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RESEARCH

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Development and characterization of niosomes loaded mucoadhesive biodegradable ocular inserts for extended release of pilocarpine HCl

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Abstract

Background Pilocarpine HCl is a non-selective muscarinic receptor agonist that is prescribed for the treatment of glaucoma. The use of pilocarpine conventional eye drops is associated with several side effects, such as loss of visual acuity, and the need for several applications due to rapid drainage away via the nasolacrimal duct, especially for elderly people. Such adverse effects can lead to low patient compliance and poor clinical outcomes. Therefore, the aim of this project was to develop, optimise and characterise a biodegradable pilocarpine HCl ocular insert using niosomes as a drug delivery vehicle. To achieve that, various polymers such as hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and a blend of both were investigated to prepare the ocular inserts using solvent casting technique. The niosomes of pilocarpine HCl were prepared using span-60 and cholesterol by thin film hydration method. The produced noisome-loaded ocular inserts were characterised using various analytical techniques, including Fourier Transform Infrared (FTIR), X-ray Diffractions (XRD), thermal analysis, particle size analysis, weight and content uniformity, surface pH and drug release profile, among others.

Results The results indicated that drug-free ocular inserts of the two polymers (HPMC + PVA) were better than single polymer-based ocular inserts (HPMC or PVA alone). The formed niosomes demonstrated good entrapment efficiency of 49.7% ± 7.0, with an average particle size of 325.7 ± 3.5 nm. The FTIR analysis showed no interaction between the compositions of niosomes. Four optimal formulations with various co-polymer ratios and pilocarpine content were further evaluated. Pilocarpine-containing niosomes-loaded ocular inserts provided uniformity in pilocarpine content (89–96%), with 34.8% moisture content and an average pH of 7. The release profile of niosomes-loaded inserts demonstrated an initial burst release within 2 h ranging from 26.54% (T4) to 41.22% (T2), and continuous sustained release for the next 24 h (68.32 ± 5.11% (T4) to 82.11 ± 6.01% (T2)).

Conclusions This work successfully optimised biodegradable ocular inserts containing slow-release pilocarpine HCl encapsulated in niosomes for the treatment of glaucoma without dose dumping, resulting in a user-friendly drug delivery system.

Keywords Biodegradable ocular insert, Extended-release, Nanoparticles, Niosomes, Pilocarpine HCl

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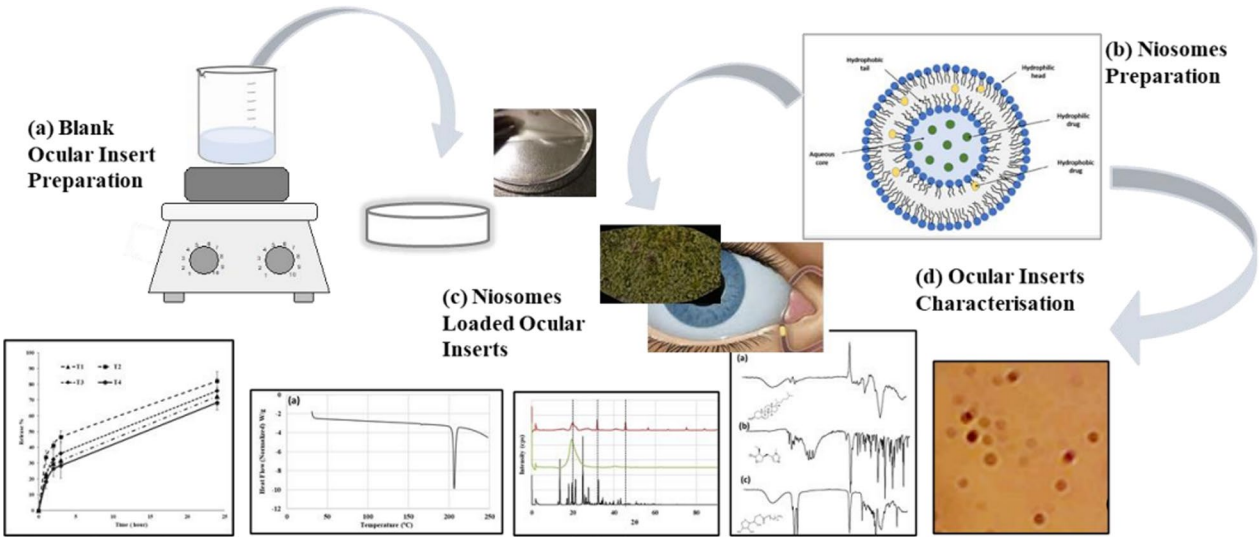
Graphical abstract



Background

The eye is an anatomically and physiologically unique organ with various structural components [1]. Although the eye is an easily accessible organ for the direct administration of medication, it is isolated by several barriers such as the cornea, which acts as the main barrier for absorption and transportation of topically applied drugs into the systemic circulation. Further, the posterior part of the eye, such as the retina, creates an additional barrier. The retinal barrier is a protective barrier for the transport of materials [2], which creates challenges to drug delivery [3, 4]. In general, small lipophilic molecules can be absorbed through the cornea, whereas hydrophilic molecules can be absorbed through the conjunctiva and sclera [2].

The main routes for ocular administration of active pharmaceutical ingredients (APIs) are topical, systemic, and intraocular. The topical route, with formulations such as eye drops, accounts for 90% of aqueous ocular administration. This is the most preferred route owing to ease of application, patient preference and reduced systemic side effects caused by the API. Eye drops have several advantages such as being easy to apply by most patients (self-administration), safe, and more comfortable [5]. Besides, eyedrops can overcome first pass metabolism and directly target the site of the action [6]. Nevertheless, the use of eye drops has several limitations particularly, short retention time in the eye [3] which requires multi-dose administration during the day, which is detrimental to patient compliance [7, 8].

Pilocarpine HCl is a non-selective muscarinic receptor agonist and is prescribed for the treatment of glaucoma. Pilocarpine HCl decreases intraocular pressure in glaucoma patients by increasing trabecular outflow [9]. Lowering high intraocular pressure aids in preventing blindness, vision loss, and nerve damage [10]. Pilocarpine HCl eye drops are commonly used for the treatment of glaucoma with different concentrations (1%, 2%, 4%) available. The use of these conventional eye drops has been associated with several side effects, especially for elderly people, like loss of visual acuity, preservative allergy, and the need to repeat the dose to maintain therapeutic effects. Such adverse effects can lead to low patient compliance, and hence poor clinical outcomes [9].

For optimal bioavailability from ophthalmic topical formulations and effective clinical outcomes, these formulations need to be designed to increase retention time of the dosage form and enhance ocular drug permeability [11]. Novel drug delivery systems (DDSs) have been designed to deliver ocular drugs with reduced side effects. These formulations are based on nanotechnology to achieve desired drug particle size and the associated reduction of eye irritation, plus improved bioavailability. These formulations include microparticles, nanoparticles like liposomes (acyclovir), niosomes aqueous gels, or dendrimers (tropicamide) [5].

Niosomes are nano-sized vesicles containing non-ionic surfactants arranged in bilayers. Depending on the preparation method, niosomes may be unilamellar or

multilamellar. Niosomes are made of a surfactant bilayer with the hydrophilic heads found on the surface, and inside, of the vesicle while the hydrophobic tails form the bilayer; this allows for two different areas for drug entrapment [12]. Features that make niosomes interesting for research include capacity for different API entrapment, osmotic activity and stability, presence of an amphiphilic structure that contains hydrophobic and hydrophilic portions and provide applications for dissolving drugs with varying solubilities. In addition, niosomes release the drug in a controlled manner through the bilayer, which can protect the encapsulated API during transit. Therefore, niosomes act as a store of medication in the body and enable targeted drug delivery [13]. Niosomal formulations are versatile owing to their structural flexibility, in terms of composition, fluidity, and size [12]. Niosomes are compatible, will not stimulate immunogenic reactions, and are decomposed by the biological system [14]. Furthermore, niosomes do not require special storage conditions [13]. These characteristics make niosomes promising nanocarriers in the treatment of ocular diseases. For example, timolol maleate, brimonidine tartrate, atenolol, dorzolamide HCl, bimatoprost and acetazolamide have been developed as niosomes for glaucoma treatment, while lomefloxacin HCI and chloramphenicol niosomes have been developed for treatment of conjunctivitis. Flurbiprofen and prednisolone niosomes have also been prepared for treatment of ocular inflammation and epalrestat for diabetic eyes [12, 15, 16].

Ocular inserts as novel drug delivery systems are gaining traction in research. Ocular inserts of pilocarpine HCl, marketed as Ocusert®, were an alternative topical dosage form that provided extended release of pilocarpine HCl over seven days. Ocusert® was easy to insert in the upper or lower lid, soft, flexible and had two drug release options: 20 µg/hour or 40 µg/hour. It was based on a reservoir system with zero order release pattern and pilocarpine HCl released by diffusion [17]. Ocusert ® was withdrawn from the market due to dose dumping and frequent loss of insert especially during sleep [18]. Therefore, development of pilocarpine HCl as an extended-release dosage form, such as niosomes, to be loaded into hydrophilic soluble ocular inserts, which would release the drug over 24 h and be biodegradable, would be advantageous. Other work by Lin et al. [19] reported the use of alginate and pluronic solution as the in-situ gelling vehicles for ophthalmic drug delivery of pilocarpine HCl. The mixture of 0.1% alginate and 14% pluronic solutions showed improvements in gel strength and clinical outcomes: with the main objective of improving the ocular bioavailability of pilocarpine HCl.

