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FORMULATION AND EVALUATION OF NIOSOMAL GEL OF TIMOLOL MALEATE FOR OCULAR DRUG DELIVERY

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ABSTRACT

The main purpose of the study was to develop niosomal gel of timolol maleate with increased bioavailability (enhanced permeation) and sustained action (drug retention at the target site). Using different ratios of span 60 and cholesterol, niosomes were prepared by Hand Shaking method and optimized by evaluating different parameters like drug content, entrapment efficiency, particle size and *in-vitro* drug diffusion study. The niosomal pellets were further incorporated in gel, prepared by the method and further optimized by parameters like gelling parameters, mucoadhesive strength and *in-vitro* drug release study. The optimized niosomal formulation containing span 60 and cholesterol in equal proportion (1:1) showed better drug content (DC) i.e. 86.3±0.39% and entrapment efficiency (EE) i.e. 83.4±0.22 with vesicle size of 465±0.24 nm. The in vitro drug diffusion study indicated t_{90} value of 490 min thus proving sustained action of the formulation. The optimized gel containing poloxamer 407 (P407) and poloxamer 188 (P188) in the ratio of 1:2.7 showed gelation temperature at 37 ºC (physiological temperature of the body) and t90 value of 10 h thus depicting sustained action. Thus, sustained drug delivery with increased bioavailability was designed for timolol maleate for the treatment of ocular disease.

KEYWORDS: Niosomes, niosomal gel, Sustained drug release, Ocular drug delivery, timolol maleate

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INTRODUCTION

Poor bioavailability of ocularly administered drug can be attributed to factors which include tear dynamics (blinking reflex and tear turnover) [(1)], non-productive absorption, transient residence time in the cul-de-sac, relative impermeability through corneal epithelial membrane, rapid precorneal elimination, drainage by gravity, frequent installation, enzymatic metabolism, nasolacrimal drainage, and the absence of controlled release [(2-8)]. Due to these physiological and anatomical constraints, a very small fraction of the administered drug (approx.1% or even less) of the instilled dose is available for ocular absorption [(9-10)]. Frequent dosing of drugs thus becomes a necessity to achieve the therapeutic concentration at the targeted site. This often results in the corresponding increase in local and systemic side effects. The high dose and dosing frequency cause unavoidable systemic side effects like stomach upset and disturbed GI motility [(11)].

The systemic route can overcome this but due to the presence of the blood-aqueous barrier and blood-retinal barrier, it ultimately leads to high loading dose at the target site. Various approaches, like viscosity enhancement, use of mucoadhesive, particulate drug delivery, vesicular drug delivery, prodrugs, and other controlled systems like ocuserts, iontophoresis, bioadhesive gels, ocular insert, contact lenses etc. are being explored [(3,12-14)]. Vesicular systems (niosomes and liposomes) can act as drug reservoirs. Niosomes offers advantages like no variation in the purity of surfactants, cost-effective, chemically stable, low

toxicity because of their non-ionic nature, flexibility in the structure which helps them to form micelles and can improve the performance of the drug via better availability and controlled delivery at a particular site. Niosomes are capable of encapsulating both hydrophilic and lipophilic drugs and can serve as effective drug carriers [(15)]. However, non-ionic surfactant vesicles may promote drug absorption by preferentially modifying the permeability characteristics of the conjunctival and scleral membranes as surfactants in lower concentration are used as penetration enhancers [(16, 17)].

The term gel represents a physical state with properties intermediate between those of solid and liquids. However, it is often wrongly used to describe any fluid system that exhibits some degree of rigidity. It is therefore recommended that the term should be restricted to those systems that satisfy the following criteria, which are similar to suggested by Herman [(18)]:

1. They are coherent colloidal system of at least two components (the gelling agent and a fluid component).
2. They exhibit mechanical properties characteristic of the solid state.
3. Each component is continuous throughout the system.

The term "gels" is broad, encompassing semisolid of a wide range of characteristics from fairly rigid gelatin slabs to suspensions of colloidal clays, to certain greases. A gel can be looked upon as being composed of two interpenetrating phases (the gelling agent and a fluid component).

