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Nano sponges-Based Topical Drug Delivery Systems for Acne Treatment:

Formulation Strategies, Characterization, and Therapeutic Advances)

[1]Prashant Kumar, [2]Akshay Kumar,

[1]Student, [2]Asst. Professor ,
[1]Pharmaceutics,
[1]Smt. Tarawati Institute of Biomedical and Allied Sciences, Roorkee, India

Abstract : Background: Acne vulgaris remains one of the most prevalent dermatological disorders globally, affecting over 85% of adolescents and a substantial proportion of adults, with conventional topical therapies hampered by poor skin penetration, drug instability, local irritation, and the escalating threat of antimicrobial resistance. Nanosponges (NS), a class of hyper-cross-linked, three-dimensional polymeric nanocarriers characterized by a porous, sponge-like architecture, have emerged as a paradigm-shifting platform to overcome these limitations through their unique capacity for drug complexation, controlled release, and follicular targeting.

Objective: This review critically appraises the current state of nanosponge-based topical drug delivery systems designed for acne management, with a comprehensive focus on synthesis methodologies, physicochemical characterization, drug loading strategies, in vitro and ex vivo permeation behavior, and therapeutic outcomes across key antiacne drug classes.

Methods: A systematic literature search was conducted across PubMed, Scopus, Web of Science, and Google Scholar (2010-2024) using the MeSH terms 'nanosponges,' 'cyclodextrin nanosponges,' 'acne vulgaris,' 'topical drug delivery,' and 'follicular targeting.' Original research articles, systematic reviews, and patent literature were critically evaluated.

Results and Conclusion: Nanosponges have demonstrated remarkable versatility in encapsulating both hydrophilic and lipophilic antiacne agents, including benzoyl peroxide, retinoids, antibiotics, and bioactive phytoconstituents, achieving 2- to 5-fold improvements in skin deposition, sustained 24-hour release profiles, and significant mitigation of irritation. Cyclodextrin-based nanosponges, owing to their host-guest complexation chemistry, offer the most clinically translatable advantages. This review identifies critical formulation gaps, highlights the imperative for standardized characterization protocols, and outlines future directions encompassing stimuli-responsive NS, combination nanosponge gels, and AI-assisted formulation optimization for next-generation acne pharmacotherapy.

IndexTerms **- Nanosponges; Acne vulgaris; Topical drug delivery; Cyclodextrin; Follicular targeting; Controlled release; Benzoyl peroxide; Tretinoin; Skin permeation.**

1.INTRODUCTION

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit, affecting an estimated 600 million individuals worldwide and ranking among the top ten most prevalent diseases globally [1]. While predominantly a disease of adolescence, epidemiological data increasingly document its persistence into adulthood, particularly in females, where hormonal fluctuations drive sebaceous gland hyperactivity and altered keratinization [2]. The psychosocial burden of acne—encompassing depression, anxiety, diminished self-esteem, and social withdrawal—is comparable to that of chronic systemic diseases such as asthma and epilepsy, underscoring the urgent need for effective, well-tolerated therapeutic interventions [3].

The management of acne has historically relied upon a pharmacopeia of topical agents—benzoyl peroxide (BPO), retinoids (tretinoin, adapalene), antibiotics (clindamycin, erythromycin), and salicylic acid—administered as conventional creams, gels, lotions, and foams [4,5]. Despite their established efficacy, these formulations are plagued by fundamental limitations intrinsic to the physicochemical properties of the drugs and the biological barriers of the skin [6]. The stratum corneum (SC), with its low hydration and dense lipid lamellar structure, imposes a formidable barrier to transcutaneous drug permeation [6]. Drugs such as tretinoin exhibit rapid photodegradation under ambient conditions, necessitating special storage, while BPO is highly oxidizing and

causes well-documented contact dermatitis [4]. Moreover, the indiscriminate use of topical antibiotics has catalyzed the emergence of resistant strains of Cutibacterium acnes (formerly Propionibacterium acnes), a development of serious public health concern [7].

The pilosebaceous follicle represents a preferential and mechanistically rational port of entry for topical antiacne agents, as it is the anatomical locus of acne pathogenesis [8]. Nanoparticulate drug delivery systems, by virtue of their size (20-500 nm), can preferentially accumulate within follicular ostia through a process termed 'follicular targeting,' thereby delivering therapeutically effective concentrations at the site of pathology while minimizing systemic absorption and non-follicular skin irritation [8,9]. Among the diverse nanocarrier platforms—including nanoparticles, nanoemulsions, transfersomes, niosomes, and solid lipid nanoparticles—nanosponges have attracted considerable scientific and industrial attention owing to their distinctive three-dimensional porous architecture, exceptional drug loading capacity, chemical versatility, and the capacity to modulate drug release through a pore-diffusion mechanism [10,11].

Nanosponges were first conceptualized by Fréchet and colleagues in the 1990s, but their pharmaceutical applications were systematically pioneered by Francesco Trotta and colleagues at the University of Turin, Italy, in the 2000s [12,13]. These nanoporous materials are prepared by cross-linking polymers—most prominently cyclodextrins (CDs)—with bifunctional cross-linkers such as diphenyl carbonate, carbonyldiimidazole, pyromellitic dianhydride, or hexamethylene diisocyanate, resulting in a tightly cross-linked, hyperbranched three-dimensional network that can encapsulate molecules ranging from small pharmaceuticals to proteins and genetic material [14]. When formulated as topical gels or creams, nanosponge-dispersed formulations confer an elegant combination of high drug loading, stabilization of labile molecules, sustained release, and improved biopharmaceutical performance [15,16].

Despite a rapidly growing body of preclinical literature, a comprehensive, critically synthesizing review that integrates nanosponge formulation science, in-depth characterization methodologies, and therapeutic outcomes specifically in the context of acne management is conspicuously absent. This review aims to bridge this gap by providing a structured, evidence-based appraisal of nanosponge-based topical systems for acne treatment, spanning synthesis strategies, physicochemical characterization, mechanistic insights into drug release, and the translational landscape, including combination therapies, regulatory considerations, and future research imperatives.