Therefore, there is a need to develop a user-friendly dosage form for pilocarpine HCl that releases pilocarpine HCl slowly over extended period of time and hence reduces the anticipated side-effects, especially for elderly patients, which are manifested in loss of visual acuity and annoyance for repeated dosing to maintain therapeutic effect. Such adverse effects can lead to low patient compliance and hence this will affect clinical outcome. Therefore, the aim of this project was to develop a formulation of biodegradable mucoadhesive ocular insert loaded with pilocarpine HCl containing niosomes to provide an extended-release effect over 24 h which would provide an effective treatment of glaucoma with sustained release effect of drug. This would result in an increase in contact time between drug and cornea, reduction in the number of daily doses of the traditional ophthalmic dosage forms and sustained API delivery to the targeted site, using as little API dose as possible [7].

Methods

Materials

Pilocarpine HCl powder (≥98%) and polyvinyl alcohol (PVA) were obtained from Sigma-Aldrich (Taufkirchen, Germany). Methanol (HPLC grade) was purchased from Honey well (Saint-Germain-en-Laye, France), water (HPLC grade) and chloroform were obtained from Alpha Chemika (Mumbai, India), while triethyl amine was obtained from Tedia (Fairfield, Ohio, USA). Orthophosphoric acid and hydroxypropyl methylcellulose (HPMC) were purchased from Alzchem for chemical (Trostberg, Germany). Glycerine, span 60 and sodium hydroxide were obtained from Fischer (Guangzhou, China). Cholesterol and phosphate buffered saline were obtained from Carlsson (Maryland, USA). All materials were used as supplied.

Development of drug free (blank) ocular inserts

Hydroxypropyl methylcellulose (HPMC) and polyvinyl alcohol (PVA) in different concentrations (see Table 1) were investigated to prepare the blank ocular inserts. Accurately weighed HPMC was sprinkled over 100 mL distilled water placed on a hotplate magnetic stirrer (Dlab ms-h280 (Beijing, China)) with temperature set at 30–40 °C and 1500 rpm for 1–2 h to ensure complete swelling and hydration of the polymer. Then, the required volume of glycerine (as plasticiser) was added and stirred for 15 min. After that, the polymer solutions were sonicated for 30 min continuously using a Bandelin Sonorex Digitec sonicator to remove bubbles. The final solution was cast onto plastic petri-dishes (area 56.71 cm^2). To prevent quick drying and films cracking, the samples were placed on the bench for 12 h at ambient temperature before placing them in the hot air oven at 40 °C for 4 h to complete drying. PVA containing ocular inserts were prepared in a similar manner but using cold distilled

Table 1 Summary of the composition of the drug free (blank) ocular inserts formulations

Formula	Polymer	Polymer concentration %w/v	Plasticiser (glycerine) (%v/v)	Solvent volume (mL)
F1	HPMC	0.5	0.25	50
F2				30
F3				20
F4	HPMC	1.0	0.25	50
F5				30
F6				20
F7	HPMC	1.5	0.25	50
F8				30
F9				20
F10	HPMC	2.0	0.25	50
F11				30
F12				20
F13	PVA	0.5	1.0	50
F14				30
F15				20
F16	PVA	1.0	1.0	50
F17				30
F18				20
F19	PVA	1.5	1.0	50
F20				30
F21				20
F22	PVA	2.0	1.0	50
F23				30
F24				20
F25	PVA	3.0	1.0	50
F26				30
F27				20
F28	HPMC + PVA	1.5 + 2.0	1.0	50
F29				30
F30	HPMC + PVA	1.0 + 1.5	1.0	50
F31				30
F32				20
F33	HPMC + PVA	1.0 + 1.0	1.0	50
F34				30
F35				20

water initially and stirring at 1500 rpm for 30 min. The temperature of the PVA solution was then increased to 100 °C for 1 h to ensure complete swelling and hydration. Hot air oven drying time was only 30 min.

Blank ocular inserts containing a blend of HPMC and PVA were prepared starting with PVA solution as discussed above, after which the solution was kept on the bench at ambient temperature to cool to about 37 °C. This solution was returned to the hotplate and HPMC powder (0.5 g, 1 g or 1.5 g) was sprinkled with stirring at 1500 rpm and 37 °C for 30 min. Glycerine was added and solution further stirred for 15 min, then sonicated for 30 min to remove bubbles. The solution was cast on plastic petri-dishes (area 56.71 cm ^{2}). To prevent quick drying and films cracking; the samples were placed on the bench for 12 h before putting it in the hot air oven for 30 min to complete drying.

Preparation of niosomes

The niosomes were prepared according to [7] using thin film hydration method. Accurately weighed span 60 (200 mg), cholesterol (100 mg) and pilocarpine HCl (20 mg) were added to 10 mL chloroform in a round bottom flask. The solution was rotated at 150 rpm for 1 h on a Heidolph rotary evaporator (Kelheim, Bayern, Germany) to evaporate the chloroform under low pressure at 60 °C. This step led to the formation of a thin film on the wall of flask. Then 10 mL of phosphate buffer (pH 7.4) was added to the flask to hydrate the film and left on the rotatory evaporator for 1 h at 60 °C and 150 rpm to remove the residual solvent. To produce niosomes, the dispersion was vortexed for 5 min at 60 °C. Finally, the produced niosomes were sonicated for 10 min at 60 °C using a Bandelin Sonorex Digitec sonicator.

Preparation of niosomes loaded ocular inserts

The prepared niosomes were loaded in selected preparations of blank ocular inserts. The ocular inserts were prepared as described above. An appropriate weight of niosomes containing 1 mg or 2 mg of pilocarpine HCl (calculated based on the entrapment efficiency results) was incorporated into the produced polymer blend solution (at room temperature) and stirred on a magnetic stirrer Dlab ms-h280 (Beijing, China), 200 rpm for 10 min to ensure homogeneous dispersion. The resulting dispersion was poured into silicon moulds and placed on the bench top for complete drying at room temperature. The quantity of added niosomes was based on the average daily dose of pilocarpine HCl (1–2 mg) [9]. Table 2 summarises the composition of all prepared pilocarpine HCl loaded ocular inserts.

Analytical method optimisation and validation for pilocarpine HCl

High performance liquid chromatography (HPLC) was employed for the quantitative analysis of pilocarpine HCl. The method was based on [7] with modification. A Dionex Ultimat HPLC System from Thermo Fisher Scientific Inc. (Sunnyvale, California, USA), with gradient pump, UV detector set at 215 nm, and C-18 analytical column from Phenomenex® (Luna® 5 µm, LC column 250 × 4.6 mm, particle size 5 µm) was used. The mobile

Table 2 Summary of the composition of pilocarpine HCl loaded ocular inserts

Formula	Polymer (type and concentration (%w/v))	Plasticiser (glycerine) (mL)	Amount of pilocarpine HCl (mg)	Solvent volume (mL)
T1	1% HPMC + 1.5% PVA	1.0	1.0	50
T2	1% HPMC + 1% PVA	1.0	1.0	50
T3	1% HPMC + 1% PVA	1.0	2.0	50
T4	1% HPMC + 1.5% PVA	1.0	2.0	50

phase was composed of solution A (1.35% v/v phosphoric acid and 0.3% v/v mL triethylamine in HPLC grade distilled water (pH adjusted to 3 using 10 M NaOH)) and solution B (methanol). The two solutions ratio A:B was 90:10%v/v, column temperature (20 °C), flow rate (1.5 mL/min), and sample injection volume (10 µL). Pilocarpine HCl samples were analysed over the concentration range of 3.9–1000 µg/mL using solution A as diluent. The HPLC method was validated according to ICH guidelines in terms of specificity, accuracy, precision, and linearity, limits of detection, and limit of quantification [20].

Characterization of the drug free ocular inserts

Ocular insert/film quality

The blank ocular inserts were evaluated based on multidimensional criteria such as smoothness, transparency, flexibility, good wetting and spreading ability, non-sticky and easy peeling according to the method described in [21, 22]. Evaluation scores were given for each feature out of 20 (0 bad, 10 good, 20 very good) based on visual inspection. The total of scores were calculated out of 100.

Weight uniformity

The blank and the niosome loaded films were cut into small pieces with dimensions of 0.5 × 1.0 cm. Each piece was weighed individually using a Sartorius analytical lab scale digital balance (AC/120 S MC-1). The mean, standard deviation, and relative standard deviation for the values were calculated using 5 replicates.

Disintegration time

One piece with a dimension of 0.5 × 1.0 cm for each formulation of the blank ocular insert was placed in 3 mL artificial tears on a hotplate set at 37 °C. The disintegration time was monitored. Disintegration time was defined as the time required to start breaking down of the films into small pieces. This test was repeated for three samples.