Gels are semisolid, being either suspensions of small inorganic particle or large organic molecule interpenetrated with liquid. In the first case, the inorganic particles, such as bentonite, form a three-dimensional "house of cards" structure throughout the gel. This is a true two-phase system, as the inorganic particles are not soluble but merely dispersed throughout the continuous phase.

Large organic molecules tend to exist in solution as randomly coiled flexible chains. These molecules, either natural or synthetic polymers, tends to entangle with each other because of there random motion. It is interaction between the units of the colloidal phase, inorganic or organic, that sets up the "structural viscosity" immobilizing the liquid continuous phase. Thus, gels exhibit characteristics intermediate to those of liquid and solids [(19)].

Timolol is a drug used either as an eye drop or as a mouth drop. It is used as an eye drop to treat elevated pressure inside the eye, such as ocular hypertension and glaucoma. It is used by mouth for high blood pressure, chest pain due to poor blood supply to the heart, to prevent more complications after a heart attack and to stop migraines.

MATERIALS AND METHODS

Materials:

Timolol maleate was obtained from Sun Pharma Pvt. Ltd., Gujarat. Span 60 from Loba chemicals, cholesterol from Analab fine chemicals, P407and P188 from BASF Chemicals were procured. All the chemicals used were of analytical grade.

Methods:

Compatibility Studies:

I) Interaction Studies by Fourier Transform InfraRed Spectroscopy (FT-IR) Studies:

In order to detect any interaction between drug and excipients in the range of 400-4000 cm^{-1} by FT-IR spectroscopy (JASCO FT / IR-4100) using potassium bromide (KBr) disc technique, FT-IR spectra of timolol maleate, span 60, cholesterol and physical mixture in the ratio of 1:1 (drug and excipient) were performed. [(20, 21)]

II) Interaction Studies by Differential Scanning Calorimetry (DSC) Studies:

Timolol Maleate, span 60, cholesterol and physical mixture 1:1 ratio (drug and excipient) DSC studies were conducted using DSC 60 (Shimadzu). Samples were sealed separately in aluminium cells and placed between 50 °C and 350 °C respectively. Thermal analysis was conducted in a nitrogen atmosphere at a heating rate sustained at 10oC per minute. In each case, an empty pan of alumina was used as the reference[(22)].

Formulation of Niosomes of Timolol Maleate by Hand Shaking Technique:

As the irritation power of surfactants decreases in the following order, i.e. cationic > anionic > ampholytic > non-ionic, niosomes of the ocular drug delivery were prepared by non-ionic

surfactants. Timolol Maleate niosomes were prepared with different molar ratios of non-ionic surfactant (span series) and drug cholesterol using the thin film hydration process. Twelve research formulations (TMF1 to TMF12) have been performed.

Set concentrations of correctly weighed surfactant (1: 2: 3: 4) in different molar ratios (30 µM: 60 µM: 90 µM) and cholesterol (30 µM) were dissolved in a solvent mixture of chloroform and methanol (2:1 v/v) and agitated until fully dissolved. It was then vortexed at a temperature of 55 °C in a round bottom flask to extract the solvent under decreased pressure in the rotary flask evaporator for 30-40 minutes at 100 rpm. After evaporation of solvents, the surfactants and cholesterol lead to formation of thin film on the inner sides of round bottom flask (RBF).

In order to obtain yellowish white dispersion of niosomes, the thin film was hydrated with aqueous phase containing drug (200 mg) in 10 ml of phosphate buffer pH 7.4 for 30 minutes at 55°C temperature. The above white dispersion of niosomes was cooled in an ice bath and then sonicated at 150V for 3 minutes using a probe type ultrasonicator. The resulting niosome vesicles were deposited in a refrigerator at 4 °C for further studies. Plain niosomes have also been prepared without drug use. [23, 24, 25, 26, 27]

Characterization Studies of Niosomes of Timolol Maleate:

Drug Content Analysis:

After lysing the niosomes, the amount of drug in the formulation was calculated using 50 percent n-propanol and shaken well for complete lysis of the vesicles. Solution absorption was measured at 254 nm in UV visible spectroscopy (Perkin Elmer) with empty niosomes as blank after sufficient dilution with the phosphate buffer saline pH7.4. From the standard curve, the drug content was computed [28].

