

Review Article

Nanosponge-Based Topical Delivery of Anti-Acne Agents: Formulation Strategies, Published Evidence and Translational Prospects

Shyammurti Kumar¹, Pankaj Kumar¹, Basit Fazal², Shantanu Ranjan³ and Manish Kumar²

¹Department of Pharmaceutical Chemistry, Nibha Institute of Pharmaceutical Sciences, Rajgir, Nalanda, India

²Department of Pharmacology, Nibha Institute of Pharmaceutical Sciences, Rajgir, Nalanda, India

³Department of Pharmaceutics, Nibha Institute of Pharmaceutical Sciences, Rajgir, India

ARTICLE INFO

Received: 13 July 2026

Revised: 30 August 2026

Available Online: 12 September 2026

*Corresponding author:

Mr. Pankaj Kumar; Department of Pharmaceutical Chemistry, Nibha Institute of Pharmaceutical Sciences, Rajgir, India.

ABSTRACT

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit driven by interacting abnormalities in sebum production, follicular keratinization, Cutibacterium acnes-associated inflammation and host immune responses. Benzoyl peroxide, topical retinoids and other guideline-supported agents remain effective, but local irritation, formulation-dependent tolerability, instability of some actives and adherence challenges continue to motivate advanced topical delivery approaches. Nanosponges are porous, cross-linked particulate carriers—frequently based on cyclodextrins or polymers such as ethyl cellulose—with internal cavities and high surface area that can modify drug solubility, retention and release. This project critically verifies published evidence on anti-acne nanosponge systems, with particular emphasis on benzoyl peroxide and azelaic acid. The published benzoyl peroxide study identified an ethyl-cellulose formulation (F9) with a particle-size range of 80–200 nm and loading efficiency of $87.9 \pm 1.38\%$. Its 5% nanosponge-gel formulation (F9C) showed 98.39% cumulative release/permeation at 12 h in the reported in-vitro study, a flux of $0.1672 \text{ mg/cm}^2\text{-h}$, a drug content of 95.74%, and non-Fickian release behavior. The formulation remained physically acceptable during 60 days of accelerated storage. Independent work with β -cyclodextrin nanosponges loaded with azelaic acid reported approximately five-fold improvement in aqueous solubility, 228 nm mean particle size, 0.14 polydispersity index, -21 mV zeta potential, approximately 88% encapsulation efficiency and controlled 24-h release. These data support nanosponges as promising topical carriers, but they do not establish clinical superiority. The main translational gaps are limited human clinical evidence, inconsistent terminology and characterization, scale-up, long-term safety, standardization of release/permeation methods, and the need to demonstrate clinically meaningful improvement over optimized conventional formulations.

Keywords: Acne Vulgaris; Benzoyl Peroxide; Azelaic Acid; Nanosponges; Cyclodextrin; Ethyl Cellulose; Topical Drug Delivery; Controlled Release; Skin Permeation; Nanocarrier.

Introduction

Acne vulgaris is among the most common inflammatory skin disorders and is characterized by comedones, papules, pustules and, in more severe disease, nodules, cysts and scarring. Global Burden of Disease 2019 analyses estimated approximately 231.2 million prevalent cases worldwide and 117.4 million incident cases, illustrating the scale of the condition. Acne is not simply a cosmetic problem: persistent lesions and scarring can affect psychosocial functioning and quality of life. [1,2]

The pathophysiology is multifactorial. Androgen-driven sebaceous activity increases sebum production; abnormal follicular keratinization promotes microcomedone formation; changes in the follicular microbial environment involving *C. acnes* contribute to innate and adaptive inflammatory signaling; and rupture of the follicular unit amplifies inflammation. Modern models therefore emphasize the interaction of sebogenesis, hyperkeratinization, microbial ecology and inflammation rather than attributing acne to a single organism. [3–5]

Current evidence-based management supports benzoyl peroxide (BPO), topical retinoids, topical antibiotics in appropriate combinations, azelaic acid and selected systemic therapies. The 2024 American Academy of Dermatology guideline strongly recommends BPO and topical retinoids and recommends combining topical agents with complementary mechanisms. Importantly, topical antibiotic monotherapy is discouraged and BPO is recommended in combination regimens to reduce the risk of antimicrobial resistance. [6]

