

RESEARCH PAPER

Preparation and ex-vivo ocular delivery of Thermo-responsive pluronic F- 127 hydrogel containing propranolol hydrochloride-loaded Liposomes

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ABSTRACT

Objective(s): Poor bioavailability of ophthalmic drops is mainly due to rapid nasolacrimal drainage and eye impermeability of corneal epithelium. The main aim of this study is to prepare a liposomal hydrogel for the ocular delivery of propranolol hydrochloride as a β -blocker drug to enhance drug concentration at the desired site of action.

Materials and Methods: In this study liposome formulations were designed and prepared by homogenization and thin-layer methods and then dispersed into the pluronic based hydrogel. The optimized liposomes and liposomal hydrogel were used in Ex-vivo ocular permeation studies through the rabbit's eye.

Results: liposomes showed 170-380 nm particle size, 34-65% entrapment efficiency, and sustained release profiles that 30-60 % of loaded drug released after 24 h. liposomes dispersed in hydrogels demonstrated a lower release rate. Liposomes and liposomal hydrogel increased ocular bioavailability of more than 3-folds.

Conclusion: In this study, the administration of thermo-responsive factors (pluronic) led to longer resistance time of the dosage form in the eye because the drug would turn into gel structures at the body temperature. Therefore, a system consisting of both pluronic factor and liposomes will be of great interest because it will pair up the Thermo gelling properties of the pluronic factor and the carrier characteristics of the liposome formulations.

Keywords: Drug delivery, Liposome, Thermo-responsive hydrogel, Ocular, Rabbit, Propranolol hydrochloride

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INTRODUCTION

Glaucoma is an ocular disorder characterized by changes in the optic disc and loss of visual accuracy and field. There are two major types of glaucomas; open-angle glaucoma and closed-angle glaucoma. Open-angle glaucoma is associated with intraocular pressure (IOP) increasing [1].

Glaucoma treatment usually is started by drug therapy. It is usually started with a single well-tolerated topical agent. The goal of drug therapy in patients with glaucoma is to preserve visual function by reducing the IOP to a level at which no further optic nerve damage occurs. Topical β -blockers reduce the intraocular pressure (IOP) by blockade of sympathetic nerve endings in the ciliary epithelium causing a fall in aqueous humor

production [2]. β -blockers to have the advantage of low cost owing to generic formulations [1]. Timolol, betaxolol, and levobutnolol are the most frequent topical beta-blockers that are used for glaucoma. They demonstrate similar IOP efficacy but differ in the pharmacological properties and side effects. They have systematic absorption and can affect bronco-pulmonary and cardiovascular function especially in patients with heart failure, asthma, or chronic obstructive airways. Betaxolol is beta-1-selective which demonstrates systematic tolerability more than non-selective beta-blockers such as timolol. Topical application of Betaxolol is associated with stinging up to 30-40% of patients that limits its use as a first choice beta-blocker [2]. Although Propranolol hydrochloride is a beta-blocker and can be used for the treatment of glaucoma the ocular hypotensive effect of Propranolol was reported in patients with various

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types of open-angle glaucoma [3]. The effective ocular delivery system for Propranolol can introduce a new beta-blocker for the treatment of IOP with good tolerability. Providing and maintaining an efficient drug concentration in the precorneal area of the eye is one of the most challenging problems of ocular drug delivery [3,4]. Many drugs that are manufactured in solution formulations display poor penetration through the corneal barrier. When a drug in solution form is instilled in the eye, initially the rate of its diffusion from the tear fluid to ocular tissues is high, but it rapidly declines. This phenomenon may result in a transient period of overdose which is associated with an increase in the risk of side-effects. Rapid nasolacrimal drainage of the instilled drug may lead to a short duration of action. Most of the instilled drug is lost within the first 15-30 seconds after instillation, and less than 3-5% of the drug penetrates the cornea and reaches the intraocular area that may result in a long duration of sub-therapeutic levels before the next dose is administered [5]. This indicates the need for an ocular drug delivery system that has the convenience of a drop but will serve as a slow-release depot [6]. Colloidal dosage forms such as nanoparticles, liposomes, and microemulsions have been widely explored to overcome various static and dynamic barriers of the eye [7].