Optical Microscopy Study:

By optical microscopy, the particle size of the niosomal suspension was determined. On a glass slide, a drop of niosomal suspension was inserted. A cover slip was placed over the suspension of the niosome, and an optical microscope and a pre-calibrated micrometre of the ocular eye piece measured the average vesicle dimension. The prepared vesicles were studied to observe the formation of vesicles under a magnification of 40 X. [29, 30]

Estimation of Entrapment Efficiency:

Ultra-centrifugation methods estimated the Entrapment efficiency of niosomes where the niosomal dispersions were centrifuged for 90 minutes at 14000 rotations per minute. The clear supernatant from the resulting solution was diluted correctly using phosphate buffer pH 7.4 and spectrophotometrically analysed for the drug concentration. The percentage encapsulation efficiency (EE %) was calculated using equation [31].

% EE = [(Drug added - Free "unentrapped drug") / Drug added] ×100

***In-vitro* Drug Release Studies of Niosomes:**

The niosomal formulation *in-vitro* drug release analysis was studied using the technique of membrane diffusion. The *in-vitro* diffusion cell was developed as a semi-permeable membrane using the cellophane membrane. The diffusion cell is composed of a beaker, a temperature regulated magnetic stirrer and a test tube with both ends open. One end of the test tube was closed as a semi-permeable membrane using a treated cellophane membrane and the other end was left open to add niosomal formulation. The freshly prepared phosphate buffer saline pH 7.4 of 100 ml balanced at 37 °C ± 0.5 °C was the diffusion medium. The niosomal 5 ml formulation was put through the open end of the test tube on the cellophane membrane within the diffusion cell. The diffusion medium used was 100 ml of phosphate buffer pH 7.4, freshly prepared. It was placed inside the beaker in such a way that contact was made with the buffer on the lower surface of the cellophane membrane.

The buffer solution temperature was held at 37 °C± 0.5 °C and stirred during the study period with a magnetic stirrer. Aliquots (5 ml) of medium were regularly removed and replaced with a new pH 7.4 buffer diffusion medium to maintain constant volume (sink condition). The samples were examined spectroscopically at 254 nm for the Timolol Maleate concentration. [32]

Formulation and Evaluation of Gels:

By dispersing 1 percent Carbopol 940 w / w in distilled water, the gel base was prepared and then allowed to swell for 1 hour. After that, with continuous homogenization, glycerine was applied

to the dispersion. The pH of triethanolamine was modified by [33, 34].

Preparation of Niosomal Gel:

By using a cooling centrifuge for 90 minutes at 4 °C and 12,000 rpm, the calculated volume of TMF-7 niosomal formulation was centrifuged. The semisolid mass of niosomes was removed from the supernatant and combined with the electric homogenizer in the 1% Carbopol gel base [34].

pH Measurements:

An automated pH meter was used to deliver the pH of the gel formulations. The pH meter was calibrated before measurement and readings were taken by dipping the glass rod into the gel formulations [35].

Viscosity Measurement:

A Brookfield viscometer was used to assess the viscosity of gel formulations. In the beaker, 25.0 g of gel was taken, and spindle number 4 was rotated at 50 rpm and the sample viscosity was determined [35].

Spreadability:

Using a spreadability apparatus, the spreadability of gel formulations was determined. On the lower slide, 1.0 g of gel sample was mounted and the upper slide was positioned on the top of the sample [35].

Drug Permeation Studies:

In-vitro Permeation studies were performed using a cellophane membrane of molecular weight of 12000D (Glycerin treated). The cellophane membrane was clamped into a hollow open-end glass tube and dipped into a beaker (receptor) within the media (100 ml). In both PBS saline and STF, which were taken in the receptor compartment, permeation studies were performed. In the donor compartment (hollow glass tube), exactly 1gm of formulation was weighed and placed on the membrane.