Moisture content

To measure the moisture content of the drug free ocular inserts, each film was weighed to attain its initial weight (W_i) and then heated at 100–120 °C in a hot air oven until a constant final weight was achieved. The final weight (W_f) of the dried film was then measured, and the moisture content (MC) was calculated using Eq. (1).

$$\mathrm{MC}\ (\%) = \frac{(W_i - W_f)}{W_i} \times 100 \tag{1}$$

Characterization of pilocarpine HCl niosomes

Entrapment efficiency

The amount of pilocarpine HCl entrapped within the niosomes was investigated by placing 1 mL of the formula in 1.5 mL Eppendorf tubes followed by centrifugation using a DLAB refrigerated centrifuge (D3024R) at 7000 rpm and 4℃ for 1 h. The supernatant was collected, then, 1 mL of phosphate buffer pH 7.4 was added to wash the vesicles and re-centrifuged for 1 h. This step was repeated twice, and supernatant was collected each time. Then, 1 mL of isopropyl alcohol was added to lyse the washed niosomes and the mixture was centrifuged for 30 min at 7000 rpm. A 100 µL sample was withdrawn and transferred into a 5 mL volumetric flask containing 1 mL isopropyl alcohol. The solution was then made up to 5 mL using phosphate buffer pH 7.4. The drug content was analysed using HPLC at 215 nm to calculate the total entrapped drug within the niosomes. The collected supernatants were combined in a 10 mL volumetric flask and made up to volume using phosphate buffer pH 7.4. The drug content was then analysed by HPLC at 215 nm to calculate total free drug in supernatant which was used to calculate the recovery and entrapment efficiency ENT (%) according to the following equations:

$$\mathrm{PIL_T} = \mathrm{PIL_N} + \mathrm{PIL_S} \tag{2}$$

$\mathrm{PIL_T}$ is the total amount of used pilocarpine HCl, $\mathrm{PIL_N}$ is the amount of pilocarpine HCl within the niosomes, whereas $\mathrm{PIL_S}$ is the total amount of the pilocarpine HCl within the supernatant (i.e., free drug).

$$\mathrm{ENT}\ (\%) = \frac{\mathrm{PIL_N}}{\mathrm{PIL_T}} \times 100\% \tag{3}$$

Microscopic analysis of niosomes

One drop of the pilocarpine HCl loaded niosomes was placed on a glass slide and an optical Nikon microscope (Tokyo, Japan) was used to assess the prepared niosomes at 100× magnification.

Laser diffraction analysis

Laser diffraction was employed to analyse average particle size of the niosome, polydispersity index (PDI), and zeta potential. The parameters were measured via photon correlation spectroscopy using a Zetasizer Nano ZS90 instrument from Malvern Instruments (Worcestershire, UK). Niosomes were diluted with deionised water and sonicated at low amplitude (~ 30 Hz) for 10 s prior to analysis. Results were reported as mean ± standard deviation (SD) using triplicate samples.

Characterization of drug loaded inserts

Content and thickness uniformity

The content uniformity of each ocular insert was evaluated by measuring the amount of pilocarpine HCl in each insert. Each ocular insert was placed in a 10 mL volumetric flask containing 8 mL phosphate buffer (pH 7.4) and 2 mL isopropyl alcohol. The flask was sonicated for 8 h using a Bandelin Sonorex Digitec sonicator to ensure complete dissolution of the film. Each experiment was repeated three times. Samples were withdrawn from the flask and analysed by HPLC. Film thickness was measured using an Erweka TBH 30 tester (Hessen, Germany), and the average, standard deviations, and relative standard deviations were calculated.

Surface pH

Measurement of the surface pH of the final pilocarpine HCl loaded ocular inserts was carried out according to the method described in [23], where 1 mL of distilled water was applied onto the film in a petri dish and allowed to spread evenly over the surface of the film. The surface pH was determined using a digital pH meter, and the results were recorded as mean ± SD using triplicate samples.

Fourier transform infrared (FTIR) spectroscopy analysis

FTIR spectra of pilocarpine HCl, span 60, cholesterol, pilocarpine HCl containing niosomes, blank films and niosome-loaded films were recorded using a Perkin Elmer FTIR spectrometer (OH, USA), associated with Spectrum 10 software. A sample was loaded onto the sample holder and each sample's FTIR spectrum scans was recorded over the range of 450–4000 cm^{-1} with a resolution of 2 cm^{-1}.

Drug release study

Niosome loaded ocular inserts containing 1 or 2 mg pilocarpine HCl were used in the donor compartment model using cellulose dialysis membrane and 2 mL phosphate buffer pH 7.4, which was used to mimic in vivo cornea epithelial membrane conditions. This donor compartment model was placed in a beaker containing 50 mL of phosphate buffer, pH 7.4. The beaker was placed on a magnetic stirrer plate at a temperature of 37 °C and set at 60 rpm. At time intervals of 1 h for the duration of 3 h and then after 24-h, 1 mL samples of the release medium were removed and placed in separate vials and then analysed by HPLC. 1 mL of phosphate buffer pH 7.4 maintained at the same temperature was replaced to maintain sink conditions [24].

Differential scanning calorimetry (DSC) analysis

DSC analysis of pilocarpine HCl and niosomes was carried out using a DSC Q200- TA instrument (USA). Around 5 mg of each sample was placed onto an aluminium pan and heated at a rate of 10 °C/minute under continuous nitrogen purging (50 mL/minute).

X-ray diffraction (XRD) analysis

An X-ray diffractometer (MiniFlex 600 benchtop diffractometer (RigaKu, Tokyo, Japan)) was used to investigate the physical form of niosomes, pilocarpine HCl and niosome loaded ocular inserts. The XRD experiments were performed over the 2θ range from 5 to 90°, with Cu Kα radiation (1.5148227 Å) and a voltage set at 40 kV and a 15 mA current. Designated samples were placed on a holder and scanned in triplicate. Data was recorded at a scanning speed of 5°/minute. OriginPro® software was employed to analyse the scans (OriginLab Corporation, USA).

Statistical analysis

Statistical analysis was performed using SPSS statistical pack (version 25) with $p < 0.05$ quotes as the level of significance for the calculation of one-way ANOVA test. Results were reported as mean ± SD (standard deviation).

Results

Quantification of pilocarpine HCl

A calibration curve for pilocarpine HCl was obtained over a concentration range of 3.9–1000 μg/mL. The curve demonstrated linearity with high degree of corelation (coefficient of determination $R^2 = 0.9999$, regression equation $Y = 0.1135 \times - 0.0591$). The method was specific to pilocarpine HCl and none of used materials

(HPMC, PVA, glycerine, cholesterol, span 60) interfered with the pilocarpine HCl peak that eluted at 5.72 ± 0.18 min. A peak representing the blank ocular insert appeared before 2 min. Recovery experiments for three concentrations in triplicate over three days were conducted to determine the intraday repeatability and (inter-day) reproducibility as an indication of the method's accuracy. The results are shown in Table 3 and demonstrate method precision with RSD below 6.04%. All recovery results ranged between 96.7 and 101.8% with low RSD (between 0.96 and 6.04%) indicating an accurate method. RSD between 0 and 15% is an indication of method accuracy. Similar results were reported in a previous study on pilocarpine HCl [22]. Equipment precision was evaluated using repeated measures of one selected concentration (62.5 μg/mL) of pilocarpine HCl solution and the results demonstrated precise equipment owing to low RSD (0.44%) and according to the ICH guidelines [20] a RSD of less than 2%, indicates an accurate and precise technique. The method limit of detection (LOD) and limit of quantification (LOQ) of pilocarpine HCl were 1.2 μg/mL and 3.65 μg/mL respectively. Overall, the employed method demonstrated a valid and reproducible process for the analysis of pilocarpine HCl.

Characterization of drug free (blank) ocular inserts

The first part of the project aimed to optimise a drug-free (blank) ocular insert by enhancing its smoothness, transparency, flexibility, wetting/ spreadability, and ease of peeling off. Additionally, the project aimed to develop films that disintegrate within a specific time frame.

To do that, various formulations of drug-free ocular inserts were investigated (Table 1). The produced blank ocular inserts were characterised based on film quality, weight uniformity and disintegration time. The prepared HPMC containing formulations are shown in Fig. 1, revealed films with a transparent and smooth appearance. Increasing the HPMC content above 1%

Table 3 Accuracy of pilocarpine HCl HPLC method (intraday and inter-day reproducibility)

Pilocarpine HCl concentration (μg/mL)	Intraday recovery % (mean ± SD), n = 3	RSD%	Inter-day recovery % (mean ± SD), n = 9	RSD%
250	100.54 ± 1.45	5.11	101.8 ± 0.41	1.42
125	98.95 ± 0.84	6.04	101.2 ± 0.14	0.96
62.5	96.71 ± 0.52	4.60	101.7 ± 0.18	2.53

