Original Article

Face Mask Embedded with Nanoemulsion for Reducing Facial Skin Adverse Effects Caused by Prolonged Wearing the Mask during COVID-19 Management

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ABSTRACT

Background: Wearing a facemask is one of the precautionary measures for preventing coronavirus disease spread, which causes many facial skin adverse effects. Vitamin-E (TPGS) and olive oil have an efficient effect on skin moistening. Therefore, in this study, face-masks embedded with NE; prepared using olive oil and TPGS, were developed to reduce the long-wearing face mask adverse effect. **Methods:** Box-Behnken design was used to develop NE formulations which were physically evaluated to select the most stable formulation. Fibroblast cell lines (3T3) were used to examine NE efficacy on dermal cell proliferation and *in vitro* cytotoxicity possibilities. Face-masks were also examined for 6 hr wearing dermal compatibility on healthy participants. **Results:** The formulated NE didn't significantly affect cell proliferation nor had a toxic effect on dermal cells ($p<0.05$). More than 60% of the respondents were satisfied with masks containing NE. **Conclusion:** In particular, a face mask embedded with the preparaed selected NE formula could produce emollient feelings during application without retarding the breathing or causing any irritant sensation.

Keywords: Nanoemulsions, Face-mask, Coronavirus disease virus, Olive oil, Vitamin E.

INTRODUCTION

The spread of the coronavirus disease virus (COVID-19) has been reported worldwide since December 2019. One of the necessities to reduce the possibility of this airborne infection transmission is wearing facemasks. Prolonged wear of face masks could cause increases in the facial skin's temperature. The later causes skin damage, redness, dryness, and contact dermatitis.[1,2] Many researchers suggested that using hydrocolloid dressings, protectant film, or daily skin emollient as a barrier prior to mask application to avoid the mask tightening effect.[3-5]

Nanoemulsions are considered a dermal delivery system that enables high and fast skin permeation. The small droplet size provides a large surface area that fastens the actives' release onto the skin and enhances stratum corneum penetration through. Using nanoemulsion, especially O/W, helps in moistening the skin.[6] Its fluidic nature improves its ability to adhere to the stratum corneum as a thin lipid film, which facilitates its skin emollient effect.[7,8] Nanoemulsions, unlike emulsions, are pseudoternary stable systems, with no creaming or glossy effect and easy skin flow. Nanoemulsions could be fabricated with cosmetics formulations ingredients' as many emollient lipids.[9] Nanoemulsions' high storage stability and ease preparation technique, which does not require high energy or complicated procedures, facilitate its cost-effectiveness the.[10]

Vitamin E, alpha-tocopherol, is easily oxidized by atmospheric oxygen and water-insoluble, in which this characteristic can make it difficult for the development of

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topical products with high water content.[11] The unique nanoemulsions' characteristics facilitate using them as an appropriate vehicle to deliver Vitamin E and other lipophilic compounds onto the skin. Vitamin E could be used in dermatological-cosmetic applications as an endogenous cellular antioxidant, to lubricate the skin and improve skin tone, moisturizing properties, elasticity, density, and collagen production. Topical application of Alpha-tocopherol significantly reduces the severity of erythema and edema,[12] which all result from the prolonged wearing of face masks the adverse effects.

Olive (*Olea europea*) oil is a bioactive phenolic compounds with antioxidant,[13] anti-inflammatory,[14] and photo-protector activities.[15] Additionally, it could be used in different topical delivery systems or cosmetics for the treatment of skin diseases.[13] Olive oil formulation in NE form reduces the unaccepted oil odor and creasy effect.[16] Olive oil is highly compatible with oil-soluble substances as Vitamins E. The later improves its soothing and protective effects (antioxidant effects) on the skin.[17]

Therefore in this study nanoemulsions were prepared using olive oil and vitamin E to reduce the long-wearing face mask adverse effect. Using nanoemulsin on the mask facilitates during time emollient effect with no breath retarding or greasy effect with high skin absorption.

MATERIALS AND METHODS

Materials

Olive oil, PEG 400 and vitamin E (Alpha-tocopherol) have been bought from Sigma-Aldrich Co (St. Louis, MO, USA). Tween 80 and glycerol were purchased from El-Gomheria Co., Cairo, Egypt. All additional chemicals were acquired from El-Gomhoria Co. in Egypt.

