Volume 4, Issue 3, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

DUAL-RESPONSIVE SUPRAMOLECULAR NANOGELS: ENHANCING TOPICAL ANTIBIOTIC DELIVERY VIA HOST-GUEST COMPLEXES

Azizullah Mukhtar[1], Hassan Ali[2], Abdul Jabbar[3], Shafiullah[*4], Momina Mukhtar[5], Zaib-un-Nisa[6], Abid Hussain[7]

[1,2]*Department of Pharmaceutical Sciences, Faculty of Pharmacy, Superior University, Lahore, Pakistan*
[3]*Imran Idrees College of Pharmacy, Sialkot, Pakistan*
[*4,5]*Imran Idrees College of Pharmacy, Sialkot, Pakistan*
[6]*Department of Zoology, GC Women University, Sialkot Pakistan*
[7]*Department of Pharmacy. University of Poonch Rawalakot, AJK Pakistan*

[1]drazizullahmukhtarrph@gmail.com, [2]hassanhafiz600@gmail.com, [3]abdujabbar333414@gmail.com, [*4]shafi.ullah@superior.edu.pk, [5]mominamukhtar498@gmail.com

DOI: https://doi.org/10.5281/zenodo.20266749

Keywords
Nanogels; Host-Guest Chemistry; Stimuli-responsive Delivery; Dermal Penetration; Antibiotic Resistance; Supramolecular Chemistry.

Article History
Received: 31 January 2026
Accepted: 16 March 2026
Published: 30 March 2026

Corresponding Author:
Shafi Ullah
shafi.ullah@superior.edu.pk

Abstract

Due to an increase in incidences of multidrug-resistant bacteria and the formidable barrier of the stratum corneum, effective management of chronic, deep thermal pathologies is challenging. Inadequate bioavailability, quick metabolism of drugs, and insufficient penetration are frequently presented by preparations of conventional topical dosage forms (Guy, 2024). Stimuli-responsive supramolecular nanogels have been developed as an advanced category of hybrid platforms that combine a resilient three-dimensional framework of cross-linked polymeric network with the dynamic modularity of host-guest chemistry to overcome these limitations (Kesharwani et al., 2023). This research reviews the incorporation of macrocyclic hosts, specifically cyclodextrins, cucurbiturils, and pillararenes, into nanogel structures for drug delivery (Saji, 2022). Non-covalent and reversible interactions are applied in these systems to aid in significant loading of the drug and spatial-temporal release, which is induced by localized oxidative stress and infected wound environment with acidic pH, enhancing activities of enzymes such as matrix metalloproteinases and gelatinases (T. Das, Das, Sultana, & Swain, 2025; Dong et al., 2023). Furthermore, we evaluate the mechanism by which these supramolecular assemblies penetrate the dermis through lipid fluidization and hair follicle shunting, which is supported by evidence from ex vivo confocal Raman spectroscopy and Franz diffusion investigations (X. Wang, Ma, Li, & Yang, 2024). This review provides a critical examination of developments in biofilm eradication, cytocompatibility, and regulatory problems faced during the practical application of these smart nanotherapeutic device.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

1. Introduction: The Convergence of Supramolecular Chemistry and Dermal Therapeutics

1.1 The Clinical Conundrum: Antibiotic Resistance in Chronic Wounds and Burns

An important worldwide healthcare burden marked by an increase inmorbidity and mortalityis the management of chronic wounds, such as diabetic wounds,vascular, and pressure ulcers, along with critical burn injuries (Ding et al., 2022). The transition from an acute contamination to a long-term infection is a significant outcome of these illnesses, usually aided by the progression ofcomplex microbial biofilms (Maslova, Eisaiankhongi, Sjöberg, & McCarthy, 2021). By serving as a biological fortress at places where bacteriareside within a cell, working as a physical obstacle to thepenetration of antibiotics (Singh et al., 2025).

In these situations, pathways for physiological resistance arecomplex, consisting of decreased drug permeability, elevated efflux pumpactivity, and direct chemical transformations of antibiotics (S. Das & Baker, 2016). An opportunistic gateway for microorganisms that are progressivelyresistant to standard therapies is developed by structural disruptions of thedermal barrier in cases of burns and chronic ulcers(Al-Dahmoshi, Al-Obaidi, & Al-Khafaji, 2020). Conventional topicalformulations are usually hampered by suboptimal permeation into deep-seatedbiofilm reservoirs (Kaiser, Wächter, & Windbergs, 2021).Development of an advanced drug delivery system is necessitated by the clinicalgap, including nanocarriers and hydrogels that have the capability to bypass EPS barrier, guaranteeing continuous and localized delivery of anti-microbialdrugs (Kaiser et al., 2021).

1.2 Advantages of nanogels over Liposomes and Solid Lipid Nanoparticles

Despite the fact that lipid-based carrier systems such as solid lipid nanoparticles and liposomes have typically been dominant in topical skin delivery, nanogels, cross-linked hydrophilic polymeric systems measuring between 20-200 nm possess unique advantages of physicochemical natures for the management of infected wounds(Maddiboyina et al., 2022). Liposomes typically experience limitations due to their marked instabilities, despite their biocompatibility and potential to simulate skin lipids (Camilo et al., 2020). Nanogels present a robust three-dimensional framework, which, in contrast to liposomes, ensures a surge in mechanical properties and efficacious encapsulation of drugs for both hydrophobic and hydrophilic antimicrobial drugs (Kesharwani et al., 2023).

Nanogels present greater capabilities of water retention and swelling ratio in contrast to SLNs, which utilize a solid lipid matrix for the prevention of pharmaceutical deterioration (Fei et al., 2022). The increased water levels are important to maintain a moist wound environment and elevating the softness of stratum corneum through hydration and therefore permitting deeper dermal uptake of antibiotics (Niu et al., 2022). By utilizing nanogels, a level of spatiotemporal control is obtained, which is challenging to achieve with simple lipid vesicles (Alkanawati, Machtakova, Landfester, & Thérien-Aubin, 2021).

1.3 The Supramolecular Edge: From Covalent Crosslinking to Dynamic Host-Guest Interactions

A significant development in nontherapeutic design is the shift from conventional covalently crossed polymers to supramolecular structures. Conventional polymers typically rely on irreversible chemical linkages like those developed via radical polymerization or click chemistry to safeguard the integrity of the network and often develop in flexible structures with limited dynamic wound environment adaptability (Siafaka, Özcan Bülbül, Okur, Karantas, & Üstündağ Okur, 2023). On the other hand, non-covalent reversible interaction, particularly host-guest complexation, is utilized in supramolecular nanogels to aid in crosslinking and gelation. Macrocyclic hosts such as cyclodextrins, cucurbiturils, and pillararenes lead to the development of inclusion complexes with specific guest molecules like hydrophobic drug

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

molecules or polymeric site changes and hence work as physical cross-linkers(Saji, 2022).