Despite efficacy, conventional topical therapy can be limited by concentration- and vehicle-dependent burning, stinging, dryness, erythema, peeling and irritation. BPO is particularly effective but may cause local irritation and bleaching of fabrics. Such limitations create a rational formulation target: maintain sufficient drug exposure at the skin site while reducing unnecessary free-drug exposure and controlling release. [6,7]

Nanosponges have attracted attention as porous drug carriers capable of accommodating molecules through inclusion, adsorption or matrix entrapment. Cyclodextrin-based nanosponges are three-dimensional cross-linked networks, whereas polymeric systems may use ethyl cellulose and other polymers. For topical delivery, the intended benefit is not systemic 'movement' of nanoparticles through the body, as suggested in the supplied thesis, but modification of drug solubility, stability, skin retention, release kinetics and, where demonstrated experimentally, local deposition. [8,9]. This project

provides a broad discussion of acne, nanosponges, anti-acne actives and published nanosponge studies.

Objectives

- To critically synthesize the formulation rationale for nanosponge-based topical delivery of anti-acne agents.
- To verify and correct key scientific statements in the supplied thesis using current guidelines and peer-reviewed literature.
- To summarize quantitative formulation and performance data from traceable published studies, especially benzoyl peroxide and azelaic acid systems.
- To identify formulation, analytical, safety and translational gaps that must be addressed before clinical adoption.

Methods of Evidence Synthesis

The supplied thesis was examined for its stated rationale, formulation concepts, cited studies, quantitative results and conclusions. The scientific claims were cross-checked against accessible peer-reviewed publications, PubMed-indexed literature, current acne guidelines and published primary formulation studies. Priority was given to primary studies for numerical formulation data and to contemporary guidelines/reviews for clinical context. Data that could not be verified were not converted into invented values. Where the thesis conflated general nanosponge properties with acne-specific evidence, the claim was narrowed to the level supported by the literature.

For the benzoyl peroxide nanosponge study, the published formulation tables and release/permeation data were transcribed and interpreted without alteration. For azelaic acid, quantitative findings were cross-checked against the published Polymer Bulletin study and a recent comprehensive formulation review. Because the present manuscript is an evidence synthesis rather than a new experiment, no human or animal ethics approval was required for this manuscript itself.

Results and Evidence Synthesis

Corrected scientific basis for nanosponge delivery

The thesis correctly identifies nanosponges as porous carriers with potential for controlled release, solubility enhancement and topical delivery, but several statements require correction. First, nanosponge size is not universally fixed at a single range; reported systems span the nano- to submicron scale depending

on composition and preparation. Second, 'targeting' the pilosebaceous unit should not be stated as an established clinical property unless follicular deposition or localization is experimentally demonstrated. Third, nanosponges should not automatically be described as non-toxic, non-irritant or non-mutagenic: these are formulation-specific claims requiring appropriate safety studies. Finally, antibacterial effects against acne should not be inferred from testing against an unrelated organism; *C. acnes*-specific testing is preferable when acne efficacy is the question. [8–10]

The most defensible formulation hypothesis is therefore that nanosponge encapsulation can alter the physicochemical and release behavior of a topical active and may increase skin retention or controlled delivery. Whether these changes translate into superior clinical outcomes depends on the active, polymer, cross-link density, particle size, surface properties, gel vehicle, dose and patient skin biology.

Published benzoyl peroxide nanosponge evidence

Raytthatha et al. developed BPO-loaded nanosponges by a quasi-emulsion solvent-diffusion method using HPMC K4M, Eudragit RL100 or ethyl cellulose as the polymer and PVA as the external-phase stabilizer. Nine batches were prepared. The HPMC and Eudragit batches produced yields below 50%, whereas the ethyl-cellulose batches F7–F9 produced yields of $77.5 \pm 0.45\%$, $78.6 \pm 2.86\%$ and $82.1 \pm 2.31\%$, respectively. F9 had the highest reported loading efficiency ($87.9 \pm 1.38\%$) and a particle-size range of 80–200 nm, and was therefore selected for gel development. [11]

