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Optimization and Characterization of Naringenin Transfersomes with Simplex Lattice Design and Anti-Aging In Vivo Study

Sinta Yuliana*, Ilham Kuncahyo, Nuraini Harmastuti

Department of Pharmaceutics, Faculty of Pharmacy, Setia Budi University, Indonesia

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*Corresponding Author:
Sinta Yuliana
Email: yulianasinta303@gmail.com

ABSTRACT

Naringenin acts as an antioxidant, neutralizing free radicals that are present in the atmosphere and which are responsible for a number of adverse effects on the skin, including photoaging, the formation of wrinkles, and a loss of radiance. The objective of this study is to determine the effect of varying phospatidilcholine, cholesterole, and tween 80 on the characteristics of naringenin transfersome and their efficacy as anti-aging agents. A total of 14 naringenin transfersome formulas were subjected to testing using the Design-Expert application, using simplex lattice design method. The particle size, polidispersity index, zeta potential, and % Entrapment efficiency were evaluated. Subsequently, the optimal formula was subjected to in vivo anti-aging testing. The characterization results obtained for the PSA test indicate a range of values between 70 and 90 nm for the naringenin transfersomes. The % Efficiency of Absorption test yielded results between 80 and 92%, while the PDI test exhibited a range close to. The value of zero is obtained for the zeta potential, and the results are distant from this value. The optimum formula, as predicted by the Simplex lattice design method, provides results for the characterization test that are in close alignment with the actual outcomes.

Keywords : Naringenin Transfersome, Optimization, Simplex Lattice Design, Anti-aging

INTRODUCTION

Naringenin is a compound that is present in a substantial number of natural plants, including citrus fruits, tomatoes, cherries, and cocoa. Naringenin is a flavonoid compound belonging to a class of compounds that have been demonstrated to exert a range of pharmacological effects on biological systems. These effects include anti-inflammatory, anticancer, antiatherogenic, and antioxidant properties (Salehi *et al.*, 2019). However, the majority of the data obtained from previous studies were neither in vitro nor in vivo. Flavanones in naringenin, a compound found in citrus fruits, have been demonstrated to possess antioxidant and free radical scavenging properties. Furthermore, previous research has indicated that naringenin may be employed as a means of preventing oxidative damage to the skin (Tsai *et al.*, 2015).

Transdermal delivery systems have recently emerged as a subject of considerable interest, largely on account of the advantages they offer over conventional oral and parenteral delivery systems. These delivery systems are non-invasive and can be self-administered by patients, thus improving patient compliance and providing a controlled release of therapeutic agents (Ambarwati & Yulianita, 2019).

Transfersomes are nanocarriers in the form of elastic vesicles, comprising phospholipids and surfactants as their primary components. The combination of phospholipid and surfactant components endows transfersomes with the ability to penetrate the skin elastomechanically through intercellular pores or fuse with the stratum corneum layer, thereby carrying a greater quantity of drugs to the receptor (Darajat et al., 2023a). Consequently, transfersomes are said to exhibit superior skin penetration properties in comparison to other forms of delivery in the form of rigid conventional vesicles (Ambarwati & Yulianita, 2022).

Some researchers have explored the formulation of transfersome with various phospholipids and surfactants. One such

phospholipid is phospatidilcholine, a triglyceride-functional group amphiphilic molecule derived from soybeans. This phospholipid is odourless, in contrast to phospholipids derived from eggs. The research conducted by (Ambarwati & Yulianita, 2021) on the surfactant component in the form of Tween 80 indicated that Tween 80 exhibits superior flexibility and skin penetration properties compared to sodium cholate.

Furthermore, the research conducted by (Opatha *et al.*, 2020) demonstrated that Tween 80 produces particles with smaller sizes and higher % absorption efficiency compared to Span 80. The surfactant selected for the optimisationnof this transfersome formulation is Tween 80. The research conducted by (Zubaydah *et al.*, 2023) demonstrated that the use of tween 80 resulted in the optimal characteristics of transfersomes, as evidenced by the highest percentage of absorption efficiency, the smallest particle size distribution, the best polydispersity index (PDI), and the highest penetration.