Using a magnetic stirrer with a Teflon coated magnetic bead, the solution is continuously stirred in the receptor compartment. Both compartments should be in contact and held at a temperature of 37±2 °C. Samples of 5 ml were collected at pre-determined intervals and supplemented with fresh buffer solutions to preserve the sink conditions. Samples were analysed and drug concentrations were measured in the samples using a UV-Spectrophotometer of 295 nm for STF and 293.60 nm for PBS. The experiment was conducted in triplicate and average values were reported [36].

RESULTS AND DISCUSSION

Compatibility Study by FTIR:

FTIR Spectra of Drug:

The IR spectrum of the sample obtained was performed according to the material and methods referred to in the procedure and complied with the reference norm IR spectrum of Timolol maleate. Test drug IR spectra exhibit identical characteristic peaks. The IR spectrum of the sample drug is shown in **Figure 1**, and **Table 1** shows the explanation.

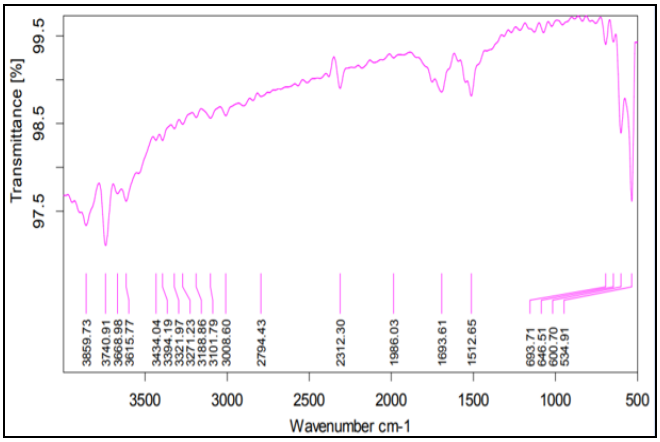

Figure 1: IR Spectra Analysis of Timolol Maleate (Sample)

Table 1: Interpretation of Timolol Maleate

S. No.	Frequency (cm^{-1}) Standard	Frequency (cm^{-1}) sample	Assignments
1	3534.23, 3331.67, 3301.56	3434.04, 3394.19, 3321.97	N-H stretching (primary amine)
2	3205.78, 3199.09	3271.23, 3188.86	N-H Stretching (Secondary amine)
3	2999.53	3008.60	CH_3 symmetric stretching
4	2785.89	2794.43	CH_2 symmetric stretching
5	2378.10	2312.30	C-H Stretching
6	1899.09	1986.03	N-H deformation
7	1699.78, 1567.46	1693.61, 1512.65	N–H bending strongly coupled with C–N stretching (amide II band)
8	687.20, 689.21	693.71, 646.51	N-H out of plane bending

FTIR Spectra of Drug with Polymer:

In order to evaluate the compatibility of the drugs and excipients, FTIR spectra have been registered. The research was conducted according to the technique referred to in the material and methods in the section. The FTIR spectra are represented in **Figure 2**.

