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Recent advances in polymer-based drug delivery systems for atopic dermatitis: enhancing therapeutic efficacy and outcomes

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ABSTRACT

Atopic dermatitis (AD) is a chronic, multifactorial skin condition characterized by impaired skin barrier function, immune dysregulation, and persistent inflammation. It significantly diminishes patients' quality of life due to frequent relapses and exacerbations. Despite advancements in therapeutic strategies, current treatments often fail to achieve long-term remission and are commonly associated with adverse side effects, including skin thinning and systemic complications. Polymer-based formulations have emerged as promising alternatives, offering enhanced drug delivery, improved skin penetration, and precise, controlled release mechanisms. This review critically examines recent advances in polymeric systems for AD treatment, focusing on smart polymers that respond to environmental stimuli such as pH, temperature, and inflammation. These systems enable sustained, site-specific drug release, enhancing therapeutic efficacy, minimizing side effects, and improving patient compliance. Moreover, responsive polymer delivery systems optimize therapeutic outcomes by targeting the underlying pathophysiology of AD, paving the way for more personalized and effective treatment strategies. Challenges associated with current polymer-based therapies are also discussed, alongside future research directions aimed at overcoming these limitations. The continued development of innovative polymer-based systems holds significant potential for delivering long-term, targeted, and effective AD treatments. By modulating key disease mechanisms rather than merely alleviating symptoms, these advances are expected to substantially improve patient outcomes and overall quality of life.

1. Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disorder characterized by intense itching, erythematous patches, and edematous scabs [1–3]. Persistent itching often leads to continuous scratching, which aggravates skin irritation and can progress to eczema, skin thickening, and roughness. Affecting a significant portion of the global population, AD significantly diminishes patients' quality of life, highlighting the critical demand for effective and sustainable treatment. This review explores the causes, pathophysiology, and epidemiology of AD, focusing on its impact on patients and the limitations of existing therapies. Addressing these challenges requires the development of more targeted and efficient treatment strategies.

Recent advancements in biomaterials, particularly polymer-based technologies, have introduced promising opportunities to improve AD treatment [4]. Biocompatible polymers are pivotal in promoting skin barrier recovery, reducing inflammation, and enhancing moisture retention—critical factors in managing AD [5]. For instance, hyaluronic acid (HA) is renowned for its remarkable moisturizing properties and ability to restore the skin barrier, while natural polymers such as chitosan offer additional antibacterial and anti-inflammatory benefits, aiding in infection prevention and inflammation control [6].

Innovative drug delivery systems, particularly smart polymers that respond to environmental stimuli such as pH, temperature, and inflammation, are transforming AD therapy. These systems are engineered to enable sustained and site-specific drug release, providing prolonged therapeutic effects that outperform conventional treatments [7]. By responding dynamically to changes in the disease microenvironment, such as altered pH or temperature, or to external triggers like light or electricity, smart polymers offer precise and controlled drug delivery tailored to the severity of inflammation [8,9]. This targeted approach minimizes drug exposure to healthy tissues, reducing systemic

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side effects and enhancing treatment efficacy [10,11]. Moreover, the adaptability of these polymers allows for customizable treatment strategies, aligning closely with the chronic and relapsing nature of AD. As a result, smart polymer systems present a significant advancement in addressing the limitations of existing therapies while improving patient outcomes and compliance.

This review delves into the pathogenesis of AD, existing treatment modalities, and drug classes, with a particular emphasis on innovative polymer-based technologies such as smart polymers (Fig. 1). These advanced formulations offer significant potential in enhancing skin barrier repair, reducing inflammation, and preventing infections [12]. By exploring these advancements, the review provides a comprehensive foundation for future research, paving the way for the development of more effective, personalized, and patient-centered treatment strategies for AD.

2. Epidemiology of atopy

2.1. AD prevalence

Recent global surveys estimate that approximately 200–250 million people are affected by AD worldwide, although prevalence rates vary considerably across regions and age groups [13]. In high-income countries in Northern Europe and North America, childhood prevalence often exceeds 15 %–20 %, whereas adult prevalence is typically 2 %–5 %. In contrast, population-based studies in East Asia (e.g., Korea, Japan, China) report increasing prevalence in both children (10 %–15 %) and adults (3 %–4 %), likely influenced by rapid urbanization and changing environmental exposures [14,15]. In low- and middle-income regions, prevalence remains lower but is steadily rising, with urban children being disproportionately affected compared with those in rural areas. Additionally, ethnic differences have been observed; for instance, African American and Asian populations tend to experience earlier onset and greater disease severity than Caucasian populations [16]. These epidemiological variations underscore the complex interplay of genetic background, socioeconomic conditions, and environmental triggers that shape the global burden of AD.