O/W nanoemulsions preparation and optimization

O/W nanoemulsions were prepared using olive oil and alpha-tocopherol as the disperse phase, while deionized water containing glycerol was used as the continuous phase. Box-Behnken statistical design was used for the development of different formulations according to Table 1. In brief, alpha tocopherol was dissolved in the olive oil. Tween 80 was added, and the dispersed phase was heated up to 60°C. The aqueous phase containing different concentrations of glycerol and 10 ml phosphate buffer at pH 7.4 was heated to the same temperature. Drop-wise addition of oil phase to aqueous solution with agitation using magnetic stirring at 200 nm resulted in a coarse emulsion, and then continuous agitation until it reached room temperature. For the preparation of nanoemulsion, the prepared emulsion was mixed using a high-speed homogenizer (KRH-I, Shanghai, China) at different speed rates for various times according to Table 1. For emulsion stabilization, the prepared emulsions were subjected to ultrasonic homogenization using an ultrasonic processor at 20 kHz, 750 Watts for 5 min.

Table 1: The composition of the prepared nanoemulsions (Independent factors, the selected levels and the studying responses) for Box-Behnken design process.

Factors	Levels		
	Low (-1)- High (1)		
A: Olive oil	10	20	30
B: Surfactant mix (Tween 80: alpha tocopherol; 2:1)	5	10	15
C_3: Glycerol	1	2	3
D: Speed (rpm)	10000	12500	15000
F: Time (min)	10	15	20
Responses			
Particle size (PS)	Minimize		

Evaluation of the prepared nanoemulsions

Vesicles size, size distribution and Zeta potential determination

The vesicle size, size distribution (pdi), and zeta potential of the formulated nanoemulsions were conducted using Malvern Instruments Ltd.'s Zetasizer, which had an avalanche photodiode detector and was adjusted at 632.8 nm laser. They were measured immediately after nanoemulsion preparation.

pH Determination

The prepared stable NE formulation pH values were determined using (Jenway pH meter, UK) by inserting the electrode directly into the sample at room temperature (25 ± 0.5°C).

Rheology Study

Brookfield viscometer, DVIII (MIDDLEBORO, MASSACHUSETTS 02346, USA) rheometer was used to characterize the formulations, and the measurements were conducted in stainless steel utilizing cone–plate geometry, with a diameter of 40 cm and a spacing of 0.052 mm. The formulations were tested at 32 ± 0.1°C. The experiments were carried out in an oscillating condition. Flow curves were established with shear rates ranging from 0.01 to 100/s.

Emulsion Stability

The stability of the formulated nanoemulsions was evaluated macroscopically by the bottle test method. The prepared nanoemulsion formulae were transferred into a tightly closed graduated cylinder at room

temperature. The emulsion was monitored for creaming, phase separation, coalescence, flocculation, and any color changes for 30 days, which indicated the system instability. Accelerated stability tests were also conducted using centrifugation and thermal accelerated stability tests. In the centrifugation test, 10 mL of samples were centrifuged at 5000rpm for 10 min (Laborezentrifugen, 2k15; Sigma, Darmstadt, Germany) at 25.0±0.5°C while the thermal stability test was conducted using a freeze–thaw cycle stability test. 10mL of the suspected emulsion was placed in a vial and refrigerated at -5°C for 24 hr before allowing it to thaw at ambient temperature for another 24 hr. The sample was visually inspected, and the particle size, Pdi and Zeta value were determined by the same previously described steps in section 2.3.1.

In vitro assay of the Prepared NE on Dermal Cell

Cell culture

At 37°C, fibroblast cell lines (3T3) were cultivated in an incubator with a humidified atmosphere containing 5% CO_2. The cells were maintained alive with 100 units/mL penicillin, 100 g/mL streptomycin, and 10% heat-inactivated fetal bovine serum (Life Technologies, USA) added to Dulbecco's Modified Eagle Medium (DMEM), Sigma–Aldrich, USA to maintain the cells alive. When the cells had achieved 80% confluence, the media was withdrawn and the cells were washed twice with sterile phosphate buffer saline (PBS, pH 7.4). To detach the cells from the flask, 1 mL of trypsin–EDTA was added. After centrifugation, the supernatant was discarded, and the cell pellets were re-suspended in a cell medium. An updated Neubauer hemocytometer was used to evaluate cell density.