2. Fundamentals of Host-Guest Chemistry in Nanogel Architectures

2.1 Macrocyclic Hosts: Cyclodextrins, Cucurbiturils, and Pillararenes

The preference of macrocyclic host molecules mainly dictates the architectural coherence and functional array of supramolecular nanogels. These molecular containers aid in transformation from a stationary polymeric framework to dynamic responsive platforms by serving as elementary cross-linking nodes or gating elements(Hu, Huang, Redshaw, Tao, & Xiao, 2023). Due to their exceptional biocompatibility and toroidal framework consisting of a hydrophobic interior and hydrophilic exterior, cyclodextrins, particularly beta cyclodextrin, are among the most frequently utilized hosts and regarded as the gold standards (Topuz & Uyar, 2024). Cyclodextrins are usually incorporated into a nanogel matrix in cutaneous therapy to solubilize lipophilic pharmaceuticals and increase their diffusion via lipid-rich stratum corneum(H. Wang et al., 2024).

Distinct by their pumpkin-shaped symmetry and polar carbonyl-fringed portals, cucurbiturils (CB[n]) provide a significant advantage of extraordinarily high binding affinity and specificity for cationic occupants (Wu, Zhang, Lin, & Gao, 2023). Gated release properties are enabled by the inflexible and lipophilic cavity of CB[n], whereupon there is retention of the antibiotic until its displacement(Kakuta, Yamagishi, & Ogoshi, 2018).Pillararenes facilitating the development of stable and linear supramolecular polymer and cross linked assembly(Z. Li & Yang, 2021).

2.2 Mechanisms of Supramolecular Crosslinking and Gelation

The careful regulation of non-covalent bonds aids in the transformation of polymeric precursors into an integrated framework of nanogels along with host-guest complexation functioning as the prime mechanism of cross-linking (Addonizio et al., 2024). Supramolecular nanogels are usually referred to by their dynamic and reversible non-covalent interactions, contrasting to covalent hydrogels, which rely on chemical bonds of a permanent nature (Yang et al., 2022). One of the two structural patterns is followed by the process of gelation. First is the modification of precursor polymer with either a host or its analogous guest molecule, and second is the development of ternary complexes in which the cucurbituril macrocyclic host engages with two different guests from separate guest-bearing polymeric chains(Gómez-Florit et al., 2020; Panzer, 2022).For instance, the capability of beta cyclodextrin to form an inclusion complex with adamantine units is leveraged by systems employing it as a cross-linking agent(Yoshida et al., 2023).

2.3 Integrating the Cargo: Competitive Binding versus Prodrug Conjugation

Two primary principles demonstrate the preferential encapsulation of antimicrobial agents into supramolecular nanogels, physical confinement via competitive bindingand prodrug conjugation aided chemical bonding. Distinctive advantages are demonstrated by each mechanism in modulating the release profile and maintaining the therapeutic window inside the infected dermal microenvironment (Pinelli, Saadati, Rossetti, Rossi, & Sacchetti, 2023). In the competitive binding model, antibiotics function as a guest molecule located inside a macrocyclic host's hydrophobic cavity. Drug release is mainly triggered by endogenous competitive binders or by changes in the environment, which reduce the association constant (M.-P. Li, Yang, & Xu, 2022). Significantly alleviated affinities for cationic antibiotics are indicated by cucurbituril (CB[n]) based systems, remarkably returning drug uptake until its substitution by competitive entities like spermine or other biogenic amines, commonly increased in inflamed or necrotic tissues (Chernikova & Berdnikova, 2020; Colaco et al., 2025). Prodrug conjugation involves covalent binding of an antibiotic to the guest entity by a stimuli-responsive linker, such as an enzyme-cleavable peptide sequence (Boyce et al.,

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

2020; Wharton, Crawshay-Williams, Schober, Floto, & Spring, 2024).

3. Design of Stimuli-Responsive Hybrid Platforms for Topical Application

3.1 pH-Responsive Systems: Exploiting the Acidic Mantle and Infected Wound Milieu

The microenvironment of an infected wound in its chronic stage serves as a dynamic chemical landscape which can be exploited for on-demand administration of drugs. A particular acidic range is established by healthy skin generally. However, the pathological conditions of infected wounds and mature biofilms commonly develop characteristic nature and, as an outcome of bacterial metabolic reactions and buildup of lactic acid, the local pH levels decrease to about 5.5. Smart nano-micelles with bacterial infection-responsive disassembly for selective antimicrobial applications(Pranantyo, Kang, & Chan-Park, 2021). Utilizing host guest interactions which can react to protonation states, pH-responsive supramolecular nanogels are developed to detect these differences. A notable strategy utilizes carboxylatopillararene (CPA) as a macrocyclic host (Yan et al., 2019).

Furthermore, advanced method incorporates pH-responsive supramolecular nanofiber networks. These systems are usually comprised of self-assembling amphiphilic peptides (e.g., IKFQFHFD or pentapeptides) that maintain a stable hydrogel structure at neutral pH but go through fast network destabilization and disintegration when the pH approaches ~5.5 (H. Chen et al., 2022). Conversely, certain platforms are specifically engineered to address the alkaline shifts (pH > 7.4) noted in other phases of chronic inflammation (Haidari, Vasilev, Cowin, & Kopecki, 2022).

3.2 Enzyme-Responsive Mechanisms: Targeting Bacterial Secretions and Matrix Metalloproteinases

The enzymatic landscape of damaged dermal tissue offers a highly specific biological impetus for the spatiotemporal dispersal of antimicrobials. In chronic wound healing, the overabundance of host-derived matrix metalloproteinase, in particular MMP-2 and MMP-9, in fusion with bacterial-secreted enzymes including lipase and gelatinase, establishes a systematic organisation to correlate therapeutic interventions with the overall existence of pathogens (Mihai et al., 2024). Supramolecular nanogels use these signatures by including enzyme-cleavable moieties into host-guest complexes or the polymeric backbone, which alters the nanogel into a bio-responsive barrier (Pottanam Chali, Hüwel, Rentmeister, & Ravoo, 2021).

An upgraded strategy encompasses the application of hyaluronidase-responsive macrocyclic building blocks. Nanogels cross linked with hyaluronic acid, or HA-guests, experience localized degradation following exposure to the bacterial milieu (Monroe & Fikhman, 2023). This localized degradation starts the disintegration of the supramolecular network, so "releasing" the enclosed antibiotics(Patel et al., 2024).

