Bull. Pharm. Sci., AssiutUniversity, Vol. 48, Issue1, 2025, pp. 107-119.

Bulletin of Pharmaceutical Sciences
AssiutUniversity
Website: http://bpsa.journals.ekb.eg/

BULL. PHARM. SCI. Assiut Univ.

# ELASTIC VESICLES FOR ENHANCING THE TOPICAL REPURPOSED EFFECT OF PROPRANOLOL AGAINST *CANDIDA ALBICANS*

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*The goal of this investigation was to load transferosomes with the repurposed antifungal drug propranolol to treat candida albicans topically. The production of transferosomes for enhancing propranolol topical administration was the focus of this study. By a $2^1.3^1$ full-factorial experiment with different surfactants and phospholipid amounts, transferosomes formulas were fabricated. Transferosomes were assembled by ethanol injection approach. Transferosmes were evaluated for entrapment efficiency (EE%), particle size (PS), polydispersity index (PDI), and zeta potential (ZP). Employing Design Expert®, the optimum-formula (F3) was opted, revealing ZP of -28.15±1.11 mV, PDI of 0.476±0.001, PS of 207.05±0.45nm, and EE% of 71.00±0.94%. Further, the optimum formulation illustrated spherical transferosomes with no aggregation under transmission electron microscope inspection. In-vitro release investigation verified that the optimum formula was released in a sustained manner than propranolol solution. In addition, during storage the optimum formula was stable. The histological inspection confirmed the tolerability of the optimum transferosomes*

**Keywords:** *Propranolol; candida albicans; factorial design; transferosomes; histopathological study*

## INTRODUCTION

Drug repurposing is an approach used to find another uses for licensed or under exploratory medications that go beyond their initial prescribed use.[1] Azole compounds are the most often used antifungal bioactives due to their safety.[2] Despite azoles' exceptional therapeutic efficiency against yeasts and molds, their extensive use has led to the development of azole resistance. It is necessary to create new antifungals to solve this issue.[3]

The improvement of repurposed antifungals is the topic of several research papers. As an illustration, statins are initially identified as lipid-depressing drugs due to their ability to inhibit HMG-CoA reductase. Though, they have also been revealed to have a wide extent of antifungal actions on *Aspergillus spp*., and *Candida spp*. In addition, antidepressant medicines prove the capability to destroy azole-resistant *Candida spp*. *in-vitro* if Fluconazole is present or not. Moreover, β-receptor blockers and antiarrhythmic medications such as potassium, calcium, and sodium channel antagonists have demonstrated antifungal effectiveness against *Candida albicans*.[4] Aforementioned experiment endorsed that Propranolol might be useful against *Candida albicans*.[5] Further, previous studies Propranolol as antifungal for vaginal inection.[6] It worth mentioning that Propranolol has been opted as a drug as it has MW 259.34 g/mol, logP = 3.22, it is a BCS class 1 (it has high solubility and permeability).[7]

Skin infections have been distributed universally lately. Fungal contagions are more often appearing related to the rise in the patients because of cancer treatment, and human immunodeficiency virus infections.[8]

*Received : 4/12/2024& Accepted : 4/2/2025*

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Antifungal medicines are mostly treated by topical application or systemic oral administration. While oral management of systemic antifungals is acknowledged to be more efficient, it commonly outcomes in toxic shortcomings and boosted danger of drug interaction.[9]

Liposomes are phospholipid (PC) vesicles that have an aqueous compartment enclosed by one or more lipid bilayers. While several studies relate liposomes to topical drug administration, only a few investigations have explored the probability of topical drug delivery utilizing liposomes.[10] A novel group of vesicles identified transferosomes were presented by Cevc et al[11] as a system comprised of a PC and surfactant (SAA). Transferosomes have both hydrophilic and hydrophobic components that can surround a variety of solubility-ranging medicinal compounds. They can twist and go via the narrow constriction with no considerable loss. This high flexibility provides safer deposition of vesicles. Further, SAA can interrupt the proteins in the SC.[12] Various research have proven that topical delivery from transferosomes was efficient than from firm liposomes.

Therefore, the current study's objectives were to assess the safety of transferosomes when applied to the skin topically, as well as the potential of these vesicles to increase propranolol's topical deposition. To do that, several factors influencing the aspects of vesicles were examined using full factorial $2^1.3^1$ design and Design Expert® to determine the ideal formula. Entrapment efficiency percentage ($Y_1$), particle size ($Y_2$), polydispersity index ($Y_3$), and zeta potential ($Y_4$) were chosen as dependent factors, and SAA type ($X_1$) and PC amount (mg) ($X_2$) were examined as independent variables. The best transferosomes were assessed in terms of stability and shape. Additionally, male Wistar rats were employed in histopathology investigations of propranolol from the optimum transferosomes.