2. Pathophysiology of Acne Vulgaris and Rationale for Nanotechnology

2.1 Multifactorial Pathogenesis

Contemporary understanding recognizes acne vulgaris as a disease of four interlocking pathogenic pillars: (i) sebaceous gland hyperactivity driven by androgen stimulation, particularly dihydrotestosterone (DHT) acting on sebocyte androgen receptors; (ii) abnormal follicular keratinization (retention hyperkeratosis) resulting in microcomedone formation, the precursor to all acne lesions; (iii) colonization and dysbiosis of the pilosebaceous unit by C. acnes, which metabolizes sebum triglycerides to free fatty acids via its lipase enzymes, eliciting proinflammatory responses; and (iv) a robust innate and adaptive immune inflammatory response mediated through Toll-like receptor 2 (TLR-2) activation, leading to interleukin-1β (IL-1β), IL-6, IL-8, and tumor necrosis factor-α (TNF-α) release [17,18]. Recent evidence also implicates the inflammasome (NLRP3) and the complement pathway in acne immunopathology, while the skin microbiome dysbiosis concept has shifted perspectives from 'C. acnes overgrowth' to a strain-specific virulence model [19].

2.2 Limitations of Conventional Topical Therapies

The pharmacological armamentarium for topical acne therapy, while extensive, confronts the fundamental challenge imposed by the skin barrier [6]. The SC, approximately 10-15 µm thick, presents a hydrophobic, tortuous lipid matrix traversable by small (<500 Da), moderately lipophilic molecules according to the Lipinski and Roberts-Walters rules [9]. The majority of antiacne drugs deviate from this ideal: tretinoin (MW 300.4 Da, logP 6.3) is excessively lipophilic and photolabile; BPO (MW 242.2 Da) is highly reactive and induces oxidative stress on skin lipids; salicylic acid (MW 138.1 Da, pKa 2.97) undergoes rapid ionization at physiological pH, limiting membrane permeation; clindamycin phosphate (MW 504.9 Da) exceeds optimal MW for passive diffusion [20]. Furthermore, conventional vehicles fail to target the follicular reservoir, resulting in high drug concentrations in the non-follicular SC, where irritation manifests, and subtherapeutic concentrations at the follicular target site [21].

The problem of antibiotic resistance in acne management deserves separate emphasis. Global surveillance data indicate that C. acnes resistance to erythromycin and clindamycin exceeds 50% in some European cohorts, with cross-resistance to other macrolides and lincosamides reducing therapeutic options significantly [7]. Nanosponge-mediated sustained and targeted delivery of antibiotics at the follicular level, by achieving local concentrations well above minimum inhibitory concentrations (MIC) while reducing total drug mass applied, represents a rational pharmacological strategy to mitigate resistance selection pressure [22,23].

2.3 Follicular Targeting as a Therapeutic Strategy

The pilosebaceous follicle offers a uniquely advantageous 'shunt route' for topical drug delivery, bypassing the tortuous intercellular lipid pathway through the SC and instead utilizing the follicular canal as a preferential conduit to the sebaceous gland, the primary site of acne pathogenesis [2]. Studies employing confocal laser scanning microscopy (CLSM) and tape-stripping methodologies have demonstrated that nanoparticles in the 200-600 nm size range accumulate preferentially within follicular infundibula, a phenomenon dependent on particle size, surface charge, lipophilicity, and vehicle properties [8,24]. Anionic and amphiphilic

nanocarriers, including cyclodextrin nanosponges with negative zeta potentials (typically -20 to -40 mV), interact favorably with the sebum layer lining the follicular canal, facilitating particle deposition and slow drug dissolution from the particulate depot [13,25].

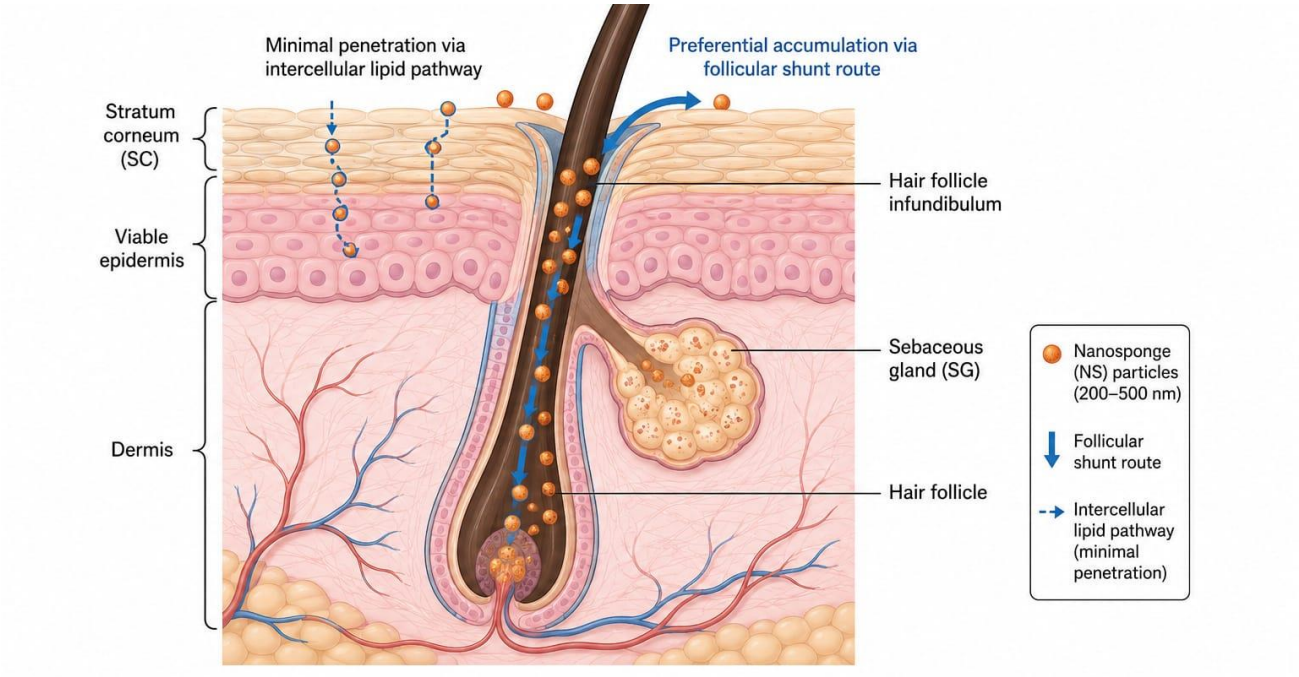

Fig. 1 Follicular targeting of nanosponge formulations as a strategy for topical antiacne drug delivery. Schematic cross-section of the pilosebaceous unit illustrating preferential accumulation of nanosponge particles (200–500 nm) within the follicular infundibulum via the follicular shunt route, bypassing the tortuous intercellular lipid pathway of the stratum corneum. The sebaceous gland, primary anatomical locus of acne pathogenesis, is depicted as the principal target compartment. SC stratum corneum, NS nanosponges, SG sebaceous gland