Three F9-based Carbopol 934 gels containing 1%, 3% and 5% nanosponge were evaluated. Their reported viscosities were 3285, 3353 and 3462 cP, respectively, with pH values of 6.8, 7.1 and 6.9. The 5% nanosponge gel (F9C) showed the highest cumulative release/permeation values across the reported 12-h study. The authors reported a flux of $0.1672 \text{ mg/cm}^2 \cdot \text{h}$ for F9C. In antimicrobial testing against *Staphylococcus aureus*, the zones of inhibition were 5.5, 11.3 and 17.4 mm for F9A, F9B and F9C, respectively. [11]

The selected F9C gel was compared with a marketed 5% BPO gel. F9C had a viscosity of 3462 cP, pH 6.5, clear appearance and 95.74% drug content, whereas the marketed formulation had 3321 cP, pH 6.8 and 97.73% drug content. In the reported diffusion experiment, the marketed product reached 91.81% at 9 h, whereas F9C reached 98.39% at 12 h. The authors fitted release data to several kinetic models; the Korsmeyer–Peppas model gave the highest R^2 for F9C (0.9989) with $n = 0.6444$, interpreted as non-Fickian transport. [11]

The formulation was reported to remain stable for 60 days under $40 \pm 0.5^\circ \text{C}/75 \pm 5\%$ relative humidity, with viscosity decreasing from 3415 to 3254 cP and 12-h permeation decreasing from 98.39% initially to 96.79% at 60 days. These findings support formulation feasibility but should not be interpreted as evidence of long-term clinical stability because the study duration was only 60 days and did not establish a formal shelf life. [11]

Table 1: Published quantitative profile of the optimized BPO nanosponge system.

Parameter	F9 nanosponge / F9C gel	Interpretation
Polymer	Ethyl cellulose	Highest-yield polymer among tested groups
Particle size	80–200 nm	Nano/submicron range reported
Loading efficiency	$87.9 \pm 1.38\%$	Highest among F7–F9
Gel nanosponge level	5% w/w (F9C)	Selected concentration
Viscosity	3462 cP	Within the study's target range
pH	6.5	Compatible with topical skin application
Drug content	95.74%	High assay value
12-h cumulative release / permeation	98.39%	Controlled/prolonged profile in study
Flux	$0.1672 \text{ mg/cm}^2 \cdot \text{h}$	Highest reported among F9A–F9C
Antimicrobial zone	17.4 mm	Against <i>S. aureus</i> ; not <i>C. acnes</i>
Korsmeyer–Peppas n	0.6444	Consistent with anomalous/non-Fickian transport in the authors' model

Azelaic acid as an independent nanosponge example

Azelaic acid is an established topical option for acne and post-inflammatory hyperpigmentation, but formulation performance is constrained by physicochemical properties and local tolerability. Kumar and Rao developed β -cyclodextrin nanosponges using diphenyl carbonate as cross-linker. Their optimized 1:6 β -cyclodextrin formulation produced spherical porous particles with a mean diameter of approximately 228 nm, PDI 0.14 and zeta potential -21 mV, with approximately 88% encapsulation efficiency. The formulation increased

aqueous solubility from 1.97 to 9.28 $\mu\text{g/mL}$ —approximately five-fold—and provided controlled release over 24 h. [12,13]

The azelaic acid study also reported antimicrobial testing and cell-based safety assessment. The nanosponge showed stronger activity against *S. aureus* and *C. acnes* than free azelaic acid in the reported MIC/MBC experiments, while overall cytotoxicity was not interpreted as indicating a major additional risk. However, these results are preclinical and cannot be equated with clinical efficacy or reduced irritation in patients. This distinction is essential for publication-quality interpretation.

Table 2: Comparison of the two best-documented anti-acne nanosponge examples.

