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Original Research Article

Ex-Vivo and In-Vivo Evaluation of Benzophenone-3 Loaded Microspheres Incorporated Sunscreen Cream for Enhanced Photoprotection

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Abstract

Excessive exposure to ultraviolet (UV) radiation is a major cause of skin damage, premature aging, and photocarcinogenesis. The present study is aimed to develop and evaluate a microsphere-based sunscreen cream incorporating Benzophenone-3 as an organic UV filter in combination with inorganic UV blockers (zinc oxide and titanium dioxide) to enhance photoprotective efficacy and dermal safety. Benzophenone-3 was encapsulated into ethyl cellulose microspheres to improve photostability and control release characteristics. Five formulations were prepared, including placebo, free drug, microsphere-loaded, inorganic-only, and combined microsphere–inorganic systems. Ex-vivo permeation studies were conducted using Franz diffusion cells with porcine flank skin. In-vivo skin irritation and sun protection factor (SPF) studies were performed using Wistar albino rats. The combined microsphere–inorganic formulation demonstrated the maximum SPF value of 21. Ex-vivo studies showed negligible transdermal permeation (<1%) with predominant drug retention (>90%) in the stratum corneum. All formulations were classified as non-irritant according to the Draize scoring system. The findings confirm that microencapsulation combined with inorganic UV filters significantly enhances sunscreen efficacy, improves photostability, minimizes systemic exposure, and ensures dermal safety. The developed formulation represents a promising strategy for advanced broad-spectrum topical photoprotection.

Keywords: Benzophenone-3; Microspheres; Sunscreen cream; Photoprotection; Franz diffusion cell; In-vivo SPF; Zinc oxide; Titanium dioxide; Skin retention; UV radiation.

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Introduction

Ultraviolet (UV) radiation from sunlight is one of the primary environmental factors responsible for acute and chronic skin damage. Prolonged exposure to UV radiation can lead to erythema, photoaging, hyperpigmentation, immune suppression, and an increased risk of skin cancer. UV radiation is broadly classified into UV-A (320–400 nm), UV-B (280–320 nm), and UV-C (100–280 nm), of which UV-A and UV-B reach the earth's surface and significantly affect human skin. Therefore, the development of effective and safe sunscreen formulations is essential for skin protection. [1-3]

Sunscreens are topical preparations designed to protect the skin by absorbing, reflecting, or scattering UV radiation. Organic (chemical) UV filters function primarily by absorbing UV radiation and converting it into less harmful energy, whereas inorganic (physical) filters reflect and scatter UV rays. [4-5] Among organic UV filters, Benzophenone-3 (Oxybenzone) is widely used due to its ability to absorb UV-B and partial UV-A radiation. However, concerns related to photostability, skin penetration, and potential irritation have prompted the need for improved delivery systems. Microencapsulation technology offers an effective strategy to enhance the stability and safety of topical actives. Incorporating Benzophenone-3 into polymeric microspheres can improve photostability, provide controlled release, minimize direct skin contact, and reduce irritation potential. Ethyl cellulose, a hydrophobic and biocompatible polymer, is commonly used for microsphere preparation due to its film-forming and controlled-release properties. [6-8]

Inorganic UV filters such as zinc oxide (ZnO) and titanium dioxide (TiO_2) are widely recognized for their broad-spectrum protection and excellent skin compatibility. These agents primarily act by reflecting and scattering UV radiation. The combination of organic and inorganic UV filters

may provide synergistic photoprotection, offering enhanced broad-spectrum coverage while improving formulation stability and safety.

Despite the availability of numerous sunscreen products, achieving optimal balance between efficacy, photostability, minimal systemic absorption, and dermal safety remains a formulation challenge. In this context, the present study was designed to develop a microsphere-based sunscreen cream incorporating Benzophenone-3 along with inorganic UV filters and to evaluate it for ex-vivo, and in-vivo performance. [9-10]

The objectives of the study were:

1. To study sunscreen creams containing free drug, drug-loaded microspheres, inorganic UV filters, and their combination.
2. To assess ex-vivo skin permeation using Franz diffusion cell studies.
3. To determine in-vivo dermal safety through skin irritation testing.
4. To evaluate in-vivo Sun Protection Factor (SPF) and compare the photoprotective efficacy of different formulations.

