RESEARCH PAPER

Formulation Development and Characterization of Benzoyl Peroxide–Emodin Nanostructured Proniosomal Gel for Topical Antifungal Activity against *Candida albicans*

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ABSTRACT
The development of localized topical drug delivery systems is of interest for the management of cutaneous fungal infections. This study aimed to develop and characterize a benzoyl peroxide–emodin nanostructured proniosomal gel for topical application and evaluate its in-vitro antifungal activity against *Candida albicans*. Benzoyl peroxide and emodin proniosomal gels were prepared separately using the coacervation phase separation method with cholesterol, soya lecithin, Span 60, and Tween 80. The optimized formulations were incorporated into Carbopol 934 gel to obtain a combination formulation. The formulations were evaluated for compatibility by FTIR and DSC and characterized for entrapment efficiency, drug content, pH, viscosity, spreadability, vesicle size, polydispersity index, zeta potential, surface morphology, and in-vitro drug release. BPPG5 and EmPG5 exhibited the highest entrapment efficiencies of 91.07 ± 1.19% and 85.44 ± 0.63%, respectively, with drug contents of 93.82 ± 0.73% and 90.43 ± 0.81%, respectively. The optimized BPPG5–EmPG5 formulation showed a pH of 6.8 ± 0.93, viscosity of 8639 ± 3.78 cP, and spreadability of 45 ± 1.09 mm. The mean vesicle size, PDI, and zeta potential were 488.1 nm, 0.183, and −32.1 mV, respectively. At 24 h, the cumulative drug release reached 93.21 ± 1.64% for benzoyl peroxide and 90.76 ± 2.19% for emodin. The combination formulation showed a 17 mm zone of inhibition against *C. albicans*, compared with 16 and 15 mm for BPPG5 and EmPG5, respectively. Overall, the developed formulation exhibited suitable physicochemical characteristics, measurable drug release over 24 h, and promising in-vitro antifungal activity against *C. albicans*.

Keywords: Benzoyl peroxide; emodin; proniosomal gel; nanostructured vesicles; *Candida albicans*; antifungal activity; topical drug delivery.
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.INTRODUCTION

Skin infections are an important public health concern because of their substantial disease burden, treatment limitations, and increasing antimicrobial resistance. The World Health Organization (WHO) established the Fungal Priority Pathogens List to prioritize research and development against fungal pathogens associated with significant public health impacts and unmet therapeutic needs[1]. *Candida albicans* is classified as a critical-priority pathogen, emphasizing the need for effective antifungal interventions and improved therapeutic approaches[2]. The continuing emergence of antifungal resistance and limitations in the antifungal development pipeline further support the investigation of alternative bioactive agents and innovative drug delivery systems.[3]

Cutaneous fungal infections commonly affect the skin, hair, and nails and may be caused by dermatophytes and yeasts, such as Candida spp.[4] *C. albicans* is an opportunistic pathogen capable of morphological transition and biofilm formation, characteristics that contribute to its persistence and pathogenicity.[5] Although topical therapy provides localized drug administration, inadequate residence time, variable drug release, and limitations in drug deposition may influence therapeutic performance.[6,7] Therefore, vesicular topical systems that can improve formulation retention and modify drug release are of considerable interest.

Benzoyl peroxide (BPO) is an established topical antimicrobial and keratolytic agent widely used in dermatological formulations, particularly for the treatment of acne. Its antimicrobial activity is primarily associated with the generation of reactive oxygen species (ROS)[6,7] However, its topical performance can be influenced by the formulation characteristics, drug release, and localization within the skin. In this study, BPO was incorporated as an established topical antimicrobial component rather than as a conventional antifungal drug, and its combination with a phytoconstituent was investigated as a topical formulation strategy[8–10].