Feature	BPO nanosponge	Azelaic acid nanosponge	Translational implication
Carrier	Ethyl cellulose polymeric nanosponge	β -cyclodextrin/DPC nanosponge	Carrier chemistry strongly affects performance
Preparation	Quasi-emulsion solvent diffusion	Melt synthesis + drug loading	Method must be optimized for active/polymer
Particle size	80–200 nm	228 nm mean	Both are within a nanoscale range
Drug loading/EE	87.9 $\pm$ 1.38% loading efficiency	$\approx$ 88% encapsulation efficiency	High loading is achievable but metrics are not identical
Release	$\approx$ 98.39% by 12 h in reported permeation study	$\approx$ 66% by 24 h	Release profile is formulation-specific
Biological evidence	<i>S. aureus</i> antimicrobial test; rat-skin permeation	<i>C. acnes</i> / <i>S. aureus</i> assays; HaCaT testing	<i>C. acnes</i> and human skin models are more clinically relevant
Clinical evidence	None established	None established for nanosponge superiority	Human comparative trials remain a major gap

Formulation variables that govern nanosponge performance

The evidence indicates that polymer identity, drug-to-polymer ratio, cross-linking density, solvent system, stabilizer concentration, stirring conditions and incorporation into the final gel can materially change particle size, yield, loading, release and skin delivery. Higher cross-linking generally reduces pore accessibility and can slow release, although the direction and magnitude depend on the drug and network chemistry. Particle size alone is not an

adequate quality attribute; PDI, surface charge, morphology, drug state, residual solvent, loading, release kinetics and physical stability should be considered together. [8,9]

For topical products, the nanosponge is not the final dosage form. The gel or cream vehicle determines rheology, spreadability, skin contact, evaporation, hydration of the stratum corneum and ultimately patient acceptability. Carbopol-based gels are attractive because they can provide a reproducible semisolid matrix, but pH and neutralization must be

controlled and the nanosponge must remain physically dispersed without aggregation.

Analytical characterization required for a publication-ready formulation

A robust anti-acne nanosponge study should include: (i) particle size and PDI by dynamic light scattering; (ii) zeta potential; (iii) morphology by SEM/TEM or an appropriately justified alternative; (iv) drug content and encapsulation/loading efficiency using a validated analytical method; (v) FTIR, DSC and/or XRD to investigate drug-carrier interactions and changes in crystallinity; (vi) residual-solvent assessment when organic solvents are used; (vii) in-vitro release under physiologically relevant conditions; (viii) ex-vivo permeation and skin-retention studies using Franz diffusion cells; (ix) rheology, pH, spreadability and drug-content uniformity of the final gel; (x) antimicrobial testing against clinically relevant organisms, including *C. acnes* when feasible; and (xi) stability studies using predefined acceptance criteria.

Clinical and translational relevance

The clinical rationale for nanosponge delivery is strongest where the active is effective but limited by local irritation, poor solubility, instability or undesirable release kinetics. For BPO, the principal opportunity is to preserve antimicrobial efficacy while modulating free-drug exposure. For azelaic acid, solubility and tolerability are important formulation targets. Nevertheless, the benchmark should be an optimized conventional product, not merely an unformulated drug. A nanosponge should be considered clinically meaningful only if it demonstrates better lesion outcomes, tolerability, adherence, pharmacodynamic effect, or a clearly useful reduction in dose/frequency.

The current acne guideline evidence does not establish nanosponge formulations as standard therapy. Therefore, statements in the supplied thesis that nanosponges are 'superior to conventional formulations' or already represent an important clinical treatment should be softened. The evidence currently supports 'promising preclinical and formulation technology' rather than established clinical superiority. [6]

Discussion

The combined evidence supports a coherent formulation-development pathway for anti-acne nanosponges. The BPO study demonstrates that polymer selection can markedly affect manufacturing yield: ethyl cellulose produced substantially higher

yields than the tested HPMC and Eudragit systems. Within the selected ethyl-cellulose series, increasing polymer concentration was associated with a reduction in particle-size range and a marked improvement in loading efficiency in the reported batches, culminating in F9. This provides a useful formulation-development example, but the relationship should not be generalized without additional experiments because particle size and loading are affected by multiple process variables.

The BPO study also illustrates why release kinetics must be interpreted carefully. The optimized nanosponge gel had a high Korsmeyer–Peppas R^2 and an n value of 0.6444, which is compatible with anomalous transport in a simplified empirical model. Calling this simply 'zero-order diffusion' is imprecise because zero-order release and diffusion mechanism are separate concepts. A better statement is that the cumulative release data showed the strongest fit to the reported Korsmeyer–Peppas model, while the zero-order model also showed a high R^2 . Mechanistic claims should therefore be supported by complementary diffusion, swelling or matrix-erosion evidence.

