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Original Article

Formulation and Evaluation of Timolol Maleate Proniosomal Gel for Ocular Drug Delivery

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ABSTRACT

Introduction: The objective of this task is to succeed with the trial of an ocularly efficient Timolol maleate formulation produced from prolonged proniosomal gel niosomes to get significant therapy for glaucoma. **Methods:** Cholesterol, Lecithin, Span 60, Brij 72, and Tween 80 in various concentrations were used to create Timolol maleate loaded proniosomal gel derived niosomes utilizing the phase coacervation method. Found on these outcomes of entrapment efficiency and *in-vitro* release, an optimised batch of proniosomal gel-produced niosomes was chosen. By spreading proniosomes in an *in-situ* gelling method, timolol maleate proniosomal gel-derived niosomes were created. Fourier transforms infrared spectroscopy (FTIR) experiments confirmed each interaction study. Wetting agent with additive effects on entrapment efficiency along with *in-vitro* drug release manner based on proniosomal gel-produced niosomes was investigated. Cholesterol, Lecithin, Span 60, Brij 72, and Tween 80 in various quantities were used in a coacervation technique, by dispersing proniosomes in an *in-situ* gelling method, a timolol maleate proniosomal gel was created. **Results:** The FTIR analyses revealed no signs of interaction between the medicine and the excipients, indicating that they are compatible. At the end of 12 hr, formulations T2 and T10 had 99.98 percent and 99.90 percent drug release, respectively. **Conclusion:** Starting with these findings secured, it can be closed this one proniosomal gel derived niosomes might be a satisfactory alternative to conventional eye drops as they exhibited elevated penetrability with sustained-release actions.

Keywords: Timolol maleate, Proniosomal gel, Phase co-acervation technique, Ocular delivery, Niosomes.

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INTRODUCTION

The primary goal of ocular medicine administration is to get better the already accessible conventional dosage shape as well as to make use of innovative drug delivery systems to improve therapeutic efficacy. The use of eye drops as a topical treatment for people with eye problems is extremely prevalent, because of continual lachrymal secretion, tear turnover, blinking, reflex, moreover quick nasolachrymal drainage, traditional eye drops have a low ocular bioavailability. Usual drainage of an administered dosage begins almost instantly after administration furthermore is finished in less than 5 min.[1] As a decision, a regular influx of concerted mixture ensures required to obtain these expected healing effects. To address these issues, researchers have looked into a variety of ocular formulations, including viscous solutions, ointments, gels, nanoparticles, and polymeric inserts.[2] These vehicles occupy enhanced corneal contact time to varying degrees, but they have not been universally adopted due to obscured vision or a lack of patient compliance. As a decision, achieving adequate ocular bioavailability after topical distribution of a medicine to the eye is a difficulty that has yet to be overcome.[3] Timolol maleate (TM) was used as the model medication in this investigation. The most often used medicine in the treatment of glaucoma is TM, which is a non-selective beta-blocker. Glaucoma is the world's next to the mass routine source of darkness. It affects around 70 million people all over the world.[4] TM was chosen above other medications in the same class because it had a faster onset, better tolerance, and fewer adverse effects. This medication reduces intraocular pressure by inhibiting the generation of aqueous humor in the ciliary epithelium by blocking sympathetic nerve terminals. The goal of this work was to find a way for dispersing proniosomal gel including TM within *the in-situ* gel to improve the mucoadhesive and long-term release behaviour of the gel.

MATERIALS AND METHODS

Materials

Yarrow chem products, Mumbai, India, provided Timolol maleate, Lecithin, and Poloxamer. Loba Chemie Pvt. Ltd, Mumbai, India, provided the cholesterol. Rolex Chemical Industries in Mumbai, India, provided Span 60. Spectrum Chemicals in Mumbai, India, provided Brij 72. S D Fine Chemicals in Mumbai, India, provided Tween 80. Each chemical utilised were of the highest quality.