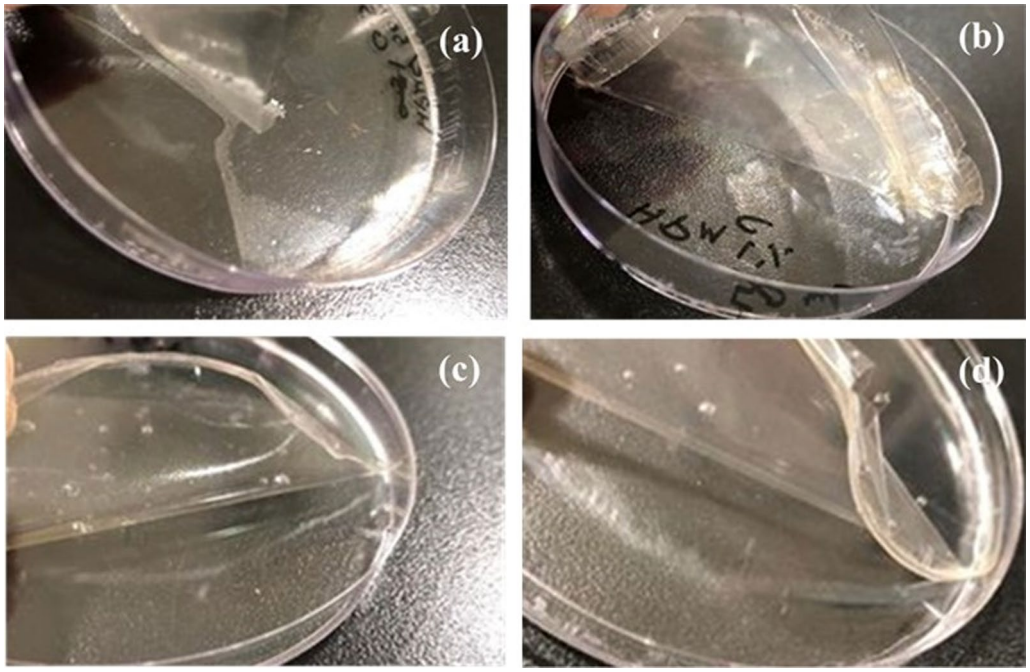


Fig. 1 Images of HPMC blank ocular inserts at different concentrations (w/v), **a** HPMC 0.5% -F1 **b** HPMC 1%-F4, **c** HPMC 1.5%-F8, **d** HPMC 2%-F11

(w/v) resulted in thick films with reduced flexibility, even at lower volumes. However, the transparent appearance, which was observed in all the HPMC films, was not affected by increasing HPMC content from 0.5% to 2% w/v.

Representative samples of PVA containing blank ocular inserts are shown in Fig. 2. Increasing PVA content from 0.5 to 2% w/v led to harder films, which were less flexible, and difficult to handle. Transparent and smooth appearance was observed in all preparations regardless of the PVA content. PVA 2% w/v films demonstrated a hard and less flexible appearance like a paper sheet (Fig. 2d), despite increasing the plasticiser (glycerine) concentration from 0.25 to 1% v/v. Several researchers employing HPMC and/or PVA in the development of ophthalmic films observed similar trends [25, 26].

Blank ocular inserts made of a blend between PVA and HPMC are presented in Fig. 3: Films (a) and (b)—containing 1% HPMC with 1% and 1.5% PVA respectively—produced very smooth, flexible, and transparent appearance. However, increasing the amount of the PVA in the blend, led to a reduction in the flexibility, transparent appearance, and an increase in the hardness of the films. Film (c) presented a harder film than (a) and (b); because of the high percentages of PVA (2%) and HPMC (1.5%). Blending polymers in the formulation of films produced smooth and flexible films with suitable disintegration time for ocular insertion, due to inherent characteristics of the individual polymers.

Quality of blank ocular inserts

The blank ocular inserts were further evaluated according to multifaceted criteria. Each criterion was given a score and the total score for each film is depicted in Table 4. F30 and F33 demonstrated superior properties with a score of 100 and were chosen for incorporation of pilocarpine HCl niosomes. From Table 4, lower concentrations of HPMC (0.5–1.5%) fail the extended disintegration time target, while higher HPMC concentrations had longer disintegration times but were hard to cast on casting dishes. All PVA containing films exhibited very long disintegration time. However, the co-polymer films particularly F30 (1% HPMC, 1.5% PVA) and F33 (1% HPMC, 1% PVA) retained the excellent properties of the films in terms of smoothness, transparency, flexibility, wetting / spreadability and ease to peel off; as well as produced films that had a disintegration time within the targeted window.

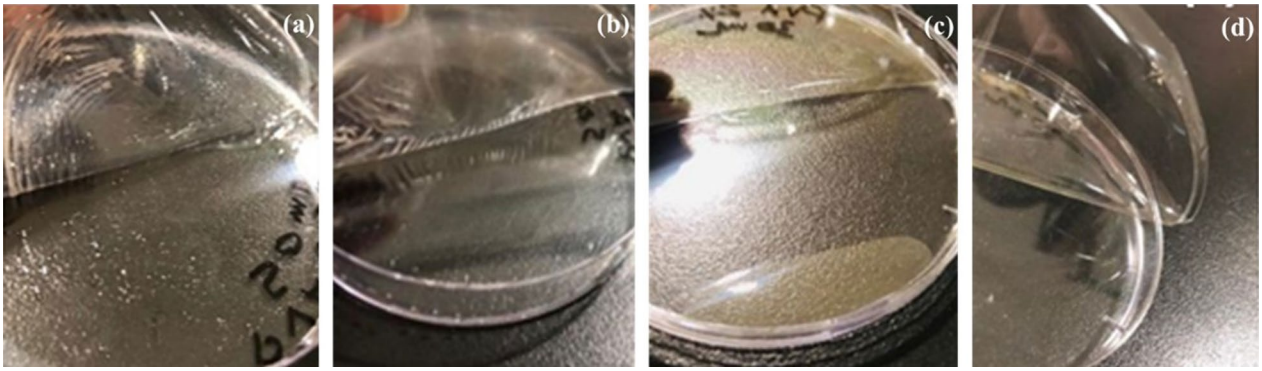


Fig. 2 Images of blank ocular inserts at different PVA concentrations (w/v), **a** PVA 0.5% -F13, **b** PVA 1% -F16, **c** PVA 1.5% -F19, **d** PVA 2% -F23

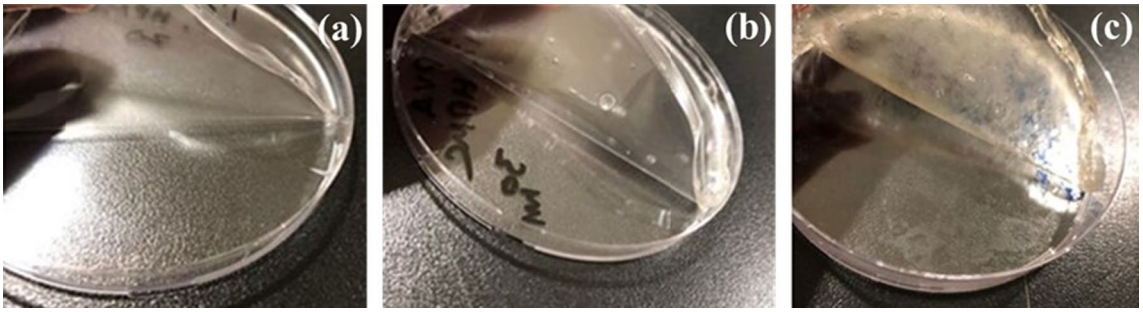


Fig. 3 Images of blend films (HPMC + PVA) at different concentrations (w/v), **a** HPMC1% + PVA 1% -F34, **b** HPMC 1% + PVA 1.5% -F30 **c** HPMC 1.5% + PVA 2% -F29

Table 4 Ocular inserts/ films quality characterization and scoring based on the evaluation criteria

Formula	Characterization of the films evaluation score (0 bad/10 good/20 very good)						Disintegration time score 10 very good interval (3–5 h) other value bad (0)
	Smoothness	Transparent appearance	Flexibility	Good wetting and spreading ability	Non-sticky and easily peeled off	Total/100	
F1	20	20	20	20	20	100	0
F2	20	20	10	20	0	70	0
F3	20	20	20	20	20	100	0
F4	20	20	20	20	20	100	0
F5	20	20	20	20	20	100	0
F6	20	20	20	20	20	100	0
F7	20	20	20	10	20	90	0
F8	20	20	20	10	20	100	0
F9	20	20	10	10	20	80	0
F10	20	20	10	0	20	70	10
F11	20	20	10	0	20	70	10
F12	20	20	10	0	20	70	10
F13	20	20	20	20	20	100	0
F14	20	20	20	20	20	100	0
F15	20	20	10	20	0	70	0
F16	20	20	20	20	20	90	0
F17	20	20	20	20	10	90	0
F18	20	20	20	20	10	90	0
F19	20	20	20	20	20	100	0
F20	20	20	20	20	20	100	0
F21	20	20	20	20	20	100	0
F22	20	20	10	20	20	90	0
F23	20	20	10	20	20	90	0
F24	20	20	10	20	20	90	0
F25	10	10	0	10	20	50	0
F26	10	10	0	10	20	50	0
F27	10	10	0	10	20	50	0
F28	10	10	0	0	20	40	0
F29	10	10	0	0	20	40	0
F30	20	20	20	20	20	100	10
F31	20	20	20	10	20	90	10
F32	20	20	20	10	20	90	10
F33	20	20	20	20	20	100	10
F34	20	20	20	20	20	100	0
F35	20	20	20	20	20	100	0

Weight uniformity and disintegration time

The results of weight uniformity and disintegration time of the blank films are presented in Table 5. The produced films showed good weight uniformity as evident from the low %RSD value, except for few batches. Good spreadability of the liquid polymer is related to weight uniformity of the final dry film. Overall, the two selected batches (F30 and F33) demonstrated good weight uniformity and low RSD.