The range employed in the study comprised cholesterol, phospholipon, and tween 80. The phospholipon dosage ranged from 700 to 800 mg, the tween 80 dosage from 100 to 200 mg, and the cholesterol dosage from 50 to 150 mg (Ambarwati & Yulianita, 2022). The transfersome formula of naringenin was optimised and characterised with varying weights of cholesterol, phosphotidicin, and tween 80 using a factorial design. The determination of the optimum transfersome formula was conducted through the calculation of the percentage of absorption efficiency, particle size, zeta potential, polydispersity index (PDI), and the assessment of efficacy as an anti-aging agent in vivo through the use of a Simplex Lattice Design (SLD) (Darajat *et al.*, 2023b).

RESEARCH METHODS

Materials

Naringenin was purchased from Changzou (China), Phospatidilcholine, Tween 80, and Cholsesterol from Sigma-Aldrich (Germany), Phospate buffer and Ethanol from Merck (Germany), and Purified water (Smart-Lab).

Naringenin Transfersome Preparation

The following formula will be the basis for the subsequent calculations:

Table 1. Naringenin Transfersome Preparation

No.	Item	Weight (mg)
1	Naringenin	40
2	Fosfolipid	700 – 800
3	Tween 80	100 – 200
4	Cholesterol	50 – 150
5	Phospate Buffer (PBS) 7,4 ad	20mL

The formula that has been inputted into the application is then subjected to a process of trial and error with the primary variables of the combination of cholesterol, phospatidilcholine, and tween 80, with the aim of identifying the extent to which these variables influence the percent absorption efficiency (%EP), PDI, zeta potential value, and particle size. The formula generated from the trial and error run mixture has the same value or replication. This value is used to identify any errors in the test or potential errors (Zubaydah *et al.*, 2023).

The naringenin transfersomes were prepared using the thin layer hydration method. The procedure involves combining all the ingredients, including the active substance, in a round-bottom flask. Subsequently, ethanol and chloroform are added in a 1:1 ratio, up to a maximum of 10ml, and stirred until fully dissolved. The solution is then evaporated at 50°C and 60rpm until a thin layer is formed.

Finally, the solution is cooled and diluted with 20 ml of 0.1N NaOH in PBS (pH 7.4) (Kuncahyo *et al.*, 2021). The second stage of the colloidal evaporation process was conducted using an ultrasonicator for a duration of 10 minutes, with an amplitude of 50% and a pulse on and off cycle of 5 minutes each.

Particle Size Analysis

The polydisperse index and particle size were observed using a particle size analyser (PSA) (Malvern, UK). The samples were loaded into a cuvette and measured for particle size at a wavelength of 633 nm with a refractive index of 1.333 and an angle of 173° at 25°C. The z-average value and polydispersity index were utilised to characterise the particle size and particle size distribution of the naringenin transfersomes (Rajkumar *et al.*, 2022).

Entrapment Efficiency

The centrifugation procedure should be conducted for approximately one hour at 6000 rpm

for each colloidal naringenin transfersome. The transparent solution obtained after centrifugation was analysed using a validated UV-Vis spectrophotometer. The entrapment efficiency (EE) was calculated as the percentage difference between the amount of drug incorporated into the transfersome system and the amount of drug that remained in the supernatant (Ratnasari & Anwar, 2016).

The percentage entrapment efficiency (EP) is calculated using the following formula:

$$\%EP=\frac{TD-FD}{TD} \times 100\%$$

Where, TD is the total compound of drug in the formula. FD is the amount of drug in the supernatant.

