**In vitro characterization & Pharmacokinetic evaluation of ion activated in situ gelling system for Betaxolol Hydrochloride**

A.Geethalakshmi¹*, K Mahalingan¹, Sajal Kumar Jha²

¹*, ¹ Department of Pharmaceutics, The Oxford College of Pharmacy, Begur Road, Bangalore, Karnataka, India.
² Department of Pharmaceutics, School of Pharmacy, Guru Nanak Institutions Technical Campus, Hyderabad, India.

E-Mail: geeshwar@gmail.com

**Abstract**

Formulation of Betaxolol HCl *in-situ* gelling system by ion activated method for the treatment of glaucoma with the aim to improve patient compliance as the dosage regimen is one drop of the dosage form twice a day. Betaxolol HCl *in-situ* gelling system was prepared by using gelrite for ion activated method. The gelrite was selected as polymer, when instilled as a liquid solution in to the *cul-de-sac* can be initiated gelation by the electrolytes (Na⁺, Ca²⁺ and Mg²⁺ cations) present in tear fluid. The preparation was subjected to physico-chemical evaluation, *in-vitro* diffusion study, sterility study, isotonicity testing, eye irritation testing, stability testing, *in-vivo* studies, pharmacokinetic parameters such as Cmax, tmax and AUC and the comparative evaluation of *in-vitro* and *in-vivo* studies with marketed product. A significant ocular bioavailability (relative bioavailability 119.96) was observed in 0.6 % gelrite containing 0.25% betaxolol HCl of formulation F3 exhibited sustained release of drug from formulation over a period of 8hrs thus increasing residence time of the drug, non-irritating with no ocular damage or abnormal clinical signs to the eye. Therefore, it was concluded that the selected formulation satisfies the entire necessary requisite for a stable, sterile and sustained release formulation with enhanced bioavailability.

**Key words** - Betaxolol HCl, gelrite, *in situ* gel, ocular, *in vivo* studies

**INTRODUCTION**

Betaxolol hydrochloride was the topical, cardio selective β₁-adrenergic antagonist to be used in ophthalmology [1]. It is available dose is 0.25 and 0.5% solutions [2]. β-blockers are the most widely prescribed drugs for the treatment of glaucoma alone or in combination with other agents. Betaxolol works by suppression of aqueous humor formation by blocking the β-adreno receptors in the ciliary body. All agents are available as solutions and are usually administered one to two times daily [3-5]. Ocular residence time is shortened as a consequence of rapid elimination from the corneal surface by the lacrimal flow [6-8]. Treatment compliance can, therefore, be insufficient due to the high frequency of Administration [9,10]. As the ocular efficacy of topically applied drugs is influenced by the corneal contact time, the most common method of improving the corneal availability of drugs is to increase preconveal residence time by using hydrogels [11-13]. Therefore, in this research work, formulation and evaluation of ion activated *in situ* gelling system for Betaxolol HCl and its bioavailability determination was carried out [14-16]. The polymer when instilled as a liquid solution in to the *cul-de-sac* can be initiated gelation by the electrolytes (Na⁺, Ca²⁺ and Mg²⁺ cations), present in tear fluid. Gelation by this method is influenced by osmolality of the solution due to absorption of polymers by electrolytes from the tear fluid. The concentration of sodium ion in human tears is 2.6 gm/l, which is particularly suitable to cause gelation of polymers[17-20]. The objective of the present study was to develop an ion activated *in situ* gelling system of Betaxolol HCl used in the treatment of glaucoma using gellan gum as a polymer. Gellan gum was investigated for the formulation of eye drops of Betaxolol HCl (0.25% w/v), which undergo gelation when instilled into the *cul-de-sac* of the eye and provide sustained release of the drug during the treatment of glaucoma [17].

**MATERIALS AND METHODS**

**Materials**

Betaxolol hydrochloride sample was gifted from Medigraph Pharmaceuticals (P) Ltd. Maharashtra, Gelrite was obtained from Sigma Aldrich, Bangalore, Karnataka, Sodium chloride, sodium bi carbonate, calcium chloride dihydrate and sodium hydroxide pellets were purchased from Karnataka fine chem., Bangalore, Karnataka.