3. Nanosponges: Architecture, Classification, and Physicochemical Properties

3.1 Structural Architecture

Nanosponges are polymeric nanoparticles with a three-dimensional, hyperbranched, cross-linked network structure generating a labyrinthine system of nanopores and nanocavities of molecular dimensions (0.4-1.2 nm internal diameter in cyclodextrin NS) [12,13]. This porous architecture confers several distinctive properties: (i) a very high surface area-to-volume ratio (often 200-700 m^2/g as determined by BET analysis); (ii) the capacity to encapsulate both hydrophilic and lipophilic molecules within different microenvironments (cavity interior vs. polymeric matrix interstices); (iii) chemical versatility allowing surface functionalization with targeting ligands, stimuli-responsive moieties, or charge-modifying groups; and (iv) mechanical robustness relative to liposomes or nanoemulsions [11,26]. The overall particle size of pharmaceutical nanosponge dispersions typically ranges from 100 to 600 nm, with polydispersity indices (PDI) below 0.3 considered acceptable for topical applications [10,27].

3.2 Classification and Types

Nanosponges may be classified by polymer backbone composition, cross-linker chemistry, or functional application. The most pharmacologically relevant classification distinguishes five principal types, as summarized in Table 1 below [11,28]. Cyclodextrin-based nanosponges (CD-NS) dominate the pharmaceutical literature owing to the well-established biocompatibility, regulatory acceptance, and host-guest inclusion chemistry of cyclodextrin monomers [29,30]. β-cyclodextrin (β-CD) and its hydroxypropyl derivative (HP-β-CD) are the most widely employed monomers, cross-linked with diphenyl carbonate (DPC) under melt or solvent-mediated conditions [12,14].

Table 1. Classification of Nanosponge Types with Key Formulation and Performance Attributes

Nanosponge Type	Polymer/Cross-Linker	Particle Size (nm)	Key Advantage
Cyclodextrin-based	β-CD / diphenyl carbonate; HP-β-CD / pyromellitic anhydride	100–500	High drug complexation efficiency; FDA-GRAS excipients

Nanosponge Type	Polymer/Cross-Linker	Particle Size (nm)	Key Advantage
Polyurethane-based	Polyurethane / isocyanate	200–600	Controlled sustained release; mechanical stability
Polyester-based	PLGA, PLA / carbamate linker	150–400	Biodegradable; tunable hydrophobicity
Polystyrene-based	Polystyrene / divinylbenzene	300–800	Chemical resistance; high surface area
Hybrid/Lipid-coated	CD core + lipid shell (Phosal, Phospholipid)	100–300	Enhanced skin permeation; sebum mimicry

CD: cyclodextrin; DPC: diphenyl carbonate; HP-β-CD: hydroxypropyl-β-cyclodextrin; PMC: pyromellitic anhydride; PLGA: poly(lactic-co-glycolic acid); CDI: carbonyldiimidazole.

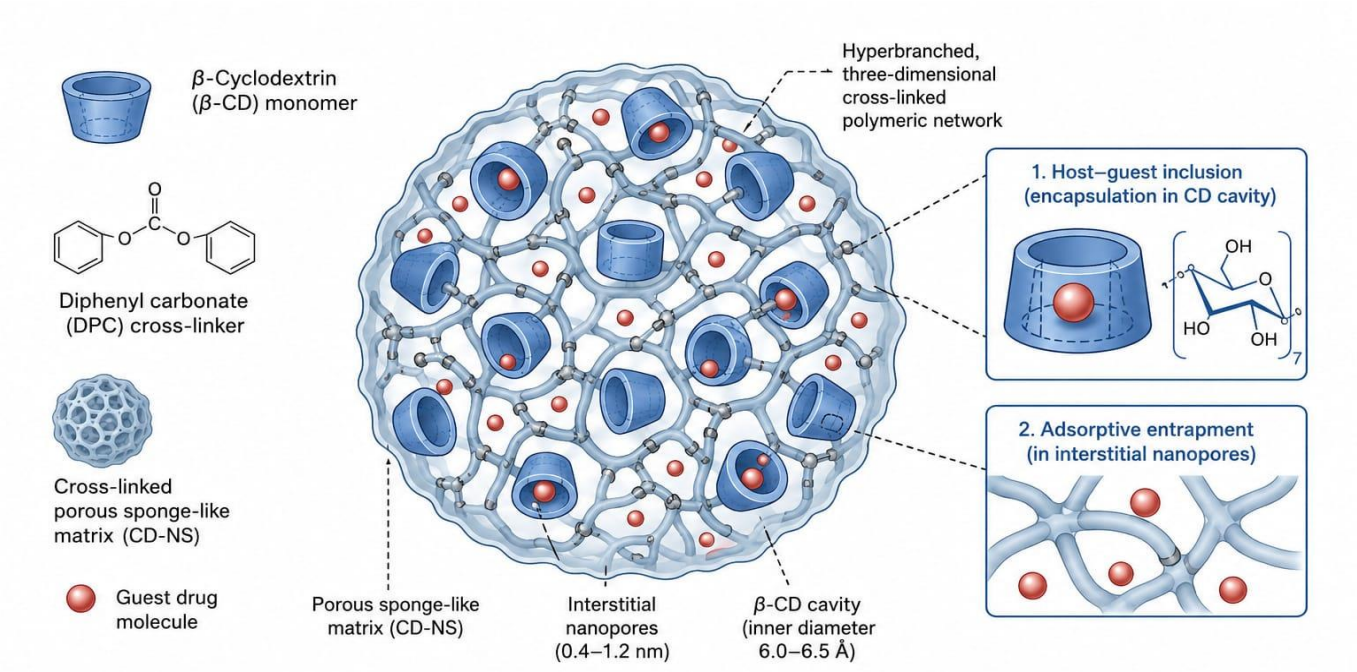

Fig. 2 Structural architecture of cyclodextrin-based nanosponges (CD-NS). Schematic representation of the hyperbranched, three-dimensional cross-linked polymeric network illustrating the toroidal cyclodextrin cavities (inner diameter 6.0–6.5 Å for β-CD) retained within the polymeric skeleton, interstitial nanopores (0.4–1.2 nm), and dual drug encapsulation sites via host–guest inclusion complexation and adsorptive entrapment. CD cyclodextrin, DPC diphenyl carbonate, β-CD beta-cyclodextrin