The study aims to provide a scientifically validated approach for developing advanced topical sunscreen systems with improved efficacy and enhanced dermal safety.

Materials and Methods

Materials: Benzophenone-3 (Oxybenzone) was used as the active pharmaceutical ingredient (API). Ethyl cellulose (EC) was used as the polymer for microsphere preparation. Sodium carboxymethyl cellulose (CMC) and Tween 80 served as stabilizer and emulsifying agent, respectively. Polyethylene glycol (PEG) was used as a co-solvent. Chloroform and methanol were used as analytical grade solvents. Zinc oxide and titanium dioxide were used as inorganic UV filters. Aloe vera gel was used as a herbal additive. Phosphate buffer (pH 7.4) was prepared according to standard procedures. All chemicals and reagents used were of analytical grade.

Preparation of Benzophenone-3 Loaded Microspheres [11]: Benzophenone-3 loaded microspheres were prepared using the solvent evaporation technique. The organic phase was prepared by dissolving 500 mg of Benzophenone-3 in 2 mL PEG and incorporating it into ethyl cellulose dissolved in 50 mL chloroform under continuous stirring to obtain a homogeneous solution. The aqueous phase consisted of 0.05% w/v CMC and 1% w/v Tween 80 dissolved in distilled water. The organic phase was added dropwise into the aqueous phase under mechanical stirring at speeds ranging from 1000 to 2000 rpm, and stirring was continued for 2–3 h at room temperature to allow complete evaporation of chloroform and formation of solid microspheres. The formed microspheres were collected by decantation, washed three times with distilled water, air-dried for 24 h, and stored in a desiccator until further evaluation

Preparation of Sunscreen Cream Formulations: The sunscreen cream formulations were prepared using a combination of organic and inorganic UV filters incorporated into a pre-formulated hydrophilic–lipophilic cream base. In the present study, plain cream base was procured from Inc Formulator and used as received. An accurately weighed quantity of the plain cream base was taken in a clean beaker. For formulations containing the organic UV filter, either Benzophenone-3 (F2) or Benzophenone-3 loaded microspheres (F3 and F5) were incorporated. The required amount of Benzophenone-3 was directly dispersed into the cream base under gentle stirring to ensure uniform distribution. In the case of microsphere-loaded formulations, the microspheres were carefully blended into the base using slow and uniform mixing to avoid rupture or structural damage of the microspheres. For formulations containing inorganic UV filters (F4 and F5), zinc oxide and titanium dioxide were gradually incorporated into the cream base with continuous stirring to prevent agglomeration and ensure homogeneous dispersion. Aloe vera gel, where applicable, was also added slowly and mixed thoroughly to maintain uniformity.

The mixture was stirred at 500–700 rpm until a smooth and uniform cream consistency was achieved. Mechanical homogenization was then carried out for 5–10 minutes to enhance dispersion, improve texture, and ensure even distribution of all active ingredients within the base. The prepared sunscreen creams were transferred into clean, dry, airtight containers and stored at room temperature for further evaluation.

Table 1: Formulation Batches

Product Type	Formulation Components	Weight (g)
F1	Placebo (cream base only, unprotected)	20
F2	Cream base + Benzophenone-3 drug	19 + 1
F3	Cream base + Benzophenone-3 microspheres	16 + 4
F4	Cream base + Inorganic agents (ZnO + TiO_2 + Aloe vera gel)	17 + 1 + 1 + 1
F5	Cream base + Organic + Inorganic agents	13 + 4 + 1 + 1 + 1

Evaluation of Sunscreen Cream Formulations: The ex-vivo evaluation of the prepared formulations was done using porcine flank skin to study the permeation of drug across the skin layers.

Ex-Vivo Skin Penetration Studies (Franz Diffusion Cell) [12]: Ex-vivo permeation and skin deposition studies of Benzophenone-3 were performed using a vertical Franz diffusion cell assembly.

