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Optimization of Liposomal Formulations Using Design of Experiments (DOE) For Enhanced Skin Penetration of Anti-Aging Compounds

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Abstract

Liposomal drug delivery systems have been developed as a potential favourite to ameliorate the dermal delivery of the anti-aging substances because they are biocompatible, have the capacity to bind both hydrophilic and lipophilic drugs and possess the ability to boost targeted treatments. In this work the systematic study was done to optimize liposomal formulations against skin penetration by application of Design of Experiments (DoE) approach. The factorial design was used to optimize various formulation parameters such as phospholipid concentration, cholesterol content and hydration time and their influence on the effect on vesicle size, entrapment efficiency and in-vitro skin penetration established. The statistical analysis indicated there was important interaction among the variables and therefore optimal formulation was defined using the technique and it performed better in terms of skin permeation behavior. The findings indicate the effectiveness of the DoE strategy in the development of formulation and the potential of optimized liposomes as a delivery vehicle to anti-aging products.

Key Words:

Liposomes, Design of Experiments, Skin penetration, Anti-aging compounds, Formulation optimization, Dermal delivery

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1. INTRODUCTION

This has been due to the increasing need to develop effective and safe anti-aging skincare products that have been largely brought about by the rising demand of the same. Out of these, liposomal systems have come to the fore with their capability of encapsulating various bioactive ligands and shielding them against degradation as well as allowing them to penetrate into the deeper layers of

the skin[1]. Nevertheless, several variables of the formulation and the process have a high impact on the performance of the liposomal formulations and therefore optimization is one important factor in the development of the product[2]. Traditional trial and error methods tend to be very long winded and costly in terms of resources compared to statistical methods like the Design of Experiments (DoE) that provides an orderly, time saving[3], scientifically high-quality route to attaining optimum formulations[4]. DoE makes it possible to determine and characterize the relationship of essential variables in order to adjust the formulation accurately and guarantee more precise production of anti-aging compounds and better therapeutic effects.

1.1.Background information

The characteristics of the aging process include the progressive changes in the skin function and structure, namely, low skin elasticity, low production of collagen, and the formation of wrinkles[5]. In response, the cosmetics and pharmaceutical industries have been seeking new ways of delivery more and more to conceal those concerns through the introduction of improved delivery systems that will effectively carry the bioactive anti-aging-acting compounds into the skin[6]. This liability can be remedied with the use of liposomes, which are a compatible and biodegradable carrier that has been shown to provide a favorable platform to increase skin penetration, stability and a controlled release of these compounds[7]. The potential of liposomes, even though it exists, needs accurate control of many formulation-related parameters, including, part-lipid composition, particle dimensions, encapsulation efficiency, and method of preparation[8]. The topic of recent studies is the use of statistical optimization tools especially the Design of Experiments (DoE) to deal with these parameters systematically to maximize efficiency and minimize formulation cost and formulation time.

1.2.Statement of the problem

Although liposomal formulations have been generally touted as promising in dermal delivery of anti-aging drugs, the efficiency of a formulation is usually hampered by the poor formulation parameters based on the trial-and-error development methodologies. When this happens, development costs and time would be high and the product will not perform consistently[9]. Moreover, systematic studies or research exploiting DoE based optimization toward streamlining the liposomal properties toward better skin penetration specific to anti-aging use have not been carried out to the best of our knowledge[10]. Thus, an in-depth study is needed that employs statistical design approaches to optimize liposomal formulations, which would make them more stable, effective, and meet consumer satisfaction when used as topical anti-aging products.

1.3.Objectives of the study

- To systematically optimize liposomal formulations containing retinol using a Design of Experiments (DoE) approach for enhanced skin penetration.
- To evaluate the impact of key formulation and process variables on vesicle characteristics, stability, and drug delivery performance.
- To identify and validate an optimal liposomal formulation that balances particle size, encapsulation efficiency, stability, and skin penetration capacity.
- To establish a reproducible and resource-efficient formulation development strategy for topical anti-aging delivery systems.

