Advanced Bioactive PLGA Nanogels for the Management of Atopic Dermatitis

Taniya A. Bhawani, Anushree A. Gaidhane, Krutika R. Channe

NAGPUR COLLEGE OF PHARMACY, WANADONGRI, HINGNA-441110

Abstract

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disorder marked by immune dysregulation and impaired barrier function. Conventional therapies often fall short due to limited skin penetration, systemic side effects, and poor drug stability. Nanotechnology has emerged as a transformative approach in dermatology, offering targeted, controlled, and biocompatible delivery systems. Among these, poly (lactic-co-glycolic acid) (PLGA) nanogels have gained attention for their ability to encapsulate bioactive compounds, enhance skin absorption, and modulate immune responses. This review explores the application of advanced bioactive PLGA nanogels in AD therapy, detailing their physicochemical properties, mechanism of action, and therapeutic advantages. These nanogels facilitate sustained drug release, inhibit key inflammatory pathways such as STAT6 and IL-4 signaling, and promote skin barrier restoration. Safety profiles, biodegradability, and reduced systemic toxicity are also discussed, alongside limitations such as production cost and potential immunogenicity. Scope for further advancements includes the development of multifunctional and stimuli-responsive PLGA nanogels, microneedle-assisted delivery systems, and personalized formulations tailored to individual patient profiles. With ongoing research and clinical validation, PLGA nanogels exhibit considerable potential as next-generation therapeutics for the effective and patient-centric management of atopic dermatitis.

Keywords- Atopic dermatitis, PLGA nanogels, Nanotechnology, controlled and sustained release, anti-inflammatory therapy, skin barrier repair.

Introduction

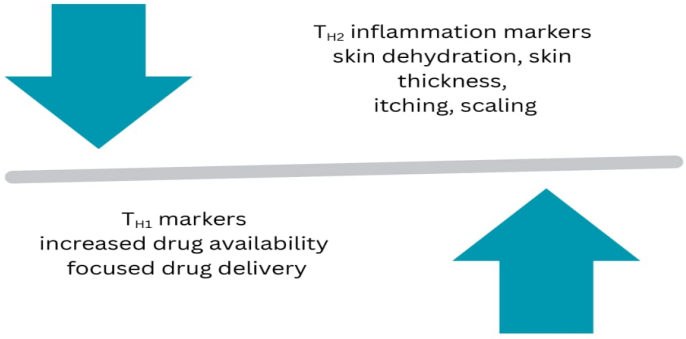
Atopic dermatitis, also called atopic eczema, is a chronic pruritic skin condition affecting approximately 17.8 million persons in the United States. Atopic dermatitis is often associated with other allergic conditions such as asthma and allergic rhinitis, forming what is commonly referred to as the allergic triad. Atopic dermatitis (AD) is a chronic disease that causes redness, irritation, itching, and inflammation of the skin (1). Research indicates that approximately 30% of children diagnosed with atopic dermatitis may go on to develop asthma as they grow older (2,3). Mutations in the filaggrin gene can compromise the skin's barrier function, allowing external antigens to interact with immune cells and trigger inflammation. Such inflammation leads to itching and scratching, which further damages the epidermis—a cycle commonly referred to as the itch-scratch loop (2,4).

A drug delivery system facilitates the precise administration of the active pharmaceutical ingredient (API), ensuring it reaches the targeted site at a regulated pace to produce the intended therapeutic effect (5,6). Controlled drug delivery refers to the administration of therapeutic agents at a defined rate, either locally or throughout the body, over a designated duration. This approach offers several advantages, including (i) maintaining a stable and effective drug concentration, (ii) enhancing patient adherence to treatment regimens, (iii) enabling site-specific targeting of the medication, and (iv) extending the duration of drug activity for sustained therapeutic benefit (7,8). Nanotechnology has significantly advanced the efficiency of drug delivery systems, marking a major milestone in modern therapeutics. Its integration into medicine—commonly referred to as nanomedicine—leverages materials and devices at the nanoscale (typically under 100 nanometers) to support diagnostic, therapeutic, and monitoring functions within biological systems (9). Key medical applications include targeted drug delivery, gene therapy, and innovative approaches to cancer treatment (10). Poly (lactic-co-glycolic acid) (PLGA), synthesized from poly (lactic acid) (PLA) and poly (glycolic acid) (PGA), is a widely utilized polymer in drug delivery applications (11). Its broad acceptance is attributed to its favorable biocompatibility, predictable biodegradation into safe metabolites—namely lactic and glycolic acid—and its approval by regulatory bodies such as the FDA for medical use. PLGA's adaptability makes it an excellent candidate for sustained and controlled drug release. By modifying the ratio of PLA to PGA, its degradation profile can be tailored to specific therapeutic needs. Additionally, PLGA is capable of encapsulating both water-soluble and lipid-soluble drugs and supports multiple administration routes, including oral, injectable, and implantable formats (12,13). Apparent diffusion coefficient measurements reveal that drug mobility within PLGA-based delivery platforms is governed not only by the physicochemical properties of the drug and the composition of the PLGA polymer, but also by the geometric attributes—such as size and shape—of the delivery system itself (14). Consequently, these variables play a critical role in the formulation and refinement of advanced controlled-release technologies (15). Upon degradation, PLGA breaks down into its constituent monomers—lactic acid and glycolic acid—which are biocompatible and

non-toxicity to developing cells (16). These byproducts are readily processed and cleared from the body through normal metabolic pathways, making PLGA an ideal material for biomedical applications (12).