Proliferation Studies

3T3 cells were seeded in 60 × 15 mm Petri plates ($1.0 – 5 \times 10^5$ cells /dish) and cultured in supplemented media as described in section 2.5.1. The medium was discarded the next day, and 1 ml of fresh medium with various concentrations of the prepared selected NE formula was added. Every 24 hr, 3T3cells were counted for 72 hr, in a Neubauer chamber, after mild trypsinization.[18]

In vitro Cytotoxicity Study

The *in vitro* cytotoxicity of the prepared selected nanoemulsions was investigated using (MTT) cell viability assay. 4 x 104 3T3 cells were cultured for attachment in 96-well plates at a density of 6 × 104 wells for 24 hr under 5% CO_2, 90% relative humidity, and at 37°C. Cells were incubated for 48 hr with increasing concentrations of NE (0.1-1000 g/mL). Subsequently, 20 µl of 5mg/ml of MTT solution was added to the obtained cultured media and incubated for 4 hr at 37°C. All MTT tests were carried out in triplicate. The cell toxicity was analyzed by measuring absorbance at 570nm with the Synergy 2 Multi-Detection Microplate Reader by BioTek Instruments, Inc. The inhibitory concentration (50%) was determined, and the result was expressed as a mean ± standard deviation. The negative control was prepared by adding culture medium alone (100% proliferation).

Safety Evaluation *in vivo*

Cutaneous compatibility of NE was assessed according to the WMA Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects with a protocol approved by the ethical committee of Al-Taif University, KSA; Approval number: 43- 049. It was evaluated by a single application to 12 volunteers ranged in ages from 16 to 55 years (6 males and 6 females) after receiving their written informed consent.[19] The volunteers were selected who have intact skin with no lesions or irritation. Each volunteer underwent a double-blind study over the course of 24 hr. In order to evaluate the safety, 2 face masks embedded with, 20 µL of NE and water (negative control) were applied to the normal face skin. NE or water (negative control) was sprayed on the face mask 30 min before wearing the face mask by the volunteer. The face masks were removed after 6 hr of application. The responses were evaluated at 30 min, 2hr, 4hr and 6hr after face masks removal.[20] The films were evaluated in terms of their emollient feelings during application; good breathing, and any irritant sensation. Evaluation parameters were feeling of discomfort in the breathing (1/0), skin irritation sensation (acceptable; 1/0), and an emollient sensation (acceptable; 1/0).[21]

Statistical Analysis

Each experiment was carried out three times. The statistical differences between groups were assessed by one-way ANOVA with Tukey's HSD, using SPSS 18 (Chicago, IL, USA). A P-value less than 0.05 was considered significant throughout the research.

RESULTS AND DISCUSSION

Preparation and Evaluation of the Nanoemulsion

Nanoemulsion preparation was done using high-energy emulsification techniques to form a system that is thermo-kinetically stable.[22] The large droplets size converted into smaller droplets (nanosized) by applying a high shear zone, which depends on the rotation speed and time.[23]

The prepared NE was O/W emulsion, which facilitates the emollient effect with a little greasy effect. The HLB value required for O/W nanoemulsion preparation was around 8-18.[24,25] Therefore, a mixture of surfactants was preferred. The surfactant ratio was chosen to achieve the required HLB value. The amount of the used surfactant was calculated using equation one as when the used HLB value was facing the required HLB that might help in developing a stable emulsion.[26] Equation 1 was used to calculate the quantity of each surfactant required to attain the target HLB value.[27]

$$HLB = HLB(S1) \times 0.01*S1 + HLB(S2) \times 0.01*S2 \quad \text{Eq (1)}$$

Where HLB = emulsion hydrophilic-lipophilic balance, S1, S2 = amount of the used surfactant % (w/w), HLB (S1) or (S2) = HLB value of the used surfactants, S1+S2 = 100% (w/w).

The main goal of nanoemulsion formulation is to obtain formulae with uniform nanoparticle sizes. Table 2 shows the effect of different variables on the PS of the prepared NE. Design Expert 10.0.1 [Stat Ease. Inc.] software was used to obtain 48 experimental runs using Quadratic Box-Behnken design. Only 31 out of 48 nanoemulsions were successfully obtained. Increased glycerol concentration > 1% improves NE stability and formation.[28] Glycerol could improve NE system stability as it acts as a co-solvent in the NE system, increases the NE viscosity and decreases the droplet collision frequency.[29]

All factors have a significant effect on the tested responses, with a non-significant lack of fit, and follow a linear model with R^2 value = 0.9693. Statistical analysis results and the final equations in terms of coded factors are represented are shown in Table 3.