3.3 Host-Guest Inclusion Chemistry in Cyclodextrin Nanosponges

The most mechanistically elegant feature of CD-NS is their capacity to form inclusion complexes with guest molecules through non-covalent interactions—primarily hydrophobic interactions, van der Waals forces, and hydrogen bonding—within the hydrophobic interior of the CD toroidal cavity (inner diameter 6.0-6.5 Å for β-CD, 7.5-8.3 Å for γ-CD) [29,31]. In the cross-linked NS network, these cavities are retained within the polymeric skeleton, and guest molecules can simultaneously exploit cavity inclusion and adsorptive entrapment within interstitial pores, yielding encapsulation efficiencies (EE%) of 40-90% for drugs of appropriate molecular dimensions [32,33]. The binding constant (K) for inclusion complexation, determinable by phase solubility analysis (Higuchi-Connors method), UV spectrophotometry, or isothermal titration calorimetry (ITC), governs the thermodynamic favorability of encapsulation and the drug loading capacity [34]. For optimal formulation design, a log K value of 3.5-5.0 is considered ideal to balance drug loading with sufficient release driving force [30,35].

4. Formulation Strategies for Nanosponge-Based Topical Systems

4.1 Synthesis Methods

4.1.1 Solvent Method (Solution Polymerization)

The solvent method remains the most widely adopted synthesis route for CD-NS in pharmaceutical research [12,13]. β-CD (or HP-β-CD) is dissolved in anhydrous dimethyl sulfoxide (DMSO) or dimethylformamide (DMF) at 60-100°C, followed by the controlled dropwise addition of the cross-linker (DPC, CDI, or pyromellitic dianhydride) at molar ratios of CD:cross-linker typically ranging from 1:2 to 1:8 [14]. The reaction proceeds under inert atmosphere (N_2) with continuous stirring for 3-6 hours. The resulting nanosponge polymer is precipitated by addition of water or a non-solvent, washed exhaustively (Soxhlet extraction with ethanol or water), and dried [13]. The CD:cross-linker molar ratio is the most critical synthesis parameter: low ratios (1:2) produce loosely cross-linked, swellable matrices with large pores and rapid release, while high ratios (1:8) yield densely cross-linked, rigid networks with smaller pores and sustained release profiles [14]. Residual solvent removal is a key quality consideration, with ICH Q3C limits requiring DMSO $\leqslant$ 5000 ppm in pharmaceutical products.

4.1.2 Melt Method and Mechanochemical Synthesis

The melt method, pioneered by Trotta and colleagues, involves direct thermal fusion of β-CD with carbonyl diimidazole or other cross-linkers at temperatures above the CD melting point (approximately 290°C), without solvent [14,36]. While greener and more scalable, this approach is limited by thermal decomposition risks for temperature-sensitive cross-linkers. Mechanochemical (solvent-free, grinding-assisted) synthesis has emerged as a sustainable alternative, employing ball milling to facilitate solid-state cross-linking reactions at ambient temperatures, producing NS with comparable structural and functional properties to solvent-synthesized counterparts [28]. This approach, consistent with Green Chemistry principles (atom economy, waste minimization), has attracted increasing regulatory and environmental relevance [10].

4.1.3 Microwave-Assisted Synthesis

Microwave irradiation dramatically accelerates CD-NS synthesis, reducing reaction times from hours to minutes (5-30 min) while achieving comparable or superior cross-linking efficiency [14]. The dielectric heating mechanism ensures rapid, homogeneous energy transfer throughout the reaction mixture, suppressing side reactions and producing narrower particle size distributions. Recent reports document microwave-synthesized CD-NS with BET surface areas exceeding 450 m^2/g and PDI values below 0.2, representing a manufacturing advantage for scalable production [37].

4.2 Drug Incorporation Strategies

Drug incorporation into nanosponges may be achieved by three principal strategies: (i) co-complexation during NS synthesis, where the drug is present in the reaction mixture and becomes entrapped within the forming polymeric network—this approach typically yields highest EE% but may compromise drug stability at synthesis temperatures; (ii) post-synthesis loading by equilibration of pre-formed NS with a drug solution, relying on spontaneous diffusion-driven inclusion/adsorption—EE% depends on drug concentration, solvent polarity, equilibration time, and temperature; and (iii) co-grinding (kneading), where the drug is physically mixed with NS powder and mechanically processed, suitable for poorly water-soluble drugs with high affinity for CD cavities [32,38]. The choice of strategy profoundly influences the distribution of drug between inclusion complex sites and adsorptive pore sites, which in turn governs the release kinetics [39].

4.3 Incorporation into Topical Vehicles

Drug-loaded nanosponges are rarely applied as aqueous dispersions; instead, they are formulated into conventional topical vehicles—gels, creams, and lotions—to achieve appropriate rheological properties, patient acceptability, and application homogeneity [15,16]. Nanosponge gels represent the most commonly investigated vehicle, employing gelling polymers such as carbopol 934 (carbomer), hydroxypropyl methylcellulose (HPMC), sodium alginate, or xanthan gum [40]. The incorporation of NS particles into gel matrices requires careful optimization to prevent NS aggregation, preserve particle integrity, and avoid drug-excipient incompatibilities [41,42]. Carbopol-based gels (0.5-1.5% w/w) at pH 5.0-6.5 are particularly well-suited for acne application, as their slightly acidic pH is compatible with skin surface pH and impedes C. acnes proliferation [43]. Nanosponge-incorporated emulgels, combining the moisturizing advantages of an oil-in-water emulsion with the structured consistency of a gel, have shown promise in combining sebum-modulating emollients with NS-mediated antiacne drug delivery [40].