The receptor compartment (approximately 20 mL capacity) of the vertical Franz diffusion cell was filled with phosphate buffer (pH 7.4) to maintain sink conditions and continuously stirred using a magnetic stirrer while maintaining the temperature at 37 ± 0.5 °C throughout the experiment. Porcine flank skin, selected due to its structural and permeability similarity to human skin, was carefully cleaned to remove hair and underlying adipose tissue and stored at −20 °C until use. Prior to the study, the skin was thawed, equilibrated to room temperature, and hydrated with phosphate buffer (pH 7.4). The prepared skin (approximately 0.5 mm thickness) was mounted between the donor and receptor compartments with the stratum corneum facing the donor side, ensuring no air entrapment at the interface. The test formulation was applied uniformly over the exposed skin surface at a dose of 5 mg/cm² in the donor compartment, and the assembly was properly sealed to prevent leakage. Aliquots were withdrawn from the receptor compartment at 5-minute intervals for 120 minutes and immediately replaced with an equal volume of fresh phosphate buffer to maintain constant volume and sink conditions. The collected samples were analyzed spectrophotometrically at 286 λ_{max} and cumulative drug permeation was calculated using a previously established calibration curve.

Determination of Drug Deposition in Stratum Corneum (Tape Stripping Method) [13]: After completion of the permeation study, the skin surface was gently blotted to remove residual formulation. The stratum corneum was removed using adhesive tape stripping. Scotch® adhesive tape was repeatedly applied and removed from the same skin area.

The collected strips were placed in methanol and sonicated for 10 minutes to extract the deposited drug. The solution was filtered if necessary and analyzed spectrophotometrically.

Determination of Drug Retention in Skin Tissue: Following tape stripping, the remaining skin tissue was finely cut into small pieces and immersed in 10 mL of methanol. The tissue was sonicated for 10 minutes to extract drug retained in the viable epidermis and dermis. The extract was analyzed using UV–Visible spectrophotometry, and drug retention was quantified using the calibration curve.

In-Vivo Studies: All animal experiments were conducted in accordance with Istitutional ethical guidelines for the care and use of laboratory animals (IAEC No. 08/BNCP/IAEC/2025 B.N. College of Pharmacy, Udaipur, and Rajasthan, India)

In-Vivo Skin Irritation Study[14-15]

Animals and Housing Conditions: Wistar albino rats (n = 30) were used for the study. Animals were housed under controlled environmental conditions (25 ± 2 °C temperature, 60–90% relative humidity, and 12 h light/dark cycle) with free access to standard pellet diet and water. Animals were acclimatized for seven days prior to experimentation.

Experimental Design

The animals were divided into five groups (n = 6):

- **Group I:** Cream base (Control)
- **Group II:** Cream base + Drug
- **Group III:** Cream base + Microspheres
- **Group IV:** Cream base + Inorganic agents
- **Group V:** Cream base + Microspheres + Inorganic agents

The dorsal surface of each rat was shaved 24 h prior to the experiment to expose an area of 6.25 cm². Approximately 0.5 g of formulation was applied uniformly over the marked area. After 30 minutes, the site was gently washed and dried.

Erythema was evaluated at 1, 24, and 72 hours post-application using the Draize scoring scale (0–4). The mean erythema score for each group was calculated.

In-Vivo Sun Protection Factor (SPF) Determination

Preparation of Test Sites: The dorsal skin was depilated using Anne French® depilatory cream 24 h prior to the experiment. The exposed area was divided into designated test sites.

Treatment Groups

Animals were randomly divided into five groups (n = 6):

- **Group I:** Untreated control
- **Group II:** Cream base + 5% pure drug
- **Group III:** Cream base + 5% drug-loaded microspheres
- **Group IV:** Cream base + inorganic agents (ZnO, TiO_2, Aloe vera gel; 5% each)
- **Group V:** Cream base + drug-loaded microspheres + ZnO + TiO_2+ aloevera gel; 5% each)

Application of Formulation: Formulations were applied at 2 mg/cm² and allowed to equilibrate for 30 minutes prior to UV exposure.

UV Exposure: Test sites were exposed to a Xenon arc lamp emitting within the erythemogenic

wavelength range at an intensity of 0.5 mW/cm². Exposure time was gradually increased until minimal erythema dose (MED) was achieved.

