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Research Article

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Abstract

The present research work focusses on the improvement and assessment of ophthalmic medication delivery system based on the idea of pH dependent in situ gelation for betaxolol hydrochloride (betaxolol HCl), an anti-glaucoma operator, to conquer the issues of poor bioavailability and therapeutic response showed by conventional formulations based a sol-to-gel change in the parkway up on instillation. Carbopol 940 was utilized as pH sensitive gelling agent alongside HPMC as consistency upgrading specialist. Plans were assessed for pH, clearness, sedate substance, gelling limit, and in-vitro drug discharge. The defined framework was clear in appearance; pH of framework was inside scope of 5.1 – 5.6 and gave supported arrival of the medication over an eight-hour time span. The created framework in this manner is a reasonable option to customary eye drops and can be utilized as an in-situ gelling vehicle to improve ocular bioavailability and the reduction in the recurrence of instillation along these lines bringing better patient compliance.

Key words: Betaxolol HCl, Carbopol 940, fluid gel-stage progress, in situ gelation, medication conveyance, managed discharge, ophthalmic

Introduction

The one of a kind life structures, physiology, and natural chemistry of an eye offer many challenges to creating compelling ophthalmic medication delivery system. Topical delivery into circular drive is, by a long shot the most widely recognized course of visual medication delivery. Despite the fact that different ophthalmic plans exist in advertise, however are not ready to give most elevated bioavailability identified with controlled dose.[1] Whenever an ophthalmic medication is applied to the anterior segment of the eye, only 5% really enters the cornea and achieves concentration inside the eye. There are different variables that influence medication bioavailability, such as, rapid solution drainage by gravity, instigated lacrimation, squinting reflex, ordinary tear turnover, superficial absorption of medication into the conjunctiva and sclera and fast expulsion by the peripheral blood stream, low corneal penetrability (act as lipid barrier).[2&3]

β-adrenergic antagonist records for around 70% of all the solutions for glaucoma and are valuable in the treatment of chronic open angle glaucoma. These medications lessen intra ocular pressure by contending with catecholamine for β 2-adrenoreceptor on the non-pigmented ciliary epithelium and subsequently diminishing aqueous humor creation. β-blockers have a few advantages over cholinergic and adrenergic antagonist, as these have little impact on pupil size and do not cause mydriasis or responsive hyperaemia.[4]

The aim of this study was to prepare and evaluate pH dependent in situ ophthalmic gel of an anti-glaucoma

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medication for sustained ocular delivery, which is utilized for the treatment of glaucoma, to decrease raised intraocular pressure (IOP), to show signs of improvement persistent consistence by expanding living arrangement time and bioavailability.

Betaxolol hydrochloride or betaxolol HCl (2-propanol, 1-4-2 (cyclopropylmethoxy) ethylphenoxy-3 (1-methylethyl) amino-hydrochloride) was utilized as model medication.

Materials and methods

Materials

Betaxolol HCl was benevolently gifted from Hikal Labs, Bangalore. Carbopol 940 and HPMC were bought from HiMedia Labs Pvt Ltd Mumbai. Benzalkonium chloride was bought from Ozone chemicals, Mumbai. All other reagents and solvents utilized were of analytical grade. Cellophane membrane and distilled water were alternate materials utilized.

Instruments used

UV-spectrophotometer (Shimadzu), Brookfield DV Rheometer (Brookfield Engineering Laboratories), Magnetic stirrer, Autoclave were the instruments utilized for this investigation.