## MATERIALS AND METHODS

### Materials

Propranolol hydrochloride, phospholipid (PC) from egg yolk, Cremophor RH 40, and Cremophor EL werepurchased from Sigma Aldrich Co. (St. Louis, MO, USA). Ethanol was obtained from El-Nasr Pharmaceutical Co. (Cairo, Egypt).

### Methods

#### Preparation of propranolol transferosomes

By employing the ethanol-injection method using hot plate magnetic stirrer (MSH-20D, GmbH, Germany) [13]. Two surfactants, Cremophor RH40, and Cremophor EL with various quantities of PC were mixed to make the transferosomes. In a 2 mL ethanol, PC (100 mg), and the surfactants (Cremophor® RH40 or EL) were dispersed (10 mg). The organic mixture was included to a 10 mL hot (60 ℃) water that had formerly encompassed propranolol (170 mg). After 30 minutes of mixing at 800 rpm, the generated mix was preserved in the fridge. To acquire mature vesicles, the vesicles were stored at 4°C.[14]

#### Characterization of Propranolol transferosomes

#### Entrapment efficiency (EE%)

The transferosomes dispersion was centrifuged (20,000 rpm) using cooling-centrifuge (3-30KS; Sigma Zentrifugen, Germany) for 1 hr using centrifuge at 4°C. The pellet was then lysed in methanol and assessed at $\lambda_{max}$ 289 nm [15]via spectrophotometer (UV-1601PC; Shimadzu, Kyoto, Japan),.[16]EE% was found operating the direct method. [17]

$$EE\% = \left(\frac{ED}{TD}\right) \times 100 \quad \text{(Eq. 1)}$$

where EE% is the entrapment efficiency percentage, ED is the concentration of entrapped drug and TD is the total drug concentration.

#### Particle size (PS), polydispersity index (PDI) and zeta potential (ZP)

Via a Zetasizer (Malvern Panalytical Ltd, UK), the PS, PDI, and ZP of the transferosomes were evaluated. Following dilution, the measurements were carried out. Every measurement was done three times.[18] The ZP evaluation was carried out by monitoring the electrophoretic movement of the particles in the electrical field..

#### Measurement of the impact of formulation constraints by $2^1.3^1$ factorial design

Applying the lowest experimental runs, a $2^1.3^1$ factorial study was utilized to decide the

effect of numerous factors on the aspects of propranolol loaded transferosomes.[19] Two factors were measured in the selected, $X_1$: SAA type, and $X_2$: PC amount (mg). As dependent variables, the EE% ($Y_1$), PS ($Y_2$), PDI ($Y_3$), and ZP ($X_4$) were recognized **(Table 1)**. To fabricate propranolol loaded transferosomes, all possible formulae were tested in the experiments **(Table 1)**. The experimental data were inspected via Design Expert® to independently source the influences of these ingredients, and then ANOVA was used to estimate the significance.

**Optimization of propranolol transferosomes**

To elect which formulation should be chosen for further inspection, the desirability function was constructed. This function predicts the optimal levels of selected components. Selecting the optimal formulation amended meeting specific criteria, including reaching the lowest PS and PDI and the maximum EE%, and ZP.

**Determination of the amount of drug release**

The extent of medication released was evaluated for six hours at 37°C via the USP dissolution tester equipment II (USP) dissolution apparatus (Pharma Test, Hainburg, Germany). The optimal transferosomes were added into 2 mL samples in 3.14 $cm^2$ plastic cylindrical tubes, each of which held 5 mg of propranolol. The formulations were immersed in 50 milliliters of pH 5.5 phosphate buffer release medium.[20] At 1, 2, 3, 4, 5, and 6 hours, aliquots were eliminated and estimated at estimated $\lambda_{max}$of 289nm was used to evaluate aliquots of propranolol. Three experiments were carried out.

**Transmission electron microscopy (TEM)**

Using a transmission electron microscope TEM (JEOL JEM 1230; Tokyo, Japan), the optimal transferosomes shape was examined. A thin layer of the transferosomes was employed to a copper grid faced with carbon, dyed phosphotungstic acid 1.5%, observed, and photographed.[21]

**Effect of storage**

For forty-five days, the ideal transferosomes were kept at 4°C. At 0 and 45 days, samples were taken out. Relating the initial assessment with the values obtained after storage allowed for the estimation of stability. As previously mentioned, measurements of the EE%, PS, PDI, ZP, and Q6h (%) from the transferosomes were made. Statistical analysis was analyzed by Student's t-test.[22]

**pH assessment**

The pH of the optimum transferosomes was estimated, by a calibrated pH meter (Hanna, type 211, Romania).