**Preformulation studies**

The studies include drug appearance, solubility in different solvents (water and pH 7.4 buffer), melting point, infrared spectra, DSC studies, determination of λmax in saline phosphate buffer pH 7.4 [21].
Drug-excipient compatibility studies using FT-IR

Drug-excipient compatibility studies were performed to analyse the compatibility between drug and selected polymers and to develop a suitable analytical method for the drug. The interaction studies between the drug and gelrite was studied on FT-IR (Bruker optics, Tensor 27) spectroscopy. Spectra of Betaxolol Hydrochloride, Gelrite and physical mixture Betaxolol Hydrochloride with Gelrite were studied at 400 to 4000 cm\(^{-1}\).

DSC Studies

DSC analysis was carried out to confirm the incompatibility between the drug and the polymer. DSC measurements were conducted by means of a Mettler Toledo DSC1 STAre SW 8.10 system equipped with refrigerated cooling system (Hubert Te45). Approximately 5-10 mg of the samples were weighed into hermetic aluminum pans and quickly sealed to prevent water evaporation from the samples, simultaneously an empty hermetically sealed pan was used as a reference. Samples were exposed to temperature ranging from 30.0 to 300.0°C (scan rate: 10 ºC/min). All the measurements were preferred at least in triplicate [22].

Formulation of Ion-activated in-situ gelling system

Gelrite was dissolved in deionised water and heated up to 85°C for 15 min. The solution was cooled by continuous stirring in open air. Benzalkonium chloride and drug solution were added to the above polymer solution. The volume was made up to 100 ml with deionised water followed by suitable filtration by using filter paper (0.2 mm). The prepared formulations were terminally sterilized by autoclaving at 121°C and 15 Psi for 20 min [19-21]. Five such formulations were formulated and the formulation chart of in-situ gel systems by ion activated method is shown in table: 1

<table>
<thead>
<tr>
<th>Ingredients(%W/V)</th>
<th>Formulation code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Betaxolol HCl</td>
<td>0.25</td>
</tr>
<tr>
<td>Gelrite</td>
<td>0.2</td>
</tr>
<tr>
<td>BKC</td>
<td>0.02</td>
</tr>
<tr>
<td>De ionized water(ml) q.s</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table: 1 Formulation chart of Betaxolol HCl in situ gel

General Appearance and pH

The general appearance of the prepared formulations was observed, which included color and clarity of solution. The pH of the prepared formulations was measured by using pocket pen pH meter [23-26].

Drug Content Estimation

Drug content estimation was done by pipetted out 0.1ml (0.25 mg) of 0.25% sample solution was diluted to 10ml with simulated tear fluid in 10ml volumetric flask. The absorbance of the resulting sample solution was measured at 222.5nm [23-26].

Gelling capacity

Gelling capacity test was carried out to find optimum viscosity, which is the main criterion for sol-to-gel transition. A drop of prepared formulations was added to 2ml of simulated tear fluid. Gelling capacity and gelling time was observed [27,28].

Rheological Studies

The rheological studies were done by Brookfield DV-II+ viscometer using SC4 - 18 spindles for solution form. The samples were poured into the adapter of the viscometer. The angular velocity was slowly increased from 10 to 100 rpm and then reversibly performed from 100 rpm to10 rpm. By adding STF in the ratio of 25:7 formulations and STF respectively and the formulations were made into gel form, the viscosity was determined as specified above using LV-2 spindle [29-32].

In vitro diffusion study

The study was carried out using Franz diffusion cell by using 0.2μ cellophane membrane previously soaked overnight in the STF and placed in between the donor and receptor compartment. 130 ml of STF was placed in the receptor compartment and accurately 1ml of the formulation was instilled into the donor compartment of the Franz diffusion cell. The temperature was maintained at 37°C ± 0.5°C by placing the whole assembly on the thermostatically controlled magnetic stirrer. The magnetic bead was rotated such that it produced a vortex and touched the cellophane membrane. 1 ml of samples were withdrawn at periodic time interval (0-8h) and replaced with an equal volume of STF. Samples were diluted and measured by UV-visible-spectrophotometer at 222.8nm [24].
Isotonicity Study

The selected formulation F3 was subjected to isotonicity measurement. 1 ml sample was mixed with 4 drops of blood and viewed under electronic microscope at 45X. The shapes of blood cell were compared against standard marketed product [31].