Liposomes are spherical vesicles consisting of amphiphilic lipids, enclosing an aqueous core. Liposomes, first described by Bangham, are biocompatible and biodegradable phospholipids microcapsules which have been considered as good candidates for the encapsulation and delivery of pharmacological agents [8-10]. Liposomes have been used for ocular delivery of different drugs such as ciprofloxacin [11], Timolol [12], gene therapy [13], Acetazolamide [14], and Tacrolimus [15]. Liposomes have been applied for the treatment of anterior and posterior eye disorders. Liposomes improve drug delivery to anterior and posterior segments by increasing cornea adhesion, permeation through the cornea, and decrease drug clearance [16]. In this study, the application of thermo-responsive factors (pluronic) can lead to longer drug residence periods in the eye because the new formulation would form the gel structure at the body temperature. Therefore, a liposome consisting of pluronic as a thermoresponsive polymer will be of great interest to increase the ocular bioavailability of Propranolol hydrochloride.

MATERIALS AND METHODS

Materials

Propranolol hydrochloride was purchased

from Hakim industrial Company (Tehran, Iran). Phosphatidylcholine, Cholesterol, Pluronic F-127, Ethanol, and chloroform were purchased from Merck (Germany). Stearylamine was purchased from Fluka (Germany). 12 kDa Cellulose acetate membranes were provided from Toba Azma, (Tehran, Iran). All other materials were of the highest quality commercially available.

Propranolol hydrochloride assay method

For determination of drug concentration in loading and release tests, UV spectroscopy (Cecil, England) was used at the wavelength of 289 nm. Selectivity, accuracy, precision, repeatability and the limit of quantification (LOQ) were evaluated as validity tests.

Experimental design for preparation of liposomes and permeation

Final properties of liposome and permeation through the cornea can be affected by several factors. 3 variables at 2 levels full-factorial method was used for experimental design. Method of Liposome preparation, lipids ratio, and drug amount were our three explored variables (Table 1). Drug loading, particle size, and drug release were selected as dependent variables. According to full-factorial design, 8 formulations were prepared and their characterizations were described. Table 1 shows independent variables and levels for all 16 formulations.

Table 1. Independent variables and levels

variable	Variable's level	
	+	-
Lipid ratio (C:L:S)	1:1:0.1	1.5:0.5:0.5
Drug/Lipid ratio	0.2	0.1
method	2	1

(-): the low amounts or ratio

(+): the high amounts or ratio

2: the high pressure homogenization method

1: the Solvent Evaporation Method

C: L: S indicates cholesterol: lecithin: stearylamine ratio

Liposomes preparation

Liposomes were prepared by solvent evaporation and homogenization methods

Solvent evaporation method

Lipids consisting of cholesterol, lecithin, and stearylamine with a definite ratio were dissolved in the organic solvent (chloroform). Afterward, the lipid solution was kept in a rotary evaporator (Buchi, Switzerland) for 2 hours at 50°C and an average rate of 40 rpm. The organic solvent was

completely removed under vacuum conditions until a thin lipid film formed. The film was hydrated with the Propranolol hydrochloride 0.2-0.4 % aqueous solution. After proper handshaking for about 20 minutes, the suspension was kept in the refrigerator for 30 minutes and then sonicated (Elma, Germany) to achieve the desired particle size [17].

Homogenization method

In this method, all lipids were dissolved in ethanol. The drug was dissolved in phosphate buffer (pH=7) separately and added to the ethanolic phase. This mixture was homogenized at the rate of 7000 rpm for 5 minutes and then sonicated several definite times. Finally, the suspension homogenized 3 times under 15000 bar pressure with High Pressure Homogenizer [18].

Preparation of the hydrogel

The cold method that was previously described by Soga et al [19] was used for the production of the hydrogel. 1.65 g pluronic was mixed with 10 ml PBS (pH 7.4) aqueous solution in flat-bottomed glass vials for 24 h at 4 °C until the pluronic was dissolved.

Preparation of liposomal gel

The defined amount of pluronic was added to Propranolol hydrochloride-loaded liposomes in flat-bottomed glass vials and mixed for 24 hr at 4 °C with the magnetic stirrer until the pluronic was dissolved and a clear solution was provided.

Phase transition behavior

The gelation temperature of the liposomal gel was measured by determining the optical transmittance at 500 nm over a range of the temperature at a rate of 0.2 °C/min by ultraviolet-visible spectrophotometer (Cecil, England) [20].