Method

Standard calibration curve

Standard medication solution of betaxolol HCL was set up by dissolving 100 mg of unadulterated betaxolol hydrochloride in a little measure of Simulated Tear Fluid in 100 ml volumetric flask and later the volume was balanced with Simulated Tear Fluid solvent. The resultant solution gives the concentration of 1mg/ml i.e. 1000µg/ml. From above stock solution 10 ml solution was taken and later diluted up to 100 ml with a similar solvent in a volumetric flask. The concentration of this stock was 100µg/ml. From this stock solution 02, 04, 06, 08, 10, 12, 14, 16, 18, 20, 30, 40, 50, 60, 70, 80, 90, and 100 ml solution pipette volume was made with 100 ml utilizing STF as a solvent to get centralizations of 02, 04, 06, 08, 10, 12, 14, 16, 18, 20, 30, 40, 50, 60, 70, 80, 90, and 100µg/ml individually. The absorbance was measured at 224 nm (lambda max of betaxolol HCl). The standard calibration curve was obtained from information of concentration v/s absorbance.[5]

pH dependent in situ hydrogel

The buffer salts were dissolved in 75ml of distilled water, HPMC was added and permitted to hydrate, Carbopol was sprinkled over this solution and permitted to hydrate overnight. The solution was mixed with an overhead stirrer, betaxolol HCl was dissolved in a little amount of water, benzalkonium chloride was added to this solution, and the medication solution was then added to make up the volume to 100 ml. This solution was sifted through 0.2 mm filter paper.[6] (Table 1)

Table 1: Formulation of pH triggered in situ gel of Betaxolol HCl

Sl No	Ingredients	Quantity in grams				
		F1	F2	F3	F4	F5
1	Betaxolol hydrochloride	0.2	0.2	0.2	0.2	0.2
2	Carbopol 940	0.2	0.3	0.4	0.5	0.6
3	HPMC	1.5	1.5	1.5	1.5	1.5
4	Citric acid IP	0.407	0.407	0.407	0.407	0.407
5	Disodium hydrogen phosphate IP	1.125	1.125	1.125	1.125	1.125
6	Benzalkonium chloride	0.02	0.02	0.02	0.02	0.02
7	Purified water	100ml	100ml	100ml	100ml	100ml

Assessment parameters

A. Appearance
B. pH
C. *In vitro* gelation studies and viscosity
D. Rheological studies
E. Drug content
F. *In vitro* drug release
G. Sterility

Appearance

Clarity of formulation is the most vital parameter, highlighting an ophthalmic preparation. Every created formulation was assessed for clarity by visual inspection against a highly contrasting background for the presence of any particulate matter, if present.[7]

pH determination

The two regions of basic significance are the impact of pH on the solubility and stability of ophthalmic preparation. The pH of ophthalmic dosage forms should be such that the preparation should be steady at that pH and in the meantime, there would be no irritation to the patient upon administration of the formulation. Ophthalmic dosage forms should have a pH range of 5 – 7.4. The created formulations were assessed for pH by utilizing equiptronic digital pH meter.[7]

In vitro gelation study

All the prepared ophthalmic formulations were assessed for gelling limit so as to distinguish the pieces appropriate for use as in situ gelling system. The gelling limit of formulation was determined by putting a drop of the system in a vial containing 2 ml of simulated tear fluid freshly prepared and equilibrated at 37° C and visually surveying the gel development and taking note of the ideal opportunity for gelation and the time taken for the gel dissolved. The composition of simulated or artificial tear fluid utilized was sodium chloride 0.670g, sodium bicarbonate 0.200g, calcium chloride 0.008g and purified water qs 100 ml.[8]

Rheological studies

Viscosity of ophthalmic formulation is an essential factor in deciding residence time of medication in the eye. The prepared sol was permitted to gel in STF and later viscosity was measured. Viscosity of the sample was measured at various angular velocities. A typical run comprised changing angular velocity from 10 to 100 rpm with measure up to weight for every rpm. The average of two readings was utilized to ascertain the viscosity.[9]

Drug content

The drug content of in situ gel was determined by taking sample (5ml) of in situ gel in 10 ml of volumetric cup and diluted with STF of pH 7.4 to get the concentration of 10 µg/ml. At that point, the absorbance was measured at 224nm utilizing UV-spectrophotometer to compute the level of drug content.[10]

In vitro release studies

The Franz-diffusion cell was utilized for studying in vitro release of the in situ gel. A cellulose acetate membrane (membrane with 25mm diameter) was adjusted to the terminal bit of the cylindrical donor compartment. 1ml in situ gel containing drug, adequate for establishing sink states of the measure was put into the donor compartment. The receptor compartment containing 16 ml of simulated tear fluid of pH 7.4 was kept up at 37° C under mild agitation utilizing magnetic stirrer. At particular time intervals, aliquots of 1ml were withdrawn and quickly replaced with a similar volume of crisp STF. Measuring the absorbance at 224 nm utilizing UV spectrophotometer[11] assessed the measure of medication released.

