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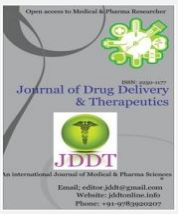

Open Access Research Article

ENHANCEMENT OF TRANSCORNEAL PERMEATION AND SUSTAIN RELEASE OF TIMOLOL MALEATE FROM DEVELOPED AND OPTIMIZED *IN SITU* GEL WITH BETTER SAFETY PROFILE

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ABSTRACT

Glaucoma is a chronic disease that causes irreversible blindness. Timolol Maleate is used as first line drug in treatment of glaucoma. Poor ocular bioavailability and therapeutic response shown by conventional ophthalmic system can be overcome by use of *in situ* gelling system which undergoes reversible sol to gel transition in cul-de-sac by physical stimulation. Present work describes formulation and evaluation of pH sensitive *in situ* gel system of Timolol Maleate. Carbopol 974P was used as pH sensitive polymer with HPMC K15M as viscosity modifier. 3^2 factorial design was used to study the effect of independent variables viz. concentrations of Carbopol 974P and HPMC K15M on dependent variables like *in vitro* drug diffusion and viscosity. Optimized batch showed 88.48% drug diffusion upto 8h. Optimized formulation was evaluated for various parameters such as drug release study, isotonicity, texture analysis, preservative efficacy studies, sterility testing as per IP 2010, accelerated stability studies. *Ex vivo* transcorneal permeability study was carried out on goat eye cornea which showed that EDTA (0.5%) increases drug penetration by 1.90 fold and showed no corneal damage after histological study. In conclusion, prepared formulation is stable and non-irritant.

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INTRODUCTION:

Glaucoma is a chronic disease of eye that is characterized by irreversible damage to the ganglionic cells and the optic nerve. Elevated intraocular pressure is most important risk factor for glaucoma. It has been established as the second leading cause of world's blindness, which may affect around 80 million in 2020. The treatment of glaucoma focuses mainly on lowering of IOP. In the last two decades several classes of topical IOP lowering drugs have been made available which includes beta blocker, prostaglandin analogue (PGA), alpha-adrenoceptor agonist (AA) and topical carbonic anhydrase inhibitors (CAI's).

Timolol Maleate (TM) is a non-selective beta-adrenergic receptor blocker used in treatment of open angle glaucoma and occasionally in secondary glaucoma. Conventionally it is available in the form of solution which gets immediately eliminated from the precorneal area. Further, shorter contact time with poor corneal permeability results into poor bioavailability (10%) and decreased patient compliance. Several novel drug delivery systems (NDDS's) have been developed which includes inserts, ointment, nanosuspension etc. However these systems suffer from several drawbacks such as blurred vision associated with ointment, low patient compliance from inserts and high cost of nano suspension. These problems can be overcome by using *in situ* gel forming systems.

In situ drug delivery systems consist of polymers that exhibit sol to gel phase transition in cul-de-sac by several physicochemical parameters. Depending upon method used for sol to gel phase transition three types of *in situ* gels are widely accepted as pH triggered system, ion activated system and temperature dependent system. Pharmaceutically significant gels can be prepared by using various materials. Carbopol 974P is pH sensitive polymer which shows sol to gel transition in aqueous solution when pH is raised above 5.5. It is polyacrylic acid (PAA) which is required in high concentration to form stiff gel. At higher concentration it forms highly acidic solution which is not easily neutralized by buffer action of tear fluid. Reduction in its concentration without affecting the gelling capacity and viscosity was achieved by addition of viscosity increasing polymers such as HPMC.

MATERIAL AND METHODS:

Material

Timolol Maleate and Carbopol 974P were gifted by FDC Limited, Mumbai and Lubrizol advanced material India Pvt. Ltd., Mumbai respectively. HPMC K15M was purchased from S. D. Fine, Mumbai. HPLC grade methanol was purchased from Qualigens Fine chemicals, Mumbai. All other ingredients were of analytical grade. IOTIM (Timolol Maleate eye drops 0.5% by FDC) was brought from local medical shop.

Analytical method development

To quantitate the content of Timolol Maleate in samples reversed phase (RP)-HPLC method was developed and validated as per ICH guidelines Q2 (R1). Shimadzu RP-HPLC instrument (CFR-21) equipped with photodiode array detector (PDA) and C_{18} column of Kromasil (250 mm × 4.6 mm, 5µm particle size) was used. Mobile phase consisted of phosphate buffer: methanol (60:40 v/v) and pH 3.5 was maintained by O-phosphoric acid. Elution was measured at 295 nm with flow rate of 1.0 ml/min.