Sterility test

Sterility test was performed for fungi, aerobic and anaerobic bacteria by using fluid thioglycollate media and soya casein digest media for F3 formulation [33,34].

Growth promotion (positive control) test

The sterile media is inoculated with about 100 viable micro-organisms and incubated as per the specified conditions. According to IP procedure two containers were selected for ophthalmic formulations. The samples were labeled as ‘negative control’, ‘test’ and ‘positive control’.

Test for aerobic, anaerobic bacteria and fungi

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), viable anaerobic microorganism bacteroides vulgatus (ATCC NO. 8482 and candida albicans (ATCC NO. 10231) aseptically. 2.5 ml of the ophthalmic preparation was added to the tube labeled as test, all three tubes were incubated at 30-35ºC for bacteria and 20-25ºC for fungi for 7 days separately.

Eye Irritation Study

The ocular irritation study was carried out by taking permission from the animal ethical committee of the institution in the albino rabbits. Six white albino rabbits (both sexes) weighing 2.0 to 2.5 kgs were used for the study. The left eye was used as control (without drug-placebo) and the right eye was used as test (sterile formulation). The samples (0.25µl) were administered to the conjunctival sac of right eye. The readings were observed at 1st, 24th and 48th h. The rabbit eye was observed for injuries and blinking rate. The scoring was noted according to Draize irritancy scale. [35-37].

Stability Study

Stability study was carried out for formulation F3 as per ICH guidelines Q1.C. Samples were placed in autoclavable transparent plastic bottles, with rubber stopper and firmly sealed with aluminum foils [38-39]. The autoclavable transparent plastic bottles were kept in stability chamber at 40°C ± 2°C & 75% ± 5% RH for 6 months. Samples were estimated for pH, clarity, drug content, gelling capacity and in vitro diffusion study were carried out at 1st, 3rd and 6th month intervals.

In-vivo release studies [31,39-45]

The CPCSEA committee of the institution gave approval to perform the studies on animals and eight male New Zealand albino rabbits each weighing 2.5 to 3.0 kg. The healthy male rabbits were selected for the study of formulation and the marketed eye drop. The samples (25µl) were instilled in to the lower cul-de-sac of both eyes and the contact time was increased by closing the eye for 2min. Later the eyes were anesthetized using xylocaine (4%). Aqueous humor samples were withdrawn using a sterile needle (28-G) at 0, 0.5, 1, 2, 4, 6, and 8th h. Extraction of drug was carried out using 100 ml methanol and samples left over in a refrigerator for 60min. Later the sample was centrifuged (3000 rpm) for 15 min. 20 ml of the supernatant liquid was used for drug content analysis by HPLC. The procedure was repeated 3 times. A calibration curve was plotted by using HPLC with the conc. range of 1–7 µg/ml.

Sample preparations

The samples (50 µL) were kept at room temperature. 10µL of marketed product (25 ng/mL) was added to the sample. The tubes were sonicated for 60 sec and centrifuged at 10,000 rpm for 5 min at 4°C. The supernatant liquid was filtrated and transferred to an auto sampler and analyzed using LC/MS/MS.

Chromatographic conditions

Table:2 Working parameters of HPLC

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPLC</td>
<td>Agilent 1200</td>
</tr>
<tr>
<td>Column</td>
<td>X-terra, C18, (4.6mm i.d. × 50mm) (Waters, Milford, MA, USA)</td>
</tr>
<tr>
<td>Chromatographic solvent</td>
<td>Acetonitrile/1mM ammonium formate (80/20, v/v)</td>
</tr>
<tr>
<td>Flow rate</td>
<td>600µL/min</td>
</tr>
</tbody>
</table>

The RT was observed for Betaxalol hydrochloride and Marketed product at 0.95 min and 0.90 min respectively.
Mass spectrometric conditions

Column effluent was introduced into the mass at 4ºC for 4 min.