Anti-Aging Test

Rabbit backs that have been shaved and have undergone safety tests are analysed using a skin analyser with parameters of %collagen, %moisture, and %elasticity. Pure naringenin and naringenin transfersomes are then applied to the rabbit's back, which is subsequently exposed to UV-A light for approximately six hours. The rabbits were treated for a period of 28 days, after which observations were conducted on the rabbit backs (Darajat *et al.*, 2023a).

Statistical Analysis

All quantitative data was presented as mean ± standard deviation. The statistical significance was determined by simplex lattice design and SPSS. A value of $p < 0,05$ was considered significant.

RESULTS AND DISCUSSION

Run Trial and Error

The formula that has been inputted into the application is then subjected to a process of trial and error with the primary variables of the combination of cholesterol, phospatidilcholine, and tween 80 as the main influence. These variables include the percent absorption efficiency (%EE), PDI, zeta potential value, and particle size. The formula derived from the trial and error run mixture, exhibits a value or replication identical to that of the original. This value serves to identify any potential errors in the testing process, or instances of pure error *(Sitti Zubaydah et al.*, 2022)

Table 2. Run Trial and Error Formula

Item	Naringenin	Phospatidilcholine	Tween	Cholesterol	PBS
F 1	40	750	150	50	20
F 2	40	700	100	150	20
F 3	40	750	150	50	20
F 4	40	700	150	100	20
F 5	40	716,667	166,667	66,6667	20
F 6	40	750	100	100	20
F 7	40	700	200	50	20
F 8	40	800	100	50	20
F 9	40	700	200	50	20
F 10	40	800	100	50	20
F 11	40	766,667	116,667	66,6667	20
F 12	40	733,333	133,333	83,3333	20
F 13	40	716,667	116,667	116,667	20
F 14	40	700	100	150	20

The evaporation-sonication method or thin layer hydration was selected for the preparation of naringenin transfersomes to enhance the efficiency of drug absorption. The lipid layer formed on the walls of the round bottom flask has a large surface area, thereby increasing the efficiency of the hydration process compared to the vortexing-sonication method.

The results demonstrated that F-1, which contained the highest concentration of phospholipids, exhibited a milky white colouration with heightened intensity. Conversely, the diminished phospholipid content in F-4 resulted in a diminished colour intensity when compared to the other formulas.

Particle Size and Polidispersity Index

The utilisation of an excess of surfactant and cholesterol will result in a reduction of the particle size of the transfersome, consequently affecting the polydispersity index value. This is due to the fact that a reduction in particle size will lead to an improvement and stabilisation of the PDI value. An increase in phospatidilcholine usage will result in a discernible change in particle size, as evidenced by a visual transition from a whiter to a yellowish hue. This indicates a proportional increase in particle size.

The capacity of surfactants to diminish particle size enhances the process of transferring surfactants from a lipophilic milieu to an aqueous environment, thereby facilitating the formation of a nanoemulsion system. The particle size results of the 14 runs fell within the range of 70 nm to 90 nm. (Abdullah & Khairurrijal, 2009) posited that transfersome systems with particle sizes below 300 nm will exhibit enhanced penetration ability and superior deformability compared to vesicular systems utilising liposomes.

Some literature posits that the three components also affect the PSA test. When viewed from the contour plot produced on the weight of phospatidilcholine, it can be seen that the phospatidilcholine percentage is inversely proportional to the available sources. The percentage of use of other components, namely tween 80 and cholesterol, is also a factor. With a larger ratio of phospatidilcholine, the particle size should be larger. However, the contour plot at the lowest weight demonstrates the largest particle size. It can be observed that the weight of Tween 80 can be reduced with a minimal ratio of phospatidilcholine and a small weight of Tween 80 and cholesterol with a small ratio can result in a larger particle size than a high ratio of phospatidilcholine. Additionally, a large ratio of Tween 80 and a small amount of cholesterol can also produce a small particle size (Zubaydah *et al.*, 2023).