2.2. AD causes

AD arises from a complex interplay of genetic, immunological, environmental, and microbiome-related factors. Genetics play a crucial role, particularly mutations in the filaggrin gene, which is essential for maintaining skin barrier integrity. When filaggrin function is impaired, the skin barrier weakens, allowing allergens to penetrate more easily. These genetic factors significantly impact both immune system regulation and skin barrier function, contributing to the development of AD [17]. In addition to genetic factors, immune system abnormalities are prevalent in AD, with patients often exhibiting an overactive immune response that results in skin inflammation and heightened sensitivity to allergens (Fig. 2) [18].

Environmental factors also contribute to the development of AD.

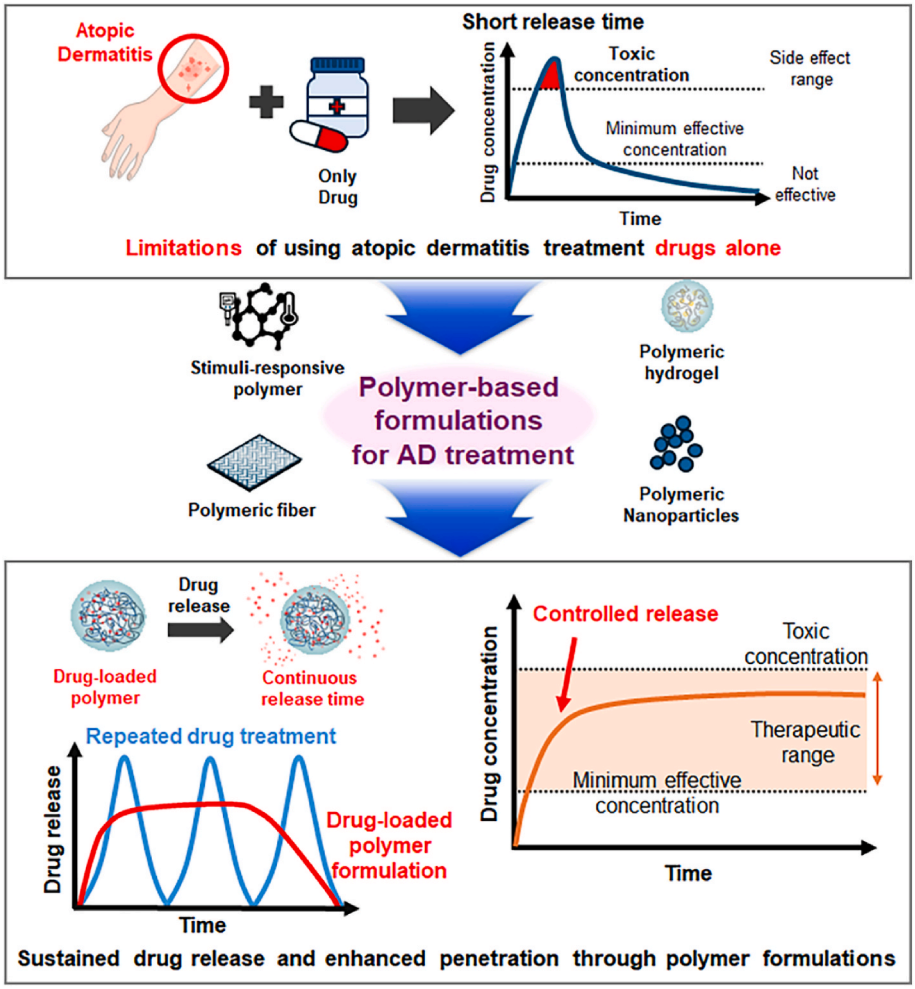

Fig. 1. Schematic illustrating drug-loaded polymer formulations for AD treatment. The diagram highlights drug-loaded polymer formulations for controlled drug release and inflammation reduction, demonstrating their role in enhancing therapeutic outcomes for AD.

