Available online on 25.12.2017 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

NON-IONIC SURFACTANT VESICLES (NIOSOMES) BASED NOVEL OPHTHALMIC FORMULATION OF TIMOLOL MALEATE

Prakash Kumar Soni, T.R. Saini

Nanotechnology Research Lab., Department of Pharmacy, Shri G.S. Institute of Technology and Science, 23- Park Road, Indore-452003, (MP) India

E-mail address: soniprakashpharma@gmail.com

ABSTRACT

The objective of the present work was to develop drug loaded niosomal ophthalmic formulation of timolol maleate (an antiglaucomal drug) for enhanced trans-corneal drug permeation and better ocular bioavailability. Timolol loaded niosomes were prepared by thin film hydration method using rotary evapoarator and ultra-sonicated for size reducation using probe sonicator. The nano-vesicle (niosomal) formulation was optimized by selecting surfactant content, cholesterol content and sonication time as independent variables and particle (vesicle) size, drug entrapment efficiency and % drug release as response variables for optimization studies. The timolol maleate niosomal (TMN) formulation was evaluated for particle size, pH and osmolality and was found to possess the desired properties. The developed TMN formulation was studied for % cumulative in-vitro drug release using bottle rotating apparatus (electrolab) and was found to be 79.98% over 8 hr period exhibiting sustained drug release profile. The ex-vivo trans-corneal drug permeation profile of developed TMN was studied using modified franz-diffusion cell apparatus (Permegear) and the % cumulative drug permeation across freshly excised goat cornea was found to be 65.90 % in 8 hrs duration, which was approximately 1.5 times higher than the conventional eye drop formulation. The developed TMN was also proved to be isotonic and non-irritant in HET-CAM ocular irritancy test. It was therefore, concluded from above studies, that the developed timolol maleate niosomal (TMN) formulation is better than conventional eye drops due to longer corneal retention, sustained drug release and better trans-corneal drug permeation and thereby higher ocular bioavailability, hence, would need less frequent administration.

Cite this article as: Soni PK, Saini TR, Non-Ionic surfactant vesicles (Niosomes) based novel ophthalmic formulation of timolol maleate , Journal of Drug Delivery and Therapeutics. 2017; 7(7):59-61

INTRODUCTION:

Timolol maleate, a non-selective beta blocker, is widely used for treatment of glaucoma in the form of eye drops, however, the conventional eye drop formulations suffer from inadequate ocular bioavailability and need to be frequently administered, due to their short pre-corneal residence, naso-lacrymal drainage and poor trans-corneal permeation. It was, therefore, aimed to develop nano-vesicular (niosomal) ophthalmic formulation of timolol maleate for enhanced trans-corneal permeation and ocular bioavailability. Niosome based novel formulations are being extensively explored due to their inherent advantages in drug delivery system [1].

MATERIAL AND METHODS:

Material

Timolol maleate was received as gift sample from M/s. Piramal Healthcare Ltd. Pihampur (MP). Span-60 (Loba Chemie) and Cholesterol (Merck) was purchased from local market. All other chemicals, reagents and solvents used were of analytical grade.

Formulation of Timolol maleate niosome (TMN)

Timolol maleate loaded niosomes were prepared by thin-film hydration method 2 using rotary evaporator (Buchi®).

Determination of particle size and entrapment efficiency

The niosomal dispersion obtained as above was sonicated for 2-3 minutes using ultra-probe sonicator (sonics) for converting the niosomes to nanometric size range and the particle (vesicle) size distribution of TMN formulation was determined by Nanotrac nano-particle size analyzer (Microtrac Inc.). The timolol maleate loaded niosomes were separated from free drug (unentrapped drug) by centrifugation at 13,000 rpm and 4°C using refrigerated centrifuge (Eppendorf). The clear supernatant so obtained was analyzed for estimation of drug content and the amount of unentrapped drug was calculated. Amount of entrapped drug was obtained by subtracting amount of unentrapped drug from the total drug amount taken [3].

$$\text{Entrapment efficiency (\%)} = \frac{\text{Amount of drug entrapped}}{\text{Total amount of drug}} \times 100$$

In vitro drug release study

In vitro drug release study of the developed TMN formulation was performed in Bottle rotating apparatus. In this method, an accurately weighed quantity of timolol maleate niosomes (equivalent to 2 mg drug), was suspended in 10 ml phosphate buffer (pH 7.4) filled in the capped glass bottle (tube) and rotated at 25 rpm and maintained at 37^0C. One test sample bottle (tube) was taken out every one hour and was analyzed for estimation of drug release till 8 hour duration and thereby, the % cumulative drug release was calculated for a period of 8 hr.

Ex vivo Trans-corneal Drug Permeation Study

Trans-corneal drug permeation study of developed TMN formulation was carried out under ex-vivo condition across freshly excised goat cornea using modified franz-diffusion cell apparatus and was compared to that of conventional eye drop product. The exposed area of goat's cornea was 1.130 cm^2 [4].

Isotonicity evaluation

Red blood cells were separated from freshly collected blood from slaughter by centrifugation applying centrifugal force of 14000G for 10 min using cooling centrifuge (Eppendorf). The recovered RBCs were suspended in appropriate amount of developed TMN formulation, 0.9% saline (isotonic) solution (negative control), and hypotonic & hypertonic saline solution (positive control) was vortexed for 5 min and was kept aside for 30 min and subsequently observed under the polarizing microscope (Leica) at 40X magnification.