Emodin is a naturally occurring anthraquinone phytoconstituent found in several medicinal plants that has attracted interest because of its diverse biological activities.[11] Importantly, Emodin has demonstrated direct antifungal activity against C. albicans. Janeczko et al. reported that Emodin inhibited the growth of reference and clinical Candida strains and suppressed hyphal development and biofilm formation, with protein kinase CK2 suggested as a possible fungal target.[8] Emodin has also been reported to reduce the activity of (1,3)-β-D-glucan synthase in *C. albicans*, suggesting an effect on fungal cell wall-associated processes.[9] Earlier experimental studies have demonstrated concentration-dependent inhibition of *C. albicans* growth.[10] These findings provide a rationale for investigating emodin as a phytoconstituent in topical formulations targeting *C. albicans*. However, its formulation development may be influenced by physicochemical and biopharmaceutical limitations, supporting the need for an appropriate delivery system.[11]

Proniosomal gel is a semisolid precursor systems that generate niosomal vesicles upon hydration. They are composed mainly of non-ionic surfactants, cholesterol, and other membrane-forming components. They have attracted interest because of their formulation flexibility, drug loading capacity, and physicochemical stability.[12–14] Proniosomal gel systems are particularly suitable for topical administration because the resulting vesicles can be incorporated into semisolid bases, combining vesicular drug delivery characteristics with the practical advantages of topical application. Niosomal and proniosomal systems have been investigated for topical and transdermal delivery, and can influence drug localization and release characteristics.[12–14] Carbopol-based gels provide suitable consistency and rheological properties for topical administration and can serve as vehicles for vesicular formulations.[15]

The combination of BPO and Emodin represents a rational formulation approach, wherein an established topical antifungal component is combined with a phytoconstituent possessing experimentally demonstrated antifungal activity against *C. albicans*.[6–10] incorporating both components into a nanostructured proniosomal gel may provide a suitable localized delivery platform and facilitate the evaluation of their formulation performance and antifungal potential. However, limited information is available on the development and characterization of a BPO–emodin combination incorporated into a nanostructured proniosomal gel and evaluated against *C. albicans*[15].

The present study aimed to develop and characterize a Benzoyl Peroxide–emodin nanostructured proniosomal gel using cholesterol, soya lecithin, Span 60, and Tween 80, followed by incorporation of the optimized proniosomal formulations into a Carbopol 934 gel base. The formulations were evaluated for compatibility by FTIR and DSC and characterized for entrapment efficiency, drug content, pH, viscosity, spreadability, vesicle size, polydispersity index, zeta potential, surface morphology, and in-vitro drug release and antifungal activity against *C. albicans* were evaluated to determine the performance of the optimized formulation.

MATERIALS AND METHODS

Drug and Chemicals

Benzoyl peroxide and emodin were used as the active pharmaceutical ingredients and were procured from Shri Kamla Educational Agency, Akola, Maharashtra, India. Cholesterol, soya lecithin, Span 60, and Tween 80 were used for proniosome preparation, while Carbopol 934 was used as the gelling polymer. Methanol, phosphate-buffered saline (PBS), methyl paraben, propyl paraben, propylene glycol, and triethanolamine were used for the formulation and evaluation. All other chemicals and reagents were of analytical grade. *Candida albicans* was used for in-vitro antifungal evaluation of the optimized formulations. The microbiological study was performed at the Department of Microbiology, Rajasthan Aryan Arts, Shri Mithulalalji Kacholiya Commerce, and Shri Satyanarayanji Ramkrishnaji Rathi Science Mahavidyalaya, Washim, Maharashtra, India.

Preformulation Studies

Benzoyl peroxide and emodin were evaluated for appearance, solubility, and melting point before formulation. The solubility was qualitatively assessed in methanol and phosphate-buffered saline (PBS), and the melting point was determined using the digital melting point apparatus[16].

UV-Visible Spectrophotometric Analysis

Standard solutions of benzoyl peroxide and emodin were prepared in methanol and diluted to 5–25 µg/mL. Benzoyl peroxide and emodin showed maximum absorbance at 235 and 224 nm, respectively. Calibration curves were prepared for the quantitative estimation of drugs[16].

FTIR Studies

FTIR spectra of the drugs and the optimized formulation were recorded over 4000–400 cm^{-1} to identify the characteristic functional groups and assess drug–excipient compatibility[16].