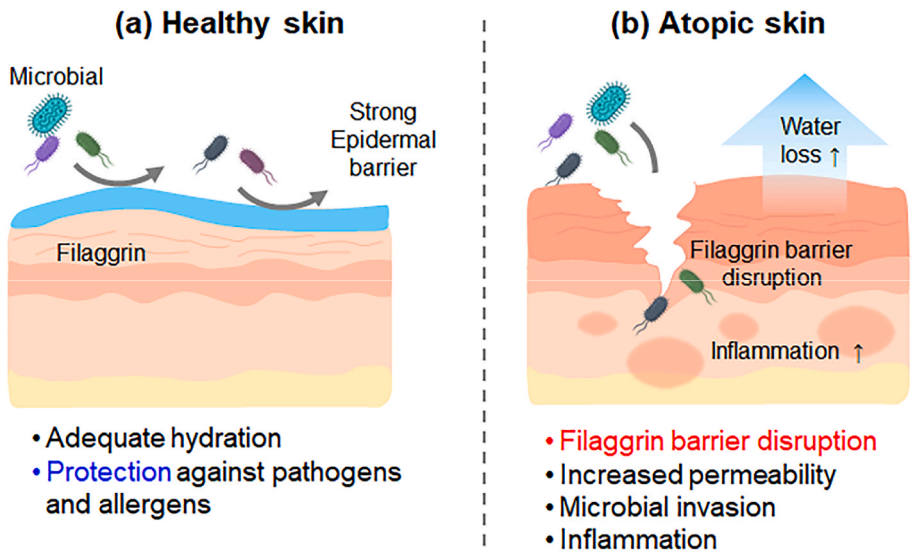

Fig. 2. Skin barrier abnormalities in AD. (a) Normal skin: The intact epidermal barrier, maintained by filaggrin and other structural proteins, retains moisture and prevents the entry of irritants, allergens, and pathogens. (b) AD skin: Filaggrin deficiency and barrier disruption lead to transepidermal water loss, dryness, and enhanced penetration of allergens and microbes, which activate immune pathways and trigger inflammation, thereby exacerbating AD symptoms.

Urbanization, air pollution, and humidity fluctuations have been associated with an increased incidence of AD, which is particularly prevalent in urban areas and high-income countries [19]. Furthermore, skin microbiome imbalance can aggravate AD symptoms. Studies have emphasized the importance of maintaining a balanced microbiome to promote skin health and reduce inflammation [20].

The skin barrier abnormalities associated with AD. Under normal conditions, the skin acts as a protective barrier, shielding the body from external irritants and pathogens while retaining moisture. This barrier is compromised in AD, leading to increased moisture loss and dry, dehydrated skin. This dryness weakens the skin's defenses, increasing its susceptibility to allergens and the risk of bacterial and viral infections. These breaches in the skin barrier can trigger allergic reactions or infections, often leading to the onset or worsening of AD and contributing to further inflammation [21].

The progression of skin barrier damage and immune response in AD occurs across the non-lesional, acute, and chronic stages. In the non-lesional stage, the early activity of T helper 1 (Th1) and Th2 cells begins to compromise the skin barrier. During the acute stage, Th2 cells dominate the inflammatory response, triggering itching and further compromising the skin barrier, while Th17 cells intensify the inflammation. In the chronic stage, prolonged activation of Th1, Th22, and Th17 cells leads to persistent inflammation, skin-barrier degradation, and abnormal sebum production. This complex interplay among immune cells creates a vicious cycle of worsening inflammation and skin damage [22,23].

2.3. Disease burden, clinical diagnosis, and unmet needs

AD imposes a substantial burden on both patients and healthcare systems. Quality-of-life studies indicate that moderate-to-severe AD ranks among the most disabling chronic skin diseases, comparable to conditions such as diabetes and depression [24]. Persistent itching and sleep disturbance often lead to psychological comorbidities, including anxiety and depression, which negatively affect school performance in children and work productivity in adults [25]. From an economic perspective, the combined direct medical costs (consultations, topical and systemic drugs, biologics) and indirect costs (missed workdays, caregiver burden) are estimated to exceed USD 5–10 billion annually in the United States alone, with similar upward trends observed in Europe and Asia [26].

Clinical diagnosis is typically based on the Hanifin and Rajka criteria or the UK Working Party criteria. However, underdiagnosis remains common, especially among adults with atypical manifestations [27]. Current treatment guidelines recommend emollients, topical corticosteroids, calcineurin inhibitors, systemic immunosuppressants, and biologics. Nonetheless, these therapies have notable limitations: corticosteroids can cause skin atrophy with long-term use, calcineurin inhibitors frequently induce local irritation, and biologics or Janus kinase (JAK) inhibitors, while effective, are expensive and require injections or continuous monitoring [28–30].