***In-vitro* antifungal estimation**

The antifungal action of Propranolol counter to *Candida albicans* was tested. The minimum inhibitory concentration (MIC) was noticed employing the microdilution approach.[23]

**Histopathological study**

The examination was accredited by the ethical-committee of the Al-Ayen Iraqi University, (reference number = AUIQ-REC-A24001). Six animals were divided into two groups where groups one behaved as control, while group two were treated with the optimum transferosomes. The treatment lasted one day. After being fixed for 24 hours in 10% formol saline, skin samples were cleaned, and alcohol was used to dehydrate them. Following a 24-hours period at 56°C, the samples were cleaned, embedded in wax blocks, and sectioned at a thickness of 4 mm. After that light microscopy utilized for histological analysis.[24]

## RESULTS AND DISCUSSION

**Results**

**Analysis of factorial design**

The experimental outcomes were estimated utilizing Design Expert® to obtain independently the influence of these factors, which were then estimated utilizing ANOVA to choose the significance of each factor. The (2 FI) model was employed, and it was seen that the predicted $R^2$ agreed with the adjusted $R^2$, with reference to the design analysis in **Table 2**, all responses displayed adequate precision with a ratio superior to 4.

**Table 1:** Factorial design for Propranolol transferosomes.

| **Factors** | **Levels** | | |
|---|---|---|---|
| **$X_1$: SAA type** | Cremophor RH 40 | | Cremophor EL |
| **$X_2$: PC amount (mg)** | 100 | 200 | 300 |
| **Responses** | **Constraints** | | |
| **$Y_1$: EE (%)** | Maximize | | |
| **$Y_2$: PS (nm)** | Minimize | | |
| **$Y_3$: PDI** | Minimize | | |
| **$Y_4$: ZP (mV)** | Maximize | | |

**EE% results**

Multilayered nanosystems can be developed into an effective delivery system for the targeted or regulated release of lipophilic medications. Depending on the lipid composition, encapsulating bioactive inside phospholipid-containing formulations provides the optimal distribution, increased stability, protection, and permeability.[25]

The effect of SAA type ($X_1$) and PC amount (mg) ($X_2$) on the EE% of propranolol loaded transferosomes is explained in **Table 2,3** and **Fig. 1A-B**. EE% ranged from 32.87±0.45 to 71.00±1.00%.

The polynomial equation for EE% is: EE%=+53.69-7.19* A-7.23* B[1]+3.43* B[2]-6.40 * AB[1]+2.74* AB[2]

It is observed that SAA type ($X_1$) had a significant impact on EE% ($p<0.0001$). It has been noted that Cremophor-RH 40 was observed to generate greater EE% values than Cremophor-EL. This could be accredited to the existence of unsaturation-locations in the alkyl chains of Cremophor-EL that might improve the infiltration of the vesicle membrane, subsequently declining EE%[26]. These results were reliable with previous research in which the authors observed that bilosomes including Cremophor RH 40 encapsulated more drug than those comprising Cremophor-EL [27].

Considering PC amount (mg) ($X_2$), it has a significant effect on EE%, it was observed that EE% augmented by the increase in the PC amount from 100 mg to 300 mg. The findings were in agreement with aforementioned literature who stated that EE% increased as PC amount augmented which could be credited to the increase in the place presented for drug load in transferosomes.[20]

**Table 2:**Output of the factorial analysis of transferosomes.

| **Responses** | **EE%** | **PS (nm)** | **PDI** | **ZP (mV)** |
|---|---|---|---|---|
| **Adjusted $R^2$** | 0.9057 | 0.9946 | 0.5471 | 0.9823 |
| **Predicted $R^2$** | 0.7943 | 0.9882 | 0.0119 | 0.9614 |
| **Adequate precision** | 12.426 | 56.794 | 5.518 | 29.585 |
| **Significant factors** | $X_1$, $X_2$ | $X_1$, $X_2$ | - | $X_1$, $X_2$ |
| **Predicted value of optimum formula (F3)** | 70.90 | 200.7 | 0.476 | -28.15 |
| **Observed value of optimum formula (F3)** | 71.00 | 200.00 | 0.475 | -28.00 |