HET-CAM Ocular irritancy test

The purpose of this test to evaluate the potential ocular irritancy of a test substance as measured by its ability to induce toxicity in the chorio-allantoic membrane (CAM) of a chicken embryo in fertilized hens egg. In this test, irritancy is assessed by the onset of hemorrhage, coagulation and vessel lysis. These assessments are considered individually and then combined to derive a score; irritation score (IS) which is used to classify the irritancy level of the test substance.

RESULTS AND DISCUSSION:

The various physico-chemical properties i.e., particle size, polydispersity index, pH, osmolality and % entrapment efficiency was studies and the results observed are presented in Table 1

Table 1: Physico-chemical properties of developed TMN formulation

S. N.	Properties	Result
1	Particle size	226.29 nm
2	Osmolality	298 mOsm/kg
3	% Entrapment efficiency	42.88%

The developed TMN formulation was studied for % cumulative in-vitro drug release using bottle rotating apparatus (electrolab) and was found to be 79.98% over 8 hr period exhibiting sustained drug release profile. The ex-vivo trans-corneal drug permeation profile of developed TMN was studied using modified franz-diffusion cell apparatus (Permegear) and the % cumulative drug permeation across freshly excised goat cornea was found to be 65.90 % in 8 hrs duration, which was approximately 1.5 times higher than the conventional eye drop formulation, as shown in figure 1.

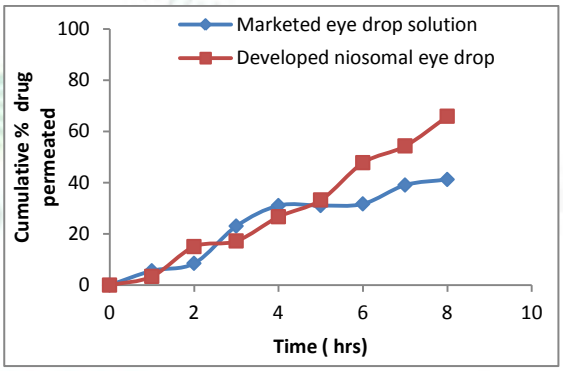
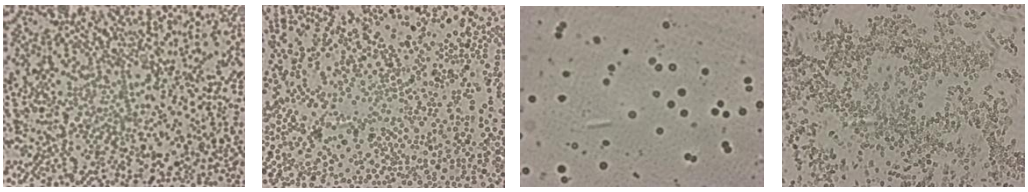


Figure 1: Trans-corneal Drug Permeation Profile of Timolol Maleate Niosomal Formulation

The developed TMN was also proved to be isotonic in isotonicity studies, as the isolated RBCs were normal in size and shape on exposure with developed TMN and isotonic saline solution, while the RBCs were shrink in hypotonic and swollen in hypotonic solution and are shown in figure 2.



(a) **(b)** **(c)** **(d)**

Figure 2: (a) RBCs with Developed Timolol Maleate Niosomal Eye Drop, (b) RBCs with Isotonic Solution (c) RBCs with Hypotonic Solution (d) RBCs with Hypertonic Solution

The developed timolol maleate niosomal formulation was also proven to be non-irritant in HET-CAM ocular irritancy test securing 0 score, as there were no signs of hemorrahage, lysis and coagulation in CAM of fertilized hens egg with developed TMN and isotonic saline solution (negative control), while hemorrahage was observed with 1% NaOH solution (positive control), as shown in fig.3.

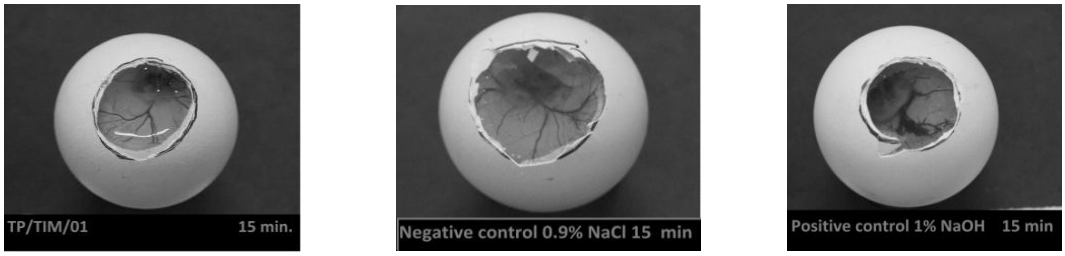


Figure 3: HET-CAM response to exposure with TMN formulation, negative control and positive control

CONCLUSION:

It can be concluded from above studies, that the developed timolol maleate niosomal (TMN) formulation is better than conventional eye drops due to longer corneal retention, sustained drug release and better trans-corneal drug permeation and thereby higher ocular bioavailability, hence, would need less frequent administration.

REFERENCES:

1. Uchegbu IF, Vyas SP, Non-ionic surfactant based vesicles (niosomes) in drug delivery, Int J Pharm, 1998, 33-70.
2. Mancon M, Sinico C, Valenti D, Loy G, Fadda AM, Accelerated photostability study of tretinoin and isotretinoin in liposome formulations, Int J Pharm, 2002, 237-248.
3. Aggarwal D, Kaur I, Improved pharmacodynamics of timolol maleate from a mucoadhesive niosomal ophthalmic drug delivery system, Int J Pharm, 155-159.
4. Zhanrong Q, Zeng W, The Development of a Butyrylcholinesterase Porous Pellet for Innovative Detection of Cholinesterase Inhibitors, Eur J of Pharm Sci, 115-123.