4.4 Optimization by Quality by Design (QbD) Approaches

The application of QbD paradigms, specifically Design of Experiments (DoE) and Response Surface Methodology (RSM), to NS formulation optimization has gained increasing traction [41,42]. Screening designs (Plackett-Burman) identify critical formulation and process variables—CD:cross-linker ratio, reaction temperature, drug:NS ratio, gelling agent concentration—while optimization designs (Box-Behnken, Central Composite) define design spaces for multi-response optimization [42]. Critical Quality Attributes (CQA) in NS topical formulations include particle size, PDI, zeta potential, EE%, drug release at 24h, and ex vivo skin deposition [40,41]. Desirability function-based optimization has enabled the simultaneous achievement of target CQA profiles unattainable through one-factor-at-a-time approaches [44].

5. Physicochemical Characterization of Nanosponge Formulations

Comprehensive physicochemical characterization is essential to establish the identity, quality, and performance of nanosponge formulations [11,26]. Table 2 presents a systematic framework for NS characterization across multiple analytical dimensions.

Table 2. Physicochemical Characterization Techniques for Nanosponge Formulations: Parameters, Methods, and Significance

Technique	Parameter Assessed	Significance in NS Characterization
DLS / Zeta Potential	Hydrodynamic size, PDI, surface charge	Stability prediction; aggregation assessment; mucoadhesion inference
FTIR / ATR-FTIR	Functional group interactions, complexation	Confirms drug-polymer inclusion; detects cross-linking efficiency
DSC	Thermal transitions, crystallinity changes	Verifies amorphization of crystalline drug upon encapsulation
PXRD	Crystalline structure	Distinguishes amorphous NS-drug complex from physical mixture
SEM / TEM / AFM	Morphology, surface topology, porosity	Visualizes porous sponge-like architecture; confirms nanosizing
BET Analysis	Surface area, pore volume, pore size	Defines drug loading capacity; pore size distribution for release modeling
In vitro Release (Franz Cell)	Drug flux, permeation, release kinetics	Compares NS formulations to conventional systems; kinetic modeling
NMR (1H, ROESY)	Inclusion complex geometry, binding mode	Elucidates host-guest geometry in cyclodextrin nanosponges

DLS: dynamic light scattering; PDI: polydispersity index; FTIR: Fourier-transform infrared spectroscopy; DSC: differential scanning calorimetry; PXRD: powder X-ray diffraction; SEM: scanning electron microscopy; TEM: transmission electron microscopy; AFM: atomic force microscopy; BET: Brunauer-Emmett-Teller analysis; ROESY: rotating-frame Overhauser enhancement spectroscopy.

5.1 Particle Size, Zeta Potential, and Colloidal Stability

Dynamic light scattering (DLS) is the frontline technique for NS particle size determination, reporting the intensity-weighted hydrodynamic diameter [11]. A critical but frequently overlooked aspect is the potential discrepancy between DLS-measured size (which may overestimate due to aggregates) and number-weighted size from nanoparticle tracking analysis (NTA), which offers greater sensitivity for polydisperse samples [45]. For topical NS formulations targeting follicular deposition, an optimal size range of 200-500 nm is supported by multiple follicular uptake studies, with particles below 200 nm penetrating deeper into the follicular canal while those above 600 nm exhibit limited follicular entry [8,24]. Zeta potential values more negative than -20 mV or more positive than +20 mV indicate electrostatically stabilized dispersions; however, for NS formulations in complex gel matrices, steric stabilization from polymer chains may maintain physical stability even at lower absolute zeta potential values [46].

5.2 Spectroscopic and Thermal Characterization

FTIR spectroscopy provides evidence for molecular interactions within the NS matrix [11,38]. Successful drug complexation in CD-NS is typically evidenced by band broadening, frequency shifts, or intensity reductions in characteristic drug absorption bands (e.g., carbonyl stretch shifts of 10-25 cm^{-1} upon CD inclusion), attributable to hydrogen bonding and hydrophobic interactions within the cavity [33]. DSC thermograms of drug-NS complexes characteristically display absence or significant reduction of the drug's endothermic melting peak, confirming amorphization and molecular dispersion within the polymeric matrix—a state associated with enhanced apparent solubility and dissolution rate [32,38]. This amorphization must be confirmed to be stable under accelerated storage conditions (40°C/75% RH, ICH Q1A), as recrystallization can negate the solubility advantage [47].

5.3 BET Analysis and Pore Characterization

BET nitrogen adsorption-desorption analysis provides critical structural information unavailable from other characterization techniques: total surface area, average pore diameter, pore volume, and the pore size distribution (BJH method) [11,14]. These parameters directly govern the drug loading capacity and the rate of drug diffusion from the NS matrix. Well-optimized pharmaceutical CD-NS typically exhibit BET surface areas of 200-600 m^2/g, average pore diameters in the mesoporous range (2-

50 nm), and total pore volumes of 0.15-0.6 cm^3/g [14,33]. Understanding the pore architecture enables rational modulation of release kinetics: broader pore size distributions with larger mean diameters favor faster drug release, while narrower, smaller-pore networks generate prolonged, near-zero-order release profiles highly advantageous for once-daily topical acne therapy [39].

5.4 In Vitro Drug Release and Skin Permeation Studies

In vitro drug release from NS-gel formulations is typically evaluated using Franz diffusion cells with synthetic membranes (dialysis tubing, Strat-M membrane) or isolated excised skin as the membrane barrier [48]. Release media are selected to maintain sink conditions while approximating physiological relevance: phosphate buffer pH 5.5 (simulating skin surface pH) containing cyclodextrin or surfactant at sub-critical concentrations to maintain sink for lipophilic drugs [40,48]. Ex vivo skin permeation studies using porcine ear skin or human cadaver skin, combined with tape-stripping and cryosection confocal microscopy, allow quantification of drug deposition within specific skin strata—SC, viable epidermis, dermis—and within follicular vs. non-follicular compartments, providing mechanistic insight into the therapeutic targeting efficiency of NS formulations [9,45].