Methods

pre-formulation studies

determination of solubility of timolol maleate

By using the shake flask method, the solubility of Timolol maleate in aqua, ethyl alcohol, PBS pH 6.8, PBS pH 7.4, and ether was measured. In a flask containing 10 ml of each solvent, an excess amount of the medication was introduced. The mixtures were then agitated at 100 rpm for 24 hours inside a thermostatically managed water bath at 370.5°C, filtered, diluted, and spectrophotometrically assessed at 294.4 nm using a UV spectrophotometer against a blank that had been treated similarly.[5]

Standard curve for timolol maleate

The medication (10 mg) was precisely weighed and put within a 100 mL measuring flask. To make this stock solution-I, the drug was dissolved in 7.4 pH buffer solution and diluted until 10 mL with the similar

buffer solution to reach a concentration of 1000 g/mL. To manufacture 100 g/mL of Timolol maleate, 10 mL of SS-I was put down in a 100 mL measuring flask and filled to the spot with water phase (stock solution-II). Transferring 0.5 to 3.0 mL of the SS-II into a 10 mL measuring flask and making up the quantity with the same buffer solution yielded serial dilutions with concentrations of 5-30 g/mL, because the sample solution was colorless, it was scanned with a UV-visible spectrophotometer between 200 and 400 nm.

Determination of partition coefficient

The drug partitioning study (Log P) was used to investigate the partitioning behaviour of the compound under research in lipophilic and hydrophilic environments. The non-aqueous phase was chosen as n-octanol, and the aqueous phase was chosen as water.

Shake flask method was used to measure the partition coefficient of Timolol maleate.

Compatibility study using FT-IR

A Thermo Nicolet FTIR spectrophotometer was used to test medication and excipient compatibility, and the spectrum was obtained in the range of 4000 to 400 cm^{-1}.[6]

Formulation of timolol maleate loaded proniosomal gel

Proniosomes were composed utilizing coacervation phase separation pattern. In-order-to each and every one preparation, exactly weighed quantity of surfactant, cholesterol, lecithin, and drugs remain merged with 2.5 mL of ethyl alcohol (95%) in a tiny stoppered glass vial. The glass vial was carried on to aqua bath at a temperature of 70-80°C for 45 min with constant vibrating up to absolute split-up of lipids. Next preheated 0.9 ml of phosphate buffer saline (PBS pH 7.4) was included to the molten lipids compound and check out on the water bath for 10 min until the product becomes a lucid liquid. The compound left to chill down to territory temperature for 24 hr and the white creamy proniosome was found. When required, the prepared proniosome was swirled with the precisely calculated quantity of PBS pH 7.4 to give drug loaded niosomal dispersion. The proniosomes were then mixed with previously prepared thermosensitive hydrogel (Chitosan 1.5% w/w) to get proniosomal gel containing 0.5% (w/w) of Timolol maleate. The acquired solution was blended for 45 min to procure a homogeneous compound, to detach bubbles developed in the production procedure, thermosensitive liquids were centrifuged (Remi Centrifuge, model RM-12C BL) at 5000 rpm for 5 min at refrigeration temperatures. The pH quantification of pre-gelling liquids were carried out at room temperature utilizing a pH meter (Techno scientific, Products). The control gel was prepared using Chitosan (1.5% w/w) containing 0.5% (w/w) of Timolol maleate and stored at 4°C for further studies. Table 1 shows admixture of proniosomal gel.

Evaluation of timolol maleate proniosomes

Determination of entrapment efficiency (%EE)

After centrifuging individual niosomal suspension at 10,000 rpm for 60 min at 4°C utilizing a cooling ultracentrifuge, the percent entrapment efficiency (percent EE) was calculated using the direct technique (Remi Centrifuge, model RM-12C BL). The precipitated cake was diffused and diluted with ethyl alcohol before spectrophotometric determination of the entrapped Timolol maleate quantity at a lambda max =294 nm using a blank of corresponding plain proniosomes handled in the uniform manner.

Formulation design

Table 1: Composition of various batches of Timolol maleate Proniosomes.