Determination of propranolol hydrochloride entrapment efficacy (EE%)

The liposomal suspension containing propranolol hydrochloride was significantly separated from the untrapped drug by centrifuging (MPW, Poland) 10ml of the suspension for 30 minutes at 30000rpm and 4 °C. The supernatant was analyzed for drug content at 289 nm on a UV spectrophotometer. The blank sample for this evaluation with a UV spectrophotometer was the supernatant of a drug-free liposome with the same compositions. By subtraction of unloaded drug from the total amount, the major amount of loaded drug achieves [21].

EE% is expressed as a percentage of total drug content by the following equation:

$$EE\% = \frac{\text{Total drug amount} - \text{Untrapped drug amount}}{\text{Total drug amount}} \times 100$$

Evaluation of bilayer structure by FT-IR

To assess the vibration band of phospholipids' hydrocarbon chain, all liposomal prepared formulations with/without drug were scanned in the range of 400-4000Cm-1 with a speed of 2cm/second with the resolution of 4cm-1 [22].

Liposomes particle size:

Particle size and polydispersity index of the liposomes, were determined by Dynamic Light Scattering system with the laser beam of He-Ne (Malvern, England). [23].

Liposome morphology examination

The morphology of liposomes was evaluated by Atomic Forced Microscopy (AFM) (NanoWizard II, JPK Company, Germany). 5 µL of the liposome was loaded in the split mica disk and AFM images were obtained in tapping mode and the average speed was 5 Hz.

Liposomes stability

To test stability, liposomes were stored for 3 months at 30 ° and 65% of relative humidity. A dramatic decrease in loading capacity or formation of cake in the suspension and also change in particle size and morphology is considered a sign of instability [24].

In-vitro Drug release studies

Drug release from liposomes

Liposomes were separated by centrifuging 10 ml of formulation for 15 minutes at 12000 rpm. The under lipid phase was diluted with 5 ml of phosphate buffer and used as a donor phase on a static diffusion cell (Malekteb, Tehran). PBS buffer (pH=7) was used as a receiver phase. In the following step, the amount of drugs passed through the acetate cellulose membrane was estimated for 60 hours. Cumulative permeated propranolol hydrochloride versus time curve shows the release pattern of the drug from thermo-responsible liposome formulation [23].

Drug release from liposomal hydrogel

For this purpose, 1 ml of Propranolol hydrochloride-loaded liposomes dispersed in 3 ml of pluronic solution and was placed in the pre-weighted glass tube and then stored in a water bath (37 °C) until a clear gel formed. The weight of each tube plus liposomal hydrogel was recorded. 3 ml of PBS buffer pre-equilibrated at 37 °C as the release medium was layered over the surface of the liposomal hydrogel. The tube was shaken at

Table 2. composition of liposomal formulations based on factorial design

Formulation No.	Variable levels	Lipids Ratio			DRUG/lipid	method
		Cholesterol	lecithin	Stearylamine		
1	--+	1.5	0.5	0.05	0.1	2
2	-++	1.5	0.5	0.05	0.2	2
3	+++	1	1	0.1	0.1	2
4	+++	1	1	0.1	0.2	2
5	---	1.5	0.5	0.05	0.1	1
6	+-	1	1	0.1	0.1	1
7	-+-	1.5	0.5	0.05	0.2	1
8	+-	1	1	0.1	0.2	1

37 °C and at predetermined intervals, the total release medium was removed and replaced with a fresh release medium. Again the weight of the tube plus liposomal hydrogel was recorded to evaluate the weight of gel dissolved [25].

Drug release kinetics study

The kinetics of drug release from the liposomal gel (as final dosage form) was evaluated by the fitting of the experimental data including the amount of released drug against time to the different mathematical models describing the kinetics behavior of drug release [25].