Determination of MED and SPF: MED was defined as the minimum UV energy required to produce perceptible erythema.

$$\text{MED (mJ/cm}^2\text{)} = \text{UV Intensity (mW/cm}^2\text{)} \times \text{Exposure Time (seconds)}$$

Sun Protection Factor (SPF) was calculated as:

$$\text{SPF} = \frac{\text{MED (Protected Skin)}}{\text{MED (Unprotected Skin)}}$$

Higher SPF values indicated greater photoprotective efficacy.

Results and Discussion

Ex-Vivo Skin Permeation Study (Franz Diffusion Cell)

Cumulative Drug Permeation: The permeation profile of Benzophenone-3 through porcine skin over 120 minutes showed negligible transdermal diffusion.

No drug was detected during the first 10 minutes (below LOQ), and only 0.13 ± 0.04 µg/cm² (0.07 ± 0.02%) permeated after 120 minutes.

Table 2: Cumulative Amount of Benzophenone-3 Permeated Through Porcine Skin Using Franz Diffusion Cell

Time (min)	Cumulative Amount Permeated (µg/cm²)	% Cumulative Permeation
5	ND	0.00
10	ND	0.00
15	0.02 ± 0.01	0.01 ± 0.00
30	0.04 ± 0.02	0.02 ± 0.01
45	0.06 ± 0.01	0.03 ± 0.01
60	0.08 ± 0.02	0.04 ± 0.01
75	0.09 ± 0.02	0.05 ± 0.01
90	0.11 ± 0.03	0.06 ± 0.02
105	0.12 ± 0.03	0.06 ± 0.02
120	0.13 ± 0.04	0.07 ± 0.02

ND – Not detected (below LOQ), Values expressed as mean ± SD (n = 3)

Table 3: Distribution of Benzophenone-3 after 120 min Permeation Study

Skin Compartment	Amount Recovered (µg/cm²)	% Drug Recovered
Stratum corneum (Tape stripping)	78.6 ± 4.2	92.4 ± 3.1
Viable epidermis + dermis	5.1 ± 0.8	6.0 ± 1.0
Receptor compartment	0.13 ± 0.04	0.7 ± 0.2
Total recovered	**83.8 ± 5.1**	**~99.1**

The minimal cumulative permeation indicates that the formulation effectively restricts systemic absorption. For sunscreen preparations, limited transdermal permeation is desirable to minimize potential systemic exposure and associated safety concerns.

The slow and negligible diffusion may be attributed to:

- High lipophilicity of Benzophenone-3
- Barrier function of the stratum corneum
- Encapsulation within ethyl cellulose microspheres
- Possible occlusive and reflective effects of inorganic agents

These findings suggest that the developed formulation is suitable for topical photoprotection with minimal risk of systemic penetration.

Skin Distribution and Drug Retention: Drug distribution analysis after 120 minutes revealed:

- **Stratum corneum:** 92.4 ± 3.1%
- **Viable epidermis + dermis:** 6.0 ± 1.0%
- **Receptor compartment:** 0.7 ± 0.2%

The majority of the drug remained confined to the stratum corneum, confirming surface-retentive behaviour. This is highly desirable for sunscreen formulations, as the protective effect should be localized to the outermost skin layer where UV exposure occurs.

Minimal drug recovery in the receptor compartment further confirms negligible systemic exposure.

The small fraction detected in viable skin layers likely represents limited partitioning into deeper tissues without significant systemic diffusion.

Overall, the permeation and deposition profile supports the safety and suitability of the microsphere-based formulation for topical use.

In-Vivo Skin Irritation Study: Dermal safety evaluation revealed excellent tolerability of all developed formulations.

The cream base (control) showed no erythema at any observation period, confirming that excipients were non-irritant.

The formulation containing free drug showed slight erythema (score = 1) at 1 hour, which resolved completely by 24 hours. This transient reaction may be due to direct interaction of free drug molecules with the skin surface.

Table 4: In Vivo Skin Irritation Test (Erythema Score)

S. No.	Formulation Type	0 h	1 h	24 h	72 h	Mean Erythema Score
1	Cream base (Control)	0	0	0	0	0.00
2	Cream base + Drug	0	1	--	--	0.25
3	Cream base + Microspheres	0	0	0	0	0.00
4	Cream base + Inorganic agents	0	0	0	0	0.00
5	Cream base + Microspheres + Inorganic agents	0	0	0	0	0.00

Notably, the microsphere-containing formulation showed no erythema at any time point. Encapsulation likely minimized direct drug–skin contact and reduced irritation potential. Similarly, the formulation containing inorganic agents did not produce any erythema. Zinc oxide and titanium dioxide are widely recognized as skin-compatible physical UV blockers, and aloe vera may have contributed anti-inflammatory effects.