3.3 Redox and ROS-Responsive Triggers in Inflamed Dermal Tissue

Perpetual oxidative stress is a characteristic associated with chronic infections and wounds, where activated neutrophils and macrophages excessively generate reactive oxygen species, including hydrogen peroxide and superoxide anions, causing a highly inflammatory microenvironment that slows down healing (Pranantyo et al., 2024). Supramolecular nanogels can be formulated to benefit from this redox imbalance as a specific trigger for the ejection of antibiotics (Alkanawati et al., 2021). Employing redox-active host-guest couples, likely the ferrocene/β-cyclodextrin (β-CD) recognition motif, is a frequent approach in this field(Sun et al., 2025). But when ROS levels are considerable, the neutral ferrocene is oxidized to the hydrophilic ferrocenium cation, which has a substantially reduced inclination for the β-CD molecule. The supramolecular network swiftly disintegrates following this redox-induced dissociation, and encapsulated medicines are released locally (Aramoto et al., 2020).

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

3.4 Hybridization Strategies for Enhanced Dermal Penetration

Hybridisation methods in supramolecular nanogels incorporate the purposeful incorporation of numerous chemical moieties to get around the lipophilic insulation of the stratum corneum. A considerable approach involves the establishment of amphiphilic nanogels that equilibrate surface hydrophobicity with network rigidity (Gruber et al., 2021).

Additionally, "nanogel-in-hydrogel" hybrid structures have emerged as advanced dual-delivery mechanisms. Researchers have effectively embedded an antibiotic-loaded supramolecular nanogel within a secondary hyper branched dendritic-linear-dendritic hydrogel configuration, supporting the sequential discharge of hydrophilic and hydrophobic agents, particularly novobiocin and ciprofloxacin, to address multi-species infections (Fan et al., 2021).

4. Mechanisms of Dermal Penetration and Tissue Integration

4.1 Overcoming the Stratum Corneum: The Role of Hydration and Lipid Fluidization

The stratum corneum operates as the fundamental rate-limiting obstacle for cutaneous antibiotic application, recognized by its "brick-and-mortar" configuration of protein-rich corneocytes positioned within a multilamellar lipid matrix of molecules (Jebbawi, Fruchon, Turrin, Blanzat, & Poupot, 2020). Supramolecular nanogels transcend this challenge via two fundamental physical mechanisms: enhanced skin hydration and the fluidization of intercellular lipids. Nanogels, especially thermoresponsive types (tNGs) can continually modulate the moisture concentration of the stratum corneum (SC). By releasing water or going through volume phase transitions at skin temperature (about 32°C), contributing to the swelling of corneocytes and widening of intercorneocyte gaps (Chauhan, Yasir, Verma, & Singh, 2020).

Besides hydration, the supramolecular functional transformation of nanogel networks supports tailored lipid fluidization. The integration of amphiphilic moieties, which may include cholesteryl groups or sulfoxide-derived side chains, facilitates the nanocarrier to copy the characteristics of chemical penetration boosters like DMSO while alleviating cytotoxicity (Işık et al., 2021).

4.2 Transfollicular versus Intercellular Shunting: Size Exclusion and Deformability

The penetration of supramolecular nanogels into the underlying dermal strata is accomplished mainly by utilizing two competing mechanisms: the intercellular lipid-rich pathway and the transfollicular (appendageal) conduit. The stratum corneum can at times be identified as a "brick and mortar" obstruction; nonetheless, its nanoscale channel-like pores function as a size-exclusion constraint on conventional rigid nanoparticles (Musazzi et al., 2018). However, supramolecular nanogels circumvent these constraints due to their intrinsic "softness" and mechanical malleability. In comparison with inflexible metallic or solid lipid nanoparticles, these dynamic polymer networks can experience a significant degree of deswelling and structural alterations, effectively "pushing" through compact intercellular gaps (Musazzi et al., 2018).

4.3 Real-Time Monitoring: In Vitro Franz Diffusion Cells and Ex Vivo Confocal Raman Spectroscopy Evidence

In vitro Franz diffusion cells are the benchmark for quantifying the bulk absorption and absorption kinetics of regionally administered antibiotics. These studies utilise a variety of them, including synthetic membranes or surgically removed human/animal dermis to identify crucial variables that include steady-state flux and the permeability index under strictly controlled sink conditions (Limón et al., 2019). The findings on cyclodextrin-based nanogels illustrate their potential to strengthen the absorption of hydrophobic medicines and modulate their discharge, hence possibly enhancing cutaneous delivery (Cirri, Nerli, Mennini, Maestrelli, & Mura, 2022).

Confocal Raman Spectroscopy and Stimulated Raman Scattering have emerged as efficient, label-free, and non-destructive approaches for

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

depth profiling(Garvie-Cook, Hoppel, & Guy, 2022). CRS permits the immediate or asynchronous imaging of drug storage embedded within the stratum corneum and viable epidermis, obtaining a depth resolution of approximately 5 µm(Krombholz, Liu, & Lunter, 2021).Recent studies have exhibited a significant quantitative correlation between the cumulative drug amount in FDCs and the intensity of Raman signals at specific skin depths, confirming CRS as a successful method for assessing bioequivalence and dermal bioavailability (Iliopoulos, Caspers, Puppels, & Lane, 2020).

5. Antibiotic Payloads: Specific Host-Guest Pairings and Antimicrobial Outcomes

5.1 Hydrophobic Antibiotics: Rifampicin and Azithromycin with Beta-Cyclodextrin Complexation

In view of their inadequate bioavailability and limited aqueous solubility, hydrophobic antibiotics, including azithromycin and rifampicin, are challenging to administer topically (Dan Córdoba et al., 2023). By establishing non-covalent inclusion complexes in which the hydrophobic antibiotic "agent" is accommodated past the lipophilic cavity of the "host," supramolecular nanogels integrated with β-cyclodextrin (β-CD) moieties get around these barriers (Anjani et al., 2021).

Rifampicin's apparent solubility and dissolution rate are substantially elevated when it is conjugated with β-CD or its derivatives (such as SBE-β-CD) (Abruzzo et al., 2022; Dan Córdoba et al., 2023). The release mechanisms alter from being solely diffusion-controlled to being deemed "affinity-controlled" when these complexes get integrated into a nanogel matrix (Thatiparti & von Recum, 2010). The latest research has demonstrated that RIF-loaded supramolecular platforms can lower the minimum inhibitory concentration against Staphylococcus aureus and achieve a 98.5% reduction in bacterial load in infected wound models compared to free drug formulations (Xu et al., 2025).

5.2 Hydrophilic Antibiotics: Vancomycin and Gentamicin with Cucurbituril Gating

Gentamicin and Vancomycin, two hydrophilic, polycationic antibiotics, have historically been problematic to administer topically due to pharmacological constraints and prospective side effects. Supramolecular nanogels incorporating cucurbiturils (CB) have been formulated as "molecular containers" that can conceal these drugs through highly specific host-guest interacting processes (Pisani et al., 2024).