Formulation	Timolol maleate (mg)	Cholesterol (mg)	Lecithin (mg)	Span 60 (mg)	Brij 72 (mg)	Tween 80 (mg)
T1	500	80	150	50	--	--
T2	500	80	150	75	--	--
T3	500	80	150	150	--	--
T4	500	80	50	150	--	--
T5	500	80	75	150	--	--
T6	500	80	150	--	50	--
T7	500	80	150	--	75	--
T8	500	80	150	--	150	--
T9	500	80	50	--	150	--
T10	500	80	75	--	150	--
T11	500	80	150	--	--	50
T12	500	80	150	--	--	75
T13	500	80	150	--	--	150
T14	500	80	50	--	--	150
T15	500	80	75	--	--	150

Characterization of timolol maleate proniosomes

In vitro delivery reports

In a Franz diffusion cell with dialysis membrane, the *in vitro* delivery was performed (molecular weight cut-off of 8000 Dalton). The receptor compartment had a capacity of 25 ml. 1.48 cm2 of donor compartment was exposed to receptor compartment connecting the donor and receptor compartments, the dialysis membrane was installed. On one side of the dialysis membrane, 1 g of proniosomal gel was applied. Simulated lacrimal fluid pH 7.4 (SLF) (NaCl 0.67 g, $NaHCO_3$ 0.20 g, $CaCl_2.2H_2O$ 0.008 g, and distilled aqua to 100 ml) was used as the receptor media.

An aqua jacket was used to keep the temperature of the receptor chamber at 370.5°C. A thermostatic heated sheet with a magnetic stirrer was used to provide heat. A Teflon-coated magnetic bead attached to a magnetic stirrer was used to stir the receptor fluid. Samples were taken at individual testing interval and restored with equivalent quantities of new receptor fluid on each time. The removed samples were spectrophotometrically examined at 294 nm. The mean values of the release experiments (n = 3) are used to calculate the results. The proportion of medication delivered at each moment spot was plotted against time to create the delivery profiles.

RESULTS

Pre-formulation reports

Analytical method determination of Timolol maleate

Solubility profile of Timolol maleate

Timolol maleate was examined for solubility in a variety of popular solvents. The results revealed that Timolol maleate was soluble in water (0.265+0.154 mg/ml), ethanol (2.151+0.262 mg/ml), pH 6.8 phosphate buffer (1.240+0.149), pH 7.4 phosphate buffer (1.721+0.353), and ether (0.047+0.024).

Determination of calibration curve

In a UV spectrophotometer, the absorbance was measured at 294 nm against a pH 7.4 phosphate buffer. In the range of 5-30 mg/mL, timolol maleate pure medication obeyed Beer-Lambert's law, by graphing absorbance versus drug concentrations, a calibration curve was created. The correlation coefficient and slope were found to be 0.9977 and 0.032, respectively, when the data was examined in MS-Excel-2007.[7]

Partition coefficient

In the n-octanol: aqua system, the partition coefficient of Timolol maleate was measured. The following equation was used to obtain the partition coefficient of Timolol maleate.

$$\textit{Partition coefficient, } PC = Co/Ca$$

Where, Co is the concentration of Timolol maleate in octanol, and Ca is the concentration of the Timolol maleate in aqueous phase.[8]

Compatibility studies using FTIR

The unique absorption peaks for C=C stretching non-conjugated at 1650.73 cm^{-1}, N-H bending at 1581.09 cm^{-1}, and N-H bending at 1581.09 cm^{-1} were discovered in the FTIR spectra of Timolol maleate. At 1218.35 cm^{-1}, -H_2C-NH- Amines stretch, -CH_2-O-R- Ethers at 1315.07 cm^{-1}, and C-H bend aromatic at 920.05 cm^{-1}. In all of the IR-spectra, there was no change in the functional group peaks of Timolol maleate.