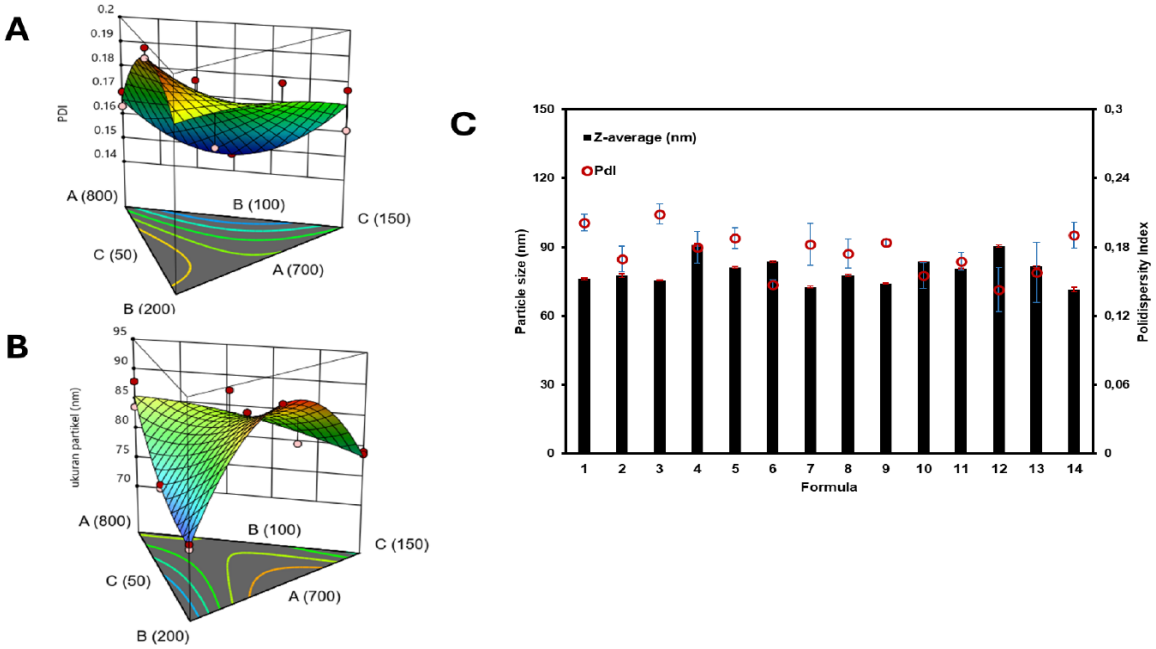

Figure 1. (A) Particle Size Analysis Result. Contour plot of particle size, (B) distribution, (C) graphical of particle size and Polydispersity index

The results of 14 runs of the naringenin transfersome formulation of the polydispersity index test yielded the results depicted in the graph above. These results fall within the range of 0.1-0.2, which indicates that the formulation meets the requisite standards. A PDI value that is indicative of a well-performing formulation is in close proximity to the value of 0. The polydispersity index (PDI) is a statistical measure that quantifies the degree of particle size homogeneity in a given formulation. A PDI value of less than 0.5, with a tendency to approach 0, indicates that the range and size of particles are homogeneous. The three ingredients used, namely phospatidilcholine, Tween 80, and cholesterol, exert a significant influence on the polydispersity index value. The use of a higher surfactant concentration will result in a PDI value that is closer to 0, while the use of phospatidilcholine in smaller quantities will also lead to a PDI value that is closer to 0. In cholesterol, the intrinsic function of cholesterol is to act as a stabilizer, thereby preventing the formation of aggregates during storage, which would otherwise affect the PDI value and particle size.

Cholesterol maintains the stability of naringenin transfersomes over extended periods, preventing any changes in their physical quality. Prior research indicates that a PDI value closer to zero is indicative of superior PDI performance and greater preparation stability. The PDI value that is closer to zero will exert an influence on the potential zeta value. In addition to the aforementioned three

components, the solvent utilized in the manufacture of transfersomes also exerts an influence on the PDI test on phospatidilcholine, which interacts with sodium diphosphate. This, in turn, can affect the zeta potential value and PDI value.