Overall, the blank films have uniformity in the weight with up to 2 standard deviations. Formulations F10, F11, F12, F30, F31, F32 and F33 achieved the ideal target disintegration times for ocular inserts (within 3–5 h).

Characterization of niosomes

The produced niosomes were based on previous work [7]. The produced niosomes were initially characterised before inclusion within the optimal blank film formulations.

Table 5 Weight uniformity and disintegration time of the formulations of the blank film

Formula	Weight uniformity (mg) (mean ± SD), RSD) n = 10	RSD (%) of weight uniformity	Disintegration time
F1	1.09 ± 0.33	30.41	15.23 ± 10.1 min
F2	0.87 ± 0.01	1.14	11.43–6.58 min
F3	0.67 ± 0.08	12.29	8.55–4.25 min
F4	1.13 ± 0.1	8.6	40.67 ± 12.25 min
F5	0.91 ± 0.1	10.99	32.0 ± 10.05 min
F6	0.75 ± 0.1	12.95	25.67 ± 5.52 min
F7	3.12 ± 0.29	9.17	68.67 ± 18.57 min
F8	2.76 ± 0.42	15.3	58.25 ± 9.25 min
F9	2.09 ± 0.14	6.56	50.52 ± 12.89 min
F10	6.03 ± 1.52	25.15	4.57 ± 0.85 h
F11	4.9 ± 0.42	8.6	3.89 ± 0.58 h
F12	3.34 ± 0.34	10.29	3.55 ± 1.61 h
F13	4.45 ± 0.52	11.76	> 7 h
F14	4.11 ± 0.13	3.13	> 7 h
F15	3.9 ± 0.54	3.1	> 7 h
F16	9.9 ± 0.84	8.48	> 7 h
F17	6.56 ± 1.4	21.36	> 7 h
F18	4.25 ± 0.41	9.62	> 7 h
F19	11.51 ± 2.69	23.33	> 7 h
F20	4.13 ± 0.13	3.24	> 7 h
F21	3.54 ± 0.46	12.86	> 7 h
F22	5.26 ± 0.71	12.54	> 7 h
F23	7.47 ± 1.28	17.11	> 7 h
F24	1.51 ± 0.18	11.87	> 7 h
F25	10.87 ± 2.73	25.15	> 7 h
F26	5.2 ± 0.40	7.69	> 7 h
F27	6.01 ± 0.54	8.96	> 7 h
F28	13.89 ± 0.79	5.66	> 7 h
F29	7.47 ± 0.85	11.36	> 7 h
F30	7.23 ± 1.23	6.95	3.80 ± 0.56 h
F31	6.61 ± 0.56	8.54	3.2 ± 0.74 h
F32	4.32 ± 0.45	10.46	3.05 ± 0.66 h
F33	13.91 ± 2.2	5.85	3.59 ± 0.35 h
F34	8.83 ± 0.89	10.09	2. 98 ± 0.25 h
F35	4.26 ± 0.15	3.53	2.12 ± 0.16 h

Microscopic analysis of niosomes

Light microscopic analysis of pilocarpine HCl loaded niosomes was done at 100× magnification. The results are presented in Fig. 4. Images of niosomes showed spherical vesicles with cavities, which could hold entrapped drug. Aggregation of the spherical niosomes appeared as lines (Fig. 4c).

However, results using laser diffraction analysis for particle size analysis are presented in Table 6. The average particle size of the niosomes was within the nanoscale. The produced particles demonstrated an acceptable distribution and a large negative zeta size which promotes particle stability.

Entrapment efficiency and pilocarpine HCl within the niosomes

The average entrapment efficiency of pilocarpine HCl within the niosomes was 49.7% ± 7.0 (n = 3). This number was employed for the calculation of the amount of niosomes to be added to each ocular insert for the preparation of the ophthalmic inserts with niosomes.

FTIR spectra

The FTIR spectrum of cholesterol (Fig. 5a) revealed characteristic bands between 2800 and 3000 cm^{-1} which are attributed to asymmetric and symmetric stretching vibrations of CH_2 and CH_3 groups. The observed broad and intense band nearly at 3400 cm^{-1} is attributed to OH stretching. Cholesterol has one double band (C=C) in the second ring. This was prominently shown at 1674 cm^{1}. The band at 1464 cm^{-1} is due to asymmetric stretching vibrations of CH_2 and CH_3. The sharp peak at 1055 cm^{-1} can be attributable to ring deformation of cholesterol. The bands between 900–675 cm^{-1} are characterised due the C–H out of plane bending which are the characteristic of the aromatic substitution pattern and mainly determined by the number of adjacent hydrogen atoms on the ring and not much affected by the nature of substitutions. Similar results were reported in [27]. FTIR analysis of pilocarpine HCl (Fig. 5b) presented a C–O stretching band at 1026 cm^{-1}. C–N stretching at 1178 cm^{-1}, N–H bending band at 1765 cm^{-1} and C–H stretching at 3079 cm^{-1}. Similar results were reported by [10]. Figure 5c presents the IR spectra of span 60 which showed a broad peak at 3384 cm^{-1} due to O–H stretch bonded, strong peak at 2916 cm^{-1} due to C–H stretch, peak at 1735 cm^{-1} due to C=O stretch, and C–O stretch peak at 1175 cm^{-1}. Similar results were reported by [28]. Therefore, the niosome spectra (Fig. 4d) showed a broad band at 3400 cm^{-1} due to O–H stretch bond in span 60, a band at 2916 cm^{-1} due to C–H alkane, N–H bending band in pilocarpine HCl at 1765 cm^{-1}, while the C–O stretch group in pilocarpine HCl caused the peak at 1175 cm^{-1}.

Characterization of pilocarpine HCl niosome loaded ocular inserts

The drug loaded insert with different concentrations of pilocarpine HCl and polymer types, appeared as thin, smooth, and flexible films, easy to handle. An amount of niosomes containing the equivalent of 1 mg pilocarpine

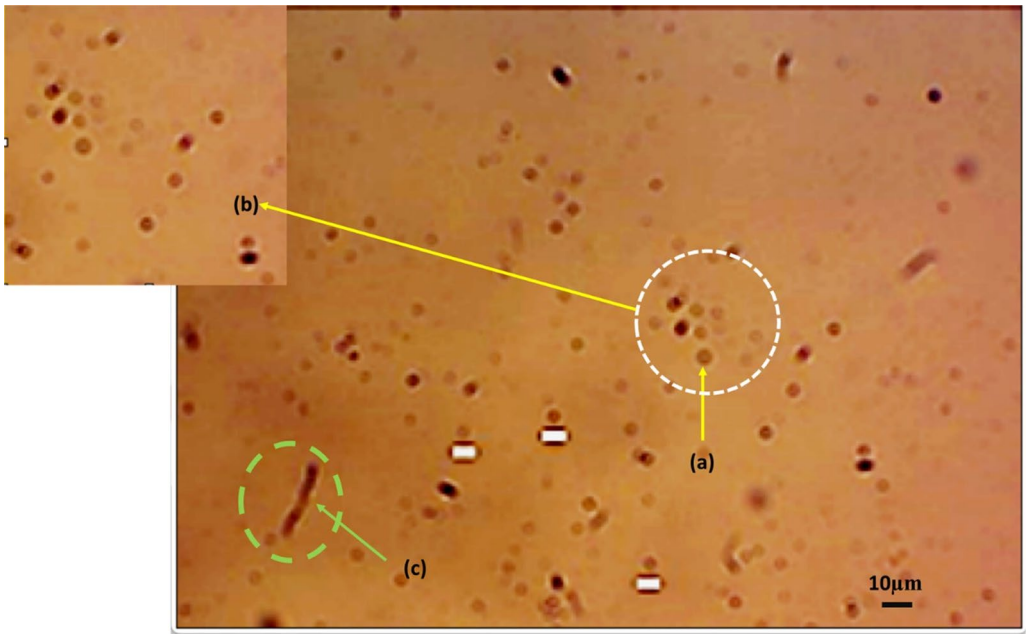


Fig. 4 Light microscopic images of niosomes loaded with pilocarpine HCl prepared by thin film hydration method at 100× magnification **a** selected area of niosomes for zoom in **b** zoomed in area highlighting the structure of the niosomes **c** Example of few aggregates

Table 6 Particle size, polydispersity index and zeta potential of pilocarpine HCl loaded niosomes (mean ± SD, n = 3)

	PSA (nm)	PDI	Zeta (mV)
Niosomes	325.7 ± 3.5	0.463 ± 0.044	− 51.32 ± 1.41

HCl for formulations T1 and T2, and 2 mg pilocarpine HCl for formulations T3 and T4 were incorporated into the films. The drug loaded inserts were cut into small pieces (2.5 × 5 mm) to be suitable to insert into the eye (see Fig. 6).

The result of the weight uniformity, content uniformity, moisture content, thickness, and surface pH are shown in Table 7.

The results revealed that the niosomal loaded ocular inserts demonstrated good content uniformity that ranged from 86.08 to 96.08% with low standard deviation that was below 2%. Further, the average moisture content of the ocular films was ranging from 30.8 to 39.6%. The surface pH of the ocular inserts is vital to ensure minimal eye irritation upon insertion. The surface pH of the drug loaded insert was in the range of 6.9–7.1.