**Table 3:** Experimental runs of the factorial design of transferosomes.

| | **SAA type** | **PC amount (mg)** | **EE%** | **PS (nm)** | **PDI** | **ZP (mV)** |
|---|---|---|---|---|---|---|
| F1 | Cremophor RH 40 | 100 | 60.05±1.92 | 117.10±1.80 | 0.510±0.005 | -20.05±0.05 |
| F2 | Cremophor RH 40 | 200 | 65.57±4.43 | 186.90±5.00 | 0.568±0.006 | -24.05±0.05 |
| F3 | Cremophor RH 40 | 300 | 71.00±1.00 | 200.70±0.10 | 0.476±0.001 | -28.15±0.15 |
| F4 | Cremophor EL | 100 | 32.87±0.45 | 145.00±0.50 | 0.558±0.084 | -17.50±0.50 |
| F5 | Cremophor EL | 200 | 52.67±0.41 | 198.50±0.00 | 0.516±0.005 | -24.50±0.50 |
| F6 | Cremophor EL | 300 | 63.96±2.71 | 243.25±1.95 | 0.544±0.006 | -26.50±0.50 |

**PS results**

The mean diameter of the vesicles is implied by the z-average diameter[28] was evaluated and presented in **Table2,3** and graphically illustrated in **Fig. 1 (C-D)**. The PS of the nano- system might impact the degree of medication deposition as well as skin penetration.[29] PS ranged from 117.10±1.80 to 243.25±1.95 nm. It is obvious that SAA type ($X_1$) and PC amount (mg) ($X_2$), affected significantly ($p<0.0001$) the PS.

The polynomial equation of PS was as follows:

PS (nm)= +181.91+13.67* A-50.86* B[1]+10.79* B[2]+0.27* AB[1]-7.87 * AB[2]

For SAA type ($X_1$), it was found that Cremophor EL generated a larger PS than Cremophor RH40. This was in agreement with previous literature, as both SAAs are assembled with hydrophilic and hydrophobic parts. The hydrophilic parts of both SAAs are responsible for decreasing vesicle aggregation and are built of polyethylene oxide (PEO) units with 40 PEO parts for Cremophor RH 40 and only 35 PEO units for Cremophor[30] Accordingly, the engagement of the previous Cremophor which has a more stabilizing capability led to the arrangement of smaller PS, the preceding outcomes agreed with former research.[31]

For PC amount (mg) ($X_2$), it was observed that PS increased by rising the quantity of PC from 100 mg to 300 mg. These findings could be due to the fact that at a high PC level, the quantity of SAA will not be sufficient to decrease the interfacial-tension indicating to the establishment of larger transferosomes.[19]

**PDI results**

The width of size distributions is determined by the PDI. Further, PDI was determined and depicted in **Table 2,3** and **Fig. 2 (A-B)**. PDI ranged from 0.476±0.001to 0.568±0.006. A homogeneous distribution shows a value of 0, whereas a totally polydisperse nanoparticles is implied by a value of 1. A PDI that is considered acceptable should be less than 0.5. The produced vesicles' polydispersity indices were often minimal, as can be seen from the data, indicating strong homogeneity and a narrow size distribution. [32]

The polynomial equation for PDI is:

PDI= +0.55-5.917E-003* A-0.011* B[1]+0.047* B[2]+0.030 * AB[1]-0.070* AB[2]

Analysis displayed that both factors SAA type ($X_1$), PC amount (mg) ($X_2$) showed no significant effect on PDI ($p=0.691$, and 0.129, respectively).

