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Section C: Drug Design, Delivery & Targeting

Formulation and Evaluation of a Skin-Compatible Sunscreen Cream

Aliaa Ismail^{1*}, David Isaac², Rahma Maged Abdallah², Ahmed Yasser²,
Ahmed Sayed², Fares Ibrahim¹, Nermeen R. Raya¹

¹Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Helwan University, Ain Helwan, Cairo 11795, Egypt

²Faculty of Pharmacy, Helwan University, Ain Helwan, Cairo 11795, Egypt

*Corresponding author: Aliaa Ismail, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Helwan University, Ain Helwan, Cairo 11795, Egypt. Tel: +2 01224328984
Email address: aliaa_adly@pharm.helwan.edu.eg

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ABSTRACT

Background: Zinc oxide (ZnO) is a key component in sunscreen products, particularly for its ability to provide a physical barrier against a broad region of the ultraviolet (UV) radiation spectrum and its soothing, non-irritating nature, which is recommended for sensitive skin. **Objectives:** This work aimed to develop a sunscreen cream using ZnO with the addition of other selected skin-friendly ingredients that are gentle and beneficial to skin and then evaluate the properties of the developed cream. **Methods:** Three formulae of sunscreen creams (F1, F2 and F3) were prepared by mixing ingredients using homogenization technique. The two homogenously appearing formulae (F2 and F3) were assessed in terms of pH and spreadability. The optimum formula (F3) was further evaluated in terms of rheological behavior, *in vitro* sun protection factor (SPF), skin irritation potential, and physical stability upon storage. **Results:** The formula (F3) showed acceptable pH, good spreadability, thixotropic non-Newtonian shear- thinning rheological behavior, and SPF value of 5.01 ± 0.55 with broad-spectrum protection against UVA and UVB. Moreover, the formula (F3) did not cause any signs of irritation on rats' skin and the normal histological structure of rats' skin appeared under a microscope. Also, F3 was physically stable and kept its color and homogeneity without any phase separation after storage for 20 days at ambient temperature. **Conclusion:** The formula (F3) composed of zinc oxide, olive oil, aloe vera gel, vitamin E, and Tween 80 is a promising skin-compatible sunscreen cream. However, further examination of this formula on human skin is needed to confirm its safety and efficiency for humans.

Keywords: Zinc oxide, Inorganic sunscreen, physical sunscreen, skin, ultraviolet

INTRODUCTION

Skin is the first immune barrier of the body against external pathogens and plays an important protective role. Skin exposure to ultraviolet (UV) radiation can indeed lead to various skin issues like sunburn, pigmentation, hyperplasia, and premature skin aging. Moreover, UV radiation is a major risk factor for skin

cancer, including basal cell carcinoma, squamous cell carcinoma, and melanoma¹. Sunscreen compounds provide protection for the skin against ultraviolet (UV) rays upon exposure to the sun and are generally classified into organic and inorganic categories. Organic sunscreens (chemical sunscreens), such as oxybenzone and avobenzone, are synthesized to be absorbed into the skin. Organic sunscreens act by capturing UV radiation

and transforming it into less damaging heat. The major disadvantages of many organic sunscreens include liability to UV-induced degradation^{2,3}, potential to disrupt the endocrine system⁴, and neurotoxic effects⁵. Inorganic sunscreens (physical sunscreens / mineral sunscreens) include zinc oxide (ZnO) and titanium dioxide (TiO₂). Inorganic sunscreens are not absorbed into the skin but tend to leave a white residue on the skin, which acts as a physical shield that blocks UVA and UVB radiations from skin penetration⁶. The use of ZnO-based sunscreen products is becoming increasingly popular because of their broad-spectrum protection against both UVA and UVB rays and excellent soothing effect and non-comedogenic properties⁷. In addition, aloe vera is well known for its beneficial effects on the skin, including sun protection, anti-oxidation, anti-aging, moisturizing, and treatment of skin wounds⁸. Furthermore, the inclusion of olive oil into sunscreen products is valuable due to its supportive functions as moisturizer, anti-oxidant, anti-inflammatory and soothing agent⁹. Vitamin E in sunscreen products acts as an antioxidant, neutralizer for UV-induced free radicals, and skin hydration enhancer¹⁰. Also, vitamin E reduces inflammation, aids in skin repair, and prevents premature aging¹¹. Thus, the aim of this work was to develop a skin-compatible sunscreen cream using the previously mentioned ingredients and evaluate the developed cream in terms of physical properties, rheological behavior, *in vitro* sun protection factor (SPF), skin irritation potential, and physical stability upon storage.