Drug permeability through isolated Rabbit cornea

The study was approved and following the guidelines for animal use by the ethics committee of the Vice Chancellor for Research and Technology of Ahvaz Jundishapur University of Medical Sciences (Approval No. N30). In vivo experiment was performed on male adult rabbits weighing 2.5-3kg which were provided by the Animals Care and Breeding Center of Ahvaz Jundishapur University of Medical Sciences. The cornea was separated from newly sacrificed rabbits with intravenous ketamine injection. Fresh corneas were excised, weighed, and maintained in glutathione bicarbonate ringer (GBR) buffer. The removed cornea was mounted on the diffusion cell (MalekTeb, Iran). It must be considered that the cornea (diffusion cell section 0.7cm², receiver, and donor volume of 11 and 0.7 ml, respectively) should cover the diffusion cell completely with the face-up. At first, receptor and donor phases were filled with GBR buffer and cornea oxygenation performed by a mix of 95% O₂ / 5% CO₂, bubbled across each phase for 15 min. thereafter, the donor phase was replaced with 0.7 ml of liposomal formulation and 11 ml of fresh GBR buffer was used to fill the receptor. During the experiments, cells were stirred in a water bath at 34 °C and 100 rpm. At each interval (0.5, 1, 2, 3, 4, 5 hours)

a volume of 1 ml was removed from the receiver phase and an equal volume of fresh GBR buffer was replaced. The concentration of permeated propranolol hydrochloride was determined based on UV spectrophotometer absorbance and then the percentage of drug permeated after 5 h was calculated and compared with an aqueous solution of Propranolol hydrochloride with the same concentration as a control.

Data analysis and statistics

The two-way t-test or variance analysis was used as statistical analysis in experimental design to determination of the relation between dependent and independent variables.

RESULTS AND DISCUSSION

Liposomal formulations based on full-factorial design

Based on full-factorial design, provided by using three variables on two levels eight formulations were prepared. Some properties of the formulations are summarized in Table 2.

Liposome characterization

%EE of liposomes

The determination of loading efficiency is essential for the assessment of therapeutic efficiency. In this experiment, EE% was estimated for all formulations Presented in Table 3. A significant direct relation was found between with the lipids ratio (p=0.006). The higher amount of Licetin caused higher EE%. The EE% of Propranolol hydrochloride was 34-66% that may be an acceptable value for a water-soluble molecule. The low encapsulation efficiency of water-soluble drugs in liposomes has been reported previously [26]. Because of the hydrophilic property of Propranolol hydrochloride, the %EE is mainly dependent on the capture volume in the liposome's internal aqueous phase. Arumugam and co-workers increased the %EE of rivastigmine

tartrate as a water-soluble molecule by increasing the internal aqueous volume which was associated with the increase in liposomal particle size [27]. But high liposomal particle size may decrease ocular penetration. Although propranolol hydrochloride is a water-soluble drug, it seems that also trapped in spaces between bilayers due to a higher amount of sterylamine as polar lipids.

Table 3. EE% and particle size of different liposomal formulations based on the factorial design (Mean ± SD, N=5)

Batch No	particle size (nm)	EE%
1	195.7 ± 20.6	34.64±1.16
2	210.3±19.3	39.68±2.22
3	177.3± 16.6	65.31±3.77
4	190.6 ± 14.6	59.92±2.47
5	346.4 ± 28.52	36.32±4.42
6	297.2 ± 22.4	47.75±3.35
7	266.2± 20.5	35.08±2.22
8	374.6 ± 29.1	64.47±0.86

Liposome’s particle size

Table 3 presents the results of the mean particle size of all prepared formulations. In this study, the effect of independent variables on the mean particle size of the liposomal formulations was evaluated. The following equation demonstrates the regression between independent variables and the particle size:

(Equation1)

$$\text{Particle size (nm)} = 3.73 - 1.69 \text{ lipid ratio} + 0.790 \text{ pluronic/lipid} - 0.132 \text{ Drug/lipid}$$

Among the three independent variables, only the method of liposome preparation showed a significant relation with particle size. The homogenization technique produces vesicles with lower particle size than the solvent evaporation method.

In vitro drug release study:

Drug release from liposomes

The percent of drug release was plotted against time and to determine the effect of independent variables on drug release and recognition the difference between formulations regarding release profile, the percentage of the released drug after 1 hour (D1) and 24 hours (D24) were measured. . D1 concerns with the rapid release of the component whereas D24 indicates a slow release rate. Fig 1 presents information about release studies for liposomes prepared in this study. The highest and lowest values of D1 were 3.45 and 1.17% provided by formulations 1 and 8, respectively. These data indicate that no burst release has been found that is a good criterion for mucoadhesive long-acting formulation. On the other hand, the highest

and lowest values of D24 were 69.44 and 27.2% provided by formulations 1 and 6, respectively. The higher amount of D24 is required for providing sufficient drug concentration in anterior and posterior segments. Therefore formulation 1 with the highest value of D24 can be introduced as the best liposomal formulation based on release results. The high amount of cholesterol as a natural lipid and using high pressure homogenization technique for liposomes preparation provided the lowest drug release.