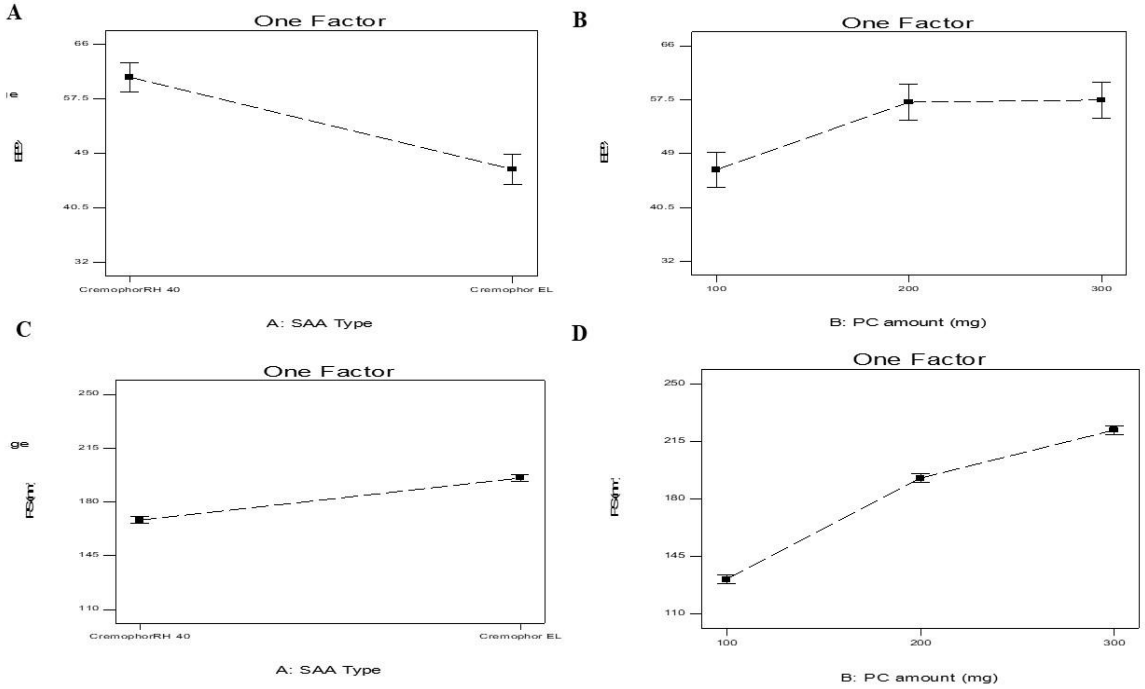


**Fig. 1:** Effect of SAA type ($X_1$) and PC amount (mg) ($X_2$) on EE%, and PS on transferosomes.

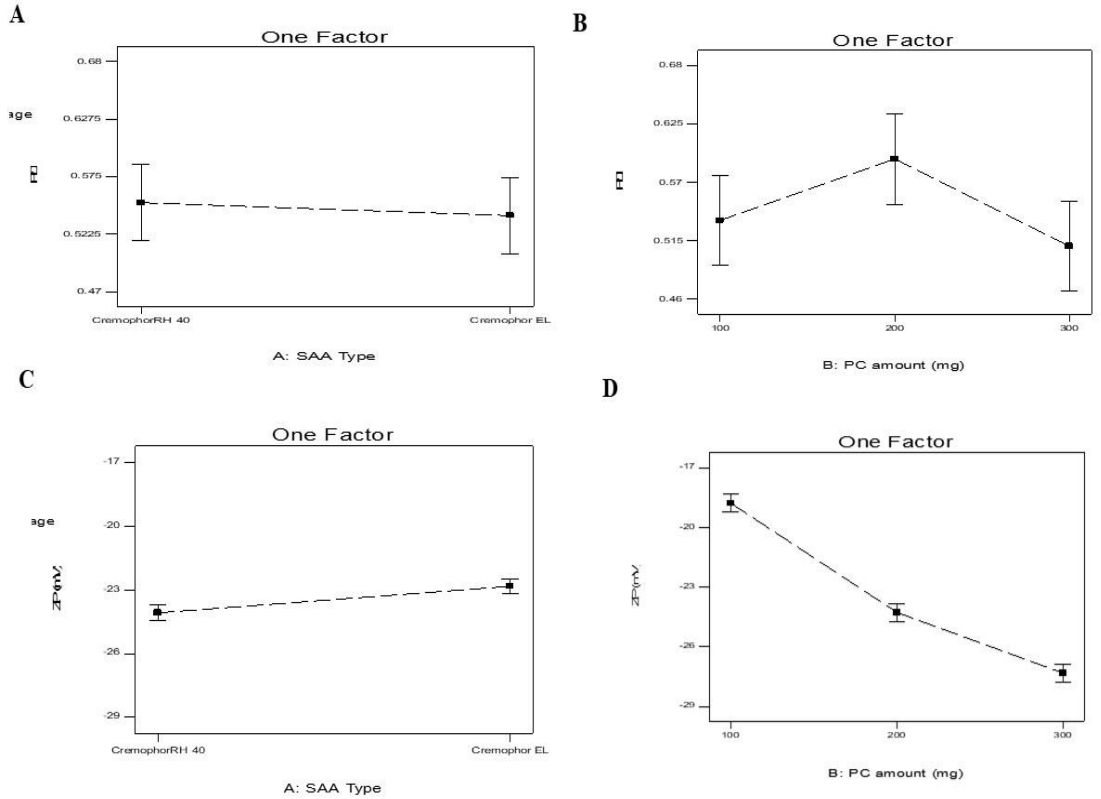


**Fig.2:**Effect of SAA type ($X_1$) and PC amount ($X_2$) on PDI, and ZP on transferosomes.

**ZP results**

ZP ranged from -17.50±0.50 to -28.15±0.15mV. Colloidal particles with (≥|15|mV) are predictable to be constant due to steric reasons.[33] For SAA type ($X_1$), it was found that Cremophor-RH 40 produced higher ZP values related to Cremophor EL, the previous results agreed with previous literature during the preparation of glyceryl monooleate-based nanoparticles for enhancing topical transport of finasteride.[34]