Sterility test

Sterility testing was performed for the aerobic and anaerobic microbes and fungi by utilizing liquid thioglycolate medium and soybean-casein medium respectively according to the Indian Pharmacopoeia. Formulation was taken in to laminar air flow and passed through a membrane filter of 0.45µm with the assistance of vacuum pump. After filtration, the filter paper was expelled from funnel and cut into two parts. One half was dropped in bacterial media (liquid thioglycolate) and the other was split dropped in fungal media (soya bean casein digest). The two media were kept for incubation at 37° C for seven days and observed for any microbial growth.[12]

Comparative evaluation of marketed product with prepared in situ gels

In vitro release studies of marketing formulation was completed utilizing bi-chambered donor receiver compartment model (Franz diffusion cell) utilizing a cellophane film soaked overnight the receptor medium (recreated tear fluid pH 7.4) The diffusion medium was 16 ml of simulated tear fluid mixed at 50 rpm at 37° C ± 0.5° C. One end of diffusion cell was secured by a cellophane membrane and 1 ml of prepared formulation was spread on the cellophane film and membrane was put in such a way, so that it simply touches the diffusion medium simulated tear fluid present in receptor compartment. The medication tests were withdrawn back at once interim of one hour for the time of eight hours from diffusion medium and investigated by UV

spectrophotometer at 224 nm utilizing simulated tear liquid as blank.

Results and discussion

Assessment of appearance, clarity, pH, and drug

All the prepared in situ gelling systems were evaluated for preliminary steps such as visual appearance, clarity, pH, and drug content. These pH-dependent formulations were transparent and clear. The pH of pH-dependent formulation was found to be in the range of 5.1 – 5.6. As concentration of Carbopol increases, pH of solution decreases. The drug content was found to be in the acceptable range of all formulations. Drug content of pH dependent in situ gel was ranging from 90.12 – 96.75%. Formulation F3 showed a drug content of 96.75%. This indicates that drug is uniformly distributed throughout the system. (Table 2)

Table 2: Preliminary evaluation of pH dependent in situ gelling system of visual appearance, clarity, pH, and drug content

Formulation code	Visual appearance	Clarity	pH	Drug content
F1	Transparent	Clear	5.64	90.12
F2	Transparent	Clear	5.53	94.31
F3	Transparent	Clear	5.37	96.75
F4	Transparent	Clear	5.23	95.84
F5	Transparent	Clear	5.12	92.61

In vitro gelation

Prepared in situ gelling systems were evaluated for the *in vitro* gelation capacity. Formulations F3, F4, F5 gelled instantaneously (less than a minute) on contact with STF. F1, F2 formulation gelled after a few minutes. By visual inspection, the formulations formed a translucent matrix in addition to the STF. (Table 3)

Table 3: Evaluation of gelling capacity

Formulation code	Gelling capacity
F1	+
F2	++
F3	++
F4	+++
F5	+++

– No gelation
+ Gels after a few minutes and remains for a few hours
++ Gels immediately and remains for a few hours
+++ Shows gelation immediately and remains for extended period

Rheological studies

For the development of optimum in situ gelling system, two major factors viscosity and gelling capacity should be taken into consideration, since the ocular shear rate is very high ranging from $0.03S^{-1}$ during blinking. During blinking, viscoelastic fluid with a viscosity is high under low shear rate condition and low under high shear rate condition, which is called pseudo plastic fluid, is often preferred, so dynamic viscosity of formulations were measured as the change of shear rate before and after gelation. Table 4 and 5 shows viscosity values obtained for all pH dependent in situ formulations using Brookfield LVDL-I PRIME. The viscosity was directly dependent on the polymeric content of the formulation. The viscosities of formulations were in following range F5> F4> F3> F2> F1. As a proportion of gelling agent Carbopol 940 and viscosifying agent HPMC increased, there is an increase in consistency of in situ gel. This is due to the characteristic of Carbopol 940 to convert into more rigid structure due to change in pH when comes in contact with pH 7.4. The addition of HPMC potentiates this rigid structural arrangement of Carbopol 940 and ultimately resulting in increased consistency.