Table: 3 working parameters of Tandem mass spectrometer

<table>
<thead>
<tr>
<th>Mass spectrophotometer</th>
<th>API-4000 triple-quadrupole, (Applied Biosystems/MDS SCIEX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Software</td>
<td>Sciex Analyst 1.4.2</td>
</tr>
<tr>
<td>Transitions</td>
<td>m/z 308.0/133.0 and m/z 268.0/133.0.</td>
</tr>
<tr>
<td>Ionisation source</td>
<td>Ionspray voltage 5500V</td>
</tr>
<tr>
<td>Temperature</td>
<td>550ºC</td>
</tr>
<tr>
<td>Parameters</td>
<td>Liquid nitrogen</td>
</tr>
<tr>
<td>Operating software</td>
<td>Dell Precision 370,1.4.1 software package (MDS Sciex)</td>
</tr>
</tbody>
</table>

Transitions of Betaxolol hydrochloride was observed: Q1-308.0 and Q3--133.0 and marketed product: (ISTD) Q1-268.0 and Q3---133.0

Preparation of Stock solution

Stock solution (1 mg/mL concentration) of betaxolol hydrochloride was prepared by using DMSO and the volume was adjusted with Methanol. (Volume of stock-5µL, matrix used – 45 µL.)

Calculation of Pharmacokinetic Parameters

AUC_{0-300} (µg.min/ml) was calculated based on the trapezoidal rule. The Cmax and tmax were obtained directly from the aqueous humor concentration-time profile. The relative bioavailability was calculated by using the following formula,

The relative bioavailability (Frel) = \{AUC_{0-300} (tested formulation) / AUC_{0-300}(commercial product)\} \times 100.

RESULTS

Preformulation studies

To confirm the identity, purity and suitability of drug for formulation and to establish a drug profile, preformulation studies were undertaken which includes Description, Solubility in water and pH (phosphate buffer pH 7.4). The identity, purity and compatibility of the drug with polymer were confirmed by FT-IR (Table: 1 & 3) and (fig: 1-3).

Table: 4 Preformulation study

<table>
<thead>
<tr>
<th>S.No</th>
<th>Drug Name</th>
<th>Description</th>
<th>Melting Point</th>
<th>Solubility Water</th>
<th>Phosphate buffer pH 7.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Betaxolol hydrochloride</td>
<td>White crystalline powder</td>
<td>114ºC</td>
<td>39mg/ml</td>
<td>27mg/ml</td>
</tr>
</tbody>
</table>

Fig: 1 FT-IR spectra of pure Betaxolol HCl

Fig: 2 FT-IR spectra of pure Gelrite

Fig: 3 FT-IR spectra of physical mixture of Betaxolol HCl and Gelrite
Appearance, Clarity and pH

The formulations of Betaxolol hydrochloride in situ gel F1-F5, were found to be clear, transparent and pH range was found to be 6.6 to 6.8.

Gelling capacity

Gelling capacity for the formulations F1-F5 was carried out and the results are shown in the table: 1

Drug Content estimation

Drug content study was carried out for the formulation F1-F5 and the results were shown in the table: 5

Note: +: gels formed within few minutes and dissolves immediately; ++: Immediate gelation remains and observed for few hours (less stiff); +++: Immediate gelation, remains for longer time and forms stiff gels, o.v: outside viscous.

Rheological studies

Rheological evaluation of formulation F1 and F2 were less viscous when compare to formulation F3. In case of formulation F4 and F5 which formed gel before the addition of STF (pH 7.4). Formulation F3 was selected as best because it exists optimum viscosity (280-839 cps).
In Vitro diffusion study

In vitro diffusion study for all the formulations was carried out. Formulation F1 released 97.28% of betaxolol hydrochloride from the gelrite solution after 4th h. In formulation F2 (96.69%) of betaxolol hydrochloride was released from the gelrite solution after 7th h. The formulation F3 (98.76%) showed better performance in drug release studies and sustained the drug action to 8th h compared to other formulations, due to higher concentration of i.e 0.6% gelrite. Formulation F4 and F5 formed gel before the addition of STF (pH 7.4.). Therefore formulations F4 and F5 were rejected for further studies. Cumulative amount releases versus time profiles are shown in the Fig: 9.