Nanotechnology in Dermatology

Nanotechnology-based therapeutic strategies have attracted significant attention for their potential in treating atopic dermatitis (17). A wide array of nanoscale delivery systems—including nanoparticles, nanogels, nanoemulsions, nanomixtures, and other engineered nanocarriers—have been explored to improve drug stability, enhance skin penetration, and reduce systemic side effects (18). These platforms offer targeted delivery of anti-inflammatory agents, immunomodulators, and barrier-repair compounds, potentially transforming the management of this chronic inflammatory skin condition (19).



Atopic dermatitis has long been characterized as a condition predominantly driven by T helper 2 (Th2) lymphocyte activity. However, recent advances in immunological research have highlighted the involvement of additional immune components, including T helper 17 (Th17) and T helper 22 (Th22) cells. Moreover, effector cells such as eosinophils and mast cells contribute to the inflammatory milieu through degranulation, further amplifying the disease's immunopathology (19,20).

Nanoparticles and nanocarriers exhibit favorable rheological behavior, possess antimicrobial properties, and show potential in enhancing skin health. Among these, silver-based nanoparticles (Ag-NPs), silver-lipid complexes, and poly (lactic acid) nanoparticles (PLA-NPs) have emerged as promising candidates for the therapeutic management of atopic dermatitis (21).

Properties

Silver-based nanoparticles (Ag-NPs) exhibit potent antibacterial activity due to their ability to interact extensively with bacterial cells. Their high surface-area-to-volume ratio facilitates adhesion to bacterial membranes and penetration into the intracellular environment, enhancing antimicrobial efficacy (22,23).

Silver-lipid complexes—A novel topical formulation combining microsilver and nanolipid carriers (NLC) has shown promising results in treating mild to moderately severe atopic dermatitis. Available as both an O/W cream and lotion, the formulation's efficacy may be attributed to the formation of a silver-NLC complex (sNLC), which potentially enhances antimicrobial activity while improving skin penetration and barrier function (24). Poly (lactic acid) nanoparticles (PLA-NPs)—Poly (lactic acid) (PLA) nanoparticles have received considerable attention as biodegradable and biocompatible nanocarriers, supported by a well-established safety profile for clinical applications (25). Their ability to facilitate sustained and controlled drug release within the epidermal skin layer for targeted dermatological therapies (26).

PLGA as a Delivery Platform

PLGA polymers can be synthesized with different terminal groups—either ester or carboxylic acid. Those with ester end groups tend to degrade more slowly in aqueous environments due to their reduced susceptibility to hydrolysis (27). In commercial settings, PLGA is available in multiple grades, each characterized by specific properties such as molecular weight, inherent viscosity, and the ratio of lactic acid to glycolic acid units (28). In biomedical contexts, PLGA is often favored over PLA due to its comparatively faster degradation profile. The monomer lactic acid, fundamental to both polymers, exists as two stereoisomers—D- and L-forms—whose relative proportions can be tailored to fine-tune the physicochemical characteristics of the resulting copolymer (13,29). By varying the lactic acid to glycolic acid ratio, typically in compositions such as 50:50, 65:35, 75:25, and 85:15, researchers can modulate key properties including degradation kinetics, mechanical integrity, and drug release behavior (30). Formulations with a higher glycolic acid fraction (e.g., 50:50) tend to degrade more rapidly due to increased hydrophilicity. Whereas those enriched in lactic acid exhibit slower degradation rates, enhanced hydrophobicity, and greater crystallinity (31).

PLGA exhibits excellent biocompatibility, and upon degradation, it yields lactic acid and glycolic acid—metabolites that are readily processed through the Krebs cycle. This metabolic compatibility, combined with its tunable degradation profile, makes PLGA a highly suitable candidate for drug delivery platforms, particularly in nanoparticle-based formulations (32).

Bioactive PLGA Nanogels for Atopic Dermatitis

Anti-inflammatory Agents

Capsaicin: Sourced from chili peppers, capsaicin modulates neuropeptide signaling and reduces itch by desensitizing sensory neurons. It is used topically to alleviate discomfort associated with chronic inflammatory skin conditions (33).

Glycyrrhizic Acid: A triterpenoid glycoside derived from licorice root, glycyrrhizic acid inhibits pro-inflammatory mediators and supports epidermal barrier recovery. Its soothing properties make it suitable for sensitive and reactive skin (34).

Piperine: An alkaloid found in black pepper; piperine suppresses inflammatory cytokines and enhances the bioavailability of co-administered compounds. It contributes to reduced inflammation and improved skin resilience (35,36).

Antioxidant Agents

Astaxanthin- A marine carotenoid with exceptional antioxidant potency, astaxanthin protects skin cells from oxidative damage, improves elasticity, and supports barrier integrity. It is particularly effective in reducing photoaging and inflammation (37,38).