Differential Scanning Calorimetry (DSC)

DSC thermograms of benzoyl peroxide, emodin, and the optimized formulation were recorded to evaluate their thermal behavior and assess possible changes following the formulation[16].

Preparation of Benzoyl Peroxide Proniosomal Gel

Benzoyl peroxide proniosomal gels (BPPG1–BPPG8) were prepared using the coacervation phase separation method. The formulations were prepared by applying two levels and three variables Factorial Design. Cholesterol, soya lecithin and combination of surfactants (Span 60 and Tween 80 in 1:1 ratio)

were the variables. Benzoyl peroxide along with excipients were dissolved in methanol and heated at 60–65°C for 5–10 min at 40 rpm. Preheated PBS was then added gradually with continuous stirring to obtain the proniosomal gel. The formulations were stored in airtight containers protected from light exposure.

Table 1. Composition of Benzoyl Peroxide proniosomal gel formulations

Formulation	BPO (mg)	Cholesterol (mg)	Soya lecithin (mg)	Span 60 (mg) + Tween 80 (mg)
BPPG1	25	90	180	90 + 90
BPPG2	25	90	180	45 + 45
BPPG3	25	90	90	90 + 90
BPPG4	25	90	90	45 + 45
BPPG5	**25**	**45**	**180**	**90 + 90**
BPPG6	25	45	180	45 + 45
BPPG7	25	45	90	90 + 90
BPPG8	25	45	90	45 + 45

Preparation of Emodin Proniosomal Gel

Emodin proniosomal gels (EmPG1–EmPG8) were prepared using the coacervation phase separation method. The formulations were prepared by applying two levels and three variables Factorial Design. Cholesterol, soya lecithin and combination of surfactants (Span 60 and Tween 80 in 1:1 ratio) were the variables. Emodin along with excipients were dissolved in methanol and heated at 60–65°C for 5–10 min at 40 rpm. Preheated PBS was then added gradually with continuous stirring to obtain the proniosomal gel. The formulations were stored in airtight containers protected from light exposure[16].

Table 2. Composition of Emodin proniosomal gel formulations

Formulation	Emodin (mg)	Cholesterol (mg)	Soya lecithin (mg)	Span 60 (mg) + Tween 80 (mg)
EmPG1	10	90	180	90 + 90
EmPG2	10	90	180	45 + 45
EmPG3	10	90	90	90 + 90
EmPG4	10	90	90	45 + 45
EmPG5	**10**	**45**	**180**	**90 + 90**
EmPG6	10	45	180	45 + 45
EmPG7	10	45	90	90 + 90
EmPG8	10	45	90	45 + 45

Preparation of Benzoyl Peroxide–Emodin Combination Formulation

Optimized BPPG5 and EmPG5 were incorporated into a 1.5% Carbopol 934 gel and mixed gently to obtain a homogeneous Benzoyl Peroxide–emodin proniosomal gel. The formulation was allowed to stand overnight to remove the entrapped air and was stored in an airtight container.

Characterization of Proniosomal Gel

The formulations were evaluated for appearance, entrapment efficiency, drug content, pH, viscosity, and spreadability. Optimized formulations were further evaluated for vesicle size, PDI, zeta potential, surface morphology, and in vitro drug release. For entrapment efficiency, approximately 1 g of the formulation was hydrated with PBS and centrifuged at 18,000 rpm for 40 min at 4°C. The free drug was quantified spectrophotometrically.

EE (%) = [(Total drug − Free drug) / Total drug] × 100

Drug content was determined after methanolic extraction and spectrophotometric estimation[16,17].

Vesicle Size and Polydispersity Index

The vesicle size and PDI of the optimized formulation were determined by dynamic light scattering (DLS) using a Zetasizer after suitable dilution with distilled water at room temperature[17].

Zeta Potential

The zeta potential of the optimized formulation was determined by electrophoretic light scattering using a Zetasizer after dilution with distilled water.

Surface Morphology by Scanning Electron Microscopy

The surface morphology of the optimized formulation was examined using scanning electron microscopy (SEM) after suitable sample preparation and mounting.