Sterility testing

Formulated pH dependent betaxolol HCl *in situ* gelling systems were evaluated for sterility. There was no appearance of turbidity and hence no evidence of microbial growth when all the formulations were incubated for seven days at 30° C – 35° C in case of fluid thioglycolate medium and at 20° C – 25° C in case of soybean-casein digest medium. The preparations being examined therefore passed the test for sterility.

In vitro diffusion studies

The *in vitro* diffusion of betaxolol hydrochloride from the prepared formulation was studied through a cellophane membrane using diffusion cell using STF of pH 7.4 as diffusion medium. The diffusion studies of prepared *in situ* gelling systems carried up to 8 hours. *In vitro* diffusion studies of marketing eye drop (IOBET) was done through a cellophane membrane using diffusion cell STF of pH 7.4 as diffusion medium and the release-marketed product was up to three hours.

Table 4: Viscosity of pH dependent in situ gel formulation before and after gelation

Angular velocity (rpm)	Viscosity of pH dependent Betaxolol HCl in situ gel (cps)									
	F1		F2		F3		F4		F5	
	Before gelation	After gelation	Before gelation	After gelation	Before gelation	After gelation	Before gelation	After gelation	Before gelation	After gelation
10	180	16110	239	22755	659	33490	1680	37940	2280	40110
20	150	15590	210	26510	539	31890	1410	35140	1710	38250
30	140	12210	180	23810	479	29240	1109	28160	1380	36510
50	132	10970	156	18740	365	27620	903	26220	1192	31490
60	130	9960	150	16550	395	22210	889	24730	1020	28420
100	120	8750	144	12470	323	18740	547	21680	839	26470

Table 5: In vitro diffusion data of pH dependent in situ gelling system and marketing eye drop

TIME	F1	F2	F3	F4	F5	Marketed eye drop
30	-	-	-	-	-	24.34
60	31.89	23.65	20.46	15.68	11.16	45.18
120	47.12	32.14	30.49	29.32	27.41	75.48
180	53.33	39.2	36.39	38.94	34.69	96.61
240	43.45	43.45	40.05	42.6	45.42	-
300	72.83	55.3	46.27	48.24	53.33	-
360	81.86	66.35	52.48	55.88	59.28	-
420	90.31	75.65	62.37	65.18	62.37	-
480	94.03	89.76	74.8	69.7	67.47	-

pH dependent Betaxolol HCl in situ gelling system

In vitro diffusion studies were carried out for F1 – F5 pH dependent *in situ* gel formulations using STF as a diffusion medium in the Franz - diffusion cell. The data of these release studies are presented in table 8. It was found that drug release was 94.03%, 89.76%, 74.80%, 69.70%, and 67.47% for the formulations F1 – F5 respectively after eight hours. These values indicate F3 showed a better optimum sustaining effect amongst all formulations. This may be due to the optimum concentration of Carbopol 940 along