Characterization of Timolol maleate Proniosomes

Entrapment Efficiency of Timolol maleate Proniosomes

Table 2 shows the entrapment efficiency values that were recorded. The efficiency of trapping ranged from 78.30.3 percent to 97.70.8 percent. T4, T9, and T14 produced with Span 60, Brij 72, and Tween 80 in a 3:1 ratio with Lecithin had the maximum entrapment efficiency (97.700.80%, 95.440.51%, and 94.60.37%, respectively). According to these findings, formulations comprising Span 60 had a better entrapment efficiency than those containing Brij 72 and Tween 80. In terms of individual formulation entrapment efficiency, the Proniosome formulation (T6) with a 3:1 ratio of lecithin: Brij 72 ensnared the least amount of the additional medication at 78.30.3 percent. After increasing the concentration of Brij 72 in the formulation T9, this number was enhanced even more (95.440.5 percent) (containing 1:3 ratio of Brij 72: Lecithin). The results demonstrated that a large percentage of Timolol maleate was entrapped in the proniosomes generated; this is mostly due to the use of Span 60 (T4), which has a longer alkyl chain than other non-

Table 2: Composition of various batches of Timolol maleate Proniosomes.

Formulation Code	Entrapment Efficiency	Drug content (%w/v)
T1	88.4±0.3	95.41±0.22
T2	92.0±0.1	99.98±0.25
T3	94.8±0.5	99.10±0.17
T4	97.7±0.8	96.34±0.53
T5	95.2±0.4	97.89±0.93
T6	78.3±0.3	97.32±0.50
T7	85.3±0.2	98.10±0.82
T8	90.5±0.1	96.09±0.57
T9	95.4±0.5	99.46±0.40
T10	93.2±0.6	99.90±0.11
T11	81.3±0.3	97.80±0.10
T12	89.3±0.3	96.39±0.77
T13	91.5±0.5	99.04±0.62
T14	94.6±0.7	96.77±0.50
T15	92.2±0.4	98.06±0.84

Table 3: *In-vitro* delivery profile of optimized proniosomal gel Vs Marketed eye drops.

Time (Hour)	T2	T10	Marketed eye drop
0	0.00	0.00	0.00
1	12.54	20.55	62.54
2	38.68	32.35	99.05
4	54.96	44.82	--
6	69.45	60.49	--
8	78.71	76.32	--
10	86.35	83.05	--
12	92.79	93.82	--
24	99.34	99.85	--

Table 4: Drug release kinetics of proniosomal gel formulation T1-T15.

Formulation code	KINETIC MODELS					Model Followed
	Higuchi	Zero order	First order	Korsmeyer-Pappas		
	R^2	R^2	R^2	R^2	*n*	Higuchi model
T1	0.994	0.876	0.956	0.927	0.953	Higuchi model
T2	0.992	0.862	0.979	0.921	0.886	Higuchi model
T3	0.997	0.872	0.934	0.932	0.896	Higuchi model
T4	0.998	0.890	0.926	0.929	0.894	Higuchi model
T5	0.995	0.878	0.979	0.978	0.932	Higuchi model
T6	0.991	0.892	0.968	0.960	0.889	Higuchi model
T7	0.990	0.890	0.972	0.989	0.919	Higuchi model
T8	0.994	0.894	0.982	0.981	0.925	Higuchi model
T9	0.994	0.897	0.947	0.980	0.921	Higuchi model
T10	0.993	0.872	0.970	0.929	0.896	Higuchi model
T11	0.994	0.877	0.971	0.978	0.944	Higuchi model
T12	0.996	0.895	0.956	0.960	0.895	Higuchi model
T13	0.992	0.858	0.988	0.989	0.953	Higuchi model
T14	0.991	0.809	0.957	0.981	0.958	Higuchi model
T15	0.995	0.846	0.947	0.963	0.906	Higuchi model

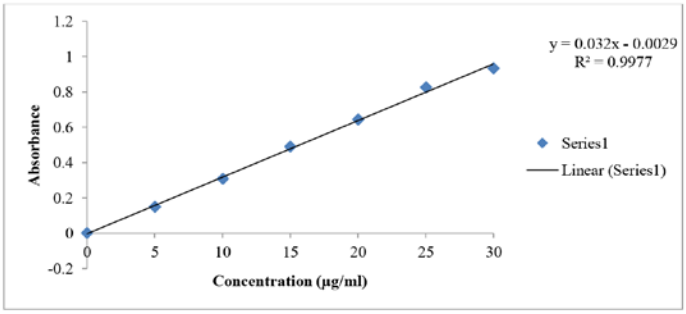

Figure 1: Calibration curve of Timolol maleate in pH 7.4 phosphate buffer.