These macrocyclic substrates simplify the formulation of "long-acting" antibiotic reservoirs in the context of antimicrobial therapy treatments(Koley, Gaur, Barooah, Bhasikuttan, & Mohanty, 2024). Researchers may exploit the dynamic nature of supramolecular crosslinking to yield stimulus-responsive release by incorporating CBs into hybrid nanogel structures (Hu et al., 2023). By keeping therapeutic levels above the minimum inhibitory concentration for an extended period of time, the potential to repurpose and construct these conventional antibiotics within nanostructured delivery systems not only augments their localized concentration but also mitigates the clinical challenge of antibiotic resistance (Koley et al., 2024).

5.3 Combination Therapy: Co-Delivery of Antibiotics with Biofilm Dispersants and Quorum Sensing Inhibitors

The progression of fully developed biofilms, in which bacteria are enveloped in a self-assembled matrix of extracellular polymeric substances that constitutes a chemical and physical protective layer against commonly used antibiotics, is primarily accountable for the proliferation of acute wound infections (Shen, Taha, Ghannoum, & Tyring, 2025). In an attempt to provide a broad spectrum of multifaceted therapeutic consequences, supramolecular nanogels are increasingly being developed as multi-component "cocktail" carriers that incorporate antibiotics together with biofilm dispersants and quorum-sensing blockers (Sikder, Chaudhuri, Mondal, & Singh, 2021).

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Implementing enzymatic dispersants, which include the cationic protease Alcalase 2.4 L FG or DNase I, to stabilize the outer coating of nanogels is a popular strategy. The proteins, polysaccharides, and eDNA in the EPS matrix are disintegrated by the enzymes in these hybrid systems, "opening" the biofilm configuration, which allows the encapsulated antibiotic to get through significantly (Blackman, Qu, Cass, & Locock, 2021). In juxtaposition with the treatment of antibiotics alone, research on alcalase-coated carbopol nanogels loaded with ciprofloxacin or clindamycin has established a strong mutually beneficial clearing impact, yielding a substantial reduction in viable biofilm-forming cells (Ali, Al Bostami, & Al-Othman, 2024).

6. Biological Performance and Safety Profile

6.1 In Vitro Antibiofilm Activity and Reduction in Minimum Biofilm Eradication Concentration

The minimum inhibitory concentration, which determines effectiveness against planktonic bacteria but fails to account for the extreme tolerance of the sessile communities residing within a biofilm matrix, is commonly utilized in conventional antimicrobial susceptibility testing (X. Chen, Thomsen, Winkler, & Xu, 2020). The basic biofilm eradication concentration in standard typical conditions can be 100–1,000 times greater than the MIC, frequently reaching values that would be systemically detrimental(Rottier, Seidelman, & Wouthuyzen-Bakker, 2023). By administering antibiotics on site and at high density unimpeded into the biofilm architecture, supramolecular nanogels successfully narrow this therapeutic gap (Weldrick, San, & Paunov, 2021).

Substantial decrease in MBEC across an array of resistant strains illustrates the numerical effect of these environments. In this regard, full-fledged Staphylococcus aureus and Pseudomonas aeruginosa biofilms have been shown to be depleted by pH-responsive supramolecular mechanics at concentrations much lower than those required for free drug solutions (Deusenbery, Gomez Casas, & Shukla, 2023). The synergistic effect of the nanogel's capacity to break into the extracellular polymeric component and the payload's provoked expulsion in response to bacterial metabolic indicators is liable for this heightened activity (Lv et al., 2023).

6.2 In Vivo Efficacy in Murine and Porcine Wound Infection Models

The effectiveness of supramolecular nanogels in animal simulations that mimic the multifaceted biological milieu of infected wounds validates their clinical prospects. It has been concluded that a supramolecular viscoelastic hydrogel composed of cholic acid and loaded with ciprofloxacin is more efficacious than ordinary therapeutic formulations at clearing wound infections brought about by Staphylococcus aureus(Kumar et al., 2021). Confirmed with gene expression and immunological profile, this system maintained a non-immunogenic profile in mouse host tissues (Kumar et al., 2021).Supramolecular nanofiber-based hydrogels have demonstrated exceptional antibacterial effectiveness in more complex models encompassing multidrug-resistant pathogens, such as MRSA skin infections (Shang et al., 2023).

6.3 Cytocompatibility and Skin Irritation: The Safety Profile of Macrocyclic Hosts

The clinical translation of supramolecular nanogels for topical use is fundamentally predicated on the non-toxic nature of their macrocyclic components. Because of their outstanding biocompatibility, cyclodextrins—more specifically Hydroxypropyl-β-cyclodextrin—are widely employed as excipients to enhance the absorption of lipophilic antibiotics without jeopardizing epidermal integrity (Ferreira et al., 2023).

Furthermore, the minimal skin porosity of cucurbiturils (CB) reinforces their safety characterization. For instance, cucurbituril (CB) has been demonstrated to stay localised within the skin's upper layers, pointing out that these hosts can deliver antibiotics locally while inhibiting systemic absorption into the bloodstream and associated toxicities (Seif,

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Impelido, Apps, & Wheate, 2014). Contemporary hybrid platforms typically employ "green" supramolecular gelation protocols, such as the use of epichlorohydrin-polymerised CDs, to further improve safety by minimizing the application of potentially detrimental small-molecule cross linkers that usually induce skin irritation (Cirri et al., 2022). Comprehensive toxicological evaluations of novel macrocycle derivatives are essential to create standardized nonclinical safety packages for dermatological applications(Zhang & Ma, 2013).

7. Challenges, Bottlenecks, and Future Perspectives

7.1 Scalability and Sterilization: GMP Hurdles for Supramolecular Systems

Scalability and terminal sterilization are substantial technical hurdles in the advancement of supramolecular nanogels from benchtop models to clinical contenders that conform to good manufacturing practices. Batch-to-batch reproducibility during mass production is intricate, in comparison with general polymers (Soni, Desale, & Bronich, 2016). Furthermore, more optimum synthetic techniques are imperative to attain high-purity macrocyclic derivatives at industrial scales (Zhang & Ma, 2013).

Conventional techniques like autoclaving might lead to undesirable secondary crosslinking or the accumulation of decomposition by-products, particularly in drug-loaded cyclodextrin systems, making terminal sterilization a specific hurdle (Agnes, Mazza, Malanga, & Manet, 2024). Emerging techniques like high hydrostatic pressure or optimized autoclaving for thermosensitive platforms show promise but need thorough validation(Agnes et al., 2024). In order to enhance these manufacturing characteristics and maintain a standardized and economical production allowing for clinical success, artificial intelligence is being put forward progressively (Escobedo, Schurr, & Nair, 2026).

