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Research Article

Development and Characterization of Liposomal Formulation for Ophthalmic Delivery of Prednisolone Acetate

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ABSTRACT

Liposomal vesicular drug carriers for ocular delivery have earned a wide potential nowadays. Prednisolone acetate liposome as ocular drug carriers has been demonstrated to be a useful mode to ameliorate bioavailability and patient abidance. The liposome was prepared by the lipid extruder method. Liposome was characterized for entrapment efficiency (EE%), vesicle size, surface morphology, and *in vitro* drug release. An *ex vivo* corneal permeation study was performed to determine the level of drug in the external eye tissue of goat, and an ocular irritation assessment was done by Hen's Egg Test-Chorioallantoic Membrane (HET-CAM) method. The optimized formulation of liposome had shown acceptable viscosity (1.21 ± 0.03 cps), refractive index (1.47 ± 0.001), osmolarity (303 ± 3 mOsm), and pH measurement (7.12 ± 0.09). Liposome as drug delivery carriers were evidenced to be an anticipating impendent to enhance corneal contact and penetration as well as a retention time in the eye ensuing in a prolonged action and enhanced bioavailability. Results of stability study exhibited a stable profile of developed liposomes.

INTRODUCTION

The domain of ocular drug delivery systems (ODDS) has dynamically advanced in the past two decades. This subsequently ensued in a novel therapeutic regimen for chronic ocular disorders. The main objective of any ODDS is to allow therapeutic drug concentrations at the desired (target) site, minimize dosing frequency, and to defeat various dynamic and static ocular barriers. The ODDS is one of the most absorbing and gainsaying attempts to confronting the formulation scientist. The anatomical and physiological profile of the eye makes it delicately imperviable to strange molecules. To circumvent the protective barriers of the eye without compromising its natural form is the challenge to the formulator. Eye drops and ointments are the most commonly available conventional ophthalmic preparations, which covers 70–80% of ophthalmic dosage forms in the market. When such formulations are administered into the cul-de-sac,

They are rapidly run out away from the ocular cavity owing to lachrymal nasal drainage and tear flow. Consequently, they are no longer adequate to battle some present virulent diseases. So, there is an urgent clinical need for an efficient ocular delivery system that can overcome drawbacks associated with conventional ophthalmic formulations.^[1-3]

High ocular drainage and poor corneal permeation are the two main factors which restrict the ocular bioavailability of drug molecule and to improve these factors at a desirable level is a key challenge. Valuable attention is to be made in the last two decades on design of efficient ODDS aiming targeting the site of action (avoid the dose frequency) and betterment in the drug effectiveness.^[4,5]

Different newer ophthalmic formulations including micro particles, *in situ* gel, nanoparticle, liposome, nanosuspension, microemulsion, iontophoresis, collagen shields, contact lenses, and ocular inserts have been

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developed and characterized.^[6] Out of these designs, in the last decade, liposomal formulations were widely explored.^[7,8]

Liposomes are microscopic vesicles comprised of lipid bilayers fencing aqueous compartments.^[9] This important feature gives the power of liposomes to encapsulate both Active Pharmaceutical Ingredients APIs (i.e., lipophilic and hydrophilic). It increases the penetration of poorly absorbed APIs via adhering to the corneal surface and ameliorating residence time. Additionally, liposomes are also biodegradable, non-toxic, and biocompatible.^[10] Moreover, manufacturing flexibility favors it in various sizes, and further, it can be incorporated into secondary vehicles (i.e., eye drops, gels, and ointments).^[11]

Chetoni *et al.* developed positively charged unilamellar liposome for acyclovir and reported improved bioavailability of drug than plain drug ointment.^[12] Kawakami *et al.* found enhanced corneal residence time of timolol when O-palmitoyl (prodrug of timolol) was encapsulated in liposomal structure.^[13]

Prednisolone (11 β , 17, 21-Trihydroxypregna-1,4-diene-3, 20-dione 21-acetate, steroidal anti-inflammatory agent), is mostly used in human and veterinary medicine. It acts binding to glucocorticoid receptors and alleviating signal transduction pathways. As it is highly hydrophobic and poorly aqueous soluble, its bioavailability is not appropriate and acceptable in a desirable level range.^[14,15]

So, in the present study, liposomes were developed for prednisolone acetate (PA), which would increase permeation across the corneal membrane and ems.