In-vitro Drug Release

In-vitro drug release was evaluated using a Franz diffusion cell with a dialysis membrane at 37 ± 0.5°C under continuous stirring. Samples were withdrawn at predetermined intervals, replaced with fresh receptor medium, and analyzed spectrophotometrically at the respective λmax. The cumulative drug release was calculated[18–20].

Antifungal Activity against Candida albicans

The antifungal activity of the optimized formulations was evaluated against *Candida albicans* using the agar well diffusion method. Formulations were filled to wells in inoculated agar plates and incubated under appropriate microbiological conditions. The zone of inhibition (ZOI) was measured in millimetres (mm) after incubation for 24 hrs[21].

RESULTS AND DISCUSSION

Preformulation Studies

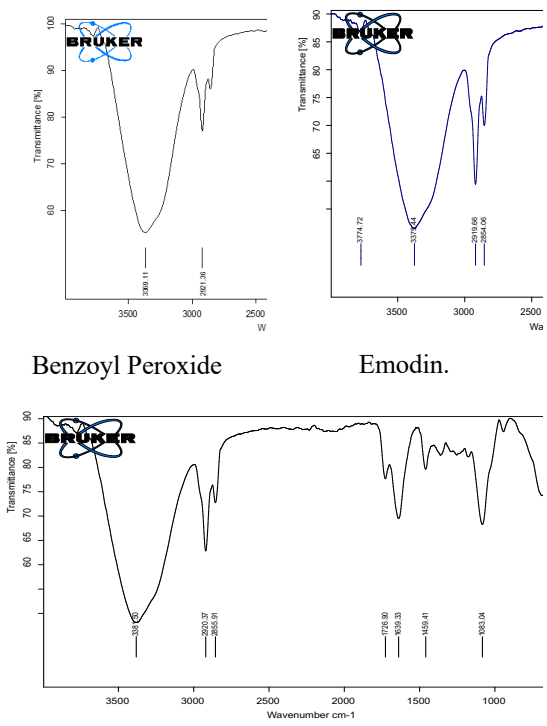
Benzoyl Peroxide and Emodin appeared as white and orange crystalline powders, respectively, and were soluble in methanol and slightly soluble in PBS. Their melting points were 105 ± 0.93°C and 255.63 ± 0.71°C, respectively, supporting their suitability for formulation development.

UV-Visible Spectrophotometric Analysis

Benzoyl Peroxide and Emodin exhibited maximum absorption at 235 and 224 nm, respectively. Calibration curves were plotted over a range of 5–25 µg/mL and were used for the subsequent quantitative estimation of the drugs.

FTIR Study

The FTIR spectra of the optimized formulation showed characteristic bands at approximately 1083, 1639, 1726, 2855, 2920, and 3381 cm^{-1}. The absence of major changes in the characteristic functional group bands indicated no evident chemical incompatibility between the active components and the formulation excipients.



Benzoyl Peroxide Emodin.

BPPG5–EmPG5 formulation.

Figure 1. FTIR spectra of Benzoyl Peroxide, Emodin, and the optimized BPPG5–EmPG5 formulation.

DSC Study

Benzoyl Peroxide and Emodin showed characteristic endothermic transitions at 112.59°C and 261.11°C, respectively. The absence of the characteristic endothermic peak of Benzoyl Peroxide and Emodin in BPPG + EmPG indicated that the drugs were molecularly dispersed and effectively entrapped within the proniosomal vesicular or lamellar structure.

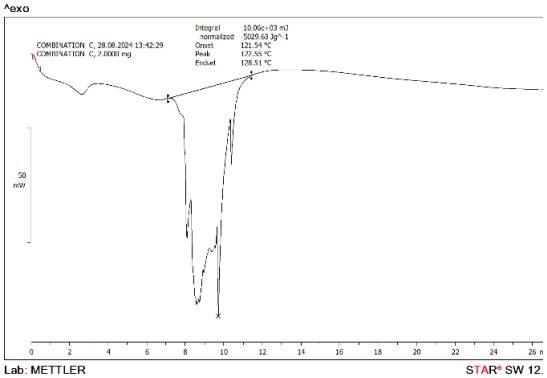


Figure 2. DSC thermograms of optimized BPPG5–EmPG5 formulation

Formulation Optimization of Benzoyl Peroxide Proniosomal Gel

Among BPPG1–BPPG8, BPPG5 exhibited the highest entrapment efficiency (91.07 ± 1.19%) and drug content (93.82 ± 0.73%) and was selected for further development.