PC amount (mg) ($X_2$), it was found that by augmenting the amount of PC the absolute negative ZP increased. Though PC are zwitterionic and thus hypothetically uncharged, they afford increase to negative ZP. This has been explained due to hydration sheets created covering the surface and the direction of lipid groups.[35]Previous research [36] claimed that the PC charge is attributable to the orientation of the dipole linking the negative phosphatidyl group and the positive choline group in the lipid. It was informed that the head is positioned in a behavior that the phosphatidyl-group is in the outer surface with the choline-group inward in the head group causing in a negative charge.

**Election of the optimized formula**

A set of criteria was first established in the Design Expert® to choose the best formula. Transferosomes having the highest EE%, ZP and lowest PS and PDI were given preference according to these parameters. The primary effects of these parameters were separately found through the use of Design Expert® to examine the experimental data. ANOVA was then performed to ascertain the importance of each element. The formula that satisfied the predetermined criteria was the best one. The optimum transferosomes (F3) had a ZP of -28.15±1.11 mV, PDI of 0.467±0.001, PS of 207.00±0.10nm, and EE% of 71.00±1.00%. The expected and examined responses of were assessed and are displayed in **Table 2** to confirm the authenticity of our testing. There was a strong association found involving the actual and anticipated values for the optimum formula F3 that is composed of 300 mg phospholipid and Cremophor RH40.

**Characterization of the optimum formula**

***In-vitro* drug release**

When anticipating a drug's *in-vivo* performance, the release profile is crucial value. High surface area and a faster rate of disintegration are the outcomes of PS

decrease.[37] Q6h for the optimum trasnsferosomes (F3) and propranolol solution is displayed in **Fig. 3**. Additionally, the results implied that the optimum transferosomes containing 300 mg PC showed a sustained release percent compared to propranolol solution.

Antimicrobial topical management by nanocarriers has proved effectiveness in treating topical microbial infections. A favorable medicine transport approach for anti-microbials is nanocarriers, which offer long release duration. They could interact with the biological surroundings and improve effectiveness *in-vivo* credited to their small size and sensitivity to charge modification. [38]From **Fig. 3** it was noticeable the release from F3 was fast then significantly ($p = 0.003$) diminished in a prolonged way associated to propranolol solution as propranolol was entirely released from propranolol solution after 1 h. The aforementioned results might be related to, firstly: propranolol is hydrophilic therefore its hydrophilic characteristics results in better release from propranolol solution. Further, the existence of PC forms a drug-PC complex inside the transferosomes, which propose the opportunity of constantly releasing propranolol in a sustained way from transferosomes that proposes a store for attacking microbial infection.[39]

**Morphology of vesicles**

TEM examination was utilized to inspect the shape of the acquired optimum transferosmes. The morphological shape revealed that they were spherical and had a reliable size distribution **(Fig. 4)**. The Zetasizer-determined transferosmes sizes did match the TEM data fairly well.

**Effect of storage**

During storage, lipid nanoparticles formulations have a capacity to combine and disintegrate, modifying PS, PDI, and ZP. Additionally, these modifications result in a decrease in the EE% and medication leakage from the vesicles.[40] Transferosomes (F3) were visually inspected for aggregation and appearance changes. Furthermore, it was determined what EE% of 71.89±2.00, PS of 203.00±2.00 nm, PDI of 0.478±0.002, ZP of -26.60±1.500 mV, and Q6h of 68.25±3.10%. After 45 days at 4°C, statistical analysis explained that there was no significant change relating the fresh and preserved transferosomes by comparing EE%, PS, PDI, ZP and Q6h. These results suggest that the ideal optimum transferosomes are stable.