MATERIALS AND METHODS

Materials

The PA was received as a gift sample from Amneal Pharmaceuticals, India. Cholesterol was purchased from Sigma-Aldrich, Dorset, UK. Hydrogenated soya phosphatidylcholine (HSPC) and 1, 2-distearoyl-sn-glycero-3-phospho-(1'-rac-glycerol) (DSPG), were obtained from Avanti Polar Lipids, Alabama. White Leghorn chicken eggs (10 days old) were obtained from Shakti poultry farm, Aanand, India. Double distilled water was used wherever required, and all chemicals used were of analytical grade and were used without further modification.

Methods

Quantification of Prednisolone Acetate (PA)

The PA was quantified by reverse-phase high-performance liquid chromatography (HPLC) (YMC Triart, C18; 250 X 4.6 mm, 5 μ). The HPLC system (SCL-10 AVP, Shimadzu, Japan) includes a binary pump (LC-10 ATVP Shimadzu, Japan), and a UV detector (SPD-10 AVP, Shimadzu, Japan). The mobile phase was IPA/water (70:30, v/v) with a flow rate of 1.0 mL/min. The detection wavelength was set at 245 nm, and the run time was 15 minutes having

23 minutes of RT. The assay was found linear with a concentration range of 0.1–50 g/mL and 0.05 g/mL LoD. The percentage of recoveries were found in a range of 98.0–101.0%. Aliquots of 10 μ L were injected into the HPLC system via an auto-injector. The samples were filtered through 0.45 m pore size membrane.

Preparation of Prednisolone Acetate Containing Liposomes (PAL)

Liposomes were prepared by the solvent evaporation method in which 9 mg of HSPC was dissolved in 1 mL of solvent system [Ethanol/methanol (8:2 % v/v)] in a 25 mL round bottom flask. The drug was dissolved in the above mixture having lipid solution. The resulting dried lipid-lipophylic drug mixed film (removed from rotary evaporator) was dissolved in 9 mL of organic solvent. A sucrose solution (9%) was added as a tonicifier. The organic solvent was removed by rotary evaporation (at 40°C under reduced pressure) to yield final multilamellar liposome (MLV) aqueous dispersion.^[16]

Size Reduction

The size of prepared MLV was reduced by adopting a microfluidizer and lipid extruder process. Prepared liposomal PSA was passed through Emulsiflex-C5 equipment conjoined with extruder holder (placed 400 nm polycarbonate membranes) under pressure at 5,000 psi (350 bar) as in Fig. 1. An investigation was done for the numbers of compressed cycles to optimize suitable parameters.

Prepared liposomal formulations were charged using cationic polymers (chitosan), mucoadhesive polymer (polycarbophil), and cationic agent (cetylpyridinium chloride and benzalkonium chloride).

Liposome Characterization^[17,18]

Zeta Potential and Particle Size Measurement

Both zeta potential and particle size distributions were analyzed using Malvern Zetasizer 2000 (Malvern

Fig. 1: Block diagram of and flow of product on lipid extruder

Instruments, UK). Particle size was determined using laser diffraction technique. All measurements were repeated three times at room temperature (30°C).