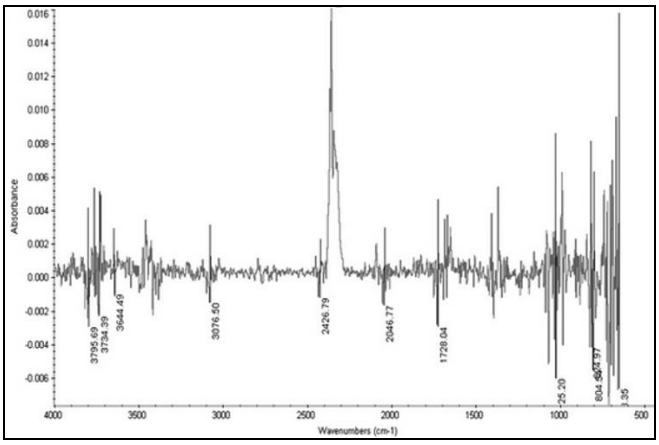

Figure 2: FT-IR Spectra of Timolol Maleate with Excipients

FTIR spectra of the timolol maleate, showed characteristic C-N, C-O, C-H, C=O(ester) stretching bands at 1025.20 cm^{-1}, 1728.04 cm^{-1}, 2046.77 cm^{-1}, 3076.50 cm^{-1}, 3644.49 cm^{-1}, 3734.39 cm^{-1} respectively. The compatibility of drugs with physical mixture of drug (s) & span 60, cholesterol. The characteristic C = O stretching band was observed at 1728.04 cm^{-1} in the FTIR spectra of timolol maleate, which is in line with the recorded values. The findings showed no chemical activity and improvements occurred in the drug's FTIR spectra and different excipients alone or in combination with both excipients exhibiting drug compatibility.

Compatibility Study by DSC:

The research was conducted according to the content and procedures apply to the technique. Timolol maleate DSC thermograms and the physical mixture of timolol maleate, span 60, and cholesterol are shown in **Figure 3**. It is observed that no any physical interaction was found between drug and polymers.

Formulation Development:

Preparation of Niosomes of Timolol Maleate by Hand Shaking Technique:

As mentioned in the procedure earlier, niosomes were prepared using the Hand Shaking technique. Twelve formulations of Timolol maleate niosomes were prepared using non-ionic surfactants (Span 20, 40, 60 and 80) along with different ratios of cholesterol (C: S) (1:1, 1:2, 1:3) with a fixed cholesterol concentration (30 µM) and a constant drug (50 mg), as shown in **Table 2**.

Table 2: Composition of Niosomes

Formulation Code	Drug Concentration (mg)	Surfactant	Cholesterol Conc. (µM) 1 ratio = 30 µM	Surfactant Conc. (µM) 1 ratio = 30 µM	Ratio of Drug, Cholesterol and Surfactant 1 ratio = 30 µM
TMF1	50	Span 20	30	30	1:1:1
TMF2	50			60	1:1:2
TMF3	50			90	1:1:3
TMF4	50	Span 40	30	30	1:1:1
TMF5	50			60	1:1:2
TMF6	50			90	1:1:3
TMF7	50	Span 60	30	30	1:1:1
TMF8	50			60	1:1:2
TMF9	50			90	1:1:3
TMF10	50	Span 80	30	30	1:1:1
TMF11	50			60	1:1:2
TMF12	50			90	1:1:3

Evaluation of Niosome:

Drug Content Analysis:

The mean percent drug content in microemulsion formulations (TMF-1 to TMF-12) was found to be respectively, (81.06 ± 0.1-2%, 75.08± 0.23%, 83.87± 0.35%, 87.76± 0.18%, 91.87± 0.23%, 85.98± 0.34%, 92.87± 0.35%, 88.54± 0.22%, 90.65± 0.12%, 87.65± 0.34%, 90.87± 0.28%, 91.09± 0.38%). TMF-7 was exhibited 92.87± 0.35% higher drug content then other formulations.

Optical Microscopy Study:

The optimized formulation optical microscopic imaging (TMF7) showed that most vesicles were spherical in shape. Compared to the other niosomal formulations, niosomes prepared using Span 60 were bigger in scale.