The predicted R-Squared (0.9504) is in reasonable agreement with the adjusted R^2; 0.9632. The adequate precision" is desirable as it was greater than 4 (40.439) indicating the adequate of this model to navigate the design space.

Changing in the olive oil and glycerol concentration have a significant effect on the particle size $p < 0.05$. As represented in Figure 1 and the statistical equation, it was found that increasing oil concentration led to an increase in the NE vesicles' size and vice versa for glycerol concentration.

NE preparation Optimization

The desired formulation was to obtain the smallest vesicle size with high oil and glycerol content to improve the emollient effect of the prepared NE and the lowest

Table 2: Experimental runs of different variables of the 2^3 full factorial designs of nanoemulsion formulations.

Block	A:Olive oil %	B:Surfactant mix %	C:Glycerol %	D:Speed rpm	E:Time min	PS nm
1	30	15	2	12500	15	290.58
2	30	10	3	12500	15	300.39
3	20	10	3	10000	15	200.06
4	10	15	2	12500	15	101.98
5	10	10	2	12500	10	119.55
6	20	10	1	10000	15	S
7	10	10	2	10000	15	128.45
8	10	10	2	15000	15	114.78
9	20	10	1	15000	15	S
10	20	15	2	12500	20	205.31
11	20	10	2	12500	15	215.04
12	30	5	2	12500	15	S
13	30	10	2	12500	20	283.43
14	20	5	2	15000	15	S
15	20	10	2	15000	10	220
16	20	10	2	10000	10	225.5
17	20	15	2	12500	10	210.56
18	10	10	3	12500	15	111.25
19	30	10	2	15000	15	260.60
20	20	10	2	12500	15	215.07
21	20	10	3	15000	15	180.83
22	20	15	2	15000	15	201.47
23	30	10	2	10000	15	279.5
24	20	5	2	12500	20	S
25	10	5	2	12500	15	S
26	20	5	2	10000	15	S
27	20	10	2	12500	15	215.04
28	10	10	1	12500	15	S
29	20	5	2	12500	10	S
30	20	10	3	12500	10	195.84
31	30	10	1	12500	15	S
32	20	10	2	15000	20	207.59
33	20	10	2	10000	20	211.58
34	20	15	3	12500	15	175.89
35	20	10	2	12500	15	214.98
36	20	15	2	10000	15	204.79
37	20	10	2	12500	15	215.18
38	20	5	1	12500	15	S
39	30	10	2	12500	10	275.40
40	20	5	3	12500	15	S
41	20	10	2	12500	15	215.21
42	20	15	1	12500	15	S
43	20	10	1	12500	10	S
44	20	10	1	12500	20	S
45	20	10	3	12500	20	190.82
46	10	10	2	12500	20	110.98

Table 3: The design expert results of all response variables and the final equation in terms of the tested independent factors.

Source	PS (nm)		
	F	*p*-value	
Model	158.06	< 0.0001	
A-Olive oil	775.90	< 0.0001	
B-Surfactant mix	3.41	0.0769	
C-Glycerol	9.03	0.0060	
D-Speed	2.02	0.1674	
E-Time	0.99	0.3289	
Lack of Fit	0.4117		
ANOVA statistics results		**Final Equation**	
Adequate precision	40.439	**Intercept**	+208.38
R^2	0.9693	A-Olive oil	+84.24
Adjusted R^2	0.9632	B-Surfactant mix	-8.35
Predicted R^2	0.9504	C-Glycerol	-13.60
SD	10.48	D-Speed	-4.30
%CV	5.15	E-Time	-3.01

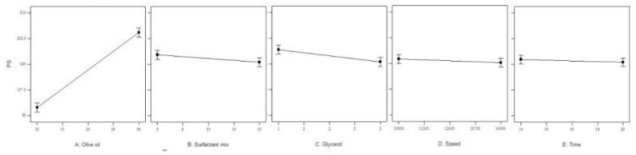

Figure 1: The effect of different preparation variables on the NE particle size.

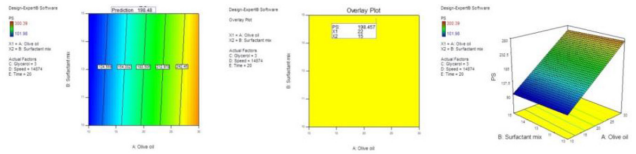

Figure 2: The optimization of the prepared NE.

surfactant amount to reduce any irritant effect. As represented in Figure 2 and from the statistical equation, it was found that olive oil concentration has a significant effect on the vesicles' size. Therefore, the optimized composition of the nanoemulsion was 3.0% glycerin, 15.0% surfactant, and 20% olive oil (all w/ w). The speed of the homogenizer was adjusted at 15000 rpm for 20 min as complementary preparation parameters to achieve the smallest vesicle size, which is approximately equal to 200 nm.