Entrapment Efficiency (EE)

With the help of buffer, the liposomal dispersion was appropriately diluted and centrifuged (15,000 rpm for 30 min) in Remi R-24 centrifuge. The supernatant was examined for drug content on a Shimadzu UV-120 spectrophotometer at 257 nm. The EE was calculated as a fraction of drug in the liposome dispersion expressed as a percentage of total drug content. The effect of shaking on EF was determined before shaking and after 3 and 6 hours of shaking. The EE was calculated by the following equation:

$$EE = \frac{\text{total drug input (mg)} - \text{drug in supernatant (mg)}}{\text{Total drug input (mg)}} \times 100$$

Morphology

In order to study liposome morphology, an optical microscope and a scanning electron microscope (SEM) were used. For light microscope, one drop of the liposomal suspension for each formula was placed on a glass slide and covered with plastic cover. One drop of the dispersion was mounted on a stub covered with clean glass. Apolaron E5100 sputter-coater was employed to sputter coat the sample with gold. For the transmission electron microscopy (TEM) study, uranyl acetate was used for negative staining of a small aliquot of the liposomal dispersion. The samples were examined using a JEOLJEM 100S electron microscope using an accelerating voltage of 80 keV.

Refractive Index and pH Measurement

Abbe type refractometer was used in studying the refractive index of selected formulations. The obvious pH of liposomal formulation was measured by digital pH meter in triplicate at $25 \pm 1^\circ\text{C}$.

In vitro Drug Release Studies

In vitro drug release, PAL was carried out Float-A lyzer (1000 KD) Dialysis Devices by filling PSA loaded liposomes into culture bottles or vials containing 0.5 G + 0.5 G media and PBS (pH 7.4). The samples were separated with a CA membrane (pore size: 4 nm) from the dissolution medium. The vials were immersed in 300 mL of simulated tear fluid (STF) having pH 7.4 + 1 % SLS. The temperature and stirring rate were $37^\circ\text{C} \pm 0.5^\circ\text{C}$ and 150 rpm, respectively. Aliquots of 1.0 mL were taken at 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours intervals from the release medium. The aliquot was properly diluted, and the amount of PA was quantified by HPLC.

Ex vivo Permeation

Vertical Franz diffusion cells with a volume of 10 mL simulated tear fluid pH 7.4 (contact area: 0.77 cm^2), $37^\circ\text{C} \pm 1^\circ\text{C}$, 200 rpm were used to determine the *ex vivo* permeation of the PSA loaded liposome. Goat corneal membranes were mounted on top of the receptor chambers. PA loaded

liposomes (150 mg) were placed into the donor chambers. The release medium (250 μL) was added to the top of the liposomes to mimic the small amount of tear secreted on the eye surface. The stirring speed of the Franz diffusion cells was set at 600 rpm. At 15, 30, 45, 60, 90, 120, 180, and 240 minutes of time intervals, an aliquot (0.15 mL) was withdrawn from the receptor chambers and replenished with fresh media. The samples were analyzed for the corneal permeation of PSA through the corneal membrane.

Stability of the Liposomal Dispersions

The empty and PA loaded liposomal dispersions were stored at $5 \pm 3^\circ\text{C}$ and $25 \pm 2^\circ\text{C}/60\% \pm 5\% \text{ RH}$. They were inspected visually as well as for microscopic appearance at the end of 15, 30, 60, and 90 days after preparation.

Ocular Irritation Study^[19,20]

The HET-CAM method employed to test substances. Pure or diluted solutions were placed directly on the exposed CAM membrane, and the membrane was examined visually by a microscope. During the period of 30, 120, and 300 seconds, time for reaction to occur on the membrane was noted. An irritation score (IS) was calculated and the substances were sorted accordingly (0–0.9: Non-irritative, 1–4.9: Slightly irritative, 5–8.9: Moderately irritative, 9–21: Strongly irritative). The reaction outcomes were observed in the context of hemorrhage, coagulation, and lysis. The test formulation was used as 0.3 mL, and the study period was 300 seconds. Negative and positive controls were also tested for comparison with the formulation.

$$IS = \left(\left(\frac{301 - \text{Hemorrhage Time}}{300} \right) \times 5 \right) + \left(\left(\frac{301 - \text{Lysis Time}}{300} \right) \times 7 \right) + \left(\left(\frac{301 - \text{Coagulation Time}}{300} \right) \times 9 \right)$$

RESULTS AND DISCUSSION

Preparation of Prednisolone Acetate Loaded Liposome

The benefit of this method is there was no precipitation/particles were found. After being prepared by the solvent evaporation method, the effects of equipment and parameters in the globule size reduction process were investigated. The concentration of lipid to cholesterol: HSPC to cholesterol ratio (60:40) and HSPC:DSPG Na ratio (80:20) was optimized by taking several trails and its observation. Then further different liposomal formulations were prepared using a varying concentration of ethanol:methanol.