MATERIAL AND METHODS

Materials

Zinc oxide (ZnO) was manufactured by PioChem laboratory chemicals, Egypt. Aloe vera gel was manufactured by Cleopatra cosmetics, Egypt. Olive oil (Extra virgin) and Lavender oil were manufactured by Imtenan, Egypt. Tween 80 [polyoxyethylene (20) sorbitan monooleate] was manufactured by Alpha Chemika, India. Viscogel UE 305® [polyacrylamide and C13-14 isoparaffin and laureth-7] was purchased from AFT chemicals, Egypt. Vitamin E soft gelatin capsules (1000mg) manufactured by Pharco Pharmaceuticals, Egypt.

Methodology

Preparation of different formulae of Sunscreen creams

Three sunscreen cream formulae (F1, F2, and F3) were prepared according to the composition shown in **Table 1**. Firstly, ZnO was ground in a porcelain mortar, followed by portion-wise addition of olive oil. The mixture was levigated thoroughly with a pestle, and then aloe vera gel and vitamin E were added. Then, both Tween 80 and viscogel UE 305® were added in F2, or Tween 80 alone was added in F3. Finally, a few drops of

lavender essential oil were added to the mixture. All the ingredients were homogenized using a homogenizer (IKA Labortechnik, Malaysia) at 300 Hz for 2 minutes. The obtained creams were kept in clean capped containers. Each formula was prepared in triplicate.

Table 1. Composition of the prepared sunscreen creams.

Components	Amount		
	F1	F2	F3
ZnO	15 g	15 g	15 g
Olive oil	10 g	7 g	10 g
Tween 80	-	8 g	5 g
Viscogel UE 305®	-	0.5 g	-
Aloe vera gel	15 g	15 g	15 g
Vitamin E	3 g	1 g	3 g
Lavender oil	2 drops	2 drops	2 drops

Examination of physical appearance of the prepared sunscreen creams

The physical appearance of the prepared sunscreen creams (F1, F2, and F3) was visually examined in terms of color, homogeneity, and phase separation.

Evaluation of the physically stable prepared sunscreen creams

Measurement of pH

The pH values of sunscreen cream formulae (F2 and F3) were measured to ensure their skin compatibility. One gram of the sample was transferred to a clean beaker and diluted with 9 grams of distilled water (10-fold dilution). Then the diluted sample was stirred using a glass rod for 5 minutes to create a uniform dispersion. The digital electrode of the pH meter (BP3001 Professional Benchtop pH Meter, Singapore) was immersed directly into the supernatant of the dispersion, and the reading of pH was recorded on the monitor. The measurements were done in triplicate¹².

Spreadability test

Spreadability testing was performed to predict the ability of sunscreen creams (F2 and F3) to spread easily upon application on the skin. Spreadability was measured in terms of the diameter of the circle produced when the sample is pressed between two glass plates of definite weight. One gram of the cream was placed on the center of a circular glass plate. Then, the glass plate was covered with another glass plate. A weight of 1000 g was placed over the cover glass plate and left for 5 minutes. The diameter of the cream circle was measured after 5 minutes. The measurements were done in triplicate¹³.

Further evaluation of the selected formula (F3)

Assessment of rheological properties

The rheological properties of the prepared sunscreen cream (F3) were studied using a B-One Plus viscometer (Lamy Rheology Instruments, France) equipped with Spindle R6 at $25^{\circ}\text{C} \pm 1^{\circ}\text{C}$. All tested creams (20 g each) were subjected to variation of speed from 10 to 100 RPM for 30 seconds each. The measurements were performed in triplicate, and the average viscosity at each speed was recorded.