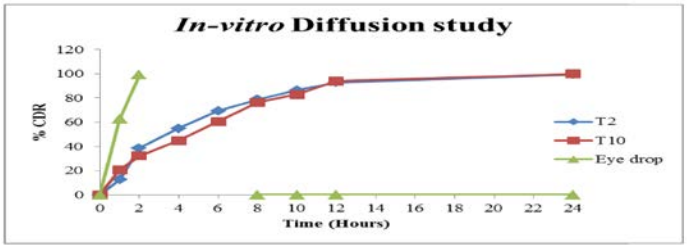

Figure 2: *In-vitro* delivery profiles of Timolol maleate loaded proniosomal gel formulae in comparison with Marketed eye drops.

ionic surfactants, resulting in increased entrapment effectiveness. The entrapment effectiveness of the medication into proniosomes decreased as the Lecithin concentration in the formulation was increased (T1, T6 and T11). This could indicate that the medication is insoluble in Lecithin.

In comparison to Brij 72 and Tween 80, Span 60 has the highest phase transition temperature (50°C) and entrapment efficiency percent. The hydrophilic lipophilic balance (HLB) value of the surfactant mixture is affected by the length of the alkyl chain, which has a direct impact on medicament entrapment efficiency. As in the case of proniosomes made with Span 60, the lower the surfactant's HLB, the better the drug entrapment efficiency and stability. This could also be due to the surfactants' structure, orientation, and packing behaviour. The greatest saturated chain length and the most entrapment are found in Span 60.

In vitro delivery reports

The Franz diffusion cell was used to perform *in-vitro* diffusion investigations on Timolol maleate proniosomal gel formulation. Over the course of 24 hr, prepared formulae revealed various release profiles, whereas marketed eye drops indicated 100 percent drug release during the first 2 hr. After 2 hr and 24 hr, the percentage of Timolol maleate delivered from the various produced proniosomal gels. The delivery of Timolol maleate after two hours ranged from 18.43 percent 0.30 to 36.59 percent 2.36, while the release after 24 hr ranged from 84.90 percent 2.19 to 99.57 percent 3.28 were shown in Table 3.

The findings of this study revealed how the amount and type of nonionic surfactants influenced the drug release profile. The addition of a non-ionic surfactant has a major impact on the drug release profile. When compared to Brij 72-based formulations, Span 60-based proniosomal gels showed prolonged release behaviour. The increased entrapment of Span 60-based compounds could justify this. Brij 72 has a lower phase transition temperature, which leads to the production of a leaky bilayer, which aids drug release.

Drug Release Kinetic Studies

Table 4 illustrates the kinetics of medicament delivery starting with a proniosomal gel is an important aspect of the rational pattern of medicament release process since it is a fundamental factor of the benefit of carrier release *in-vivo* and ensuring free drug delivery. An *in-vitro* delivery description gives crucial details about the formulation's arrangement and behaviour, as well as probable interrelationship connecting to the medicament along with carrier composition and their impact on drug release measure and method.