Full factorial experimental design

For optimization of Timolol Maleate *in situ* gel, 3^2 randomized full factorial design was selected. The design was applied to study the effect of concentration of Carbopol 974P and HPMC K15M on formulation. The amount (%) of pH sensitive polymer, Carbopol 974P (X_1) and the amount (%) of viscosity modifier, HPMC K15M (X_2) were selected as independent variables, in this study. These two factors were evaluated at 3 levels as higher, middle and lower levels. Composition of different batches of Timolol Maleate is shown in table 1.

Evaluation of formulation

Formulation was evaluated for various parameter viz. physicochemical evaluation, viscosity, drug diffusion, *ex-vivo* transcorneal permeation, histological evaluation, *in-vitro* drug release, isotonicity, texture analysis, sterility, preservative efficacy study and accelerated stability study.

Table 1: Composition of different batches of Timolol Maleate *in situ* gel

Name of excipients	Different batches of Timolol Maleate *in situ* gel (%w/v)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Timolol Maleate	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
Sodium Chloride	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80
Carbopol 974P	0.15	0.15	0.15	0.30	0.30	0.30	0.45	0.45	0.45
HPMC K15M	0.25	0.50	0.75	0.25	0.50	0.75	0.25	0.50	0.75
Benzalkonium chloride	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Water q.s.	100	100	100	100	100	100	100	100	100

RESULTS AND DISCUSSION:

The pH triggered Timolol maleate *in situ* gel was successfully formulated by using Carbopol 974P and HPMC K15M. Formulation was optimized by 3^2randomised full factorial design for two responses viz. viscosity at 20 rpm and cumulative percent drug diffused at the end of 8 h. Optimized formulation (Batch f7) was liquid at pH 4 and gel above pH 7 indicating *in situ* transition at physiological pH. Optimized *in situ* gel passes all safety tests used for evaluation of ophthalmic formulation as per regulatory guidelines. *In vitro* drug release study showed sustained release of drug from *in situ* gel over period of 8h as compared to marketed formulation IOTIM (FDC). Prepared formulation was subjected for *ex vivo* transcorneal permeability study and result was compared with IOTIM which showed need of penetration enhancer. EDTA (0.5% w/v) was found to be suitable penetration enhancer which showed significant increase in transcorneal permeability of drug (Fig. 1). Formulation showed less eye irritation as compared to SDS (positive control) during histological study on goat eye cornea (Fig. 2). Stability study performed over a period of 3 month showed that optimized formulation is stable. Hence; prepared formulation is feasible alternative for conventional eye drop for glaucoma treatment but future *in vivo* studies on human is necessary to confirm significant therapeutic effect.

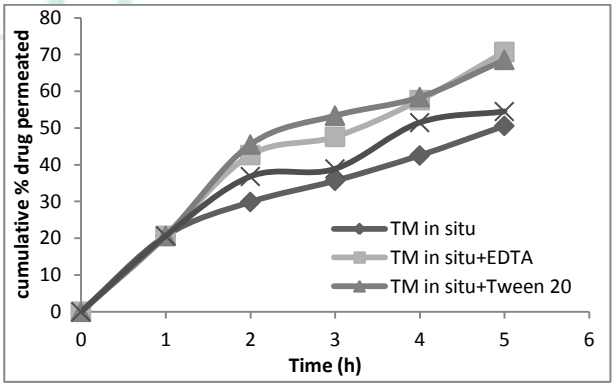

Figure 1: Comparative *ex vivo* transcorneal cumulative % drug release

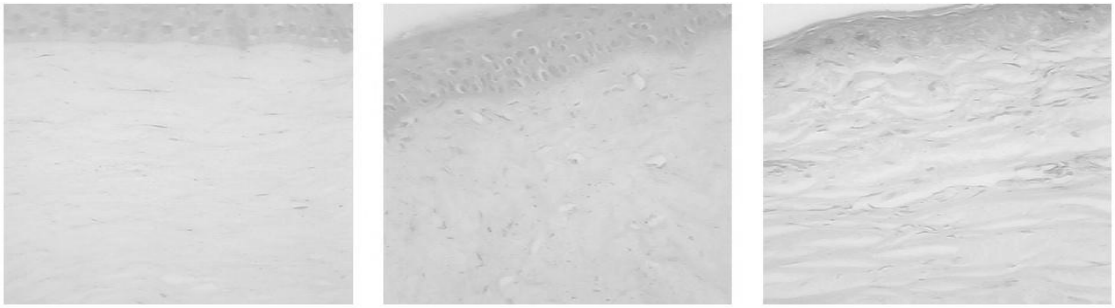

Figure 2: Histological section of goat eye cornea (magnification 40X) a) negative control: untreated cornea, b) test specimen: formulation treated cornea, c) positive control: SDS treated cornea for 5h.

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