**pH measurement**

The inspected pH assessments for optimum transferosomes ranged from 5.20 ± 0.21 to 5.12 ± 0.24, which is regarded as appropriate for topical treatment on skin.[41]

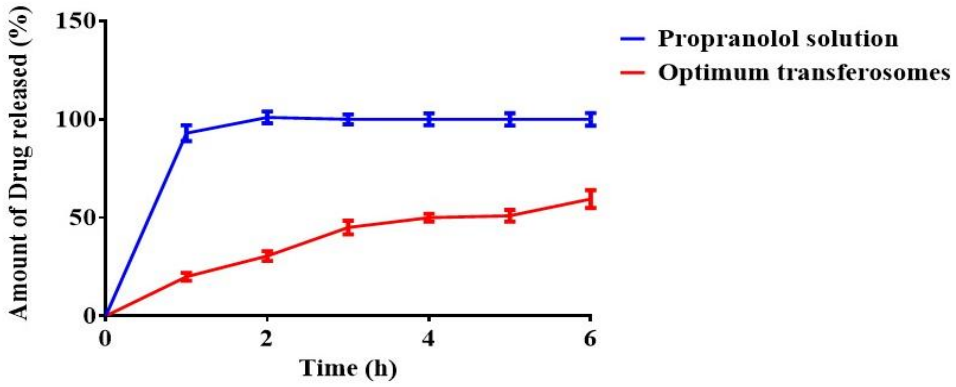


**Fig. 3:** *In-vitro* drug release for propranolol and the optimum formula (F3).

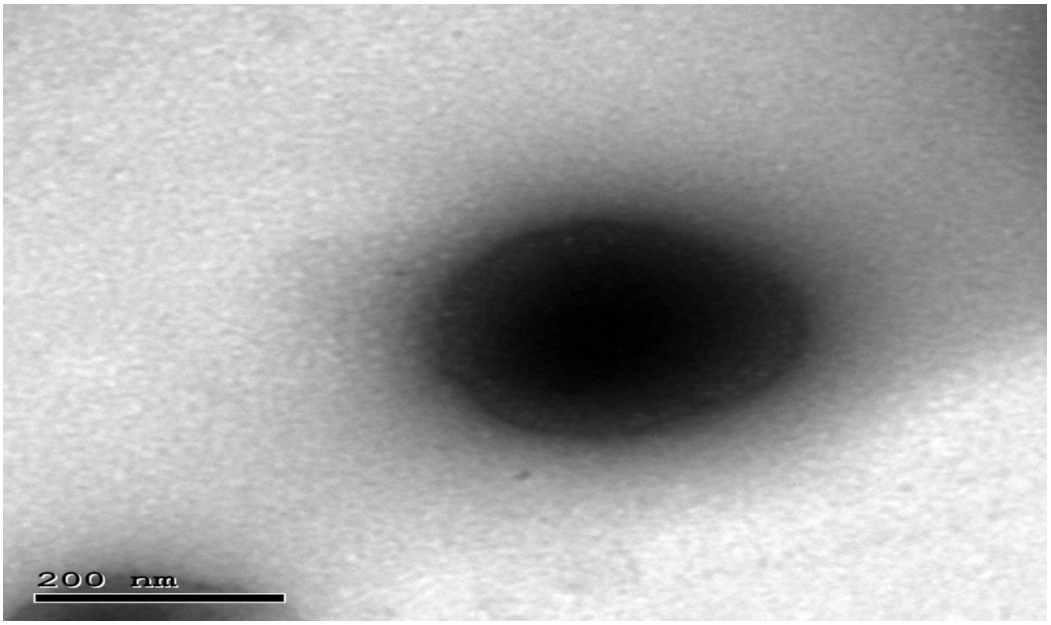


**Fig.4:** Transmission electron micrograph for the transferosomes.

***In-vitro* antifungal assessment**

Propranolol demonstrated promising antifungal action against *Candida albicans* with MIC of 1.7825 ± 0.2 mg/ml, this result suggests that propranolol has some antifungal potential, as it can inhibit the growth of *Candida albicans* at a concentration around 1.78 mg/ml. This finding suggests that propranolol could be a candidate for further research in antifungal therapy, particularly for drug repurposing in the treatment of superficial or systemic fungal infections. Although propranolol is not primarily used as an antifungal, its potential in this area suggests that repurposing known drugs could treat fungal infections, especially in patients who may not respond to antifungals. However, more studies are needed to confirm its effectiveness and mechanism of action before it can be considered for clinical use.

**Histopathological study**

Permeation enhancers are thought to be a key obstacle to topical delivery due to skin irritation.[41] When associated with untreated skin sections (group I), microscope analysis of groups II which were treated with the optimum transferosomes, respectively, proved no histological modifications in epidermal and dermal cells **(Fig. 5)**. These outcomes prove that the optimum transferosomes formulation had a reasonable level of tolerability.