Xray diffraction analysis

XRD pattern of pilocarpine HCl (Fig. 7a) demonstrated characteristic sharp peaks at 13.68°, 17.97°, 21.34°, 24.77° and 32.41° suggesting a crystalline material. Similar results were reported by Alyami et al. [7]. The blank film (Fig. 7b) demonstrated a shallow wide heap indicating the amorphous nature of the blend polymers. The niosome loaded films demonstrated characteristic peaks of the constituents of the niosomes (cholesterol and span 60). Due to the low load of pilocarpine HCl within the film, several peaks of pilocarpine HCl were not observed.

DSC analysis

The thermal profiles of pilocarpine HCl, niosomes, blank film as well as drug-loaded niosomal ocular inserts are depicted in Fig. 8. The thermogram of pilocarpine HCl (Fig. 8a) portrayed the crystalline nature of the material with sharp endothermic melting peak at 206.39 °C and an enthalpy of 20.95 J/g. Similar results were recorded by [7]. Figure 8b demonstrates the thermogram of the niosomes. This showed interesting findings, the first peak of the niosomes at around 60 °C could be attributed to span 60, while the second peak at 97.33 °C and enthalpy of 121.64 J/g probably represents cholesterol. However, the reported cholesterol melting point is between 145 and 150 °C [29, 30]. Several studies reported the effect of developing niosomes on the melting point of cholesterol with a possible shift towards a lower range [31, 32]. The blank film (Fig. 8c) showed its amorphous nature with no melting peak observed. The thermogram of niosomes loaded films (T4) as can be seen in Fig. 8d showed a sharp endothermic peak at 43.24 °C with enthalpy of 7.04

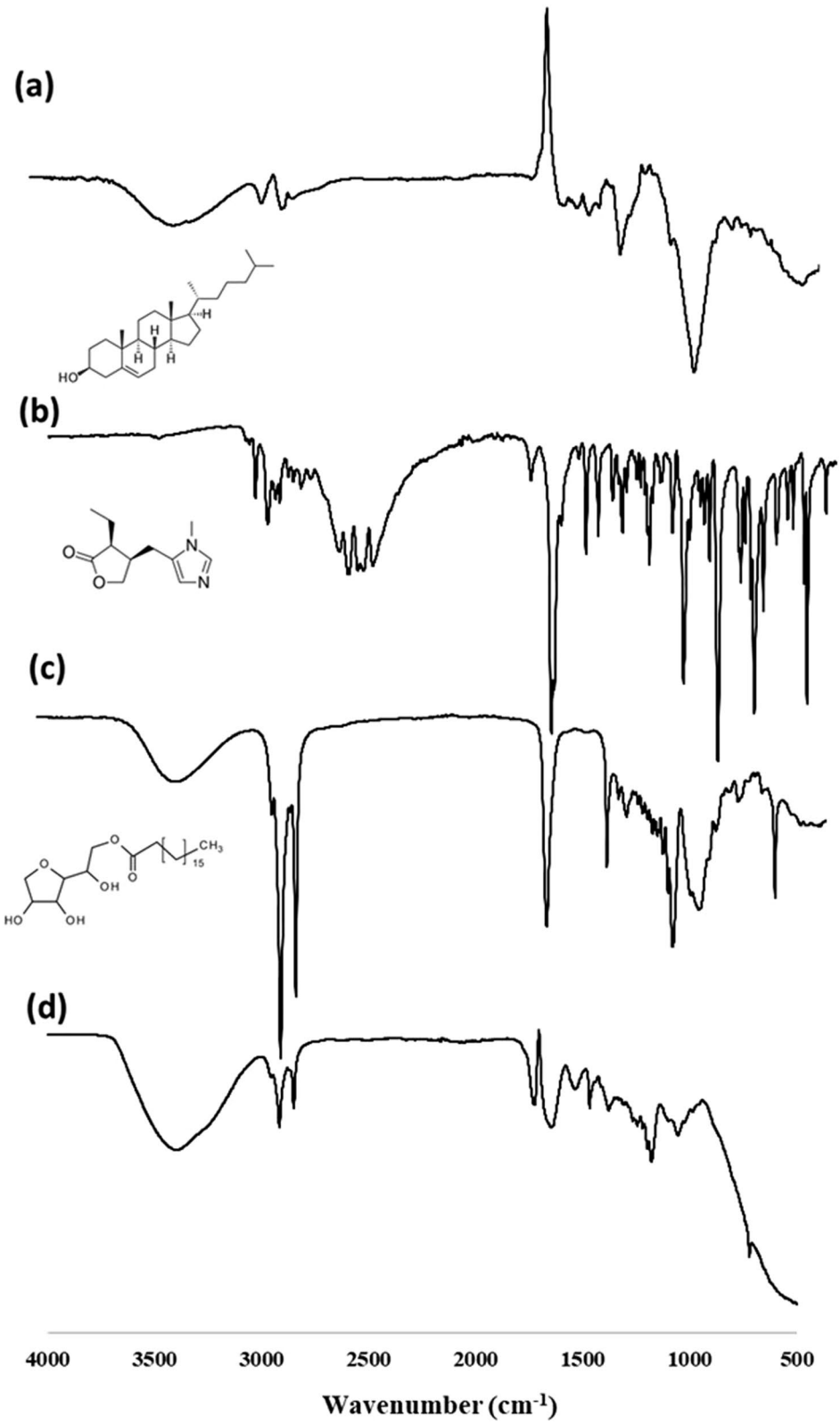


Fig. 5 FTIR Spectra and chemical structures for **a** cholesterol, **b** pilocarpine HCl, **c** span 60, and **d** niosomes

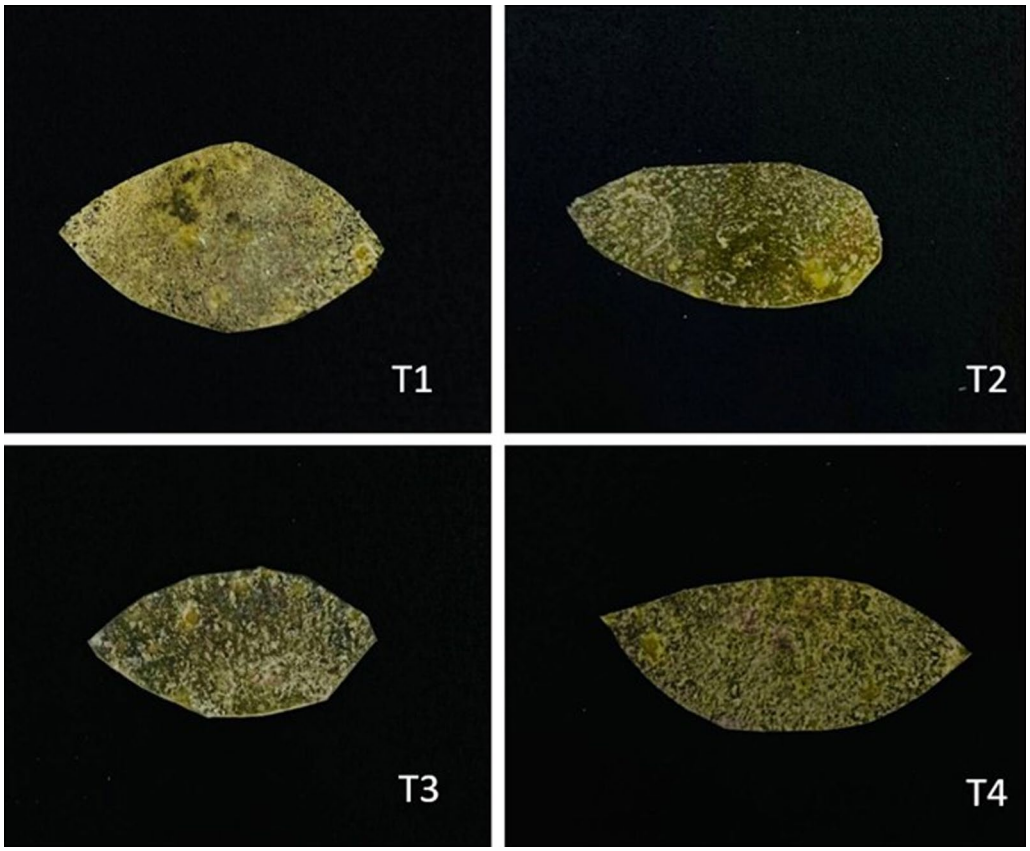


Fig. 6 Digital photographs of pilocarpine HCL niosomal loaded ocular inserts

Table 7 The result of weight uniformity, content uniformity, moisture content, thickness and pH of drug loaded niosomal inserts

Formula	Weight uniformity (mean ± SD) n = 10	Content uniformity %(Mean, n = 3)	Moisture content (mean ± SD) n = 3	Thickness (mm) (mean ± SD) n = 3	pH (mean ± SD)
T1	15.84 ± 2.06	92.5% ± 0.1	35.5% ± 2.32	0.41 ± 0.02	7.1 ± 0.1
T2	12.77 ± 2.37	89.2% ± 0.02	39.6% ± 6.63	0.55 ± 0.1	6.9 ± 0.01
T3	14.0 ± 1.23	86.08% ± 0.2	33.6% ± 8.54	0.64 ± 0.02	6.9 ± 0.2
T4	16.21 ± 1.25	96.08% ± 0.7	30.8% ± 0.72	0.95 ± 0.02	7.0 ± 0.1

J/g which represents the melting point of span 60. The second peak at 83.20 °C probably represents the melting point of cholesterol with another shift. The pilocarpine HCl melting peak does not appear probably owing to the encapsulation of the API within niosomes [31].