In vitro measurement of Sun Protection Factor (SPF)

The Sun Protection Factor (SPF) test is essential for evaluating the effectiveness in protecting against ultraviolet (UV) radiation, which can cause sunburn, skin aging, and skin cancer. The measurement of SPF value for the selected formula (F3) was conducted and calculated using a UV- 2000s Ultraviolet Transmittance Analyzer (lapsphere, USA) at wavelength range 290-400 nm. A definite amount of the formula F3 was applied as 2 mg/cm^2 over the helioplates (molded polymethylmethacrylate PMMA) to provide a standardized surface that simulates human skin roughness. These plates were certified to have topography parameters in compliance with international standards: the ISO 24443-Annex D method and Colipa 2011. The application of F3 formula on the plate was done using a micropipette, and then the plate was left to dry for at least 20 min prior to the measurements. The measurements were done in triplicate¹⁴.

Skin irritation test

A skin irritation test was performed to ensure that the selected formula (F3) is compatible for use and does not cause irritation, allergies, or adverse skin reactions. A skin irritation test evaluates immediate skin reactions like redness, swelling, or rashes. The test was performed using four female albino Wistar rats (150-200 g). The proposal of this study was revised and accepted by the Animal Research Ethics Committee of the Faculty of Pharmacy, Helwan University (Approval number 19A2025). The rats were randomly divided into two groups. Group 1 (Control) included one rat that was not subjected to any treatment to be used as a standard for comparison with normal skin. Group 2 (Test) included three rats treated with the selected formula (F3). The three rats in group 2 were labeled as test 1, test 2, and test 3 for the first, second, and third rat, respectively. Rats' hair on the dorsal area (2 cm x 2 cm) was removed one day prior to the application of the formula (F3) using a depilatory cream. Doses of 0.5 g of the selected formula (F3) were applied with uniform spreading on the shaved rats' skin twice daily for two consecutive days. The time interval between doses on the same day was 2 hours.

Visual observation and scoring systems for erythema and swelling

Skin surface morphology of the untreated control

rat and the three treated rats (test 1, test 2, and test 3) was observed and imaged at day 0 (before application of F3 on test rats), day 1 (one day after application of F3 on test rats), and day 2 (two days after application of F3 on test rats). The skin was checked visually for any sensitivity reaction (i.e., erythema, swelling, ulceration or peeling, and scratching or behavioral signs of discomfort). The mean erythema scores was recorded from 0 to 4 according to the level of erythema, where lack of erythema = 0, minor erythema = 1, distinct erythema (dark pink) = 2, moderate-to-severe erythema (light red) = 3, and severe erythema (very dark redness with or without scabbing) = 4¹⁵. The mean swelling scores were recorded (ranging from 0 to 4) depending on the degree of swelling as follows: No swelling = 0, very slight swelling = 1, slight swelling = 2, moderate swelling (skin raised significantly) = 3, and severe swelling (skin extremely raised and thickened) = 4¹⁶.

Histopathological examinations

After two days, rats were euthanized, and the defined part of the shaved skin was excised and fixed in 10 % formalin-saline solution for 24 h. The skin was washed with tap water, and then serial dilutions of alcohols (methyl, ethyl, and absolute ethyl) were used for dehydration. Specimens were cleared in xylene and embedded in paraffin at 56°C in a hot air oven for 24 h. Paraffin beeswax tissue blocks were prepared through sectioning at $4 \mu\text{m}$ thicknesses by a rotary Leitz microtome. The obtained tissue sections were collected on glass slides, deparaffinized, and stained with hematoxylin and eosin stains for histopathological examination under the light electric microscope¹⁷.

Effect of storage on physical stability of the selected formula (F3)

The effect of storage at ambient conditions was investigated as a preliminary assessment of the physical stability of the selected sunscreen formula (F3) in terms of homogeneity, color change, and phase separation. The maintenance of physical stability could ensure that F3 has the potential to retain its effectiveness, safety, and UV protection integrity throughout its shelf life. The sample was stored in an airtight container at ambient temperature away from direct sunlight and was observed visually once daily for 20 successive days to detect any phase separation and investigate color changes and homogeneity.