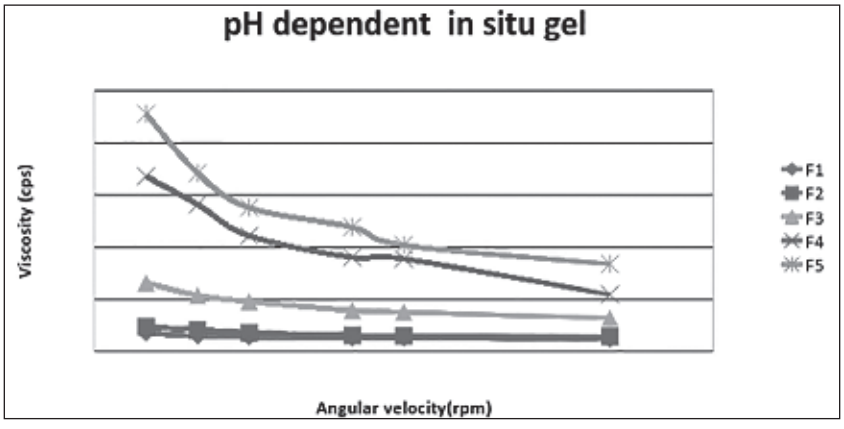

Fig 1: Viscosity of pH dependent in situ gel formulation before gelation

with HPMC in F3. Figure 4, shows the plot of *In vitro* diffusion studies for all the formulations along with a comparative study of marketing eye drop drug release profile.

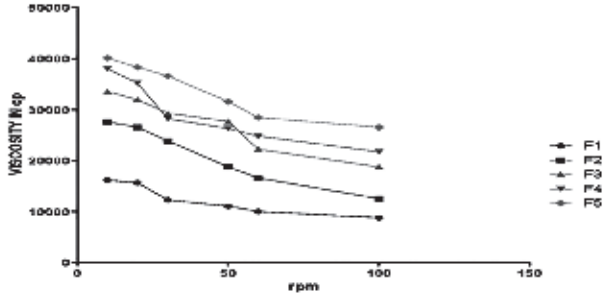

Fig 2: Viscosity of pH dependent in situ gel formulation after gelation

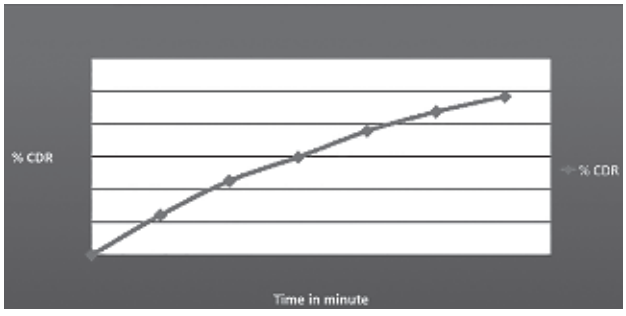

Fig 3: In vitro diffusion profile of marketed eye drop (IOBET)

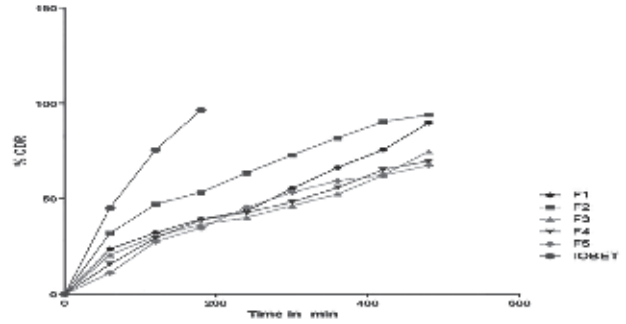

Fig 4: Shows the plot of in vitro diffusion studies for all the formulations along with a comparative study of marketed eye drop drug release profile

Conclusion

Betaxolol HCl, used in treatment of glaucoma was successfully formulated as pH dependent in situ gel forming ophthalmic solution using Carbopol as gelling agent and HPMC as a viscosity-enhancing agent. The formulation was liquid in non-physiological conditions (pH 4.0 and 25° C) and transformed to the gel form in physiological conditions (pH 7.4 and 37° C). Formulation shows sustained drug release over a period of eight hours. The developed formulation is a viable alternative dosage form to conventional eye drops by virtue of its ability to enhanced and longer therapeutic effect through its longer pre-corneal residence time and ability to sustain drug release.

Conflict of interest

"There is no conflict of interest." In case, no information was provided by authors whatsoever then by signing the Copyright Transfer Agreement, authors agree that publisher is allowed to include "The authors declared no conflict of interest."

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