The utilisation of elevated cholesterol and Tween 80 concentrations, in conjunction with phospatidilcholine, whose weight is diminished, results in a PDI value that is more proximate to zero. The source indicates that the incorporation of Tween 80 and cholesterol, which have greater weight, will influence the particle size and PDI value. Consequently, the contour plot is delineated in accordance with existing sources or literature (Zubaydah *et al.*, 2023).

Zeta Potential

In general, a zeta potential exceeding the absolute value of 30 mV is deemed essential to ensure optimal colloidal stability. The charged particles in a liquid dispersion are surrounded by ions in an electric double layer. The zeta potential has an impact on the physical stability of a drug delivery system, influencing its overall efficacy. Macrophages are capable of rapidly eliminating negatively charged particles. The 14 run transfersomes produced exhibited zeta potential values ranging from -30 to -40, indicating that the three components exert a beneficial influence on the production of qualified transfersomes.

The zeta potential value is influenced by the three components in phospatidilcholine. An excess of phospatidilcholine will increase the particle size but will decrease the zeta potential value because phospatidilcholine is a zwitterionic component with an isoelectric point between 6 and 7. The hydration media used is pH 7.4, which is above the isoelectric point. This will decrease the zeta potential value (causing it to be negative) and also affects the efficiency of absorption because the presence of surfactant molecules in the lipid bilayer can cause the formation of pores in the vesicles formed (Tsai *et al.*, 2015).

The utilization of an excess of surfactant will result in a reduction of the transfersome particle size and an impact on the polydispersity index value, given that a smaller particle size will yield a more optimal and stable PDI value. Furthermore, the zeta potential value is influenced by phospatidilcholine, which interacts with phosphate at pH 7.4. The presence of cholesterol has been observed to influence the stability and homogeneity of transfersomes. During prolonged storage, cholesterol can serve as a stabilizing agent, preventing the formation of aggregates that could otherwise compromise the integrity of transfersomes (Darajat *et al.*, 2023a).

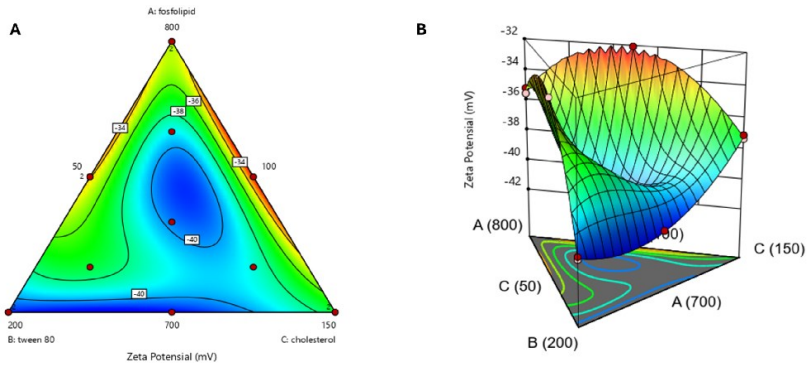

Figure 2. 2-D (A) and 3-D (B) contour plot of Zeta potential in Simplex Lattice Design

The contour plot of zeta potential indicated that an increase in the weight of Tween 80 resulted in a shift in the zeta value away from the value of 0. For phospholipids, an increase in weight led to a closer approach to the value of 0, while in cholesterol, the opposite was observed. The incorporation of cholesterol into the formulation results in a shift in the Zeta value away from the value of 0 (Ambarwati & Yulianita, 2022).