RESULTS

Examination of physical appearance of the prepared sunscreen creams

All the prepared formulae (F1, F2, and F3) appeared white and homogenous. However, the formula (F1) showed phase separation a few hours after its preparation.

Evaluation of the physically stable prepared sunscreen creams

Measurement of pH

The pH measurements of the prepared sunscreen creams (F2 and F3) were 7.9 ± 0.03 and 7.27 ± 0.06 , respectively.

Spreadability test

The results of spreadability test of the prepared sunscreen creams (F2 and F3) in terms of the diameter of circle of sample after being pressed between two glass plates were 3.53 ± 0.15 cm and 5.13 ± 0.15 cm, respectively.

Further evaluation of the selected formula (F3)

Assessment of rheological properties

Table 2. showed the viscosity (cps) of F3 at different shearing rates expressed in terms of different RPM. It can be found that the formula (F3) exhibited viscosities ranging from 53709.00 ± 1598.54 cps to 8839.33 ± 76.96 cps. Moreover, Figure 1. illustrated that F3 cream exhibited a thixotropic non-Newtonian shear-thinning behavior as its viscosity declined with increasing RPM, and also, the upflow curve (i.e., generated upon increasing RPM) and the downflow curve (i.e., generated upon decreasing RPM) were not superimposed.

In vitro measurement of Sun Protection Factor (SPF)

The SPF value of F3 cream was found to be 5.01 ± 0.55 . In addition, the UVA/UVB ratio was 0.896, and the critical wavelength was 382 nm.

Skin irritation test

Visual observation and scoring systems for erythema and swelling

Figure 2. showed the skin of rats in the control group and the treated test group throughout the period of the experiment. Throughout the two days of F3 application on rats, the observations indicated that the prepared F3 cream did not show any sign of skin reaction. The scores for both erythema and swelling were zero.

Histopathological examinations

As shown in Figure 3, both control and test groups showed normal histological structure of the epidermis, dermis with hair follicle, and underlying subcutaneous adipose tissue and muscular layer.

Effect of storage on physical stability of the selected formula (F3)

The formula (F3) did not show phase separation or any physical changes in homogeneity or color throughout the 20 days of storage.

DISCUSSION

Examination of physical appearance of the prepared sunscreen creams

The physical appearance of topical formulations is an indicator of product quality, stability, and consumer acceptability. In this study, three sunscreen cream formulations (F1, F2, and F3) were visually evaluated to assess their homogeneity and physical stability. The initial observed homogeneity of F1 could be attributed to the ability of the relatively larger amount of ZnO powder to adsorb olive oil and incorporate it temporarily into the aqueous network of aloe vera gel. However, shortly after preparation, phase separation occurred in F1, and the separation of oil and water phases was visually observed. This could be attributed to the absence of an emulsifier¹⁸. The role of emulsifier is essential in mixing oil and water phases and ensures a stable homogeneous formulation¹⁹. Tween 80 and Viscogel UE 305[®] were the emulsifiers used in the formula F2, and Tween 80 was the only emulsifiers used in formula F3. Thus, the formulae F2 and F3 were homogeneous and stable with no signs of separation, indicating successful emulsification and physical integrity over time due to the presence of the emulsifiers²⁰. This highlights the significance of effective formulation techniques, such as the careful choice of emulsifiers, surfactants, and processing conditions, to create a physically stable sunscreen cream.

Evaluation of the physically stable prepared sunscreen creams

Measurement of pH

The pH test aimed to ensure that the pH values of the formulae (F2 and F3) fall within the acceptable range for topical products to be safe and non-irritating to the skin. The results of the pH measurements of the prepared sunscreen creams (F2 and F3) were 7.9 ± 0.03 and 7.27 ± 0.06 , respectively. The tolerable pH range for the skin is between 4.5 and 7²¹. The observation of the pH test on the sunscreen cream sample showed that the pH of the sunscreen cream F3 was closer to the safe pH range for the skin.