Formulation Optimization of Emodin Proniosomal Gel

Among EmPG1–EmPG8, EmPG5 exhibited the highest entrapment efficiency (85.44 ± 0.63%) and drug content (90.43 ± 0.81%) and was selected for further development.

Physicochemical Characterization of Optimized BPPG5–EmPG5 Combination Gel

The optimized BPPG5–EmPG5 formulation showed a pH of 6.8 ± 0.93, viscosity of 8639 ± 3.78 cP, and spreadability of 45 ± 1.09 mm, indicating suitable characteristics for topical application.

Vesicle Size, PDI and Zeta Potential

The optimized BPPG5–EmPG5 formulation showed a mean vesicle size of 488.1 nm, PDI of 0.183, and zeta potential of −32.1 mV, indicating a relatively uniform vesicle population and favorable surface-charge characteristics.

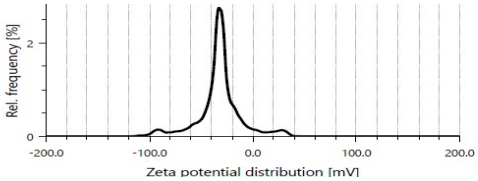


Figure 3. Zeta potential distribution of the optimized BPPG5–EmPG5 formulation.

SEM Surface Morphology

SEM analysis of the optimized BPPG5–EmPG5 formulation revealed discrete vesicular structures, supporting the formation of the proniosomal system.

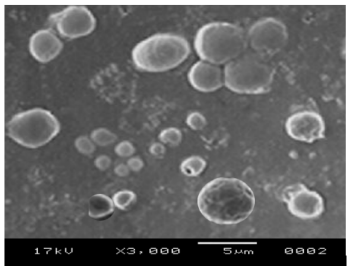


Figure 4. SEM image of the optimized BPPG5–EmPG5 proniosomal formulation.

In-vitro Drug Release

The drug release of prepared formulations were determined for 24 hrs period. BPPG5 released 93.21 ± 1.64% of Benzoyl Peroxide, whereas EmPG5 released 90.76 ± 2.19% emodin at 24 h. The observed release profile may be associated with drug diffusion from the proniosomal vesicles.

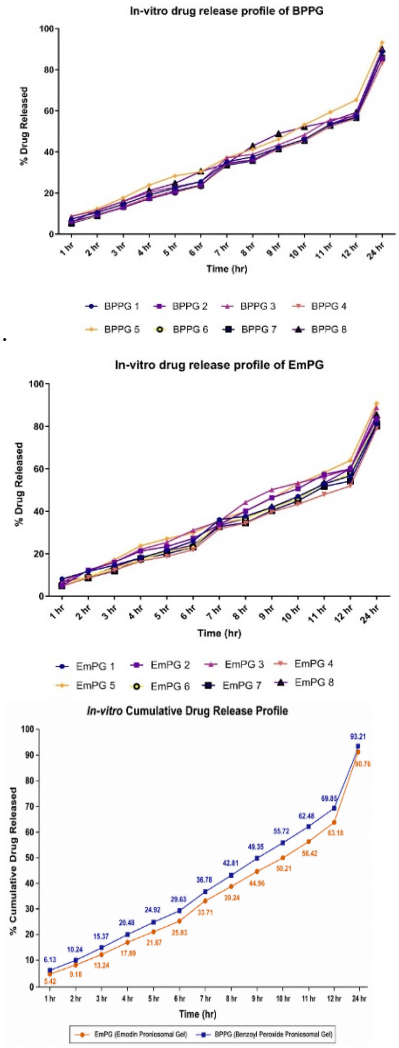
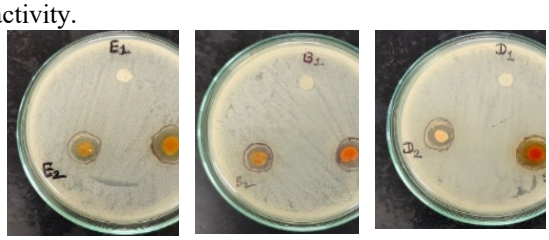


Figure 5. In-vitro cumulative drug-release profiles of BPPG5 and EmPG5 over 24 h.