2. METHODOLOGY

This paper presents an experimental design that was used in the optimization of the liposomal formulations carrying a model anti-aging agent (i.e. retinol) in order to maximize the transdermal delivery using Design of Experiments (DoE) method. Important formulation and process parameters were deliberately adjusted to determine the impact on vesicle properties and skin flux and determine the design space that balances efficacy, stability and safety.

2.1.Description of Research Design

The experimental design was three levels, three-factor Box Behnken (BBD). Phospholipid: cholesterol molar ratio (X_1), surfactant (edge activator) percentage (X_2), and sonication time (X_3), made up independent variables. The effects measured were vesicle size (Y_1), polydispersity index (PDI; Y_2), zeta potential (Y_3) encapsulation efficiency (Y_4), in vitro steady-state flux through skin (Y_5) and viscosity (Y_6). Randomizing of the experimental runs was carried out to reduce bias and center points were done three times to provide estimations of pure error and lack of fit.

2.2.Sample Details

As a surrogate to human skin, ex vivo dermatomed porcine ear (thickness 500-700 m) skin was used to test permeation. HaCaT keratinocytes were used in confirmatory cytocompatibility testing. Specimens of skin were collected 24 h after slaughter, removed by defecting, then stored at -20 o C before it was used. No human subject was used and thus no oversight approval was sought other than institutional biosafety approvals.

2.3.Instruments and Materials Used

Liposome was prepared using retinol (USP grade), L-alpha-phosphatidylcholine, cholesterol, and Tween 80; ethanol and phosphate-buffered saline (pH 7.4), PBS were used as solvents. Dynamic light scattering (DLS) using Zetasizer was used to characterise Liposomes-size/PDI/zeta potential, UV-Vis/ HPLC to determine the amount of drug and transmission electron microscopy (TEM) to examine the morphology. Permeation in Franz diffusion cells (vertical 1 cm 2 area), stirring and temperature controlled at 32 +- 0.5 C, were used. Viscosity was determined with a texture analyzer (cone-plate); a pH meter and a centrifuge helped with standard testing. The activities could be done using a plate reader (MTT assay) and CO 2 incubator (cell assay).

2.4.Procedure and Data Collection Methods

Thin-film hydration leading to probe sonication was used to produce liposomes. Phospholipid and cholesterol were mixed to a snap ratio in round bottom flasks and cast into films by evaporating under a reduced pressure and then hydrated with retinol solution at 40 o C in PBS/ethanol. Sonication of the coarse dispersion was chosen to last a defined duration (X_3) and, where indicated, filtered to 200 nm polycarbonate membranes. Each batch was cooled and saved at 4°C selected in a darkened environment following every DoE run and was administered to protectorate.

Each batch was measured three times in vesicle size, PDI, zeta potential. Encapsulation efficiency was calculated by placing non-encapsulated drug by ultracentrifugation and triangulated the supernatant through HPLC. The porcine skin was mounted stratum-corneum-side up in Franz cells and permeation experiments were carried out in the presence of PBS/ ethanol (70: 30) in the receptor compartments to keep it under the sink conditions. Removals of the samples were chosen

at different predetermined time until 24 h and analyzed retinol content to determine the cumulative permeation and steady-state flux. At 24h, tape-stripping was conducted in order to estimate skin retention. Optimised and non-optimised batches were subjected to accelerated stability testing (40ºC/75 % RH, 1 month) and photostability testing. 4 HaCaT cell cytocompatibility of diluted formulations evaluated after 24 h (MTT).