Another important correction concerns microbiology. The BPO study evaluated *S. aureus*, whereas acne pathobiology is strongly associated with *C. acnes* and host inflammation. *S. aureus* testing can demonstrate broad antibacterial activity but cannot by itself establish anti-acne activity. Future nanosponge studies should prioritize *C. acnes* assays under suitable anaerobic conditions, and where possible combine microbiological endpoints with inflammatory biomarkers and clinically relevant skin models.

The azelaic acid evidence strengthens the general formulation rationale because it provides an independent example in a cyclodextrin network and demonstrates improved solubility, controlled release and antimicrobial performance. However, the two systems should not be merged into a single 'optimized' formulation: they use different actives, carriers, preparation methods and performance endpoints. Their value is comparative and conceptual.

The major unresolved issue is clinical translation. A nanoparticle can show attractive particle size, loading and release characteristics yet fail to improve patient outcomes because skin deposition, irritation, sensory properties and adherence are governed by the complete dosage form. Consequently, the next generation of studies should use quality-by-design principles, clinically meaningful comparators, standardized skin permeation methods and adequately powered human trials.

Table 3: Important aspects of the project with limitations and explanations.

Issue	Publication-ready correction
Global acne burden	Use GBD 2019 estimates: 231.2 million prevalent cases and 117.4 million incident cases worldwide.
C. acnes terminology	Use microbial colonization/dysbiosis and inflammation; acne is not simply an infection.
Nanosponge safety	Safety is formulation-specific and requires toxicology/irritation testing.
Follicular targeting	Describe as a potential benefit requiring experimental evidence of follicular deposition/localization.
Blackhead color	Open comedone dark appearance is not dirt; pigmentation is related to melanin and optical/oxidative processes.
BPO microbiology	Report S. aureus as the organism actually tested; do not equate it with proof of anti-C. acnes efficacy.
Release mechanism	Report model fit and diffusion exponent separately.
Clinical superiority	Use 'promising' or 'potentially advantageous' until supported by comparative clinical trials.
Original results	Do not fabricate new results; use traceable published data and label them as published evidence.

Future Research Directions

- Develop anti-acne nanosponges using quality-by-design with polymer/cross-linker ratio, particle size, PDI, loading and release as predefined critical quality attributes.
- Use validated analytical methods and report full formulation composition, process parameters and replicate-level data to improve reproducibility.
- Prioritize C. acnes-specific antimicrobial and anti-inflammatory testing, together with appropriate skin models and follicular-deposition imaging.
- Compare optimized nanosponge gels directly with marketed BPO or azelaic acid products at equivalent active doses and clinically relevant application schedules.
- Conduct standardized ex-vivo skin retention/permeation studies and evaluate local irritation, barrier function and sensory acceptability.
- Progress to randomized, adequately powered clinical trials only after reproducible formulation, safety and mechanistic evidence has been established.
- Assess long-term stability, residual solvents, packaging compatibility, manufacturing scalability and cost-effectiveness before commercialization.

Conclusion

Nanosponges represent a scientifically credible platform for modifying the topical delivery of anti-acne agents, particularly when an active suffers from irritation, poor solubility, instability or an undesirable release profile. The strongest quantitative evidence

identified in this synthesis includes an ethyl-cellulose BPO nanosponge with 80–200 nm particle size and $87.9 \pm 1.38\%$ loading efficiency, and a β -cyclodextrin azelaic acid nanosponge with approximately 228 nm mean size, PDI 0.14, approximately 88% encapsulation efficiency and five-fold improved aqueous solubility. These findings demonstrate formulation potential, not clinical superiority. The principal scientific requirement for the field is now translation: standardized characterization, relevant microbiology, reproducible skin-retention studies, rigorous safety assessment and well-designed human trials. On the basis of currently available evidence, nanosponge-based topical delivery should be regarded as a promising investigational strategy for acne rather than an established replacement for guideline-recommended conventional therapy.

Funding

No financial assistance was provided for this project.

Conflict of Interest

None declared.

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