The stability studies results indicated that the selected formulation F3 was stable during the short term stability period shown in Table:7 and Fig: 12.

Table: 7 Physicochemical parameters after six months stability studies

<table>
<thead>
<tr>
<th>Stability period</th>
<th>Drug Content (%)</th>
<th>Clarity</th>
<th>pH of the Solution</th>
<th>Gelling Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before study</td>
<td>97.59±2.09</td>
<td>clear</td>
<td>6.6</td>
<td>+++</td>
</tr>
<tr>
<td>1 month</td>
<td>97.23±1.43</td>
<td>clear</td>
<td>6.6</td>
<td>+++</td>
</tr>
<tr>
<td>3 month</td>
<td>97.24±1.11</td>
<td>clear</td>
<td>6.6</td>
<td>+++</td>
</tr>
<tr>
<td>6 month</td>
<td>97.15±0.09</td>
<td>clear</td>
<td>6.6</td>
<td>+++</td>
</tr>
</tbody>
</table>

Isotonicity testing

Isotonicity was maintained in the selected F3 formulation because the blood cells were observed without change in their shape (Fig:10 and 11).

Eye irritation studies

Eye irritation test(37) was performed for the selected formulation F3. There were no inflammation was observed and blinking rates were within the normal range (2–5 times/min) [36] i.e 3–5 blink/min. Results are shown in Fig: 13-15 and table: 8.

Stability studies

Table: 6 Release kinetics of formulations F1-F5

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Korsmeyer-Peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r^2$</td>
<td>$r^2$</td>
<td>$r^2$</td>
<td>$r^2$</td>
</tr>
<tr>
<td>F1</td>
<td>0.952</td>
<td>0.951</td>
<td>0.975</td>
<td>0.974</td>
</tr>
<tr>
<td>F2</td>
<td>0.979</td>
<td>0.885</td>
<td>0.962</td>
<td>0.993</td>
</tr>
<tr>
<td>F3</td>
<td>0.992</td>
<td>0.793</td>
<td>0.946</td>
<td>0.995</td>
</tr>
<tr>
<td>F4</td>
<td>0.983</td>
<td>0.953</td>
<td>0.920</td>
<td>0.977</td>
</tr>
<tr>
<td>F5</td>
<td>0.974</td>
<td>0.977</td>
<td>0.945</td>
<td>0.973</td>
</tr>
</tbody>
</table>

Fig: 10 Photographs of Rabbits Eye after first hour
PHARMACOKINETIC STUDIES

Formulation F3 was selected as test for the in vivo study using rabbit model and compared with the commercial product Betoptic®0.25% eye drops selected as standard. Fig.16 and tables: 9 and 10 shows the Pharmacokinetic data (AUC, Cmax, and Tmax) formulation F3 and commercial product Betoptic®0.25% eye drops after instillation to 8th h.

DISCUSSION

Preformulation studies

FT-IR spectra of pure Betaxolol hydrochloride were 3239, 3082, 2931, 1513, 1247, 1048, 826 cm⁻¹ wave number as major peaks. Mixture of Betaxolol hydrochloride and excipients showed no considerable changes in the IR peaks. Therefore, it was observed that no incompatibility between the drug and polymer. The DSC thermogram of pure drug Betaxolol HCl showed a characteristic endothermic peak at 83.21°C shown in Fig-4, which is in the range of melting point of Betaxolol HCl and it showed the characteristic peak in the physical mixture of DSC thermogram. So, there was no interaction between the drug and polymer

Appearance, Clarity and pH

The formulations of Betaxolol hydrochloride in situ gel F1-F5, were found to be clear, transparent and the pH also within the limit for ocular products.

Gelling capacity

All the formulations gelled instantaneously with a translucent matrix on addition to the STF, which may due to ionic cross linking of the divalent cations and extended for few hours excluding formulation F1 showed the weakest gelation because of less amounts (0.2%) of gelrite. Formulation F4 and F5 were forming very thick stiff gel before the addition of STF due to the high concentration of gelrite (0.8%w/v & 1%w/v respectively). Formulations F2 and F3 showed good gelling capacity.