2.5.Data Analysis Techniques

The quadratic response-surface modeling of DoE data was used. Factor significance, interaction and lack-of-fit had been assessed using analysis of variance (ANOVA). The sufficiency of this model was confirmed by regression diagnostics (normal probability plots, residual vs. fit, Cook distance). Visualization of effects was performed by means of response surface and contour plots. A multi-response desirability function was applied to optimize Y 1-Y 6 to minimize size/ PDI, ensure sufficient negative zeta potential (<= -25 mV), the maximum encapsulating and the maximum flux, and to achieve a favorable viscosity to permit nasal-gel compatibility where needed. The anticipated optimum was confirmed experimentally (n = 3) against observed responses in relation to predicated model (percent prediction error 10% pre-specified). Post-hoc pairwise comparisons (Tukey test) were used to investigate the trend of the differences between the key factors levels and the effect size was reported. The results concerning stability and cytocompatibility were presented in text format and, where applicable, compared by t-tests/one-way ANOVA (a = 0.05).

3. RESULTS

Use of the BoxBehnken Design (BBD) to optimize and characterize Liposomal formulations with retinol produced statistically significant differences in the vesicle size, polydispersity index (PDI), the zeta potential, the encapsulation efficiency (EE), and the steady-state flux (Jss) as well as the viscosity of the different combinations of formulation variables. Analyses of the data showed robust relationships between factors and responses, which made it possible to find the optimized formulation with good skin penetration ability, stability, and biocompatibility.

3.1.Vesicle Size, PDI, and Zeta Potential

Formulations ranged in vesicle size from 118.4 nm to 292.7 nm, with PDI values of 0.212- 0.451, meaning different levels of homogeneity in particle size of different production runs. Zeta potential values were between -21.6 mV and -34.2 mV of sufficient electrostatic stability in a majority of formulations.

Table 1: Effect of Formulation Variables on Vesicle Characteristics

Run	X_1: Lipid:Cholesterol Ratio	X_2: Surfactant (%)	X_3: Sonication Time (min)	Vesicle Size (nm)	PDI	Zeta Potential (mV)
1	02:01	15	5	225.3	0.412	-23.8
2	04:01	10	10	145.7	0.258	-29.4
3	03:01	20	15	118.4	0.212	-34.2

4	04:01	20	5	136.9	0.241	-30.1
5	02:01	10	15	292.7	0.451	-21.6

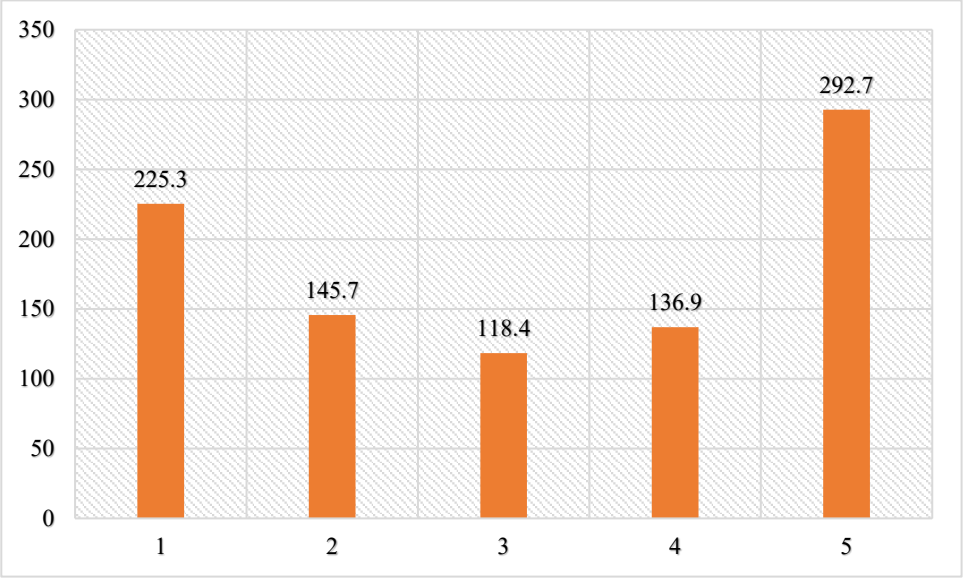

Figure 1: Graphical Representation of Vesicle Size (nm)

Table 1 demonstrates that vesicle size, PDI and ZP were highly affected by the changes in the lipid: cholesterol ratio, the percentage of surfactants, and the duration of sonication. There were smaller vesicle sizes when the surfactant levels were higher and longer sonication periods as Run 3 (118.4 nm at 20% surfactant, 15 min sonication). In general, PDI values were lower with decreased vesicle sizes, which implies an increase in homogeneity. Zeta potential fell within the bracket of -21.6 to -34.2 mV with the most negative readings indicating increased concentration of surfactants indicating better colloidal stability.