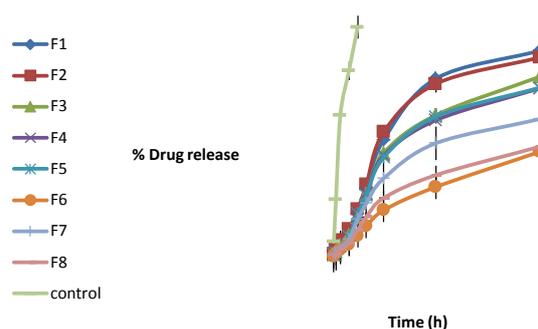


Fig 1. Propranolol hydrochloride release profiles from different liposomal formulations based on the factorial design (Mean±SD, n=5)

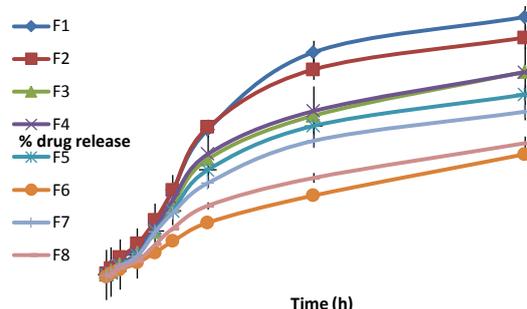


Fig 2. Propranolol hydrochloride release profiles from different liposomal hydrogel formulations based on the factorial design (Mean±SD, n=5)

Results analysis indicates that lipid ratio has an indirect significant relation with D2 (p=0.024), and D24 (p=0.012), and the similar effect of method of preparation on D1 (0.028) and D24 (p=0.019) was found. Cholesterol as a natural lipid decreased Propranolol hydrochloride diffusion through bilayer that finally caused lower drug release. The previous study showed that cholesterol increased the retention of entrapped drugs by modulating the fluidity of the liposome membrane [28]. On the other hand, the drug control solution passed through the dialysis membrane after almost 3 hours, indicating that crossing the dialysis membrane was not a limiting step in drug release and the release phase was slower than the drug

permeability through the membrane.

Drug release from liposomal hydrogel

Drug release profiles from different formulations are illustrated in Fig 2. Drug release profiles from liposomal hydrogels in the pattern are similar to drug release from liposomes but in lower amounts. The hydrogel is a semisolid formulation that drug diffusion in it is slower than liposome. The amounts of D1 and D24 in all liposomal hydrogels were lower than liposome formulations. All hydrogels demonstrated a sustained drug release pattern. Formulation No 1 with D1=3, and D24=58 also is the best liposomal hydrogel in drug release property. The results of fitting release data in three kinetic models zero order, first order, and Higuchi are presented in Table 4. The Higuchi model was more consistent with the release profile. It means that drug release was controlled by diffusion which depends mainly on the drug concentration gradient and the structure of the liposomal hydrogel. It seems that hydrogel dissolution is not a rate-limiting step in propranolol release through hydrogel and the rate of dissolution is lower than the rate of diffusion. The Higuchi was reported as the main mechanism in Propranolol hydrochloride release from solid lipid nanoparticles [29] .

Optimized liposomal hydrogel composition and evaluation

Optimization was done based on a checkpoint analysis to confirm the role of a polynomial equation in predicting the responses. Optimization was performed to finding the formulation that would obtain a maximum value of EE%, minimum particle size, and high D24. Based on obtained results, liposomal formulation 3 dispersed in the hydrogel was selected as an optimized liposomal hydrogel.

Then the characters of this optimized liposomal hydrogel such morphology, FT-IR spectrum, stability, phase transition, the release profiles

obtained by different concentrations of polymers, and permeability through excised cornea were evaluated.