Evaluation of the selected nanoemulsion formulation

According to the optimization result, the particle size and the zeta potential of the prepared selected formulation were determined. The vesicle size was 195.45 nm and –24.2 mV. The polydispersity index (Pdi) is equal to 0.124 ± 0.012 (Figure 3A), which indicates the nanoemulsion has a narrow size distribution, approximately a monodispersion system, as the Pdi value was close to zero (Pdi < 0.2).[30,31] A negative zeta value on a surface charge was dependent on the composition of the prepared nanoemulsion constituent.[32] The zeta potential assessment is critical because of its relevance to the stability of the dispersion system. When this value is >20 mV, it means the attraction between the droplets is smaller than the repulsion, which can lead to the deflocculation of the vesicles and good physical stability.[33] The negative zeta potential values may be related to a small amount of free monosaturated fatty acids (oleic acids)[34] which might adsorb hydroxyl ions at the oil-water contact and form hydrogen bonds between these ions and Tween's ethylene oxide groups.[35] The pH of the prepared selected formulations was 5.56, which is a suitable value for cutaneous application and does not interfere with the permeation characteristics of lipophilic molecules.[36] The rheological characterization was performed with selected NE and the flow curve was illustrated and studied. The system has a non-Newtonian characteristic and is considered a pseudoplastic fluid because the viscosity value decreases with increasing the shear rate value (Figure 3B).

The Nano-emulsion stability studies

The prepared selected NE formulations show no visible creaming, phase separation, or droplet aggregation. As represented in Figure 4, there was no statistically significant difference indicated in vesicle size, Pdi, and zeta potential results after storage at room temperature or even after storing for 3 months at room temperature (Figure 4) at *p*-values > 0.05. The same result was confirmed after centrifugation and a free-threw cycle (at -5°C). This result was in agreement with the previous finding that the nanoemulsion stability could be maintained up to many months the.[37] Thus, the high speed rotation utilized in NE preparation could

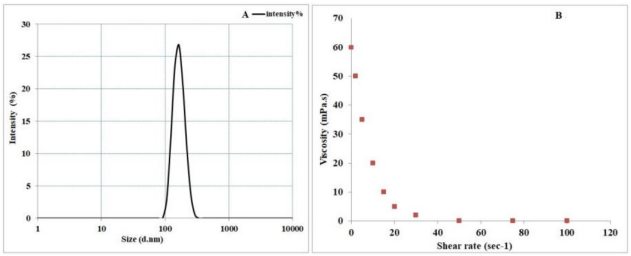

Figure 3: Size distribution (A), and Flow curve (B) of the selected nanoemulsion.

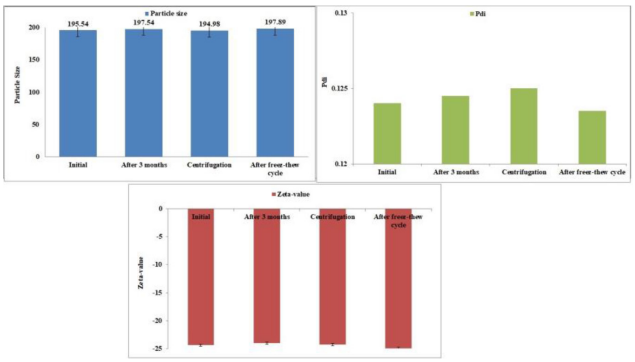

Figure 4: Storage stability assessment of nanoemulsion formulation.

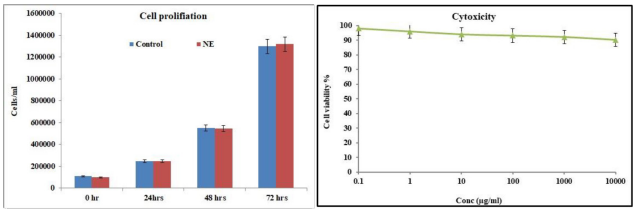

Figure 5: A. Proliferation results of the NE effect on 3T3 cells up to 72 hr, the result is mean ± SD of 3 different runs carried out in duplicate at $p< 0.001$. *B. In vitro* cytotoxicity of NE on cells.

preserve particle size, Pdi, and zeta potential and prevent nanoemulsion creaming for up to 3 months.