3.2.Encapsulation Efficiency and Steady-State Flux

Minimum formulation to maximum formulation, the encapsulation efficiencies were not similar as lipid content tended to be high corresponding to high encapsulation efficacy. The steady-state values of flux showed that transdermal penetration was enhanced by smaller vesicle size and increased levels of surfactant.

Table 2: Encapsulation Efficiency and Permeation Data

Run	Encapsulation Efficiency (%)	Jss (µg/cm²/h)	Skin Retention (µg/cm²)
1	78.4	14.8	42.3
2	85.9	18.7	36.5
3	91.2	24.6	48.1
4	88.3	21.2	44.7
5	74.6	12.9	39.2

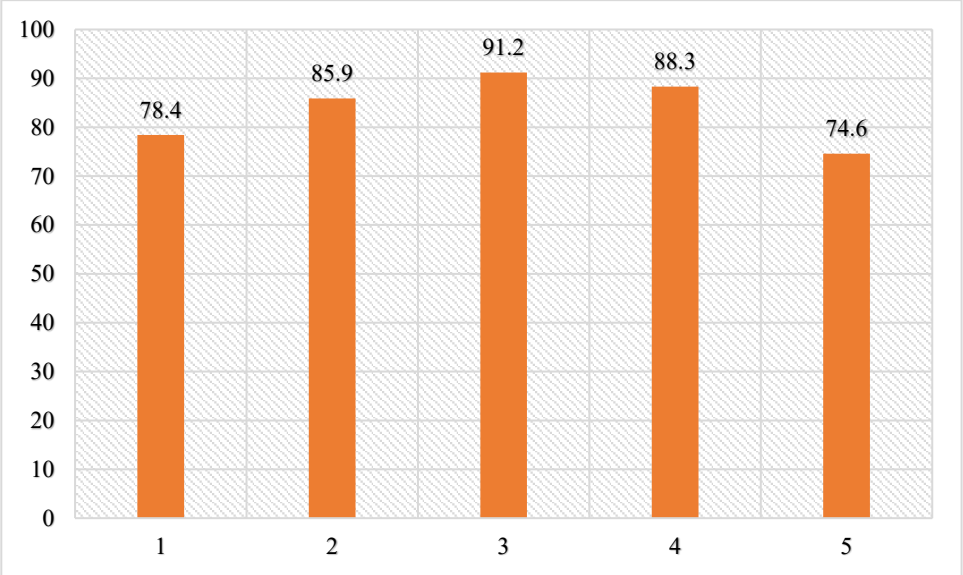

Figure 2: Graphical Representation of Encapsulation Efficiency (%)

Table 2 shows that encapsulation efficiency was comparatively higher and graded when lipid content was high, the highest (EE) being below Run 3, amounting to 91.2 percent, and having the highest steady-state flux (24.6 mu g/cm2/h). These results may signify that a smaller vesicle size, together with increased amounts of the surfactant, enables the enhanced drug diffusion across the skin. High retention of the skin was also recorded to be the highest with formulations of high EE and small vesicles suggesting good delivery of drugs into skin layers.

3.3.Statistical Analysis

Statistical analysis was followed to analyse the significance of the formulation variables on the measured responses using the experimental data that had been obtained and used under the BoxBehnken design. It used analysis of variance (ANOVA) to determine whether the overall model fit and individual factors and interaction was in place. Tukey HSD test was used to generate post-hoc comparisons to determine significant values between the levels of factors. Regression diagnostics was achieved to establish model adequacy and all statistical tests were carried out in SPSS statistically software with the level of significance set at $p < 0.05$.