7.2 Regulatory Landscape for Hybrid Platforms

A convoluted regulatory framework that inevitably involves an established category for commodities grounded in nanotechnology hampers the clinical translation of heterogeneous supramolecular nanogels (Mangla et al., 2025). The "hybrid" nature of these systems exhibits a significant hurdle. For macrocyclic hosts like cyclodextrins, deployment as effective delivery elements might call for extensive toxicological profiling (Ferreira et al., 2023). Quality risk management requires conformance to International Conference on Harmonization rules and regulations, most notably Q8 and Q11(Hwang, Ramsey, & Kabanov, 2020).

7.3 Future Trajectories: Theranostic Nanogels and 3D-Printed Smart Bandages

The introduction of "sense-and-treat" attributes into the supramolecular framework is the future of antibiotic delivery. The dynamic nature of host-guest interactions is being leveraged for both delivery and real-time diagnostic signalling, demonstrating the rapidly developing field of theranostic nanogels (Z. Wang, Sun, & Wang, 2022). These systems can be tailored to experience visible colorimetric shifts or fluorescence quenching, rendering clinicians' instant bedside data pertaining to the infection status before initiating automated drug release(Hong et al., 2020).

In the meantime, the emergence of 3D bio printing is revolutionizing the fabrication of "smart bandages" personalized to specific patients. Researchers can print anatomically contoured dressings with precise spatial control over antibiotic administration by using supramolecular nanogels as operative bio-inks (Janarthanan, Uthaman, Murugesh, & Vijayavenkataraman, 2024). In keeping with recent research, hybrid hydrogel bandages offer an improved antimicrobial efficacy as compared to traditional dressings, while matching the mechanical elasticity of human skin (2–14.7 kPa)(Fan et al., 2021). In order to achieve a fully self-sufficient, closed-loop dermal therapeutic platform, future iterations are likely to include integrated biosensors and piezoelectric factors that stimulate tissue regeneration oflocalised antibiotic dispersal (Liu et al., 2026).

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

8. Conclusion

The combination of supramolecular chemistry and nanotechnology demonstrates the shift in perspective in the medical management of pathogenic skin disease. This review has elucidated how stimuli-responsive hybrid nanogels, underpinned by dynamic host-guest interactions, offer a sophisticated solution to the clinical conundrum of antibiotic resistance in chronic wounds. Researchers have established platforms capable of withstanding high-density antibiotic loading and on-demand release triggered by the infected wound microenvironment (pH, ROS, and bacterial enzymes) by switching from conventional covalent crosslinking to retractable macrocyclic assemblies involving cyclodextrins, cucurbiturils, and pillararenes(Yang Wang, Pei, Feng, & Pei, 2019).

By inducing skin hydration, these supramolecular structures optimize penetration mechanistically and thereby ensure that treatment payloads reach deeply penetrated pathogens in the dermis (Jha et al., 2021). In both murine and porcine models, the incorporation of hybrid components enormously cuts down the minimum biofilm eradication concentration (Dey et al., 2022).

The trajectory is obvious even though there are still many hurdles to be handled, notably with implementing standardized Good Manufacturing Practices for non-covalent systems and confronting problematic regulatory frameworks for hybridized drug-device assemblies(Gupta, Tiwari, Yadav, Soni, & Joshi, 2024). “Smart” systems that integrate self-sufficient drug release with diagnostic sensing hold the key to the future of cutaneous therapies (Yuqiu Wang, Guo, He, & Gao, 2021). Supramolecular nanogels are set to go from being experimental enigmas to the foundation of precise, highly effective wound treatment as 3D bioprinting and theranostic capabilities advance, thereby lowering the worldwide burden of antimicrobial resistance.

REFERENCS

Abruzzo, A., Croatti, V., Zuccheri, G., Nicoletta, F. P., Sallustio, V., Corazza, E., . . . Bigucci, F. (2022). Drug-in-cyclodextrin-in-polymeric nanoparticles: a promising strategy for rifampicin administration. *European journal of pharmaceutics and biopharmaceutics, 180*, 190-200.

Addonizio, C. J., Braegelman, A. S., Schmidt, C. R., Ollier, R. C., Antwi, A. A., Su, B., . . . Webber, M. J. (2024). Impact of Guest Orientation in Host–Guest Supramolecular Hydrogels. *ACS macro letters, 14*(1), 8-13.

Agnes, M., Mazza, A., Malanga, M., & Manet, I. (2024). Sculpturing the future of water-soluble cyclodextrin branched polymers in pharmaceutical applications. *Journal of Materials Chemistry B, 12*(33), 7969-7976.

Al-Dahmoshi, H., Al-Obaidi, R. D., & Al-Khafaji, N. (2020). Pseudomonas aeruginosa: diseases, biofilm and antibiotic resistance *Pseudomonas Aeruginosa-Biofilm Formation, Infections and Treatments*: IntechOpen.

Ali, A. A., Al Bostami, R. D., & Al-Othman, A. (2024). Nanogel-based composites for bacterial antibiofilm activity: advances, challenges, and prospects. *RSC advances, 14*(15), 10546-10559.

Alkanawati, M. S., Machtakova, M., Landfester, K., & Thérien-Aubin, H. (2021). Bio-orthogonal nanogels for multiresponsive release. *Biomacromolecules, 22*(7), 2976-2984.

Anjani, Q. K., Domínguez-Robles, J., Utomo, E., Font, M., Martínez-Ohárriz, M. C., Permana, A. D., . . . Donnelly, R. F. (2021). Inclusion complexes of rifampicin with native and derivatized cyclodextrins: in silico modeling, formulation, and characterization. *Pharmaceuticals, 15*(1), 20.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Aramoto, H., Osaki, M., Konishi, S., Ueda, C., Kobayashi, Y., Takashima, Y., . . . Yamaguchi, H. (2020). Redox-responsive supramolecular polymeric networks having double-threaded inclusion complexes. *Chemical Science, 11*(17), 4322-4331.

Blackman, L. D., Qu, Y., Cass, P., & Locock, K. E. (2021). Approaches for the inhibition and elimination of microbial biofilms using macromolecular agents. *Chemical Society Reviews, 50*(3), 1587-1616.

Boyce, J. H., Dang, B., Ary, B., Edmondson, Q., Craik, C. S., DeGrado, W. F., & Seiple, I. B. (2020). Platform to discover protease-activated antibiotics and application to siderophore–antibiotic conjugates. *Journal of the American Chemical Society, 142*(51), 21310-21321.

Camilo, C. J., Leite, D. O., Silva, A. R., Menezes, I. R., Coutinho, H. D., & Da Costa, J. G. (2020). Lipid vesicles: Applications, principal components and methods used in their formulations. A review. *Acta Biológica Colombiana, 25*(2), 339-352.

Chauhan, I., Yasir, M., Verma, M., & Singh, A. P. (2020). Nanostructured lipid carriers: A groundbreaking approach for transdermal drug delivery. *Advanced pharmaceutical bulletin, 10*(2), 150.