The combined formulation (microspheres + inorganic agents) showed complete absence of erythema, demonstrating excellent dermal compatibility.

All formulations exhibited mean erythema scores ≤ 0.25, classifying them as non-irritant according to the Draize scale.

These findings confirm the dermatological safety of the developed sunscreen systems.

In-Vivo Sun Protection Factor (SPF) Determination: The in vivo SPF study demonstrated significant differences in photoprotective efficacy among formulations. The unprotected control exhibited a minimal erythema dose (MED) of 150 mJ/cm², representing baseline UV sensitivity.

Table 5: Determination of MED and Sun Protection Factor (SPF)

S. No.	Treatment / Formulation	Intensity	Time (seconds)	MED (mJ/cm^2)	SPF Value
1	Unprotected skin (Control)	0.5	300	150	0
2	Formulation 1: Cream base + 5% pure drug	0.5	3600	1800	12
3	Formulation 2: Cream base + 5% drug-loaded microspheres	0.5	5400	2700	18
4	Formulation 3: Cream base + inorganic agents (ZnO + TiO_2 + Aloe vera gel)	0.5	3300	1650	11
5	Formulation 4: Cream base + drug-loaded microspheres + ZnO + TiO_2+ Aloe vera gel	0.5	6300	3150	21

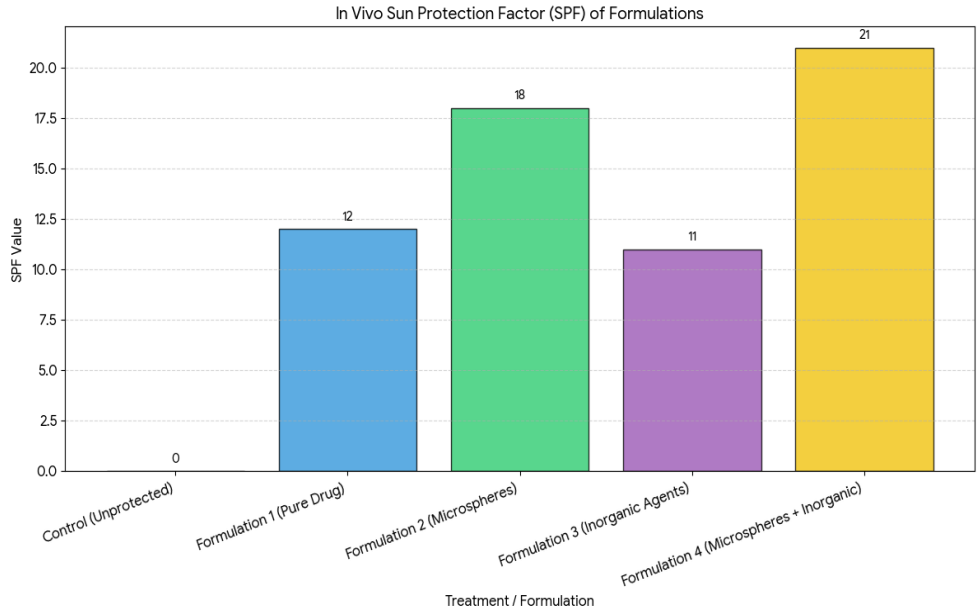

Figure 1: Bar Graph of Sun Protection Factor (SPF) Determination

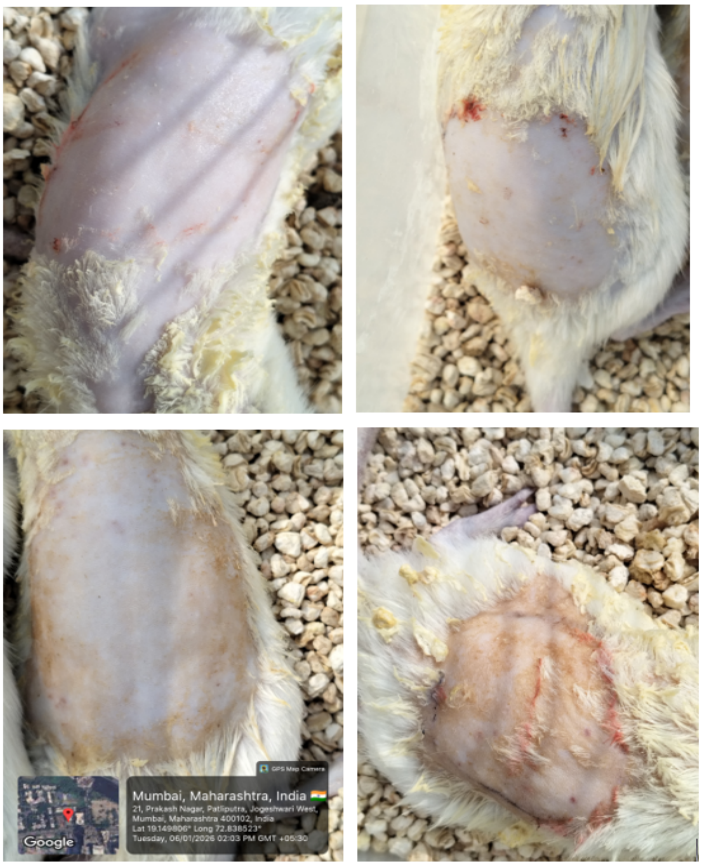

Figure :. Images of In-vivo study

The formulation containing pure drug showed an SPF of 12, indicating moderate UV protection.

Encapsulation of the drug into microspheres increased SPF to 18. The improvement can be attributed to enhanced photostability, uniform film formation, and possibly increased light absorbance from the microsphere matrix. The inorganic agent formulation produced an SPF of 11, slightly lower than the microsphere formulation but consistent with physical UV-blocking activity.

The combined formulation achieved the highest SPF value of 21, nearly doubling the protection compared to pure drug alone. This superior efficacy reflects synergistic interaction between:

- Chemical UV absorption (Benzophenone-3)
- Controlled release and photostability (microspheres)
- Physical UV reflection and scattering (ZnO and TiO_2)

The dense barrier formed by inorganic particles likely filled interstitial gaps between microspheres, enhancing uniform surface coverage and broad-spectrum protection.

Overall Interpretation