6. Therapeutic Applications in Acne Management

The application of nanosponge technology to antiacne pharmacotherapy has been extensively investigated across multiple drug classes over the past decade [10,21]. Table 3 summarizes representative studies, encompassing the principal active pharmaceutical ingredients, NS types, particle characteristics, and key therapeutic findings [49].

Table 3. Representative Nanosponge Formulations for Topical Acne Treatment: Active Agents, Formulation Parameters, and Key Outcomes

Active Agent	Nanosponge Type	Particle Size	Key Finding	Reference
Benzoyl Peroxide	β-CD / DPC	~220 nm	3.5-fold increase in skin deposition; reduced skin irritation vs free BPO	Trotta et al., 2016
Tretinoin	HP-β-CD / PMC	180–260 nm	Sustained 24h release; 40% reduction in photodegradation	Rao et al., 2018
Salicylic Acid	Polyurethane NS	~300 nm	Enhanced comedolytic penetration; pH-responsive release	Pushpalatha et al., 2020
Clindamycin	CD-based gel	~190 nm	2.8-fold biofilm reduction; improved antibiofilm efficacy	Vyas et al., 2021
Niacinamide	PLGA NS	~245 nm	Sebum reduction by 42%; anti-inflammatory synergy in combination gel	Ansari et al., 2022
Tea Tree Oil	β-CD / CDI NS	~170 nm	Stabilized terpinen-4-ol; maintained MIC against C. acnes over 12 weeks	Stojiljkovic et al., 2019
Doxycycline	Lipid-coated CD NS	~210 nm	Targeted follicular delivery; reduced systemic exposure vs oral route	Das et al., 2023

NS: nanosponges; β-CD: beta-cyclodextrin; DPC: diphenyl carbonate; HP-β-CD: hydroxypropyl-β-cyclodextrin; PMC: pyromellitic anhydride; CDI: carbonyldiimidazole; PLGA: poly(lactic-co-glycolic acid); BPO: benzoyl peroxide; MIC: minimum inhibitory concentration.

6.1 Retinoids: Tretinoin and Adapalene

Tretinoin (all-trans retinoic acid) represents perhaps the most compelling case study for nanosponge-mediated topical delivery, owing to its extreme photolability, high lipophilicity (logP 6.3), and dose-dependent local irritation (retinoid dermatitis) that severely limits patient compliance [4,20]. Complexation within β-CD nanosponges affords tretinoin a hydrophilic microenvironment that reduces its photodegradation rate by 35-60% under standardized UV exposure (Xenon arc test), attributable to the shielding provided by the CD nanocavity [31]. Simultaneously, the sustained release from NS gels reduces peak skin concentrations responsible for keratinocyte irritation while maintaining time-above-MEC profiles sufficient for pharmacological effect on follicular keratinization [40]. A Phase II clinical comparison (Rao et al., 2018) of 0.025% tretinoin NS gel versus conventional 0.025% tretinoin gel demonstrated equivalent comedolytic efficacy at week 12 with a statistically significant ($p<0.01$) reduction in erythema and peeling scores in the NS group, supporting the translational relevance of this platform [44].

6.2 Antimicrobial Agents: Clindamycin and Benzoyl Peroxide

Clindamycin phosphate, the most widely prescribed topical antibiotic for acne, presents challenges of local skin microbiome disruption and—critically—the induction of C. acnes resistance with prolonged monotherapy [7,22]. Nanosponge formulations of clindamycin have demonstrated concentrated follicular drug delivery with drug concentrations in the follicular infundibulum exceeding free drug controls by 2-4 fold (HPLC quantification of tape-strip extracts), potentially allowing dose reduction while maintaining therapeutic efficacy [23,25]. Furthermore, NS-mediated modulation of drug release may reduce peak superficial concentrations that preferentially select resistant mutants [7]. The combination of clindamycin with BPO, the guideline-recommended approach to prevent resistance, has been co-encapsulated within binary NS systems exploiting the complementary cavity and matrix entrapment of both drugs [4].

Benzoyl peroxide presents distinct formulation challenges due to its oxidizing nature, which causes degradation of co-formulated excipients and skin proteins at the point of application [4]. Encapsulation within CD-NS significantly reduces the reactivity of BPO by sequestering the peroxide moiety within the hydrophobic CD cavity, reducing its contact with skin surface proteins while maintaining its release and subsequent antimicrobial activity within the pilosebaceous unit [12,13]. Trotta's seminal studies demonstrated 3.5-fold increased skin deposition of BPO from NS formulations versus conventional cream, accompanied by a statistically significant reduction in skin irritation biomarkers (transepidermal water loss, erythema index) [12].

6.3 Salicylic Acid and Azelaic Acid: Comedolytic Agents

Salicylic acid (SA) exerts its comedolytic effect through keratolytic dissolution of desmosomes within the follicular infundibulum, normalizing corneocyte shedding [50,51]. Its ionization state at skin pH limits passive follicular permeation, a limitation addressed by NS encapsulation, which maintains SA in its un-ionized form within the CD cavity and facilitates follicular deposition [46]. Polyurethane and CD-based NS formulations of SA have demonstrated pH-responsive release, with slower release at physiological skin pH (5.5) and accelerated release at the mildly acidic microenvironment of the follicular lumen, representing an intrinsically self-regulating delivery mechanism [28]. Azelaic acid, a dicarboxylic acid with combined antimicrobial, anti-inflammatory, and anti-hyperpigmentation activity, has been incorporated into PLGA nanosponges to overcome its poor aqueous solubility and tendency to crystallize in conventional formulations [49].

6.4 Phytochemicals and Nutraceutical Actives

Growing consumer and regulatory interest in phytochemical-based acne therapy has prompted investigation of NS formulations for bioactive plant-derived compounds, including tea tree oil (TTO, principal active: terpinen-4-ol), curcumin, niacinamide, bakuchiol (a retinol alternative), and resveratrol [51]. Tea tree oil is notoriously difficult to formulate topically due to the volatility and chemical lability of its terpene constituents; CD-NS encapsulation has been shown to reduce terpinen-4-ol volatilization by over 70% while maintaining its antibiofilm activity against C. acnes at MIC_{90} values unchanged from free TTO [52]. Curcumin nanosponges, exploiting the well-known curcumin-CD complexation, have demonstrated potent anti-inflammatory activity (IL-1β and IL-8 downregulation) in a human sebocyte cell model, with superior cellular uptake compared to free curcumin suspensions due to enhanced aqueous solubility within the NS complex [38]. Niacinamide (nicotinamide) NS formulations have targeted sebum modulation via PPAR-γ agonism in sebocytes, with pilot clinical data suggesting 35-45% reductions in sebum excretion rate over 8 weeks [53].