In-vitro Antifungal Activity against Candida albicans

The optimized formulations were evaluated against *Candida albicans* using the agar well diffusion method. BPPG5, EmPG5, and BPPG5–EmPG5 showed inhibition zones of 16, 15, and 17 mm, respectively. The combination formulation showed a larger inhibition zone than the individual formulations, indicating enhanced in vitro antifungal activity.



EmPG5 BPPG5 BPPG5–EmPG5

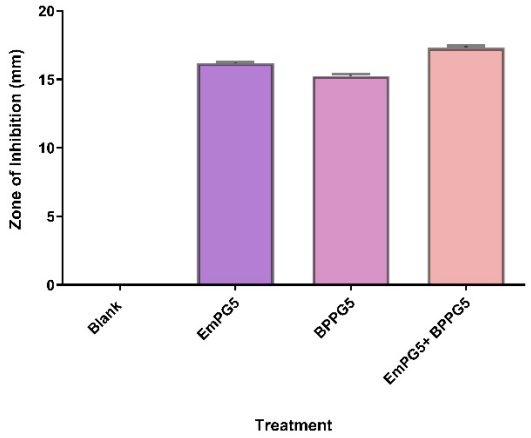


Figure 6. In-vitro antifungal activity of optimized EmPG5, BPPG5 and BPPG5–EmPG5 formulations against *Candida albicans*.

The present study successfully developed a Benzoyl Peroxide–emodin nanostructured proniosomal gel for topical delivery against *Candida albicans*. Optimization of the individual formulations identified BPPG5 and EmPG5 as the best formulations, showing high entrapment efficiencies of 91.07 ± 1.19% and 85.44 ± 0.63%, respectively. The higher entrapment may be attributed to the favorable balance of cholesterol, soya lecithin, and Span 60/Tween 80, which supported efficient vesicle formation and drug incorporation.

The optimized BPPG5–EmPG5 combination gel exhibited a pH of 6.8 ± 0.93, viscosity of 8639 ± 3.78 cP, and spreadability of 45 ± 1.09 mm, indicating suitable physicochemical properties for topical application. The vesicle size of 488.1 nm, PDI of 0.183, and zeta potential of −32.1 mV indicated a relatively uniform vesicle population with favorable surface-charge characteristics. SEM further confirmed the presence of discrete vesicular structures.

The optimized formulations showed substantial drug release over 24 h, with 93.21 ± 1.64% release of benzoyl peroxide and 90.76 ± 2.19% release of emodin.

In the antifungal study, BPPG5, EmPG5, and BPPG5–EmPG5 showed inhibition zones of 16, 15, and 17 mm, respectively, against *C. albicans*. The slightly larger inhibition zone produced by the combination formulation suggests enhanced apparent in-vitro antifungal activity compared with the individual formulations.

CONCLUSION

The present study successfully developed a Benzoyl Peroxide–emodin nanostructured proniosomal gel for topical application. BPPG5 and EmPG5 exhibited high entrapment efficiencies of 91.07 ± 1.19% and 85.44 ± 0.63%, respectively. The optimized combination showed suitable topical characteristics, including pH 6.8 ± 0.93, viscosity 8639 ± 3.78 cP, spreadability 45 ± 1.09 mm, vesicle size 488.1 nm, PDI 0.183, and zeta potential −32.1 mV. The optimized formulations showed drug release over 24 h, while BPPG5–EmPG5 showed a 17 mm zone of inhibition against *Candida albicans*, compared to 15 mm for BPPG5 and 16 mm for EmPG5. Overall, the findings support the potential of the BPO–emodin proniosomal gel as a topical vesicular formulation with promising in vitro antifungal activity.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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