Spreadability test

Spreadability is a crucial factor in sunscreen formulation, as it ensures application, uniform UV protection, and a pleasant user experience. A well-spread sunscreen prevents patchy sunburn, reduces white cast, and enhances absorption for long-lasting protection. Several factors influence spreadability, including the choice of emollients, rheological modifiers, and the particle size of UV filters. Increasing the spreadability of sunscreen improves its ease of application, uniform coverage, and overall effectiveness and optimum protection against UV lights. An excellent topical preparation usually exhibits a spreadability range of 5 to 7 cm²². The results of the spreadability test of the

prepared sunscreen creams (F2 and F3) in terms of the diameter of the circle of the sample after being pressed between two glass plates were 3.53 ± 0.15 cm and 5.13 ± 0.15 cm, respectively. From the results, F2 revealed low spreadability, while F3 showed good spreadability. The low spreadability of F2 could be attributed to the thickening effect of the emulsifier/stabilizer Viscogel UE 305®. Thus, the following evaluation tests were performed for the optimum formula F3.

Further evaluation of the selected formula (F3)

Assessment of rheological properties

Viscosity testing measures the viscosity and flow properties to ensure the right texture and

spreadability. The higher the viscosity values of the cream, the greater its resistance to skin application. Generally, a cream is considered to meet the viscosity requirements when its viscosity is in the range of 2000-50000 cps²³. **Table 2** showed that the formula (F3) exhibited viscosities ranging from 53709.00 ± 1598.54 cps to 8839.33 ± 76.96 cps, which indicated that F3 had the acceptable viscosity required for cream formulation. Moreover, the thixotropic non-Newtonian shear-thinning behavior of F3 is an important quality characteristic for a topical product for its easy, smooth, and even application on the skin.

Table 2. Viscosity values of F3 at different RPM

RPM	Viscosity of F3 (cps) $\pm$ SD (n=3)	
	Up (increasing RPM)	Down (decreasing RPM)
10	53709.00 ± 1598.54	36990.33 ± 122.20
20	28990.33 ± 799.15	22429.67 ± 90.56
40	17285.67 ± 202.84	14470.67 ± 51.19
60	12828.00 ± 218.69	11387.67 ± 24.03
80	10414.67 ± 123.58	9825.33 ± 76.66
100	8839.33 ± 76.96	8839.33 ± 76.96

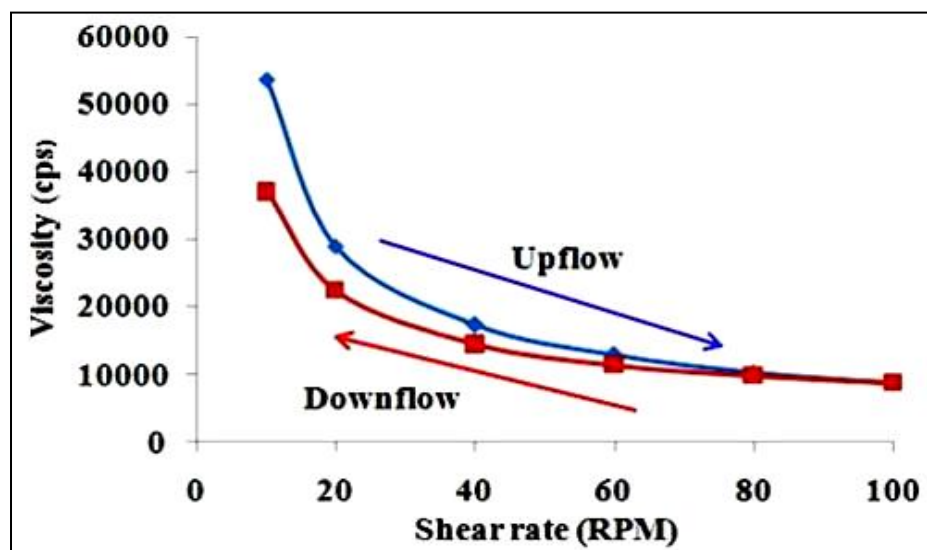


Figure1. Upflow and Downflow curves of F3



Figure 2. The images of skin surface morphology of the untreated control rat and the three treated test rats at day 0 (before application of F3 on test rats), day 1 (one day after application of F3 on test rats), and day 2 (two days after application of F3 on test rats)