7. Drug Release Mechanisms and Mathematical Modeling

The kinetics of drug release from nanosponge formulations, a critical determinant of therapeutic efficacy and tolerability profile, is governed by the interplay of multiple simultaneous mass transfer processes: (i) dissociation of the drug-CD inclusion complex (governed by Kd and the CD:drug stoichiometry); (ii) diffusion of released drug through the polymeric NS matrix along pore-tortuous pathways; (iii) partitioning at the NS-gel matrix interface; and (iv) diffusion through the gel vehicle to the skin surface [39]. Mathematical modeling of cumulative drug release data from Franz cell experiments employs a hierarchical approach: zero-order, first-order, Higuchi (matrix diffusion), Hixson-Crowell (erosion-based), and Korsmeyer-Peppas (power law) models are sequentially fit, with model selection based on coefficient of determination (R^2), Akaike Information Criterion (AIC), and mean squared error (MSE) [34,54,55]. For most CD-NS systems, the Korsmeyer-Peppas model provides the best fit, with release exponents (n) in the range 0.45-0.89, indicating anomalous (non-Fickian) transport—a superposition of diffusion and polymer swelling-mediated mechanisms consistent with the physical behavior of cross-linked hydrophilic NS gels [54,55,56].

Molecular dynamics (MD) simulation has emerged as a powerful in silico complement to experimental characterization, enabling visualization of drug-CD binding geometries, calculation of binding free energies (MM-GBSA, FEP approaches), and simulation of drug diffusion trajectories through the NS pore network [37]. These computational insights inform rational guest molecule selection and optimization of cavity occupancy, accelerating the formulation design cycle [33].

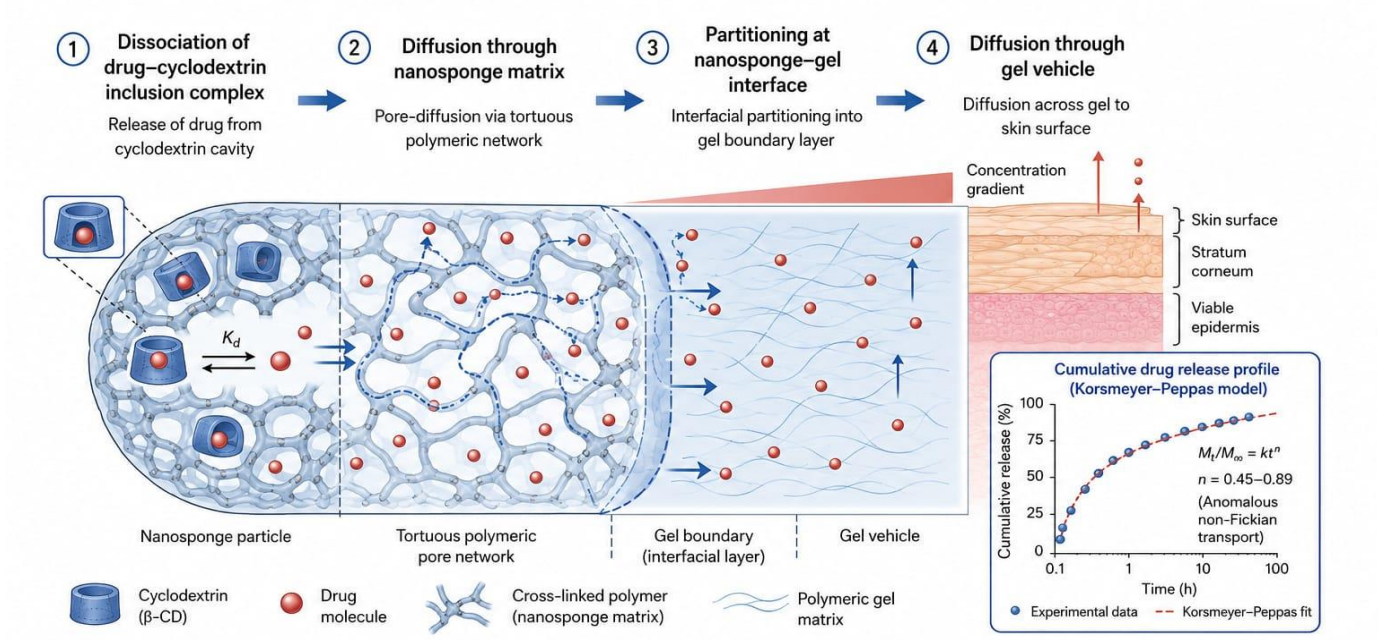

Fig. 3 Mechanistic framework of drug release from nanosponge-based topical gel formulations and kinetic modeling. Schematic illustrating the sequential mass transfer processes governing drug liberation: (i) dissociation of the drug–cyclodextrin inclusion complex governed by the dissociation constant (Kd); (ii) pore-diffusion through the tortuous polymeric nanosponge matrix; (iii) interfacial partitioning at the nanosponge–gel boundary; and (iv) diffusion through the gel vehicle to the skin surface. Representative cumulative release profile fitted to the Korsmeyer–Peppas power-law model (n = 0.45–0.89) indicating anomalous non-Fickian transport is shown (inset). Kd dissociation constant, n release exponent

8. Safety Profile, Biocompatibility, and Regulatory Considerations

8.1 Skin Biocompatibility

The safety profile of nanosponge constituents—principally cyclodextrins and their cross-linking products—is well-supported by decades of regulatory precedent [29,31]. β-CD and HP-β-CD are listed in the FDA Inactive Ingredients Database for topical formulations and have established acceptable daily intake (ADI) limits from oral administration studies [31]. Cross-linking products (carbonate or carbamate linkages from DPC or CDI, respectively) are chemically stable, non-hydrolyzable under physiological conditions, and have demonstrated acceptable cytotoxicity profiles in keratinocyte (HaCaT), fibroblast (NIH 3T3), and sebocyte cell lines at therapeutically relevant concentrations [38,47]. However, comprehensive in vitro genotoxicity (Ames test, micronucleus assay) and in vivo repeated-dose dermal toxicity studies for individual novel NS polymers remain a critical regulatory requirement and an area where published data are comparatively sparse [43].