In vitro release study

The release of pilocarpine HCl from the drug loaded ocular inserts can be seen in Fig. 9 demonstrating an initial burst release within 2 h that ranged from 26.54% (T4) to 41.22% (T2), probably due to free, unencapsulated drug; followed by a slow extended release. The extended release was attributed to the release of pilocarpine HCl from the niosomes. At 24 h, the pilocarpine HCl released from inserts ranged from 68.32 ± 5.11% (T4) to 82.11 ± 6.01% (T2). Formulation (T1 and T4) containing higher percentage of (HPMC and PVA) demonstrated slower extended-release profile. However, using one-way ANOVA and Tukey post-test, there was no significant difference among the four formulations ($p > 0.05$).

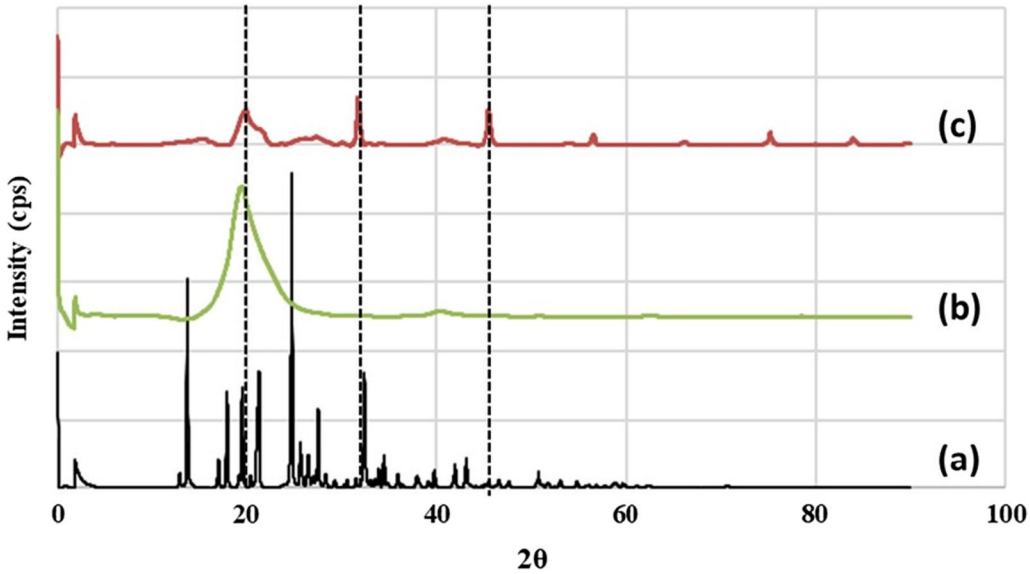


Fig. 7 XRD Spectra of **a** pilocarpine HCl, **b** the blank film and **c** pilocarpine HCl niosome loaded ocular insert

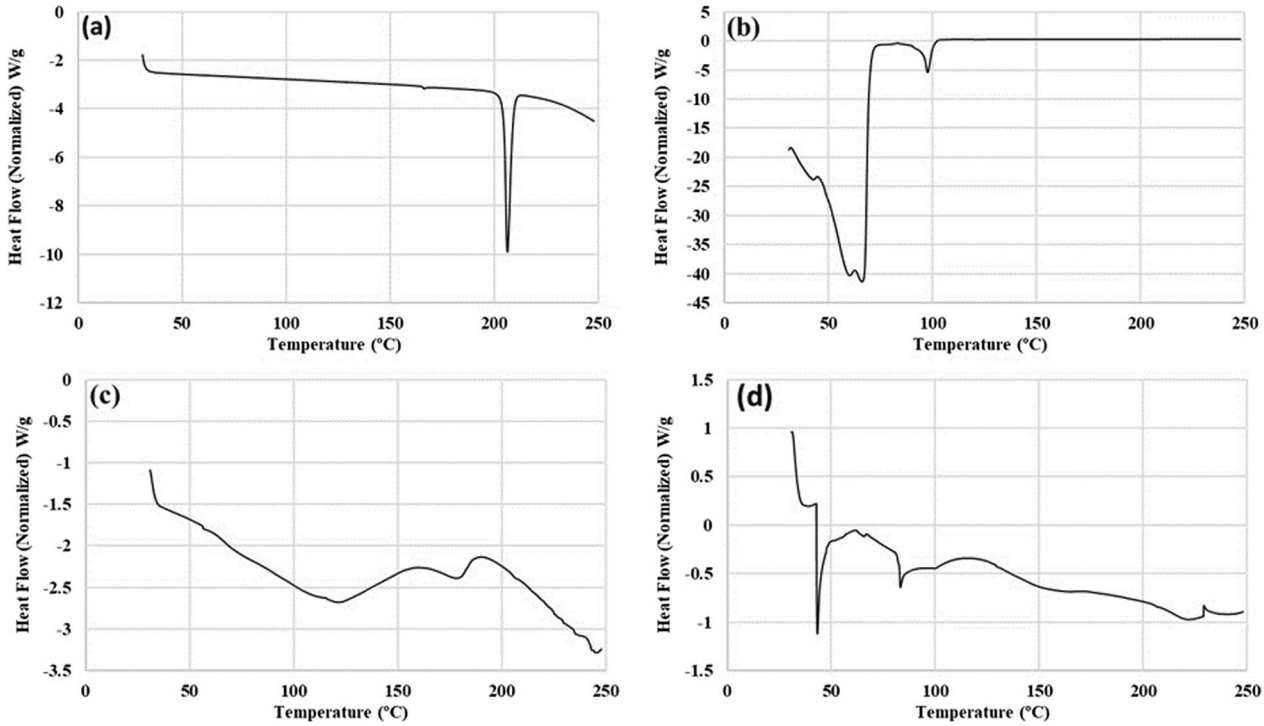


Fig. 8 DSC spectra of **a** pilocarpine HCl, **b** niosomes, **c** blank film and **d** niosome loaded ocular insert (T4)

Discussion

It has been reported that the prevalence of glaucoma, a leading cause of vision loss, is between 3 and 5% in people aged 40 years and older worldwide. Due to the rapid increase in the global population, this number is expected to rise to 112 million people by 2040 [32, 33]. This is an alarming number of anticipated patients, which demands an immediate improvement in the current therapeutic approaches. Currently, the only evidence-based treatment for glaucoma is to lower the intraocular pressure through surgery or medications [34]. However, the effectiveness and long-term efficacy

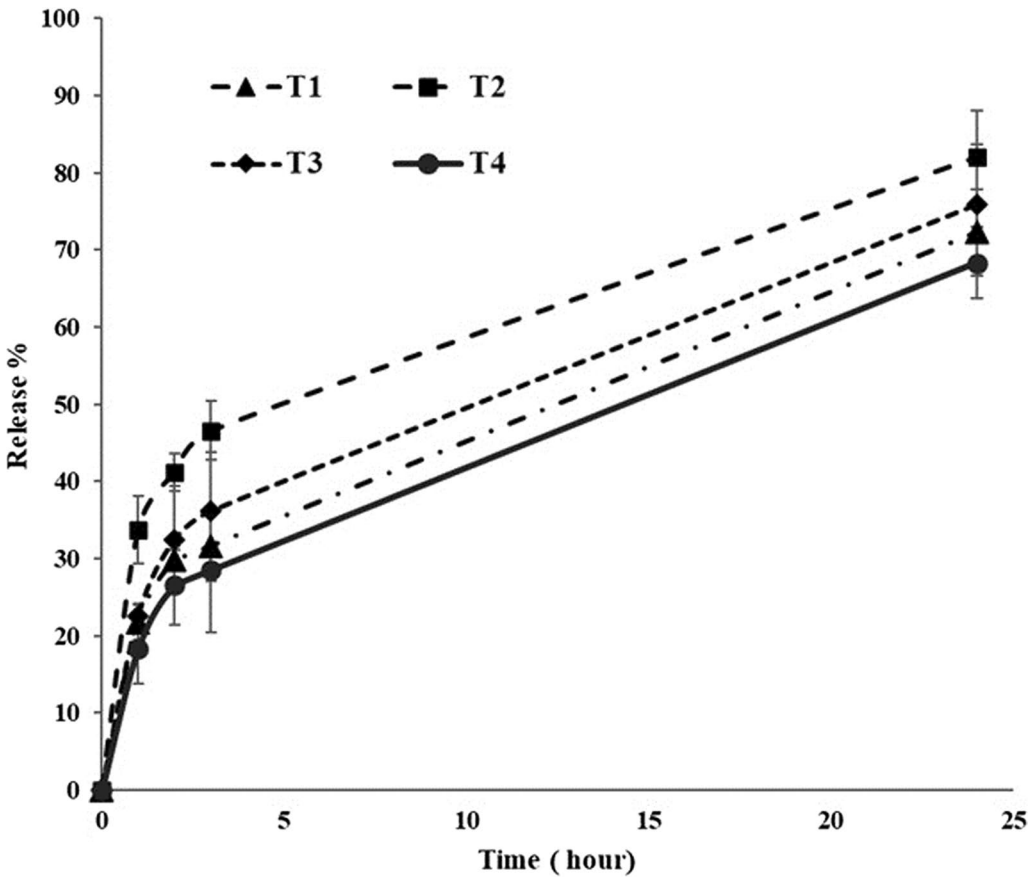


Fig. 9 Release study of pilocarpine HCl loaded niosomal ocular inserts (mean ± SD, n = 3)

of the currently available eye drops for glaucoma treatment are being questioned due to poor patient compliance. Many researchers have tried to improve the effectiveness of eye drops by increasing the pre-corneal residence time of the drugs. This can be achieved through the use of eye inserts or contact lenses. Compared to eye drops, these alternative forms of medication have demonstrated a substantial improvement in drug bioavailability [35–37].