FT-IR results

FT-IR is a non-perturbing technique, to evaluate the bi-layer structure of phospholipids by analyzing the frequency and bandwidth of vibrational modes belonging to the functional groups. Fig 3 shows the FT-IR spectra of the optimized liposomal hydrogel with the drug, and pluronic F-127 hydrogel, and pure propranolol HCL FT-IR spectra. Two main vibrational bands were found in the spectra of liposomes. A band at 3300-3500 cm-1 in the spectra is attributed to the CH2 stretching vibration of phospholipid acyl chains [18]. Another band is seen at 1600- 1800 cm-1 representing the carbonyl (C=O) stretching in the head group of the phospholipids [30, 21].

The vibrational bands of the bilayer did not change between formulations produced by the homogenization technique. It means that the physical state of bilayers did not change by independent variables. But for hydration technique, the direct and significant correlation between the percentage of pluronic and wave number of OH group in the polar head and so band slightly shifted to a higher frequency that is the reason for sol phase formation and membrane instability. It seems that in hydration techniques that a higher amount of water used, the polar group in bilayers expanded and interacted strongly with pluronic.

Liposome stability

Different physicochemical parameters can induce instability for liposomes. Oxidation and hydrolytic reaction are introduced as the main reasons for chemical instability. Low temperature storing, and protection against light can avoid instability. Liposome stability can be provided by

Table 4. correlation coefficient (r2) and release rate constant (k) of propranolol hydrochloride from liposomal hydrogel formulations in different kinetics models

Batch No	Zero-order		First-order		Higuchi	
	r ²	k	r ²	k	r ²	k
1	0.86	0.015	0.92	0.025	0.96	0.125
2	0.83	0.014	0.901	0.023	0.97	0.115
3	0.82	0.011	0.91	0.02	0.95	0.09
4	0.84	0.009	0.9	0.018	0.94	0.088
5	0.88	0.0087	0.93	0.019	0.97	0.076
6	0.94	0.0067	0.95	0.008	0.99	0.05
7	0.89	0.009	0.92	0.13	0.96	0.077
8	0.92	0.007	0.94	0.009	0.98	0.06

PH adjustment, temperature, ionic interaction, and application of cholesterol in bilayer structure. In this study, liposomes were stored at 30 ° and relative humidity 65% for 3 months. After 3 months no changes in liposomes appearance was observed. The particle size of the liposomes was increased by more than 2.5% and the loading capacity was reduced by less than 3%.

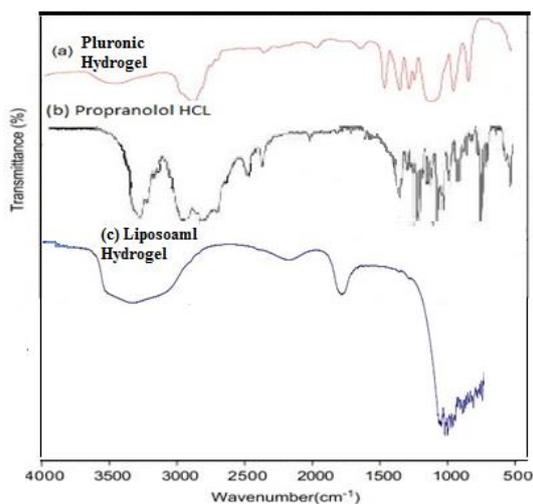


Fig 3. FT-IR spectra of F-127 hydrogel, pure propranolol HCL, and liposomal hydrogel containing propranolol HCL

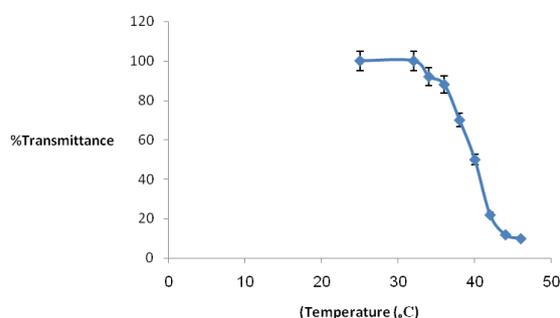


Fig 4. Temperature dependence of optimized liposomal hydrogel Transmittance

Phase transition

The relation between % Transmittance and the temperature is illustrated in Fig 4. The optimized liposomal hydrogel showed a dramatic decrease in % transmittance around 38°C. It means that hydrogel dehydrated and became hydrophobic due to the phase transition of polymer around 38°C.