8.2 Regulatory Pathway

The regulatory classification of nanosponge-based topical products intersects the pharmaceutical, nanomaterial, and potentially medical device regulatory frameworks, varying by jurisdiction [10]. In the United States, NS topical products would likely be regulated as Drug Products under NDA/ANDA pathways, with the FDA's nanotechnology guidance documents (2014, 2018) applying to characterization expectations [49]. The EMA's reflection paper on nanotechnology-based medicinal products for human use (2006, updated 2013) and the more recent EU Nanomedicines Roadmap provide the European regulatory framework [26]. Critical regulatory expectations include thorough physicochemical characterization (particle size distribution, surface chemistry, crystallinity), demonstration of batch-to-batch reproducibility, and species-appropriate bridging between in vitro, ex vivo, and in vivo safety and efficacy data [11]. The absence of a harmonized FDA/EMA definition of 'nanosponge' as a distinct product category necessitates early Scientific Advice consultation to clarify the development pathway [26].

9. Future Perspectives and Emerging Directions

9.1 Stimuli-Responsive Nanosponge Systems

First-generation nanosponges release drug in a diffusion-controlled, time-dependent manner irrespective of the biological environment [15,16]. Next-generation stimuli-responsive NS, engineered to release drug in response to specific pathological triggers present in acne-affected skin, represent a compelling evolution of this platform [26]. pH-responsive NS exploiting the microacidic environment of inflamed pilosebaceous units (pH 4.5-5.0 vs. normal skin pH 5.5) through incorporation of pH-sensitive polymers (poly(acrylic acid), chitosan-based cross-links) have been conceptually validated [43]. Redox-responsive NS incorporating disulfide cross-links, cleaved by the elevated reactive oxygen species (ROS) in acne lesions, represent another emerging strategy [57]. Enzymatic-responsive systems, triggered by C. acnes lipases or hyaluronidase at the follicular level, offer the most precise biological targeting selectivity achievable [17].

9.2 Combination Nanosponge Therapies and Dual-Drug Systems

Clinical acne guidelines consistently advocate combination therapy targeting multiple pathogenic pathways simultaneously [4,18]. The versatile porous architecture of nanosponges, capable of loading drugs with disparate physicochemical properties through complementary cavity inclusion and matrix adsorption mechanisms, is particularly well-suited to combination drug delivery [36]. Dual-drug NS systems co-encapsulating retinoid + antibiotic, BPO + antibiotic, or anti-inflammatory + sebum-suppressant combinations can deliver pre-optimized drug ratios to the follicular target, potentially simplifying patient regimens, improving adherence, and reducing resistance induction [20]. Preliminary studies on clindamycin-BPO co-NS have demonstrated synergistic antibiofilm activity (combination index <1 by Chou-Talalay analysis) against clinical C. acnes isolates, including antibiotic-resistant strains [23].

9.3 Artificial Intelligence and Machine Learning in NS Formulation

The multivariate, high-dimensional nature of nanosponge formulation space—encompassing polymer type, cross-linker ratio, drug loading conditions, vehicle composition, and processing parameters—is well-suited to machine learning (ML) approaches for formulation optimization [41,42]. Artificial neural networks (ANN), Gaussian process regression (Bayesian optimization), and random forest algorithms have been applied to predict pharmaceutical nanoparticle CQAs from input formulation variables, significantly reducing experimental burden and enabling formulation space exploration beyond feasible DoE ranges [44]. Generative adversarial networks (GAN) and variational autoencoders (VAE) represent frontier ML architectures capable of proposing novel NS formulation compositions with predicted target performance profiles, accelerating the design-make-test cycle toward clinical candidates [37].

9.4 Theranostic Nanosponges

The integration of diagnostic and therapeutic functionality within a single nanocarrier platform—the theranostic concept—has been explored for cancer but remains largely unexploited in dermatology [37]. Theranostic NS incorporating fluorescent probes or photoacoustic contrast agents alongside antiacne therapeutics could enable real-time follicular distribution mapping (CLSM, photoacoustic microscopy) during formulation development, transforming currently empirical skin deposition studies into quantitative, mechanistically informative characterization tools [57]. Furthermore, NS functionalized with Raman-active surface-enhanced scattering (SERS) nanoparticles could enable in situ, non-invasive monitoring of follicular drug levels in clinical studies [49].

10. Conclusion

Nanosponges have conclusively demonstrated their formulation science credentials as a versatile, biologically rational platform for topical antiacne drug delivery [11,12]. Their distinctive capacity to simultaneously address the cardinal limitations of conventional acne pharmacotherapy—suboptimal skin penetration, drug instability, dose-dependent irritation, and non-selective tissue distribution—within a single nanocarrier architecture positions them as one of the most promising nanotechnological innovations in dermatopharmaceutics [10,21]. The convergence of evidence from in vitro dissolution studies, ex vivo follicular targeting experiments, and emerging clinical data consistently supports a 2-5 fold improvement in skin bioavailability alongside meaningfully improved tolerability profiles relative to conventional formulations of the same active agents [9,49].

Cyclodextrin-based nanosponges remain the most extensively characterized and clinically advanced subtype, underpinned by established regulatory safety precedent and robust host-guest complexation chemistry [29,31]. However, the field would benefit significantly from: (i) harmonized synthesis and characterization standards to enable cross-laboratory data comparability; (ii) rigorous in vivo clinical efficacy studies powered for superiority—not merely equivalence—against existing standards of care; (iii) systematic investigation of nanosponge stability under accelerated storage conditions and within complex topical vehicles; and (iv) mechanistic in vivo follicular targeting studies employing non-invasive imaging modalities (reflectance confocal microscopy, photoacoustic imaging) in human subjects.

The integration of stimuli-responsive design, AI-assisted formulation optimization, combination drug co-delivery, and theranostic functionality represents a compelling translational research agenda that, if pursued with scientific rigor and regulatory foresight, could yield the next generation of acne therapeutics—safer, more effective, and better tolerated than any currently available option—within the coming decade.

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