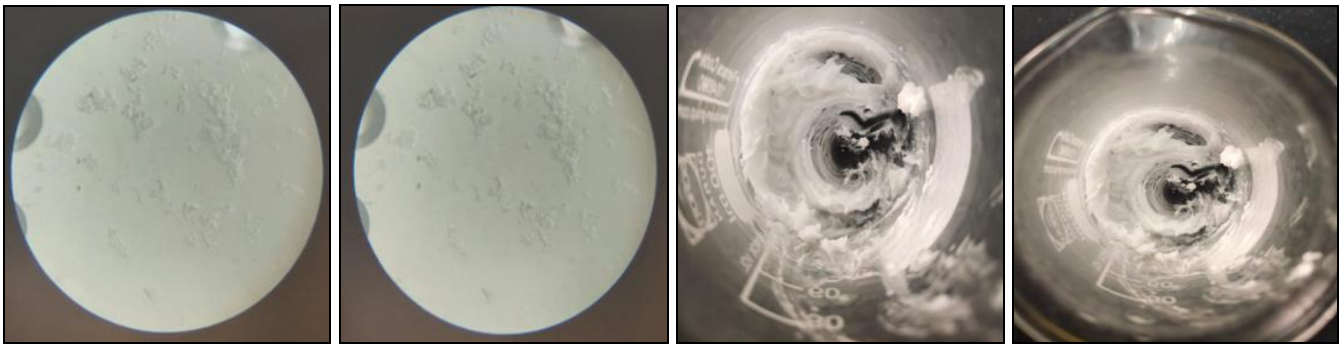

Figure 3: Optical Microscopy of Niosome

Entrapment Efficiency:

TMF7 demonstrated maximum entrapment efficiency among all the formulations compared to other formulations, as shown in **Figure 4**. This was due to its low HLB value and the high temperature of the transition. In the bilayer membranes, cholesterol has the potential to reinforce the leaking room. Increased cholesterol content begins to disturb the normal bilayer structure above a certain level, thus reducing drug capture.

***In-vitro* Drug Release of Niosomes of Timolol Maleate:**

The *in-vitro* release of all niosomal formulations produced was carried out using the method of diffusion. The studies showed that the drug release rate depends on the percentage of the efficiency of drug trapping. Formulation (TMF7), i.e. equimolar ratio of cholesterol and surfactant (Cholesterol /Span 60 / S:1:1) among all twelve established formulations, showed maximum trapping efficiency and sustained drug release of 81.34% in 12 hours. Hence, the order of drug release was found to be Span 60 > Span 40 > Span 20 > Span 80. The *in vitro* release profile of all developed formulations of niosomes of Timolol maleate as shown in the **Table 3, 4**.

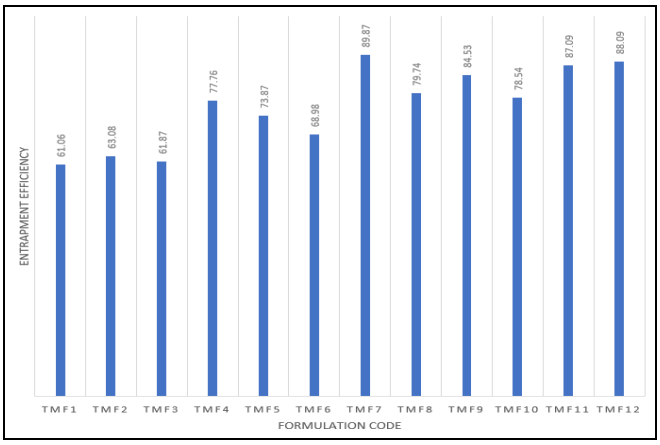

Figure 4: Entrapment Efficiency of Niosome Formulations

Table 3: Cumulative Drug Release of Niosomes of Timolol Maleate

Time (Hr)	TMF-1	TMF-2	TMF-3	TMF-4	TMF-5	TMF-6
0	0	0	0	0	0	0
1	8.45± 0.21	7.89 ± 0.12	8.34 ± 0.45	7.87 ± 0.40	9.21 ± 0.30	8.96 ± 0.34
2	14.14 ± 0.36	13.34 ± 0.23	15.32 ± 0.13	13.14 ± 0.21	15.34 ± 0.26	15.16 ± 0.24
3	21.16 ± 0.32	20.23 ± 0.41	22.06 ± 0.21	21.09 ± 0.14	22.45 ± 0.12	21.12 ± 0.45
4	28.12 ± 0.23	27.45 ± 0.42	28.16 ± 0.31	26.45 ± 0.89	27.90 ± 0.87	28.45 ± 0.21
5	33.45 ± 0.76	32.67 ± 0.56	33.12 ± 0.63	34.97 ± 0.87	33.06 ± 0.21	34.45 ± 0.47
6	41.06 ± 0.67	40.32 ± 0.21	40.06 ± 0.67	41.09 ± 0.45	40.23 ± 0.49	41.06 ± 0.56
8	48.12 ± 0.67	47.89 ± 0.78	48.23 ± 0.87	46.15 ± 0.67	48.16 ± 0.48	48.23 ± 0.48
10	59.06 ± 0.41	60.06 ± 0.42	61.08 ± 0.47	60.06 ± 0.42	61.06 ± 0.48	60.06 ± 0.45
11	68.06 ± 0.23	69.56 ± 0.48	68.43 ± 0.49	67.06 ± 0.32	68.26 ± 0.57	69.06 ± 0.48
12	79.06 ± 0.34	78.06 ± 0.47	77.43 ± 0.12	78.06 ± 0.56	79.06 ± 0.78	80.34 ± 0.67
24	88.45 ± 0.12	87.56 ± 0.23	86.26 ± 0.47	89.45 ± 0.48	91.06 ± 0.36	89.06 ± 0.45

