosity with increase in angular velocity. The viscosity of the formulations F1 –F12 ranged from 170-1500 cps at 35.6˚ C in gel form was shown in Fig. (**5**).

All the formulations exhibited pseudo-plastic rheology, a decrease in the viscosity with increase in angular velocity. Among all F6 gave the good viscosity range & gelling capacity.

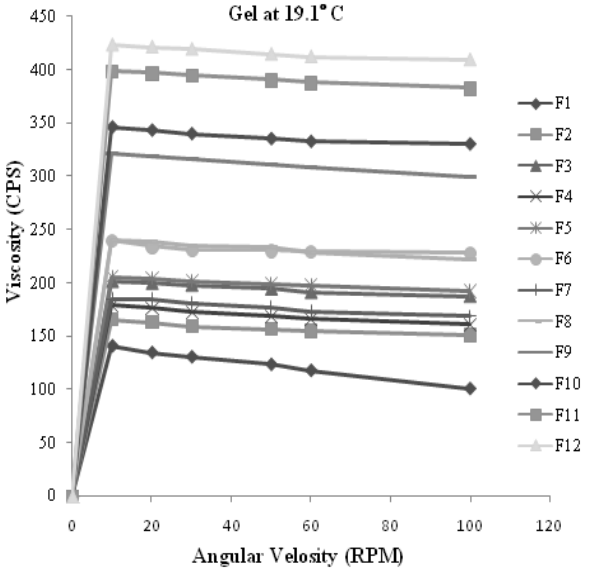

Fig. 4: Rheological profiles of formulations F1-F12 at 19.1˚ C .

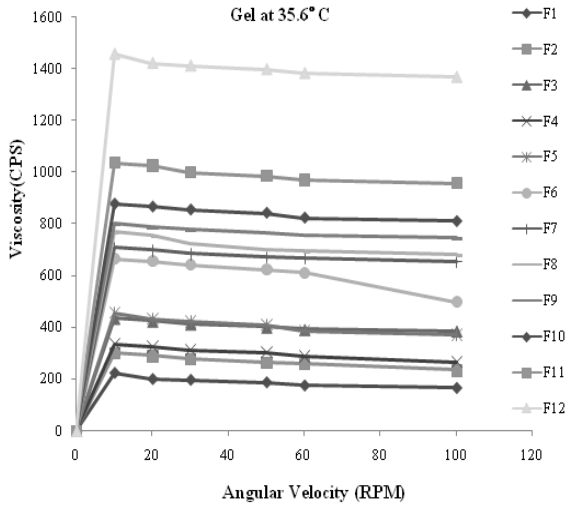

Fig. 5: Rheological profiles of formulations F1-F12 at 35.6˚ C.

In Vitro Drug Diffusion Studies

The release profile of the formulations is shown in Fig. (6). The formulation F6 showed better performance in drug release studies and sustained the drug action for 7h compared to other formulations. This may be due to the optimum concentration (15 %) of pluronic F-127 and HPMC E 50 LV (1 %) in F6. The higher regression coefficient values in Table **3** for each formulation suggested that the formulations F1 & F3 follow Higuchi Kinetics type of drug release whereas formulation F2,F4, F5, F6, F7, F8 , F9, F10 , F11 & F12 showed zero order drug release kinetics which was further proved in Fig. (**6**) by the best fit zero order models. The 'n' value obtained from Peppas equation were more than 0.5, which indicated that all the formulations showed drug release by Non-Fickian diffusion mechanism . The results are shown in Table **3**. From the results it is concluded that the high viscosity plays important role in controlling the release of drug from the formulations. When the polymer concentration increases, drug release decreases, and when polymer concentration decreases drug release from the formulation increases.

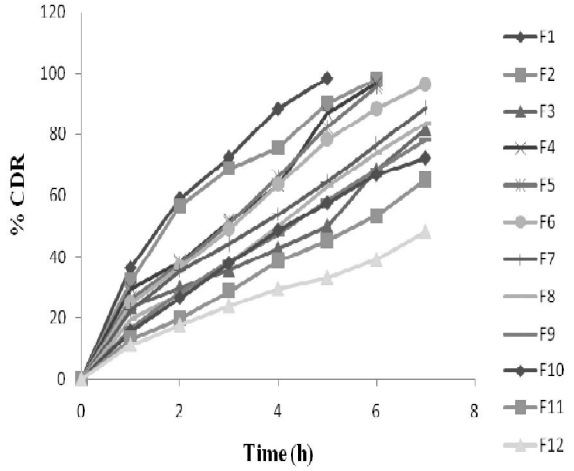

Fig. 6: Plot of *in vitro* release of F1-F12 *in situ g*elling formulations of % CDR vs.time

Table. 3: Release kinetics of formulations-F1-F12.

Formulation	Zero order	First order	Higuchi	Kosermeyer-Peppas	
	r^2	r^2	r^2	r^2	*n*
F1	0.949	0.012	0.992	0.519	1.833
F2	0.930	0.014	0.991	0.541	1.633
F3	0.959	0.086	0.911	0.592	1.402
F4	0.979	0.000	0.942	0.577	1.637
F5	0.989	0.002	0.950	0.598	1.664
F6	0.984	0.006	0.964	0.620	1.543
F7	0.984	0.032	0.962	0.615	1.490
F8	0.993	0.057	0.940	0.655	1.517
F9	0.993	0.091	0.953	0.666	1.515
F10	0.987	0.116	0.960	0.676	1.516
F11	0.994	0.174	0.929	0.703	1.474
F12	0.983	0.233	0.954	0.683	1.343

Tests for Sterility

The formulation F6 passed the sterility test as there was no appearance of turbidity and hence no evidence of microbial growth when incubated for a period of not less than 7 days at 30-35°C in case of fluid thioglycollate medium and at 20-25°C in the case of soya bean casein digest medium.

Eye Irritation Studies

In all three sections for 1st, 24th and 48th hour observations, the scores given to the rabbits were less than the maximum total scores. So, results showed that there was no irritation to the sensitive ocular tissues by the formulation and no ocular damage or abnormal clinical signs to the cornea, iris or conjunctiva were visible hence the formulation was safe to use in ocular treatment.

Stability Studies

The stability studies indicated that the formulation F6 was physically and chemically stable with no significant change in any of the parameters evaluated when stored at the ambient humidity conditions between 2-8°C, ambient temperature and 40°C except for a slight decrease in the pH with time at 40°C. From stability studies it was observed that the *in situ* gelling system of Betaxolol hydrochloride was stable at selected storage conditions with most suitable storage condition at the refrigeration temperature.

CONCLUSION

Betaxolol, β 2-adrenergic agonist used in the treatment of glaucoma is successfully formulated as a Temperature triggered *in situ* gel forming ophthalmic solution using Pluronic/HPMC based vehicle as a viscosity enhancer which sustained the drug release over a period of 7 h. The polymer used was inexpensive and easily available. The formulation also promises to reduce the frequency of drug administration, thus improving patient compliance. As the concept involved is novel, this formulation is an alternate to conventional eye drops to improve the bioavailability through its longer precorneal residence time and ability to sustain drug release and the methodology used for the preparation is simple as that of conventional ophthalmic liquid dosage form, it is industrially oriented and economical.

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