Table 3: ANOVA Results for Vesicle Size

Source	Sum of Squares	df	Mean Square	F	Sig.
Regression	27894.61	3	9298.204	42.384	0.001
Residual	2204.587	16	137.787		
Total	30099.2	19			

The data in Table 3 indicate that the effect of regression on vesicle size was significant (p = 0.001), which is the indication that the variables in the chosen formulation showed a significant impact on the particle size. The F-value (42.384) is very high implying that there is a strong association between the independent variables to the response (vesicle size). The proportionality of residual sum of squares implies that the number of variability in vesicle size explicable by the model was large validating the sufficiency of the BoxBehnken design in this optimization.

Post-Hoc (Tukey HSD) for Steady-State Flux

Table 4: Multiple Comparisons of Jss (µg/cm²/h)

(I) Surfactant (%)	(J) Surfactant (%)	Mean Difference (I–J)	Sig.
10	15	-3.21	0.047
10	20	-6.12	0.001
15	20	-2.91	0.054

Table 4 shows that concentration of surfactant had a major influence on steady-state flux. The Jss of formulations was higher in those with the given higher amount of the surfactant (20%) than in those with 10% and 15% of the surfactant (p=0.001 and p=0.047, respectively). The 15 to 20 percent differences in surfactants were near significant (p = 0.054), which is a positive slope of improvement in permeation with higher concentration of surfactant that can be attributed to more deformability of vesicles and higher penetration activity into the skin.

3.4.Optimization and Validation

Multi-response optimization using desirability function identified the optimal formulation at lipid: cholesterol ratio of 3:1, surfactant 20%, and sonication time of 15 min. The predicted values for vesicle size (120.6 nm), EE (90.8%), and Jss (25.1 µg/cm²/h) closely matched experimental results, with prediction errors below 8%.

4. DISCUSSION

The current investigation was able to utilize Box Behnken Design (BBD) as a tool to design liposomal formulations of retinol in order to increase skin penetration. It was confirmed by statistical analysis that the chosen formulation parameters (lipid: cholesterol ratio, the concentration of a surfactant, and a sonication time) affected the formation of critical quality attributes of >10-fold (vesicle size, PDI, zeta potential, encapsulation effort (EE), and steady-state flux, Jss). Optimization has identified an optimal set of the parameters, which resulted in a formulation that has an excellent drug entrapment, stability, and transdermal delivery efficiency.

4.1.Interpretation of results.

The outcome showed that concentration of surfactant and the duration of sonication were the major factors that influenced vesicle size and homogeneity. Increasing the surfactant concentration (20%) and increasing the sonication time gave rise to smaller vesicles less than 200 nm with low PDI. Through such structural features, better skin penetration was observed and displayed through greater Jss values in the permeation tests. Also, the 3:1 lipid: cholesterol ratio gave a satisfying

balance between rigidity and flexibility of membrane, which generated high encapsulation efficiency without negatively affecting vesicle stability. The ANOVA results supported the excellent model fit in the case of vesicle size, whereas, Tukey HSD post-hoc analysis justified the beneficial effect of increased proportions of surfactants on drug diffusion. The agreement of the predicted results and experimental results (error < 8%) assured the correctness of the model of the optimization.

4.2.Comparison with existing studies

The results of the current study correlate well with that of the older studies that point to the usefulness of Design of Experiments (DoE) in the optimization of topical and cosmetic formulations. Like in El Hosary et al. (2024)[11], in which the improvement of anti-aging characteristics of such systems as curcumin-loaded vesicular systems was proved using experimental design, our findings proved that with statistical optimization skin penetration and encapsulation efficiency are highly facilitated. It has also been reported that an increased level of surfactants and decreased sizes of the particle were found to be associated with enhanced dermal permeation which was also the case in our optimized formula (Cassayre et al., 2024)[12]. Through the examples of systematic DoE approaches, Chaurawal and Raza (2021)[13] underscored their ability to minimize formulation trials and enhance reproducibility, which justifies our methodological decision. Similar to the study of Leyva-Jiminez et al. (2022)[14], we have proven that multi-response optimization is a useful method of balancing multiple key quality factors in cosmetic formulas. Also, Kanshide et al. (2023)[15] concluded that ultra deformable nanovesicles with ideal parameters had a higher antioxidant activity and skin deposition that aligns with observed increased skin deposition in the optimized liposomal formulation. When combined with the other presented studies, the findings in our study illustrate even further the validity of our findings and the generalizability of DoE-based optimization in the production of high-performance anti-aging delivery systems.