Values are expressed as mean + SD of triplicates

Table 4: Cumulative Drug Release of Niosomes of Timolol Maleate

Time (Hr)	TMF-7	TMF-8	TMF-9	TMF-10	TMF-11	TMF-12
0	0	0	0	0	0	0
1	9.15 ± 0.25	8.89 ± 0.43	8.37 ± 0.12	8.17 ± 0.23	9.01 ± 0.32	8.98 ± 0.35
2	15.14 ± 0.16	14.32 ± 0.26	15.02 ± 0.25	13.44 ± 0.25	14.34 ± 0.24	14.16 ± 0.27
3	22.36 ± 0.35	21.23 ± 0.23	21.16 ± 0.25	23.09 ± 0.32	22.55 ± 0.56	25.32 ± 0.45
4	29.42 ± 0.33	27.23 ± 0.47	28.46 ± 0.36	27.45 ± 0.19	27.32 ± 0.86	28.15 ± 0.21

5	34.45 ± 0.16	33.17 ± 0.56	33.34 ± 0.13	34.12 ± 0.89	33.66 ± 0.29	34.15 ± 0.47
6	42.06 ± 0.17	42.32 ± 0.71	41.06 ± 0.17	41.99 ± 0.56	42.23 ± 0.19	41.56 ± 0.59
8	49.12 ± 0.68	47.99 ± 0.67	48.23 ± 0.87	47.15 ± 0.09	48.36 ± 0.40	48.56 ± 0.18
10	59.16 ± 0.42	60.36 ± 0.43	61.58 ± 0.42	60.56 ± 0.48	62.06 ± 0.18	61.06 ± 0.23
11	69.34 ± 0.23	69.16 ± 0.38	68.43 ± 0.19	68.06 ± 0.12	68.26 ± 0.67	69.06 ± 0.98
12	79.16 ± 0.34	77.46 ± 0.47	78.43 ± 0.15	78.56 ± 0.78	79.26 ± 0.89	81.34 ± 0.69
24	91.45 ± 0.56	87.96 ± 0.67	88.25 ± 0.42	90.45 ± 0.42	90.06 ± 0.46	89.66 ± 0.46

Values are expressed as mean + SD of triplicates

Formulation of Timolol Maleate Loaded Niosomal Gel:

The gels were prepared by dispersion method using glycerine, triethanolamine and Carbopol 934 in different ratios.

Evaluation of Timolol Maleate Niosomal Gel:

pH:

In the range of 6.09 to 6.76, the pH of the formulations was considered sufficient to avoid the possibility of ocular irritation. It was noticed that the optimised formulation (TMFG1) pH was 6.76. There was no significant change in pH values for all formulations as a function of time.

Determination of Viscosity:

The average formulation viscosity is in the 1245.479 to 3620.603 cps range. Table 7 shows the viscosities of all gel formulations and has been found to decrease by raising the shear rate, i.e. pseudo plastic behaviour has been noted.

Spreadability Study:

Niosomal gels agent exhibited spreadability values ranging from 12.35-14.77 g.cm/s. The spreading coefficient of various niosomal gel formulations are given below in table 8.