The purpose of this study was to develop and optimise an ocular insert that slowly releases pilocarpine HCl to reduce the side effects of conventional eye drops due to dose dumping and the need for frequent drug administration. Initially, we attempted to identify the best formula to make blank ocular inserts/ films. Blending polymers, enabled the incorporation of higher polymer concentrations that allowed for longer disintegration time while retaining the flexible, smooth, and transparent appearance of the inserts. In general, an ideal ophthalmic drug delivery system should be able to administer drugs accurately without causing blurred vision or irritation. It should also have suitable mucoadhesive properties to improve drug retention in the pre-corneal area, thereby increasing drug bioavailability. Additionally, the system should reduce the need for frequent dosing to improve patient compliance [8, 38].

However, individual polymer-containing films were not capable to produce the desired disintegration time and film quality. HPMC produced moderate strength films with very good elasticity and transparency, while PVA produced less flexible films but with higher strength and resilience. The selection of HPMC was based on its non-ionic, good mucoadhesive, and lubricant properties, that would allow the insert to adhere to the surface of mucosa. HPMC was used for simulated tears formulations for the management of dry eye [39]. PVA is a commonly used biocompatible, hydrophilic, good reinforcing biodegradable polymer for ophthalmic preparations [40, 41]. To the best of our knowledge, this is the first report of a blend of these two polymers for formulation of ophthalmic inserts.

The aim was to create films with optimal properties, particularly for use in the eye. The eye is a very sensitive organ; therefore, the films needed to be very smooth,

flexible, and transparency to avoid discomfort to patients. Previously marketed inserts were discontinued due to patient inconvenience and bad patient experience with the films [18]. The targeted disintegration time of the films was 3–5 h which is the time for the biodegradable components of the films began to dissolve. The hypothesis was that drug release of 12 h would still be achievable without the complete film remaining in the eyes for that duration. Therefore, F30 and F33 were selected as optimal formulations owing to their excellent properties in terms smoothness, transparency, flexibility, wetting / spreadability and ease to peel off; as well as produced films that had a disintegration time within the targeted window and were used for further analysis. Similar trends were observed in ocular films developed for the sustained release of timolol [42]. The slow disintegration of the film promotes the extended-release profile of the drug and extend the drug retention time in the pre-corneal region.

During the next step, the focus was on optimising the niosomes that would contain pilocarpine HCl. This was done to ensure that there were two barriers in place to prevent dose dumping: the biodegradable polymeric film matrix and the extended release niosomal formulation. Niosomes are commonly used vesicular nanocarriers for ophthalmic drug delivery [37, 43]. The use of niosomes minimises dose dumping, had high encapsulation efficiency when compared to liposomes and are more stable [7, 43]. Furthermore, niosomes possessed favourable photoprotection effect along with rheological characteristics pertinent to spreadability and viscosity [44]. It was crucial to maintain a small particle size for the produced niosomes. Our research showed that the average particle size for the niosomes was within the nanoscale range, which is optimal. Similar results were obtained by Alyami et al. [7]. It is important to keep the particle size of ophthalmic preparations below 10 μm to avoid ocular irritation [10]. The produced particles demonstrated an acceptable distribution and a large negative zeta size, which promotes particle stability.

The next step focused on developing the double barrier formulation comprised of the optimal ocular insert laden with the pilocarpine containing niosomes. The produced films and niosomes were subjected to molecular profiling using FTIR and XRD to understand their physical and chemical properties as well the components' compatibility profile. The analysis of the IR spectra suggests that there are no interactions or incompatibilities between the compositions of the niosomes, including the API, pilocarpine HCl. Furthermore, the XRD analysis did not reveal any shifts or changes to the main constituents of components. Furthermore, the thermal analysis using DSC suggested that pilocarpine HCL might be encapsulated within the niosomes. Similar results were reported where the disappearance of the active ingredient melting point peak could be attributed to encapsulation [7, 45].

The tears which comprises of electrolytes (Na+, K+, Cl $^{-}$), proteins such as lactoferrin, lysozyme, lipids, and mucins, serve as an excretory and delivery route of metabolic substances and nutrients [46]. The pH of the tears generally ranges from 6.5 to 7.6, with an average value of 7 [47]. Therefore, ophthalmic drug formulations should have a pH between 6.6 and 7.6 to prevent irritation. When developing ocular dosage forms, it is essential to consider the physiochemical and biopharmaceutical features of the API to be administered via the ophthalmic route, such as solubility, permeability, and stability. This should ensure sufficient dissolution of the API as well as diffusion through different ocular barriers.

Two important factors need to be addressed for eye inserts: moisture content and surface pH. The study results revealed that the moisture content of the optimal inserts ranged between 30 and 40%, which is favourable for the user's comfort and could be attributed to the hygroscopic nature of the HPMC [48]. Furthermore, the surface pH level is unlikely to cause irritation or discomfort upon application since the pH of the tears is within the range of 6.5–7.6 [47]. Therefore, all the produced formulations were not expected to have major adverse effects on the eye. The produced formulations (T1-T4) were within the recommended rage of surface pH and hence it is expected not to cause any ocular surface irritation and potentially produce good diffusion [49]. The results of this work is in agreement with other research findings for ocular formulations [43, 50].

The selected optimal formulations showed a promising release profile. The initial burst release of pilocarpine HCl is not expected cause blurred vision, because it is small amount in comparison with the traditional dose of pilocarpine HCl in eye drops. After 24 h, the pilocarpine HCl released from inserts ranged from 68.32 ± 5.11% (T4) to 82.11 ± 6.01% (T2), indicating that the formulations achieved the aim of the study. It is interesting to note that the niosomal ocular inserts loaded with pilocarpine and with a lower PVA content (1%) were able to release pilocarpine at a quicker rate. By adjusting the PVA concentration to 1.5% and increasing the initial pilocarpine content, the rate of polymer erosion and degradation can be regulated, resulting in controlled release in ocular tissues. Therefore, these ocular inserts could potentially serve as an effective delivery platform not only for pilocarpine but also for other APIs on the ocular surface for an extended period of time. Similar results were reported [51].

According to this study, combining two polymers (HPMC and PVA) with API loaded niosomes can achieve two crucial features of ocular inserts: extended retention

and sustained release of the API. This is accompanied by favourable physical and chemical properties of the insert, such as surface pH, moisture content, and compatible formulation.

Conclusions

The current study successfully produced biodegradable ocular inserts using HPMC and PVA co-polymer blend, as a drug delivery device for pilocarpine HCl loaded niosomes, to provide sustained release of pilocarpine over 24 h. The purpose was to reduce the dosing frequency, enhance patient compliance and minimize side effects associated with conventional eye drops. The optimised niosomes-loaded ocular inserts were evaluated for their mechanical and molecular performance. The findings suggested that these inserts are effective in releasing pilocarpine over an extended period while retaining a favourable pH of around 7 – entailing no possible irritation to the eye. The biodegradable ocular inserts were also found to be compatible with formulations' excipient as evident from FTIR and thermal analysis. In conclusion, these niosomes loaded HPMC-PVA ocular inserts provide a potential to be used as a platform for delivery of other pharmaceutical active ingredients for ocular delivery.

Abbreviations

API	Active pharmaceutical ingredient
SD	Standard deviation
DDSs	Drug delivery systems
DSC	Differential scanning calorimetry
FTIR	Fourier transform infrared
HPMC	Hydroxypropyl methylcellulose
LOD	Limit of detection
LOQ	Limit of quantification
PDI	Polydispersity index
PVA	Polyvinyl alcohol
RSD	Relative standard deviation
XRD	X-ray diffractions

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Author contributions

TA: investigation; data curation; formal analysis. ED: conceptualisations; formal analysis, writing—review & editing; supervision; project administration & funding acquisition. SA: review & editing; supervision; AI: conceptualisations; writing—review & editing. The manuscript has been read and approved by all the authors and each author believes that the manuscript represents honest work.

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Availability of data and materials

Any further information can be obtained from the corresponding author upon request.

Declarations

Ethics approval and consent to participate

The experiments reported in this manuscript did not involve any human or animal subjects. The experiments performed in this manuscript comply with the current laws of the country.

Consent for publication

Authors provide consent for publication in the Future Journal of Pharmaceutical Sciences.

Competing interests

The authors declare no competing interests.

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