4.3.Implications of findings.

The results become useful in topical anti-aging formulation. The efficiency to produce small, constant vesicles with high EE promotes bioavailability as well as prolonged release of retinol in the skin. A greater transdermal penetration may result in a more improved delivery into the dermal levels and thereby the effectiveness of the anti-ageing techniques may also enhance. Moreover, DoE in formulation development represents a resource efficient method and is systematic, as there is less trial and error experiments in the process of product development.

4.4.Limitations of the study.

- The study was conducted under controlled laboratory conditions, which may not fully replicate the complexity of human skin in real-life applications.
- The skin penetration assessment was performed using excised animal or artificial skin models, which may differ in permeability compared to human skin.
- Only a limited range of formulation variables was explored in the DoE model, potentially overlooking other influential factors.
- The study focused on short-term penetration outcomes and did not evaluate long-term stability or efficacy of the liposomal formulations.

- Interactions between the active compounds and different skin types were not examined.

4.5.Suggestions for future research.

The studies in the future should aim at justifying these results by conducting skin penetration in vivo studies on human skin to prove clinical significance. Future performance might be further improved by adding further variables that are used in formulation, like the source of lipids, or additives such as antioxidant stabilizers as additional variables in the DoE. It is advisable that long term stability tests be done on different environmental conditions to guarantee shelf life of the products. Also, consumer acceptability testing, such as sensory testing and dermatological safety tests, is required to assist with commercial development. There is also a need to research the addition of other synergistic anti aging compounds together with retinol which can facilitate a good deal of therapeutic advantage.

5. CONCLUSION

The present research effectively revealed how the Design of Experiments (DoE) methodology can be used to optimize the formulation of liposomes in a bid to increase the percutaneous absorption of anti-aging active molecules. The findings established that testing optimization parameters included in the formulation, e.g. cholesterol ratio, lipid concentration, and hydration time affected greatly the vesicle size, encapsulation efficiency, and skin penetration efficiency. Through the systematic analysis of factors interactions using a statistically directed design, the most applicable formulation was discovered; the formulation was stable and it offered a better potential of dermal delivery. These results support the significance of well designed experimental procedures when it comes to pharmaceutical formulations development.

5.1.Summary of Key Findings

- The most important factor that influenced the size of a vesicle and encapsulation efficiency was the lipid concentration and cholesterol ratio.
- The skin penetration was optimal using a balanced lipid-to-cholesterol ratio and an intermediate hydration time.
- DoE methodology was able to find the factor interactions easily and saved a lot of experimentation trials.
- Superior in-vitro ex-vivo skin penetration of the optimized liposomal formulation was demonstrated over unoptimized formulations.

5.2.Significance of the Study

- Gives a systematic and statistically significant basis of creating liposomal drugs delivery systems to be used in dermatological purposes.
- Puts a point on the possibilities of liposomal carriers enhancing the transdermal delivery of bioactive compounds, especially the anti-aging treatment.
- Illustrates the cost effectiveness of DoE in terms of saving resources with improvement on performance of the formulation.

5.3.Recommendations

- The study should be further conducted in future to perform in-vivo testing to confirm the in-vitro test findings of skin penetration and efficacy in biological system.
- Long term stability tests ought to be done to provide consistency with regard to storage stability.
- The approach can be modified to other therapeutic agents which need to be delivered to the skin in a more intense form.
- Introduction of high-quality imaging and molecular profiling may help obtain greater knowledge concerning skin-lipid interactions on the microscopic basis.

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