DISCUSSION

In this study reasoned those medications, which are expected for focusing on, and controlling the delivery, increment the dissolvability and saturation; vesicular medication conveyance frameworks may be favoured imprudently and proniosomes got a firm underwriting in the field of medication conveyance.[9] Proniosomes is an adaptable vesicular transporter with an assortment of matchless quality over different transporters including liposomes and niosomes. Without a doubt, proniosomes play a powerful part in medication conveyance due to their expanded entrance properties, non-poisonousness, and controlled drug discharge properties. Broad proniosomal research is unequivocal that this technique is testing.[10] Until this time, a couple of kinds of medications were advanced. This could have been the shortage of the exacting modern design and view of the provesicular drug conveyance framework. Sanctioning of the critical consideration and development in provesicles will likewise expand the new drug classes of dynamic particles like peptides, chemicals, qualities, and oligonucleotides.[11]

Proniosomes are an asset for drug research. The provesicular framework has benefits over the vesicular framework. Proniosomes are a dependable medication focusing on framework. Besides, they give the chance to grant more viable treatment than the overarching drug conveyance framework. These requirements to investigate in the space of nutraceuticals, home grown items, and beauty care products.[12] The activity of antibodies, peptides, immunizations, qualities, and sera is likewise an achievement in vesicular medication conveyance. Despite that, a large portion of the item types are right on the exploration level. In this manner, while executing tests for helpful applications, work should be completed on the size of the concentrate in a pilot plant. In this way, the improvement of modern foundation for vesicular frameworks should be introduced to lay out drug up-and-comers in a vesicular framework.[13]

Vesicular methodologies are novel procedures for shipping the medication that builds up the accessibility of medications and gives an activity for a drawn-out time frame. In addition, it enjoys distinct upper hands over customary medication conveyance frameworks. Liposomes and niosomes containing vesicles exhibit the security issues like accumulation, spillage, combination, and sedimentation of vesicles because of the fluid idea of the framework.[14] The provesicular framework created to defeat these issues for an extraordinary novel methodology incorporates proliposomes and proniosomes. Provesicles are dry, anhydrous definitions, covered with a non-ionic surfactant, go about as a transporter blended in with water when required. This article surveys provesicular drug conveyance frameworks with an emphasis on piece, readiness, the component of medication conveyance, epitome of the medication into provesicles, and portrayal procedures.[15] Similarly, this audit subtleties the synopsis of exploration discoveries and patent reports on proniosomal examinations. As upheld by the writing study, the proniosomes are a main transporter for the conveyance of different medications over various courses of organization.[16]

Proniosomal drug conveyance frameworks can catch both hydrophilic and hydrophobic medications by epitome and parceling frameworks between hydrophobic areas, in light of the size and number of the bilayer. Today, different novel medication conveyance procedures have arisen to achieve either controlled or designated conveyance, covering various courses of medication organization. Vesicular medication conveyance is an inventive procedure that exemplifies and guarantees the designated conveyance of medications like liposomes, pernicious, transferosomes, pharmacosomes and provesicles.[17]

Among every one of the vesicles, lipid vesicle transporters i.e., liposomes have acquired extraordinary importance because of the epitome of different kinds of medications. The essential limitations in the utilization of liposomes are physical and compound issues of solidness. Niosomes, otherwise called non-ionic surfactant transporters, are an incredible substitute for liposomes. Niosomes have comparative actual properties as that liposome. Niosomes generally contain cholesterol and are comprised of non-ionic surfactants. Niosomes additionally have actual solidness issues like combination, conglomeration, sedimentation on

capacity, and spillage of captured drugs on capacity, all of which limit their timeframe of realistic usability.[18]

To conquer the above-said issues related with the conventional vesicles, a potential and the latest technique to develop genuinely and synthetically stable vesicles is a provesicular transporter framework called proniosomes. Proniosomes are a transporter gotten from hydrated combinations of cholesterol and a nonionic surfactant.

The research has illustrated several aspects and from the outcomes attained, following conclusions are drawn. The preformulation parameter solubility of the drug were evaluated and satisfactory and all the values gained comply within pharmacopoeial standards.

CONCLUSION

Compatibility between drug and excipients were determined by IR studies and the results showed that there was no possible interaction between pure drug. Timolol maleate and excipients used in the preparations of proniosomal gel. *In-vitro* medicament delivery reports were carried out for 12 hr using Franz's diffusion cell. The outcome reviewed that Timolol maleate proniosomal gel prolonged the medicament delivery for extended duration of time.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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