This alteration in the Zeta value impacts the stability and homogeneity of the naringenin transfersomes. When the Zeta value deviates from the value of 0, the stability of the naringenin transfersomes is enhanced. In this context, all independent variables exert an influence on the zeta potential, particularly phospatidilcholine and tween. When these two components are combined in a drug delivery system, they enhance electrical induction, preventing the globules from attracting each other and forming aggregates. This results in a reduction in the stability of the naringenin transfersomes during long-term storage (Ambarwati & Yulianita, 2019).

Entrapment Efficiency

The term "entrapment efficiency" is related to the amount of drug loading. Drug loading is defined as the weight or percentage of the active ingredient adsorbed to the weight of the nanoparticles. Sorption efficiency, on the other hand, is the ratio between the experimentally determined drug content and the actual or theoretical mass used for the preparation of nanoparticles (Ambarwati & Yulianita, 2022).

An increase in the quantity of phosphatidylcholine will result in a greater number of vesicles, which will facilitate the absorption of a greater quantity of naringenin into the system. An increase in the quantity of Tween 80 and cholesterol will result in an enhanced absorption of the active substance within the drug delivery system. The absorption efficiency values for the 14 runs ranged from 80% to 92% (Rajkumar *et al.*, 2022).

The contour plot of %EP indicates that cholesterol and phospatidilcholine play a significant role in influencing the %EP value of naringenin transfersomes, as evidenced by the red and blue colours. The red colour indicates the highest %EP, while the blue colour indicates the lowest %EP. In the red colour, the lowest weight of cholesterol is capable of increasing %EP, while in the blue colour, the lowest weight of phospatidilcholine and tween 80 is able to further decrease %EP. The addition of Tween 80 has been demonstrated to enhance %EP, as evidenced by prior research. The utilization of Tween 80 has been shown to elevate %EP to a greater extent than the utilization of Span 80 (Zubaydah *et al.*, 2023).

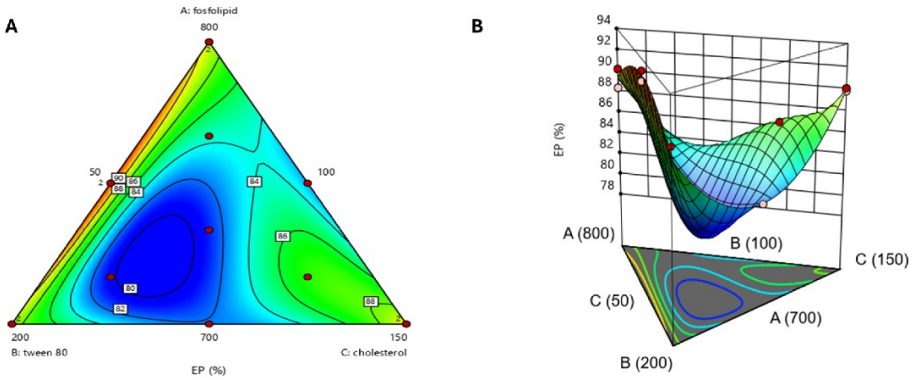

Figure 3. 2-D (A) and 3-D (B) contour plot of entrapment efficiency

Prior research indicates that the use of phospatidilcholine and Tween 80 in greater quantities will result in enhanced absorption efficiency. Similarly, the utilization of cholesterol in smaller quantities will also lead to improved absorption efficiency. The contour plot produced in this study demonstrates that of the three components, namely phospatidilcholine, Tween 80, and cholesterol, affect the percent absorption efficiency. It was observed that if phospatidilcholine is used in greater quantities, the absorption efficiency will be higher. Similarly, greater quantities of Tween 80 were found to increase the absorption efficiency. Additionally, it was noted that smaller quantities of cholesterol resulted in higher absorption efficiency (Zubaydah *et al.*, 2023).

Optimum Formula and Its Anti-Aging Test

The optimum formula and characteristics test is shown in Table 3 and Table 4.