Drug content estimation

Drug content of formulations F1- F5 was 97.59% - 98.81%, indicating the greater uniformity of drug in all the formulations.
Optimum Concentration of polymers

The composition of all the formulations are shown in the tables: 2. Gel concentration was kept at maximum of 1% (w/v). The gelrite solution 0.2% – 0.6% retained liquid state at 25°C, but 0.8% and 1.0% forms stiff gel before contact with physiological condition. Concentration of gelrite was optimized by using result of gelling capacity test and 0.6% (w/v) of gelrite forms gel after contact with physiological condition.

Rheological studies

The viscosity of the formulations F1- F5 ranged from 5-50 cps in solution form was shown in the (Fig: 4 & 5). All the formulations exhibited Newtonian flow in solution form, i.e., an increase in the viscosity with increase in angular velocity follows pseudoplastic flow \([38-40]\). Generally viscosity values in the range of 15-50 cps significantly improve the contact time in the eye. The viscosity of the formulations F1 to F5 ranged from 14-48cps with increase in the gelrite concentration within the system.

**In Vitro diffusion study**

The higher regression coefficient values in the table:6 for each formulation suggested that the formulations F1 & F2 follows Higuchi Kinetics type of drug release, whereas formulation F3 shows kosmeyer- peppas drug releases kinetics. The formulation F4 follows zero order release kinetics and F5 follows first order release kinetics. The ‘n’ value obtained from Peppas equation were more than 0.5, which indicated that formulations F1- F5 showed drug release by Non-Fickian diffusion mechanism. The results showed, drug release decreases with the increase in polymer concentration and vice versa. From the study formulation F3 was selected for further studies such as sterility, isotonicity, eye irritation and in vivo studies.

STERILITY STUDIES

The selected F3 formulation results showed there was no appearance of turbidity hence, no evidence of microbial growth. Thus, indicates the formulation F3 pass the sterility test and retained its antimicrobial efficacy.

STABILITY STUDIES

The stability studies showed that the selected formulation F3 was stable over the period of 6 months and it follows non Fickian type of drug diffusion after the stability studies.

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 and the results showed that there was no irritation to the sensitive ocular tissues by the selected formulation F3 and no ocular damage and abnormal clinical signs hence, the selected formulation F3 was safe to use in ocular treatment\([41]\).

PHARMACOKINETIC STUDIES

The drug concentration of the test formulation was significantly higher at all time periods than that of the standard formulation after instillation. After the administration of test formulation the aqueous humor drug content was higher at all time points than that of 1% commercial product \(\text{AUC}_{0-480}\text{min}\) obtained from the test formulation (15000.95ng.h/ml) was more than the standard formulation (12505.5ng.h/ml) which confirms the superior bioavailability of formulation F3 than the commercial Betoptic®0.25% eye drops. The \(C_{\text{max}}\) of the commercial product was 2282.60ng/ml compared with the \(C_{\text{max}}\) of 2996.80ng/ml for F3 formulation. High \(C_{\text{max}}\) of the test formulation may be due to the delay of precorneal clearance of the drug from the F3 formulation which able to maintain high viscosity subsequently slow release. There was no any significant difference in test and standard in case of \(T_{\text{max}}\). The \(\text{AUC}_{0-480}\) min was 1.3 times higher than the marketed product and the relative bioavailability was 119.96.

CONCLUSION

In the present work, Betaxolol Hydrochloride in-situ gel was formulated. Gel retention time, rheological studies and in vitro drug diffusion studies indicated that the developed in-situ gelling system of Betaxolol Hydrochloride will deliver the drug for prolonged period of time and reduces the frequency of dosing when compare to the marketed eye drops which is releasing the drug within one hour. The formulation F3 showed no significant changes in the in vitro parameters during accelerated stability studies. In vivo results shows that the superior bioavailability of in situ gel formulations of Betaxolol Hydrochloride (F3) when compared with the marketed eye drops (Betoptic®0.25%).Therefore it can concluded that the developed in situ gelling system of Betaxolol Hydrochloride is an alternative to conventional eye drops as it may provide better patient compliance through ease and decreased frequency of administration due to increase in bioavailability.
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