PSA loaded liposome prepared in the previous step was undergoing for size reduction by lipid extruder through polycarbonate membrane device and microfluidizer (Table 1). Particle size and PDI was significantly decreased with help of the extrusion process. However, no impact on particle size and PDI was observed with microfluidization as number of passes increased. This indicates the ineffectiveness of the microfluidization process to get the desired particle

Table 1: Different method of preparation of liposome

Process	Primary liposome	Size reduction	No. of pass	Z avg ($\pm$ SD)	PDI ($\pm$ SD)
1) Batch prepared with the solvent evaporation method	10,000 RPM at 60°C $\pm$ 3°C till solvent evaporate	--	Before extrusion	160.2 $\pm$ 9.2	0.288 $\pm$ 0.02
2) Size reduction by lipid extruder		0.1 μ membrane	1	125.6 $\pm$ 4.6	0.103 $\pm$ 0.009
			2	118.3 $\pm$ 3.6	0.096 $\pm$ 0.012
			3	108.4 $\pm$ 4.1	0.082 $\pm$ 0.005
1) Batch prepared with the solvent evaporation method	10000 RPM at 60°C $\pm$ 3°C till solvent evaporate	--	Before microfluidization	160.2 $\pm$ 9.2	0.288 $\pm$ 0.02
2) Size reduction by microfluidizer		10,000 PSI	2	145.8 $\pm$ 3.5	0.232 $\pm$ 0.03
			3	140.1 $\pm$ 3.1	0.210 $\pm$ 0.02
			5	143.8 $\pm$ 2.9	0.208 $\pm$ 0.02

Fig. 2: A. SEM photomicrograph and B. TEM image of liposome

size distribution (PSD) for nano liposomal formulation. Hence, the particle size reduction using lipid extruder was selected.

The inclusion of cationic agents increased the zeta potential of formulation to a positive side, which was beneficial as the ocular surface is anionic charge. This manifestation improved corneal penetration of the drug-loaded liposome. Cationic liposomes interact with anionic mucosa in cornea and hence improvement in cornea penetration and enhanced ocular surface time was observed.

Liposome Characterization

The encapsulation efficiency of liposomal formulations finds the ability of formulation to withstand drug molecules in the lipid bilayer of the vesicle. Cholesterol increases the fluidity property of the bilayer membrane and improves the retainability of the vesicle in a biological environment. From the drug entrapped results, it was found to be 80.0 $\pm$ 5.0%. The formulated liposome also characterized for viscosity (1.21 $\pm$ 0.03 cps), refractive index (1.47 $\pm$ 0.001), osmolarity (303 $\pm$ 3 mOsm) and pH measurement (7.12 $\pm$ 0.09). The results of a morphological study with optical microscopy and scanning electron microscopy (Fig. 2) revealed that the developed liposomes

had a smooth surface and were spherical in shape with multilamellar vesicles. The size of liposomes (> 90%) was found to be 108.4 $\pm$ 4.1 nm.

In vitro Release Study

In vitro release profiles of plain drug PA, PAL, and marketed formulation (MF) of PA, are summarized and compared in Fig. 3. The release rate of the drug was remarkably high for the liposomes, while the rate of release from