Therefore, significant unmet clinical needs persist. Patients require sustained symptom control without rebound effects or cumulative toxicity, yet current therapies often fail to provide long-term stability [31]. Another major challenge is the development of improved skin-targeted delivery systems capable of enhancing percutaneous penetration while minimizing systemic exposure. Furthermore, there remains an urgent need for affordable and accessible long-term management options, particularly for children and patients in resource-limited settings [32].

These gaps underscore the importance of advancing polymer-based drug delivery systems, which can extend therapeutic residence, selectively target inflamed lesions, and reduce adverse effects, thereby addressing the limitations of current treatments and ultimately improving patient outcomes.

3. Drug treatment: mechanisms of action and clinical significance of topical and systemic drug

AD results from a compromised skin barrier and immune system, leading to chronic inflammation and increased sensitivity to allergens [33]. Treatment strategies primarily aim to alleviate symptoms and modulate immune responses to reduce flare-ups [34,35]. Therapeutic options are typically categorized into topical treatments that are applied directly to the affected areas to reduce inflammation and itching, and systemic treatments, which target more severe or widespread symptoms throughout the body.

However, conventional topical formulations for AD treatment exhibit significant limitations, as traditional ointments often form an occlusive greasy film on the skin surface, which hinders drug permeation through the stratum corneum and restricts therapeutic penetration to the deeper epidermal layers (Fig. 3)

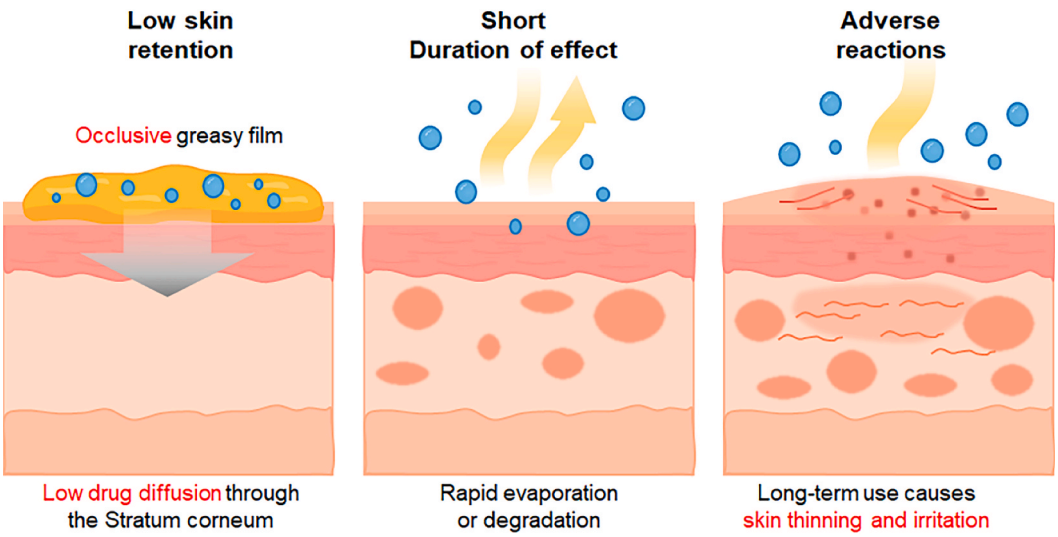

Fig. 3. Schematic illustration showing the major limitations of conventional topical formulations used for AD treatment. Traditional ointments form an occlusive greasy film on the skin surface, resulting in low drug diffusion through the stratum corneum and limited therapeutic penetration.

3.1. Topical treatment

Topical treatments are applied directly to the skin to restore the skin barrier, reduce localized inflammation, and modulate immune responses. These treatments are primarily used for patients with mild to moderate AD. The main agents used for topical treatment include steroids and topical calcineurin inhibitors (TCIs) [36,37].

3.1.1. Topical treatment agent: steroids

Topical corticosteroids remain the first-line therapy for AD because of their potent ability to suppress inflammation, vasodilation, and immune activation (Fig. 4). Their mechanism of action involves inhibition of phospholipase A2, which reduces the synthesis of prostaglandins and leukotrienes, and interference with TNF-α–driven NF-κB and MAPK signaling pathways that amplify cytokine production [38–40]. By binding to glucocorticoid receptors, corticosteroids downregulate pro-inflammatory mediators such as IL-4, IL-13, and TNF-α, thereby alleviating immune-mediated skin inflammation [41].