Chen, H., Cheng, J., Cai, X., Han, J., Chen, X., You, L., . . . Wang, S. (2022). pH-switchable antimicrobial supramolecular hydrogels for synergistically eliminating biofilm and promoting wound healing. *ACS applied materials & interfaces, 14*(16), 18120-18132.

Chen, X., Thomsen, T. R., Winkler, H., & Xu, Y. (2020). Influence of biofilm growth age, media, antibiotic concentration and exposure time on Staphylococcus aureus and Pseudomonas aeruginosa biofilm removal in vitro. *BMC microbiology, 20*(1), 264.

Chernikova, E. Y., & Berdnikova, D. V. (2020). Cucurbiturils in nucleic acids research. *Chemical Communications, 56*(98), 15360-15376.

Cirri, M., Nerli, G., Mennini, N., Maestrelli, F., & Mura, P. (2022). Development and characterization of cyclodextrin-based nanogels as a new ibuprofen cutaneous delivery system. *Pharmaceutics, 14*(12), 2567.

Colaco, V., Jadhav, S. R., Bandi, S. P., Datta, D., Dhas, N., Thakur, G., . . . Alizadeh, B. (2025). Multifunctional application of supramolecular cucurbiturils as encapsulating hosts in drug delivery: A review. *International Journal of Pharmaceutics, 681*, 125801.

Dan Córdoba, A. V., Aiassa, V., Dimmer, J. A., Barrionuevo, C. N., Quevedo, M. A., Longhi, M. R., & Zoppi, A. (2023). Development and characterization of pharmaceutical systems containing rifampicin. *Pharmaceutics, 15*(1), 198.

Das, S., & Baker, A. B. (2016). Biomaterials and nanotherapeutics for enhancing skin wound healing. *Frontiers in Bioengineering and Biotechnology, 4*, 82.

Das, T., Das, M., Sultana, S., & Swain, R. (2025). Stimuli-responsive nanogels in wound care: A comprehensive review. *Next Nanotechnology, 8*, 100260.

Deusenbery, C., Gomez Casas, C., & Shukla, A. (2023). pH-responsive swelling micelles for the treatment of methicillin-resistant Staphylococcus aureus biofilms. *ACS Applied Polymer Materials, 5*(9), 7400-7410.

Dey, A., Yadav, M., Kumar, D., Dey, A. K., Samal, S., Tanwar, S., . . . Das, A. (2022). A combination therapy strategy for treating antibiotic resistant biofilm infection using a guanidinium derivative and nanoparticulate Ag (0) derived hybrid gel conjugate. *Chemical Science, 13*(34), 10103-10118.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Ding, X., Tang, Q., Xu, Z., Xu, Y., Zhang, H., Zheng, D., . . . Maitz, P. K. (2022). Challenges and innovations in treating chronic and acute wound infections: from basic science to clinical practice. *Burns & Trauma, 10*, tkac014.

Dong, L., Huang, C., Zhao, B., Hu, G., Huang, Y., Zhang, X., . . . Qian, W. (2023). RETRACTED ARTICLE: a pH/enzyme dual responsive PMB spatiotemporal release hydrogel promoting chronic wound repair. *Journal of Nanobiotechnology, 21*(1), 213.

Escobedo, H. D., Schurr, M. J., & Nair, D. P. (2026). Nanogels for the targeted delivery of antibiotic and antimicrobial drugs. *Therapeutic Delivery*, 1-14.

Fan, Y., Lüchow, M., Zhang, Y., Lin, J., Fortuin, L., Mohanty, S., . . . Malkoch, M. (2021). Nanogel Encapsulated Hydrogels: Nanogel Encapsulated Hydrogels As Advanced Wound Dressings for the Controlled Delivery of Antibiotics (Adv. Funct. Mater. 7/2021). *Advanced Functional Materials, 31*(7).

Fei, Y., Ma, Y., Zhang, H., Li, H., Feng, G., & Fang, J. (2022). Nanotechnology for research and treatment of the intestine. *Journal of Nanobiotechnology, 20*(1), 430.

Ferreira, L., Mascarenhas-Melo, F., Rabaça, S., Mathur, A., Sharma, A., Giram, P. S., . . . Veiga, F. (2023). Cyclodextrin-based dermatological formulations: Dermopharmaceutical and cosmetic applications. *Colloids and Surfaces B: Biointerfaces, 221*, 113012.

Garvie-Cook, H., Hoppel, M., & Guy, R. H. (2022). Raman spectroscopic tools to probe the skin–(trans) dermal formulation interface. *Molecular Pharmaceutics, 19*(11), 4010-4016.

Gómez-Florit, M., Domingues, R. M., Bakht, S. M., Mendes, B. B., Reis, R. L., & Gomes, M. E. (2020). Natural materials *Biomaterials science* (pp. 361-375): Elsevier.

Gruber, A., Joshi, A. A., Graff, P., Cuéllar-Camacho, J. L., Hedtrich, S., & Klinger, D. (2021). Influence of nanogel amphiphilicity on dermal delivery: balancing surface hydrophobicity and network rigidity. *Biomacromolecules, 23*(1), 112-127.

Gupta, D. K., Tiwari, A., Yadav, Y., Soni, P., & Joshi, M. (2024). Ensuring safety and efficacy in combination products: regulatory challenges and best practices. *Frontiers in Medical Technology, 6*, 1377443.

Guy, R. H. (2024). Drug delivery to and through the skin. *Drug Delivery and Translational Research, 14*(8), 2032-2040.

Hong, S., Zheng, D.-W., Zhang, Q.-L., Deng, W.-W., Song, W.-F., Cheng, S.-X., . . . Zhang, X.-Z. (2020). An RGB-emitting molecular cocktail for the detection of bacterial fingerprints. *Chemical Science, 11*(17), 4403-4409.

Hu, J.-H., Huang, Y., Redshaw, C., Tao, Z., & Xiao, X. (2023). Cucurbit [n] uril-based supramolecular hydrogels: Synthesis, properties and applications. *Coordination Chemistry Reviews, 489*, 215194.

Hwang, D., Ramsey, J. D., & Kabanov, A. V. (2020). Polymeric micelles for the delivery of poorly soluble drugs: From nanoformulation to clinical approval. *Advanced Drug Delivery Reviews, 156*, 80-118.

Iliopoulos, F., Caspers, P. J., Puppels, G. J., & Lane, M. E. (2020). Franz cell diffusion testing and quantitative confocal raman spectroscopy: In vitro-in vivo correlation. *Pharmaceutics, 12*(9), 887.