Table 5: Formulation of Niosomal Gel

Formulation code	Niosomal Suspension (ml)	Carbopol 934 (%)	Glycerine	Triethanolamine (%v/v)	Water
TMFG-1	10	0.5	5	0.01	q.s
TMFG-2	10	1.0	5	0.01	q.s
TMFG-3	10	1.5	5	0.01	q.s
TMFG-4	10	2.0	5	0.01	q.s

Table 6: Evaluation of Niosome Formulations

S. No.	Formulation	Viscosity (CPS)	Spreadability (g.cm/s)
1	TMFG1	2236.7	13.09
2	TMFG2	1245.479	14.76
3	TMFG3	2435.896	12.35
4	TMFG4	3620.603	14.06

Permeation Studies:

Studies of drug permeation indicate that the TMFG3 formulation showed the highest release in trial 1, i.e., 54.05% in STF and 50.15% in PBS. It is therefore chosen for trail 2 as the basic formulation. Among the formulations in trial 2, TMFG3 reported the highest DR percentage of 64.38 percent in STF and 61.91 percent in PBS buffer formulations. In trail 2, the % drug release order in both PBS and STF for permeation enhancers.

The *in-vitro* bioassay of ocular irritation shows that the TMFG1 and TMFG4 formulations have a mean irritation score of less than 1, suggesting zero irritation intensity and no reaction. This confirms that the biomembrane would not have a hypersensitive reaction.

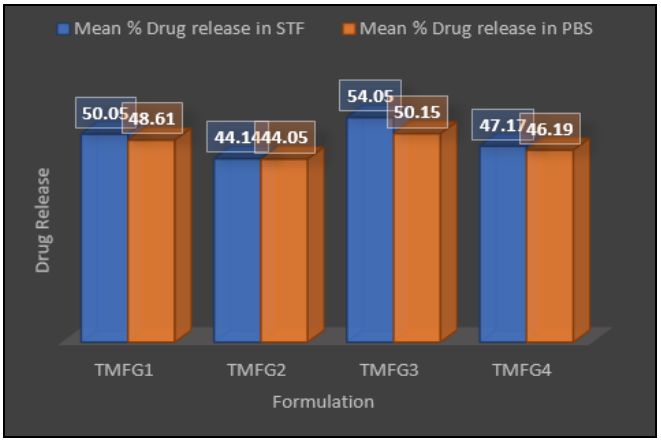

Figure 8: Drug permeation studies

Stability Study:

The stability studies of niosomal gel were performed at 5º ± 2º C and 25º ± 2º C / 60 ± 5% Relative Humidity (RH) for 3 months as per

modified ICH guidelines. The optimised formulation (TMFG3) was visually examined for any precipitation, drug content, pH, and gelling capability for 3 months every 30 days. It was found that the physical appearance of the formulation did not alter. The drug content was analysed and as shown in **Table 7**, there was a marginal difference between the formulations kept at different temperatures. When stored at refrigerator temperature, niosomal gel preparation maintained good stability during the study period.

Table 7: Stability Data for Optimized Formulation (TMG3) at 25 ± 2ºC/ 60±5% RH at Short Term Accelerated Condition

Month	TMFG3 (Optimized formulation)			
	0	1	2	3
Appearance	Milky white dispersion	Milky white dispersion	Milky white dispersion	Milky white dispersion
pH	6.02 ± 0.26	6.04 ± 0.32	6.03 ± 0.18	6.04 ± 0.54
Drug content	95.67 ± 0.44	95.41 ± 0.39	95.04 ± 0.12	94.67 ± 0.63

CONCLUSION

The newly developed timolol maleate ocular niosomal gel was found to be sterile, non-irritant and provided sustained release with improved ocular residence time by reducing dosage frequency and it was therefore inferred from the above research study that the niosomal gel system is a viable alternative compared to traditional drops because of its ability to improve bioavailability through its ability to improve bioavailability. Also, it is important in case of administration affords, by decreasing the frequency of administration and resulted in better patient acceptance. Hence, to conclude it is future magic targeted delivery in the field of ocular therapeutics.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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