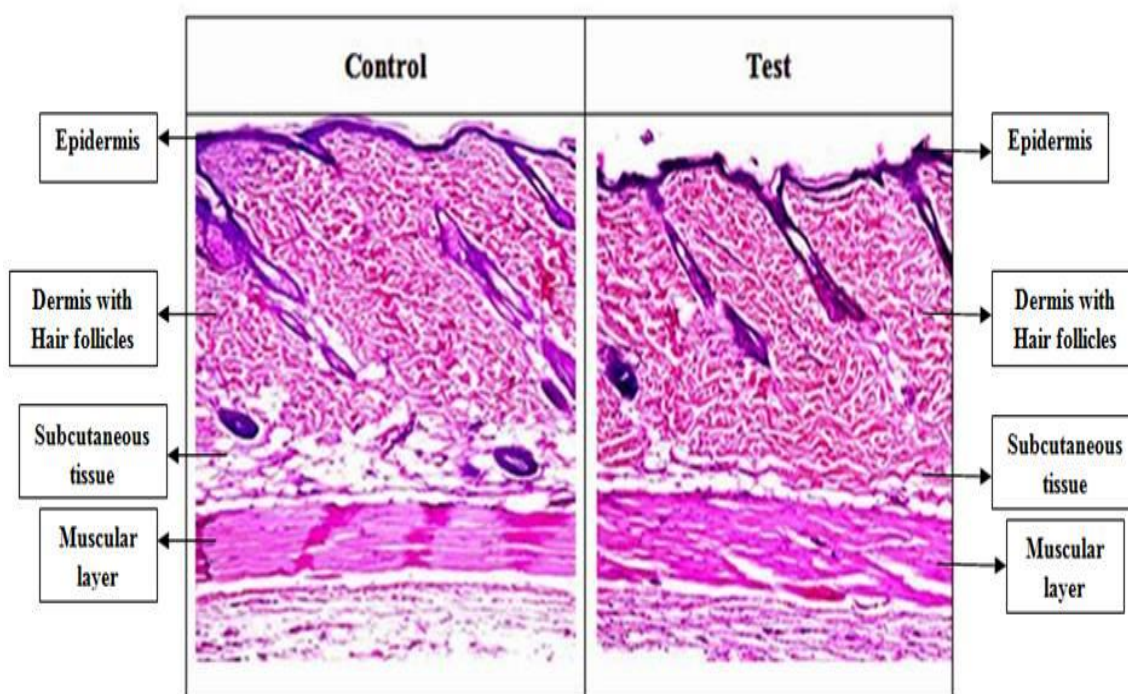


Figure 3. Histopathological examination of rat skin for control and test groups

In vitro measurement of Sun Protection Factor (SPF)

The active skin protection of a sunscreen product is indicated by the Sun Protection Factor (SPF). The SPF value indicates how long a sunscreen product can protect or block ultraviolet rays that can cause skin damage²⁴. The higher the SPF value of a sunscreen product, the better its protective activity is against the skin²⁵. The SPF value of F3 cream was found to be 5.01 ± 0.55 . However, it was previously found that the *in vitro* methods for estimation of SPF values for formulations containing zinc oxide (ZnO) at high concentrations (up to 25%) do not coincide with the labeled SPF-values that have been estimated *in vivo*²⁶. Even with their acclaimed effectiveness, sunscreen formulations having high concentrations of ZnO often yield low *in vitro* SPF values. The assumed reason for the lower *in vitro* SPF values compared to the *in vivo* SPF values of such formulations could be due to the high density of highly concentrated ZnO formulations. This could lead to the formation of a very thin film of their samples that are applied according to weight basis on the helioplates to comply with international standard methods, which might decrease their *in vitro* SPF values²⁶. Another explanation is that inorganic filters such as zinc oxide mainly scatter or reflect rather than absorb UV rays²⁷.