Işık, D., Joshi, A. A., Guo, X., Rancan, F., Klossek, A., Vogt, A., . . . Klinger, D. (2021). Sulfoxide-functionalized nanogels inspired by the skin penetration properties of DMSO. *Biomaterials science, 9*(3), 712-725.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Janarthanan, G., Uthaman, S. K., Murugesh, K., & Vijayavenkataraman, S. (2024). Exploring the potential of supramolecular hydrogels as advanced bioinks for bioprinting and biomedical applications. *International Journal of Bioprinting, 10*(3), 3223.

Jebbawi, R., Fruchon, S., Turrin, C.-O., Blanzat, M., & Poupot, R. (2020). Supramolecular and macromolecular matrix nanocarriers for drug delivery in inflammation-associated skin diseases. *Pharmaceutics, 12*(12), 1224.

Jha, A., Rama, A., Ladani, B., Verma, N., Kannan, S., & Naha, A. (2021). Temperature and pH-responsive nanogels as intelligent drug delivery systems: A comprehensive review. *Journal of Applied Pharmaceutical Science, 11*(12), 001-016.

Kaiser, P., Wächter, J., & Windbergs, M. (2021). Therapy of infected wounds: overcoming clinical challenges by advanced drug delivery systems. *Drug Delivery and Translational Research, 11*(4), 1545-1567.

Kakuta, T., Yamagishi, T.-a., & Ogoshi, T. (2018). Stimuli-responsive supramolecular assemblies constructed from pillar [n] arenes. *Accounts of chemical research, 51*(7), 1656-1666.

Kesharwani, P., Prajapati, S. K., Jain, A., Sharma, S., Mody, N., & Jain, A. (2023). Biodegradable nanogels for dermal applications: an insight. *Current Nanoscience, 19*(4), 509-524.

Koley, S., Gaur, M., Barooah, N., Bhasikuttan, A. C., & Mohanty, J. (2024). Supramolecular assemblies with macrocyclic hosts: applications in antibacterial activity. *Pure and Applied Chemistry, 96*(1), 23-42.

Krombholz, R., Liu, Y., & Lunter, D. J. (2021). In-line and off-line monitoring of skin penetration profiles using confocal Raman spectroscopy. *Pharmaceutics, 13*(1), 67.

Kumar, S., Pal, S., Thakur, J., Rani, P., Rana, K., Kar, A., . . . Pradhan, M. K. (2021). Nonimmunogenic hydrogel-mediated delivery of antibiotics outperforms clinically used formulations in mitigating wound infections. *ACS applied materials & interfaces, 13*(37), 44041-44053.

Li, M.-P., Yang, N., & Xu, W.-R. (2022). Synthesis of a new water-soluble hexacarboxylated tribenzotriquinacene derivative and its competitive host–guest interaction for drug delivery. *Beilstein Journal of Organic Chemistry, 18*(1), 539-548.

Li, Z., & Yang, Y.-W. (2021). Functional materials with pillarene struts. *Accounts of Materials Research, 2*(4), 292-305.

Limón, D., Domínguez, K. T., Garduño-Ramírez, M. L., Andrade, B., Calpena, A. C., & Pérez-García, L. (2019). Nanostructured supramolecular hydrogels: Towards the topical treatment of Psoriasis and other skin diseases. *Colloids and Surfaces B: Biointerfaces, 181*, 657-670.

Liu, Y., Luo, X., Chen, L., Qiao, Z., Si, C., & Liu, X. (2026). Dual-Layer Modular Microneedle-Based Biosensor for Advanced Precision Management of Infected Chronic Wounds. *Advanced Functional Materials, 36*(15), e17521.

Lv, X., Wang, L., Mei, A., Xu, Y., Ruan, X., Wang, W., . . . Dong, X. (2023). Recent nanotechnologies to overcome the bacterial biofilm matrix barriers. *Small, 19*(6), 2206220.

Maddiboyina, B., Desu, P. K., Vasam, M., Challa, V. T., Surendra, A. V., Rao, R. S., . . . Jhawat, V. (2022). An insight of nanogels as novel drug delivery system with potential hybrid nanogel applications. *Journal of Biomaterials Science, Polymer Edition, 33*(2), 262-278.

Mangla, B., Kumar, P., Javed, S., Pathan, T., Ahsan, W., & Aggarwal, G. (2025). Regulating nanomedicines: challenges, opportunities, and the path forward. *Nanomedicine, 20*(15), 1911-1927.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Maslova, E., Eisaiankhongi, L., Sjöberg, F., & McCarthy, R. R. (2021). Burns and biofilms: priority pathogens and in vivo models. *NPJ biofilms and microbiomes, 7*(1), 73.

Mihai, M. M., Popa, M. I., Holban, A. M., Gheorghe-Barbu, I., Popa, L. G., Chifiriuc, M.-C., . . . Lazăr, V. (2024). Clinical and microbiological features of host-bacterial interplay in chronic venous ulcers versus other types of chronic skin ulcers. *Frontiers in microbiology, 14*, 1326904.

Monroe, M. B. B., & Fikhman, D. A. (2023). Mini-review antimicrobial smart materials: the future's defense against wound infections. *Frontiers in Biomaterials Science, 2*, 1285386.

Musazzi, U. M., Cencetti, C., Franzé, S., Zoratto, N., Di Meo, C., Procacci, P., . . . Cilurzo, F. (2018). Gellan nanohydrogels: novel nanodelivery systems for cutaneous administration of piroxicam. *Molecular Pharmaceutics, 15*(3), 1028-1036.

Niu, J., Yuan, M., Liu, Y., Wang, L., Tang, Z., Wang, Y., . . . Fan, Y. (2022). Silk peptide-hyaluronic acid based nanogels for the enhancement of the topical administration of curcumin. *Frontiers in chemistry, 10*, 1028372.

Panzer, M. J. (2022). Holding it together: noncovalent cross-linking strategies for ionogels and eutectogels. *Materials Advances, 3*(21), 7709-7725.

Patel, A., Goswami, S., Hazarika, G., Sivaprakasam, S., Bhattacharjee, S., & Manna, D. (2024). Sulfonium-cross-linked hyaluronic acid-based self-healing hydrogel: stimuli-responsive drug carrier with inherent antibacterial activity to counteract antibiotic-resistant bacteria. *Advanced Healthcare Materials, 13*(6), 2302790.

Pinelli, F., Saadati, M., Rossetti, A., Rossi, F., & Sacchetti, A. (2023). On the influence of polyethyleneimine modification in nanogel-driven drug delivery. *Colloids and Surfaces A: Physicochemical and Engineering Aspects, 658*, 130623.

Pisani, S., Tufail, S., Rosalia, M., Dorati, R., Genta, I., Chiesa, E., & Conti, B. (2024). Antibiotic-loaded nano-sized delivery systems: an insight into gentamicin and vancomycin. *Journal of Functional Biomaterials, 15*(7), 194.