Fig. 3: *In vitro* release studies

Table 2: Results of stability study of PAL

Parameters	Method/ instrument	Initial	3M 25 ± 2°C/60% ± 5 % RH	3M 5 ± 3°C
Description	Visual examination	Translucent suspension	Translucent suspension	Translucent suspension
Assay (%)	HPLC	98.8 ± 1.5%	97.6 ± 1.5%	98.2 ± 1.2%
% Free drug	HPLC	14.2 ± 2.1%	17.3 ± 2.5%	14.8 ± 2.2%
Viscosity (cps)	Brookfield viscometer	1.15 ± 0.03 cps	1.18 ± 0.04 cps	1.19 ± 0.02 cps
Globule size/PDI	Dynamic light scattering/ zeta sizer	112.4 ± 3.1 nm/ 0.088 ± 0.007	115.1 ± 3.8 nm/ 0.092 ± 0.009	110.9 ± 2.9 nm/ 0.086 ± 0.006
Zeta potential (mV)	Electrophoresis/zeta sizer	+ 31.4 ± 3.9 mV	+ 28.3 ± 4.1 mV	+ 32.6 ± 3.1 mV
pH	USP <791>/ pH meter	7.12 ± 0.09	6.79 ± 0.11	7.08 ± 0.07
Osmolality (mOsm/kg)	USP 785>/ osmometer	298 ± 3 mOsm	302 ± 3 mOsm	304 ± 2 mOsm

conventional MF was less than that. In PAL, plateau was seen after 6 hours. The plateau phase may be observed due to the equilibrium of drug concentration between the donor and receptor compartment. This reaffirms the fact that lipid bilayer acts as a barrier against diffusion of the drug.

Ex-vivo Permeation

Fig. 4 indicates the cumulative amounts of PA permeated from the liposomal formulations. Significant higher amount ($p < 0.05$) of PA permeated from liposome as compared to the MF. Furthermore, liposome exhibited the highest steady-state flux (1.86 mcg/cm²hr) and permeability coefficient (0.986). Cationic liposome showed a significant increase in permeation through the corneal membrane.

Fig. 4: Ex vivo permeation study**Table 3:** Irritation score of controls and test formulation.

Formulation	Irritation score
0.9% NaCl solution	0.2
1% SDS solution	7.3
1% NaOH solution	11.7
Cationic liposome	0.3

Category of Irritation: - 0–0.9: Non-irritant, 1–4.9: Weak or slight irritation, 5–8.9 or 5–9.9: Moderate irritation, 9–21 or 10–21: Strong or severe irritation

Stability of the Liposomal Dispersions

Optimized liposomes were evaluated for their physical and chemical stability at two different temperatures (Table 2). The mean vesicle size was 112.4 ± 3.1 nm, and encapsulation efficiency was about to 86% initially; no significant changes in drug encapsulation efficiency and globule size were observed during the course of stability study for formulations stored at both conditions ($p < 0.05$). Results revealed that the prepared liposome formulation was stable for 90 days.

Ocular Irritation Study

In order to check the eye irritation potential of optimized liposomal formulation of PA, Hen's Egg chorioallantoic membrane test was performed. The experimental result of controls and test formulation is presented in

Fig. 5: A complementary and alternative medicine (CAM) treated with 0.9% Sodium chloride solution as Negative control – IS 0.1; B) CAM treated with 1% SDS solution as a positive control – IS 7.4; C) CAM treated with 0.1 N sodium hydroxide solution as positive control – IS 12.6; D) CAM treated liposomal formulation - IS 0.4

Table 3 and Fig. 5. As a negative control, 0.3 mL of 0.9% sodium chloride solution was applied and no signs of lysis, hemorrhage or coagulation on the chorioallantoic membrane were observed. However, 0.3 mL of 1% SDS and 1% sodium hydroxide solution were applied as positive controls; significant damage to the chorioallantoic membrane was observed, while, application of 0.3 mL of liposomal formulation absolutely showed no effect on the chorioallantoic membrane after 5 minutes with respect to lysis, hemorrhage or coagulation. The irritation score for controls and test formulation is presented in Table 3. The irritation score of HET-CAM test showed that the developed cationic liposome is essentially non-irritating and possess good ocular tolerability.

CONCLUSION

From the results, it can be concluded that the inclusion of PA into a lipidic vesicular system (liposomes) improved solubility and permeation across the corneal membrane. Results of short term stability study revealed stability characteristics of the developed formulation. Non-irritant nature of prepared formulation on the corneal tissue was confirmed by HET-CAM test.

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