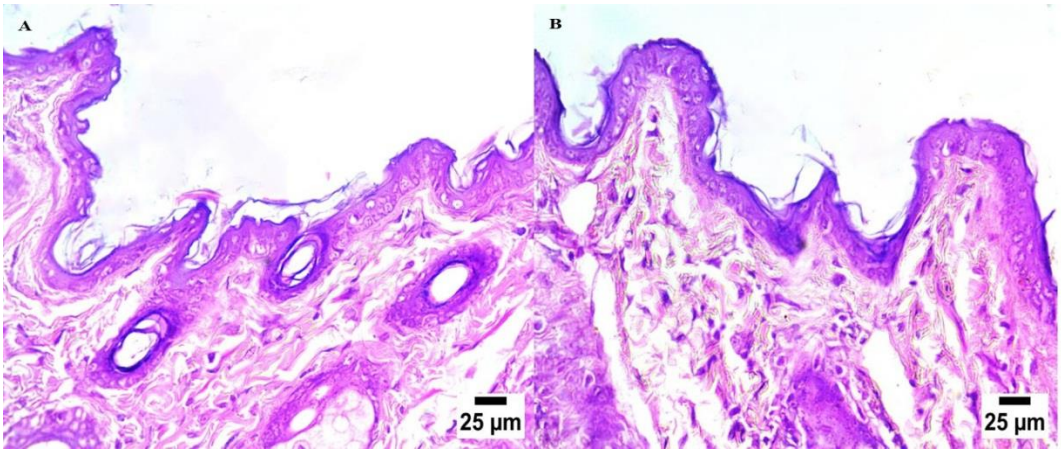


**Fig. 5:** Histopathological study for the optimum transferosomes (F3) (b) compared to the negative control (a).

**Conclusion**

In this investigation, transferosomes were created as a topical propranolol delivery drug. In accordance with the $2^1.3^1$ factorial design, formulations were created using the ethanol injection process. These formulations were then utilized to choose the best nano formula, which had spherical morphology, a sufficient drug EE%, minimal PS, PDI and good ZP values. The optimum formula was stable during storage period. The *in-vitro* release investigation proven the sustained-release of propranolol from the optimum formula related to drug solution. Additionally, the *in-vivo* histological investigation confirmed that optimum formula did not cause irritation when applied to rat skin. The results consequently implied that transferosomes applied topically without any irritation could be regarded as a potential topical administration strategy. To verify that transferosomes are therapeutically valuable in humans, more research is essential.

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Bull. Pharm. Sci., Assiut University, Vol. 48, Issue 1, 2025, pp. 107-119.

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# الحويصلات المرنة لتعزيز التأثير الموضعي لإعادة استخدام بروبرانولول ضد المبيضات البيضاء

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يهدف البحث الحالي إلى تحميل بروبرانولول، وهو عامل مضاد للفطريات مُعاد استخدامه، في الجسيمات الناقلة لعلاج فطر الكانديدا موضعياً. بروبرانولول هو دواء مضاد للفطريات. كان الهدف من الدراسه استخدام الناقلات النانومتريه لتحسين التوزيع الموضعي للبروبرانولول هو محور هذه الدراسة. وباستخدام التصميم العاملي الكامل ٢١,٣١ وكميات مختلفة من المواد الخافضة للتوتر السطحي والدهون الفوسفورية، تم إنشاء صيغ الناقلات النانومتريه. تم تصنيع الناقلات النانومتريه باستخدام طريقة حقن الإيثانول. تم تقييم الناقلات النانومتريه حول نسبة كفاءة التحوصل الدوائي (EE٪)، وحجم الجسيمات (PS)، ومؤشر تعدد التشتت (PDI)، وجهد زيتا (ZP). وأجريت المزيد من الاستكشافات على الصياغة الأمثل. باستخدام برنامج Design Expert®، تم تحديد الصيغة المثلى (F3)، حيث كشفت عن ZP قدره −٢٨,١٥±١,١١ مللي فولت، وPDI قدره ٠,٤٧٦±٠,٠٠١، و207.05±0.45 PS نانومتر، و EE% 71.00±0.94%. علاوة على ذلك، أظهرت الصيغة المثالية وجود جسيمات ناقلة كروية دون تجميع تحت تقييم المجهر الإلكتروني النافذ. أظهرت دراسة التحرر في المختبر أن الصيغة المثالية تم إطلاقها بطريقة مستدامة مقارنة بمحلول البروبرانولول. بالإضافة إلى ذلك، أثناء التخزين كانت الصيغة المثلى مستقرة. كما اثبت التحقق النسيجي من سلامة الترانسوسومات المثلى.