Pottanam Chali, S., Hüwel, S., Rentmeister, A., & Ravoo, B. J. (2021). Self-assembled cationic polypeptide supramolecular nanogels for intracellular DNA delivery. *Chemistry–A European Journal, 27*(47), 12198-12206.

Pranantyo, D., Kang, E.-T., & Chan-Park, M. B. (2021). Smart nanomicelles with bacterial infection-responsive disassembly for selective antimicrobial applications. *Biomaterials science, 9*(5), 1627-1638.

Pranantyo, D., Yeo, C. K., Wu, Y., Fan, C., Xu, X., Yip, Y. S., . . . Yang, L. (2024). Hydrogel dressings with intrinsic antibiofilm and antioxidative dual functionalities accelerate infected diabetic wound healing. *Nature Communications, 15*(1), 954.

Rottier, W., Seidelman, J., & Wouthuyzen-Bakker, M. (2023). Antimicrobial treatment of patients with a periprosthetic joint infection: basic principles. *Arthroplasty, 5*(1), 10.

Saji, V. S. (2022). Recent updates on supramolecular-based drug delivery–macrocycles and supramolecular gels. *The Chemical Record, 22*(7), e202200053.

Seif, M., Impelido, M. L., Apps, M. G., & Wheate, N. J. (2014). Topical cream-based dosage forms of the macrocyclic drug delivery vehicle cucurbit [6] uril. *PLOS one, 9*(1), e85361.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Shang, L., Liu, J., Wu, Y., Wang, M., Fei, C., Liu, Y., . . . Gu, F. (2023). Peptide supramolecular hydrogels with sustained release ability for combating multidrug-resistant bacteria. *ACS applied materials & interfaces, 15*(22), 26273-26284.

Shen, A. Z., Taha, M., Ghannoum, M., & Tyring, S. K. (2025). Biofilms and chronic wounds: pathogenesis and treatment options. *Journal of Clinical Medicine, 14*(21), 7784.

Siafaka, P. I., Özcan Bülbül, E., Okur, M. E., Karantas, I. D., & Üstündağ Okur, N. (2023). The application of nanogels as efficient drug delivery platforms for dermal/transdermal delivery. *Gels, 9*(9), 753.

Sikder, A., Chaudhuri, A., Mondal, S., & Singh, N. P. (2021). Recent advances on stimuli-responsive combination therapy against multidrug-resistant bacteria and biofilm. *ACS applied bio materials, 4*(6), 4667-4683.

Singh, B., Dahiya, M., Kumar, V., Ayyagari, A., Chaudhari, D. N., & Ahire, J. J. (2025). Biofilm and antimicrobial resistance: mechanisms, implications, and emerging solutions. *Microbiology Research, 16*(8), 183.

Soni, K. S., Desale, S. S., & Bronich, T. K. (2016). Nanogels: An overview of properties, biomedical applications and obstacles to clinical translation. *Journal of Controlled Release, 240*, 109-126.

Sun, X., Li, S., Qin, Y., Li, Y., Zhu, Y., & Wang, L. (2025). Macrocycle/ferrocene complexation-mediated smart supramolecular gel materials and their applications. *Chemical Communications, 61*(52), 9359-9369.

Thatiparti, T. R., & von Recum, H. A. (2010). Cyclodextrin complexation for affinity-based antibiotic delivery. *Macromolecular bioscience, 10*(1), 82-90.

Topuz, F., & Uyar, T. (2024). Recent advances in cyclodextrin-based nanoscale drug delivery systems. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 16*(6), e1995.

Wang, H., Tiwari, N., Orellano, M. S., Navarro, L., Beiranvand, Z., Adeli, M., & Calderón, M. (2024). Polyglycerol-functionalized β-cyclodextrins as crosslinkers in thermoresponsive nanogels for the enhanced dermal penetration of hydrophobic drugs. *Small, 20*(32), 2311166.

Wang, X., Ma, L., Li, C., & Yang, Y.-W. (2024). Macrocycle-based antibacterial materials. *Chemistry of Materials, 36*(5), 2177-2193.

Wang, Y., Guo, M., He, B., & Gao, B. (2021). Intelligent patches for wound management: in situ sensing and treatment: ACS Publications.

Wang, Y., Pei, Z., Feng, W., & Pei, Y. (2019). Stimuli-responsive supramolecular nano-systems based on pillar [n] arenes and their related applications. *Journal of Materials Chemistry B, 7*(48), 7656-7675.

Wang, Z., Sun, C., & Wang, R. (2022). Macrocycle-surfaced polymer nanocapsules: an emerging paradigm for biomedical applications. *Bioconjugate Chemistry, 33*(12), 2254-2261.

Weldrick, P. J., San, S., & Paunov, V. N. (2021). Advanced Alcalase-Coated Clindamycin-Loaded Carbopol Nanogels for Removal of Persistent Bacterial Biofilms. *ACS Applied Nano Materials, 4*(2), 1187-1201.

Wharton, T., Crawshay-Williams, F., Schober, T., Floto, R. A., & Spring, D. R. (2024). Unlocking Amides: A General Method for the Self-Immolative Release of Amide-Containing Molecules. *Angewandte Chemie International Edition, 63*(18), e202402267.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Wu, J., Zhang, B., Lin, N., & Gao, J. (2023). Recent nanotechnology-based strategies for interfering with the life cycle of bacterial biofilms. *Biomaterials science, 11*(5), 1648-1664.

Xu, J., Zou, D., Dong, E., Jiang, X., Xu, S., Xiao, Y., . . . Deng, K. (2025). Biomedical Engineering on Smart Polymeric Nanoparticle–Hydrogel Platforms for Efficient Antibiotic Delivery against Bacterial-Infected Wounds. *ACS Biomaterials Science & Engineering, 11*(7), 4166-4176.

Yan, S., Chen, S., Gou, X., Yang, J., An, J., Jin, X., . . . Gao, H. (2019). Biodegradable supramolecular materials based on cationic polyaspartamides and pillar [5] arene for targeting gram-positive bacteria and mitigating antimicrobial resistance. *Advanced Functional Materials, 29*(38), 1904683.

Yang, Q., Xu, W., Cheng, M., Zhang, S., Kovaleva, E. G., Liang, F., . . . Cheng, J. (2022). Controlled release of drug molecules by pillararene-modified nanosystems. *Chemical Communications, 58*(20), 3255-3269.

Yoshida, D., Park, J., Ikura, R., Yamashita, N., Yamaguchi, H., & Takashima, Y. (2023). Self-healable poly (dimethyl siloxane) elastomers based on host-guest complexation between methylated β-cyclodextrin and adamantane. *Chemistry Letters, 52*(2), 93-96.

Zhang, J., & Ma, P. X. (2013). Cyclodextrin-based supramolecular systems for drug delivery: recent progress and future perspective. *Advanced Drug Delivery Reviews, 65*(9), 1215-1233.