In vitro assay of the prepared NE on dermal cell

In 3T3 cells, cell proliferation was assessed. Cells were seeded on 60 × 15 mm Petri plates in 4 ml of the respective medium until the 3T3 cells grown in suspension reached maximal density after 96 hr. Tested Cells were stimulated with NE 24 hr from seeding and then counted every 24 hr. As represented in Figure 5A; NE did not significantly affect cell proliferation.

The *in vitro* concentration-dependent cytotoxicity test was performed using the MTT assay on 3T3 cells after incubation with NE for 48 hr. According to the results shown in Figure 5B, the various test samples displayed dose-dependent cytotoxicity against 3T3 cells. The relative viability with increasing samples concentration was higher than 85% at the highest NE concentration (10000 µg/mL) indicating the modest or even possible lack of cytotoxicity after 48 hr incubation periods. IC_{50} was higher than 1000 µg/mL which indicated it has a nontoxic effect.[38]

In vivo Safety Evaluation

The selected NE was tested for emollient feelings, good breathing, and any irritant sensations during application. Figure 6 represents the results. The feeling of comfort during application was expressed by yes = 1, while

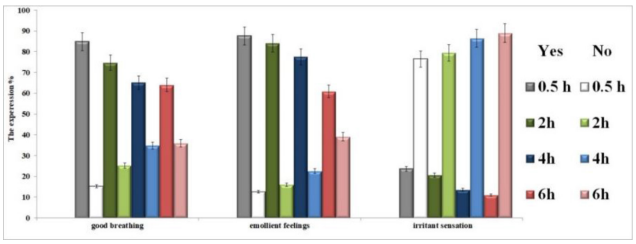

Figure 6: The *in vivo* response of the selected NE on the variables' influences, each value represents the mean ± SD (n = 3).

the unacceptance data No = 0 for emollient and good breathing effect of the tested parameters. For irritant sensation during application, expressed by yes = 1, and expressed by 0 when there was no irritant sensation.

From the reported results, we can conclude that the NE produces accepted emollient feelings and doesn't retard breathing. Additionally, it has no irritating effect. The statistical analysis of the result shows a significant difference ($p<0.05$) between the acceptance and non-acceptance results. The result explains that most patients accepted the mask containing a NE during application time up to 6hr. There was a significant difference between the volunteers' expectations after 30 min of mask application and after 6 hr, but still within the accepted range as more than 60% of the respondents were satisfied with masks containing NE.

CONCLUSION

NE contains high olive oil (20%) and glycerol concentration (3.0%) and low surfactant concentration (15.0%) could improve emollient feelings during application without retarding the breathing and didn't cause any irritant sensation. In particular, nanoemulsions preparation using high energy emulsification techniques (15000 rpm for 20 min) form a thermo-kinetically stable system with uniform nanoparticle size < 200 nm and –24.2 mV zeta value. Skin emollient effect could avoid the mask tightening effect by prolonged wearing. The later causes skin damage, redness, dryness and contact dermatitis. Face-Masks containing NE could reduce several skin adverse effects' of prolonged wearing a mask by its efficient emollient effect.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

TPGS: Vitamin E; **3T3:** Fibroblast cell lines; **COVID-19:** Coronavirus disease virus; **PS:** Particle size; **pdi:** Polydispersbility index; Size distribution; **DMEM:** Dulbecco's Modified Eagle Medium; **PBS:** Phosphate buffer saline; **HLB:** Hydrophilic Lipophilic Balance.

Ethics approval

The *in vivo* study protocol was approved by the ethics committee of Taif University, protocol code 43-485.

Author Contributions

H. A. Designed the experiments, collected, analyzed the data and drafted the manuscript (written and reviewing). R.A. Final draft revision and fund acquisition. All authors are contributed in the final manuscript revision. All authors have read and agreed to the published version of the manuscript.

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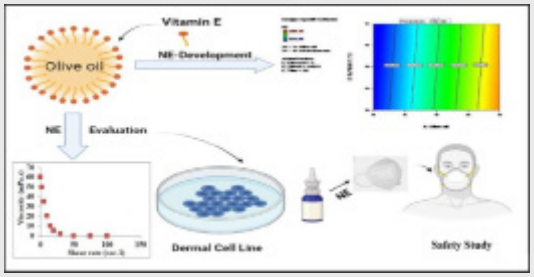
PICTORIAL ABSTRACT



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