The study demonstrates that formulation strategy significantly influences sunscreen performance.

Key findings include:

- Microencapsulation enhances photostability and sunscreen efficacy.
- Combination of organic and inorganic UV filters produces synergistic protection.
- Drug retention is primarily localized to the stratum corneum (>90%).
- Systemic permeation is negligible (<1%).
- All formulations are non-irritant and dermatologically safe.
- The combined microsphere–inorganic formulation achieved the highest SPF (21).

Collectively, these results confirm that the developed microsphere-based combination formulation offers improved efficacy, enhanced safety, and superior photoprotective performance, making it a promising candidate for advanced topical sunscreen applications.

Conclusion

The present investigation successfully developed and evaluated a microsphere-based sunscreen formulation incorporating Benzophenone-3 and inorganic UV filters. The findings clearly demonstrate that formulation strategy plays a critical role in determining sunscreen efficacy and dermal safety. Encapsulation of Benzophenone-3 into ethyl cellulose microspheres significantly improved photostability, enhanced sunscreen protection, and reduced irritation potential compared to the free drug formulation.

The combination of microspheres with inorganic agents (zinc oxide and titanium dioxide) produced a synergistic effect, resulting in the highest SPF value and superior broad-spectrum protection.

Ex-vivo permeation studies confirmed minimal systemic absorption and predominant retention of the drug within the stratum corneum, supporting the suitability of the formulation for safe topical application. In-vivo studies further validated its excellent dermal compatibility and enhanced photoprotective performance. Among all tested formulations, the combination of drug-loaded microspheres with inorganic UV filters emerged as the most effective and safest sunscreen preparation. This approach offers a promising strategy for developing advanced topical photoprotective systems with improved efficacy, reduced irritation, and enhanced skin safety.

Future studies may focus on long-term stability evaluation, clinical trials in human subjects, and assessment of water resistance and broad-spectrum UVA protection to further establish its commercial applicability.

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