Table 3. Optimum formula from Simplex Lattice Design

No.	Item	Weight (mg)
1	Naringenin	40
2	Phospatidilcholine	746
3	Tween 80	154
4	Cholesterol	50
5	PBS ad	20 mL

Table 4. Optimum characteristrics from simplex lattice design

No.	Characteristics	Results
1	Particle Size	75,83 nm
2	Polidispersity Indeks	0,195
3	Zeta Potential	-34,12 mV
4	Entrapment efficiency	92,45%

From the predictions generated from Simplex Latice Design, the optimum formula is continued to be made and then its characteristics are tested (Sitti Zubaydah *et al.*, 2022). The results between predictions in the application and real tests obtained results that are not much different (Tsai *et al.*, 2015). After obtaining the results between the predictions and the test results, statistical analysis was carried out using SPSS and from the characteristic test, the results obtained in SPSS showed that the predictions and tests carried out had no significant difference, so the predictions generated by Simplex Latice Design were in accordance with the results of the characteristic tests that had been tested (Zubaydah *et al.*, 2023).

Table 5. The parameters of Aging Test

No.	Parameter	Result				
1	Moisture	*Dry* 3-4%	*Aging* 4-10%	Normal 10-15%	*Higher* 15-30%	*Better* 30-65%
2	Elastisticity	*Loose skin* 15-35%	*Weak* 35-50%	Normal 50-65%	*Better* 65-70%	*Best* 70-71%
3	Collagen	*Serious lack* 25-50%	*Reduce* 50-65%	Normal 65-80%		

The anti-ageing test was conducted in vivo using rabbit test animals. The rabbit's dorsal surface was shaved and subsequently divided into two portions, which were then smeared with pure naringenin and naringenin transfersome, respectively. Prior to the application, the rabbit's back was evaluated using a skin analyser with three parameters: collagen, elasticity, and moisture (Windono *et al.*, 2019).

Table 6. The result of Anti Aging Test, comparing pure naringenin and naringenin transfersomes

No.	Parameter	Result		
		D-0	D-28 Naringenin	D-28 Transfersom
1	Moisture	65%	3%	48%
2	Elasticity	71%	32%	55%
3	Collagen	80%	40%	63%

The results of the anti-ageing test, comparing pure naringenin and naringenin transfersomes, demonstrated a reduction in the levels of all three parameters for both treatments when compared to H0. However, while the transfersome results exhibited a decline, the decrease in all parameters remained within the normal range, in contrast to the pure naringenin, which demonstrated a more pronounced reduction, even falling below the normal range in one instance.

Thus, it can be posited that naringenin transfersomes are more efficacious in counteracting UV radiation than pure naringenin when viewed through the lens of the aforementioned parameters. Nevertheless, despite the observed decrease, naringenin transfersomes still fall within the normal range. This may be attributed to the fact that naringenin transfersomes have not yet been formulated into topical preparations. However, if continued to such preparations, there is a possibility that the efficacy of counteracting free radicals, particularly naringenin transfersomes, may be further enhanced.

CONCLUSIONS

The combination of phosphatidicoline, Tween 80, and cholesterol has the potential to influence the characterization test of naringenin transfersomes, specifically in terms of the following parameters: PSA, %EP, PDI, and zeta potential. The combination of phospatidilcholine, Tween 80, and cholesterol at a ratio of 745.805 mg, 154.195 mg, and 50 mg, respectively, was found to be optimal for the characterization of naringenin transfersomes, resulting in a predicted value of 75,8381 for the SLD application of PSA, 0,194987 for PDI, -34,1196 for Zeta, and 92,4453% for %EP.

The optimal formula demonstrates resilience to UV light, despite a reduction in the three parameters under consideration. This is likely due to the fact that the optimal formula has not yet been formulated into a dosage form. Therefore, it can be concluded that the penetration of the optimal naringenin transfersome formula is not yet optimal in terms of UV light resistance.

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CONFLICT OF INTEREST

The authors declare that none of them have any conflicts on interest in relation to the present publication.

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