The effect of polymer concentration on drug release

The percentage of drug release after 1 and 6 h (%R1, %R6) from optimized liposomal hydrogels prepared by 1, 1.5, and 2 % of polymer are shown

in table 5. Based on obtained results no significant difference was found between batch (1%) and batch (1.5%) but both of them demonstrated more drug release compared batch (2%) significantly (P<0.05). therefore 1% polymer was selected for optimized gel preparation.

Table 5. the percent of drug release from optimized liposomal hydrogel prepared by different polymer concentration (mean ±SD, n=5)

parameter	Batch (1%)	Batch (1.5%)	Batch (2%)
%R1	5.9±0.3	5.8±0.4	5.2±0.3
%R6	25.3±1.7	26.6±1.9	20.5±2.1

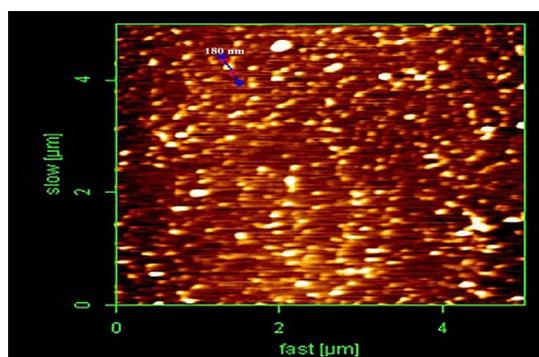


Fig 5. AFM image of optimized liposomes

Morphology of optimized liposomal formulation

As observed in Fig 5, the AFM image of optimized liposome showed vesicular structures with an average diameter of 180 nm the is following results reported by the photon correlation technique in this study. Because of force applied by AFM and convolution effect, the morphology of liposomes looks wider.

Drug permeation through rabbit cornea

The permeation profiles of formulations number 3 liposomal hydrogel, liposomal formulation, and the aqueous solution of Propranolol hydrochloride as control through excised rabbit cornea are presented in fig 6. The amount of permeated drug was measured during 5 hr for both formulations against an aqueous solution of the drug as control. The percentage of drug permeated through cornea after 5 h (Q5) was selected for assessing the effect of liposomal, and liposomal hydrogel on the permeability of cornea. The values of Q5 were improved by both formulations significantly compared to control. No significant difference was found in Q5 values provided by liposomes and liposomal hydrogels. Both formulations increased the ocular bioavailability of Propranolol hydrochloride more

than 3-folds compared with aqueous control.

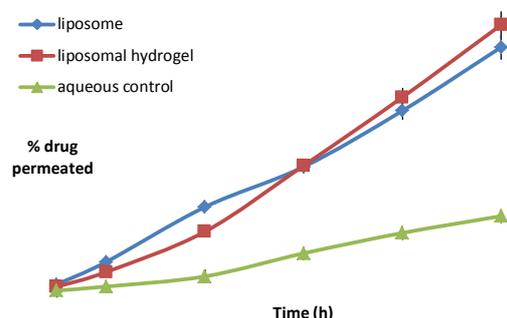


Fig 6. the permeability profiles through excised rabbit's cornea

CONCLUSION

In conclusion, thermoresponsive liposomal hydrogel formulation increased the ocular bioavailability of propranolol hydrochloride as the hydrophilic drug. It seems that the effect of liposome hydrogel was due to three reasons: delay in drug release, mucoadhesive property, and lipophilic property of liposome. Drug partitioning into the cornea is the first step for penetration that liposomal formulations by lipophilic nature increased partitioning of propranolol hydrochloride into the epithelial layer. FT-IR spectra indicated membrane stability of liposomes that decreased drug release. Drug loading efficiency for hydrophilic compounds same as propranolol hydrochloride was suitable. The drug release profile demonstrated a low burst effect and good sustained release property. On the other hand, the mucoadhesive property provided tight contact with the cornea and increased the remaining time on the surface of the cornea. This finding suggests liposomal hydrogel made by pluronic consisted of liposomes was a good carrier for sufficient delivery of Propranolol hydrochloride into the anterior and posterior segments. Sufficient drug release and drug permeation through the cornea are the reasons for the selection of pluronic based liposomal hydrogel for propranolol ocular delivery.

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