Furthermore, the results of this test revealed a UVA/UVB ratio of 0.896 and a critical wavelength of 382 nm for F3. A higher UVA/UVB ratio (closer to 1) indicates a better balance between UVA and UVB protection. The 0.896 ratio suggests the sunscreen F3 could provide substantial UVA protection, which is important for preventing premature aging and other long-term skin damage. According to the Boots Star Rating system, revised in 2008, the F3 formula falls within the range of a 4-star Boots rating, indicating its potential for a high level of UVA protection²⁸.

The critical wavelength of a sunscreen is the wavelength at which the integral of the sunscreen's absorbance spectrum from 290 nm to 400 nm reaches 90% of the total area under the curve. In simpler terms, it's the point below which 90% of the area under the absorbance curve resides. A critical wavelength of 370 nm or greater is considered by the Food and Drug Administration (FDA) to indicate broad-spectrum protection, meaning the sunscreen effectively protects against both UVA and UVB rays. Thus, a critical wavelength value of 382 nm for F3 that is above the common threshold for broad-spectrum protection approved by the FDA indicated the potential of F3 to provide broad-spectrum UV protection²⁹.

Skin irritation test

A skin irritation test evaluated the potential of the prepared sunscreen cream formula (F3) to cause redness, burning, or allergic reactions when applied to the skin. This ensures the product is safe, non-irritating,

and suitable for different skin types, including sensitive skin.

Visual observation and scoring systems for erythema and swelling

The evaluation of the safety and efficacy of zinc oxide sunscreen cream (F3) involved visual observations and scoring systems to assess erythema and swelling on rats' skin. These two parameters are commonly used to gauge the dermatological safety of topical formulations, as erythema and swelling are indicative of irritation or inflammatory responses³⁰. In this study, no signs of erythema or swelling were observed following the application of the sunscreen cream (F3), and both parameters were scored as zero. Thus, it can be assured that F3 cream does not cause any skin irritation and can be well tolerated for topical application on sensitive skin. The absence of erythema and swelling is consistent with the known gentle, non-irritating nature of ZnO, which is widely used in skin care formulations for its physical sun-blocking properties without causing skin irritation or allergic reactions³¹. Also, this study ensured the safety of the other ingredients incorporated with ZnO in the formula F3.

Histopathological examinations

The purpose of histopathological testing is to assess the microscopic effects of the tested sunscreen cream (F3) on skin tissue. Histopathological testing identifies cellular changes, inflammation, and tissue damage that may not be visible through standard visual irritation assessments. By analyzing skin biopsies under a microscope, it provides detailed insights into the extent of irritation, immune responses, and potential long-term effects. This method is crucial for distinguishing between mild irritation, allergic reactions, and severe toxicity, ensuring that dermatological products are safe for use¹⁷.

Both the control and test groups showed normal histological structure of the epidermis, dermis with hair follicles, and underlying subcutaneous adipose tissue, and muscular layer, indicating that F3 cream does not cause any histopathological changes upon application on rats' skin and could be well tolerated for topical application³². These results are consistent with research suggesting that ZnO is typically safe for use in topical applications³³. The normal skin structure observed in both groups provides further evidence supporting the biocompatibility and safety of the developed sunscreen formulation³⁴.

Effect of storage on physical stability of the selected formula (F3)

The formula (F3) did not show any physical changes in homogeneity or color throughout the 20 days of storage, indicating its promising stability upon storage under ambient conditions. However, further long-term and/or accelerated stability studies should be carried out

according to standard guidelines to confirm the obtained result.

CONCLUSION

The formula (F3) composed of zinc oxide, olive oil, aloe vera gel, vitamin E, and Tween 80 is a promising sunscreen preparation due to its good rheological properties and skin compatibility. However, further studies are required to be performed on human volunteers, such as irritation test and *in vivo* SPF measurement, to confirm the safety and efficiency of the formula (F3) for humans. Long-term and/or accelerated stability studies should be carried out according to standard guidelines to confirm F3 stability upon storage. Furthermore, a water resistance test is also required to determine how well the product maintains its protective properties when exposed to water, as in the case of submersion or sweating.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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