β-Carotene- A precursor to vitamin A, β-carotene contributes to epithelial repair and antioxidant defense. It helps maintain skin structure and reduces oxidative stress linked to inflammatory responses (39).

Quercetin- A plant-derived flavonoid known for its ability to stabilize mast cells and inhibit histamine release. Quercetin offers dual antioxidant and anti-inflammatory benefits, making it valuable in managing allergic skin reactions (40,41).

Hydrating and Barrier-Supportive Agents

Guar Gum- A natural galactomannan extracted from guar beans, guar gum functions as a stabilizer and moisturizing agent in topical formulations. It enhances skin texture, retains hydration, and provides a calming effect on irritated skin (36,42).

Mechanism of action:

Poly(lactic-co-glycolic acid) (PLGA) nanogels represent a promising nanocarrier system for the targeted treatment of atopic dermatitis (AD), owing to their biocompatibility, biodegradability, and tunable drug release properties (43). Their mechanism of action involves several synergistic pathways:

Enhanced Skin Penetration and Targeted Delivery

PLGA nanogels are engineered at the nanoscale to facilitate penetration through the compromised stratum corneum typical of AD lesions. Surface modifications with ligands such as hyaluronic acid (HA) or RGD peptides further enhance adhesion and transdermal delivery. This allows for localized deposition of therapeutic agents directly into inflamed skin layers (1,44).

Controlled and Sustained Drug Release

The polymeric matrix of PLGA enables encapsulation of anti-inflammatory compounds (e.g., curcumin, tacrolimus, corticosteroids) and ensures their controlled release over time. This sustained delivery maintains therapeutic concentrations at the site of inflammation while minimizing systemic exposure and associated side effects (45).

Immunomodulation and Anti-inflammatory Effects

Upon release, the encapsulated agents inhibit key inflammatory mediators such as interleukin-4 (IL-4), interleukin-13 (IL-13), and tumor necrosis factor-alpha (TNF-α). This downregulation of Th2-mediated immune responses leads to reduced erythema, pruritus, and edema (45).

Restoration of Skin Barrier Function

Certain PLGA nanogel formulations promote keratinocyte proliferation and lipid synthesis, contributing to the repair of the disrupted epidermal barrier. This is critical for long-term disease management and prevention of flare-ups (1,46).

Nanotechnology in Drug Delivery: Safety, Advantages, and Limitations

Nanotechnology-based drug delivery systems offer significant advantages in overcoming poor drug solubility and bioavailability (47). Their nanoscale size (10–1000 nm) provides a high surface area, enabling versatile administration routes—oral, ocular, intranasal, or subcutaneous—and facilitating targeted delivery while evading rapid clearance (48). These systems can encapsulate or bind drugs, protecting them from premature degradation and allowing sustained release at therapeutic sites. Benefits include reduced dosage requirements, minimized systemic toxicity, and enhanced efficacy (49).

Despite these advantages, several safety concerns persist. Nanoparticles may agglomerate, exhibit poor biodegradability, and pose challenges in large-scale production. Their interactions with biomolecules can lead to systemic distribution and potential accumulation in tissues (50). Toxicity profiles vary depending on particle composition, size, and morphology. For example, carbon- and metal-based nanoparticles have demonstrated cytotoxic effects in vitro and in vivo. Therefore, rigorous safety assessments—including 3D skin models (EpiSkin™, EpiDerm™), 2D cell lines (HaCaT, BALB/c 3T3), and MTT assays—are essential to determine safe concentrations for topical applications (51).

Regulatory approval of several nanomedicines underscores their clinical potential, but assumptions of universal safety are unfounded. Components such as cationic lipids, cholic acid derivatives, and targeting moieties may trigger immune responses (52). However, surface modifications and the use of biodegradable excipients have shown promise in mitigating adverse effects. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), in particular, have demonstrated favorable safety profiles and reduced skin irritation at concentrations below 1 mg/mL, making them viable candidates for dermatological therapies (36).

Conclusion

Advanced bioactive PLGA nanogels represent a promising frontier in the targeted treatment of atopic dermatitis. Their unique physicochemical properties—biodegradability, biocompatibility, and tunable drug release—enable precise delivery of therapeutic agents to inflamed skin while minimizing systemic exposure. By incorporating anti-inflammatory compounds, barrier-repair molecules, and surface ligands, these nanogels offer a multifaceted approach to managing the complex immunopathology of AD.

Recent innovations, including microneedle-assisted delivery and stimuli-responsive formulations, have further enhanced their clinical potential. Preclinical studies have demonstrated improved skin penetration, reduced cytokine expression, and restoration of epidermal integrity. However, the transition from bench to bedside requires rigorous validation through standardized safety assessments and randomized controlled trials.

Looking ahead, the integration of personalized medicine and smart nanogel systems may redefine how chronic inflammatory skin diseases are treated. With continued research and regulatory support, PLGA nanogels could become a cornerstone of next-generation dermatological therapeutics, offering safer, more effective, and patient-friendly solutions for atopic dermatitis.

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