Despite their proven efficacy, prolonged steroid use is associated with dose-dependent adverse effects, including skin atrophy,

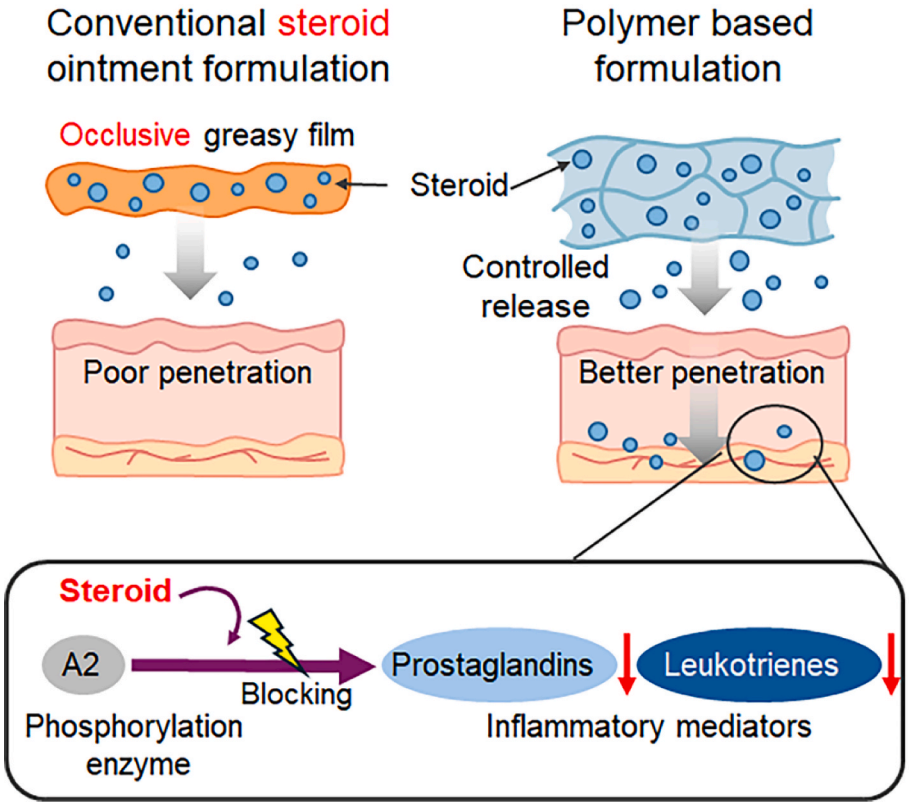

Fig. 4. Schematic illustration showing the limitations of conventional topical corticosteroid formulations in AD treatment, characterized by limited penetration through the stratum corneum and poor barrier restoration, in contrast to polymer-based systems that enable controlled release and enhanced skin delivery.

pigmentation changes, and systemic complications such as growth suppression and reduced bone density. Rebound flares following discontinuation are also common [42,43]. Importantly, while corticosteroids effectively control inflammation, they do not restore skin barrier function, leaving a critical therapeutic gap.

To overcome these limitations, formulation strategies that minimize peak concentrations and prolong local drug residence are being actively explored. For instance, polymer hydrogel depots and nanostructured carriers can provide steady transdermal flux across the stratum corneum, maintaining therapeutic efficacy while reducing irritation and systemic exposure (see Sections 5.1 and 5.2).

3.1.2. Topical treatment agent: topical calcineurin inhibitors (TCIs)

TCIs are effective AD treatments that modulate immune responses via inhibition of the enzyme calcineurin. Calcineurin inhibitors such as tacrolimus represent an alternative to corticosteroids, particularly for sensitive skin sites. Their mechanism of action involves inhibition of calcineurin, a calcium/calmodulin-dependent phosphatase essential for T-cell activation. By preventing NFAT dephosphorylation and subsequent nuclear translocation, TCIs suppress the production of IL-2, IL-6, and other pro-inflammatory cytokines, thereby reducing T-cell proliferation and downstream inflammatory cascades [44,45]. Tacrolimus binds to FKBP12 to form inhibitory complexes that block calcineurin activity while also attenuating mast cell and neutrophil activation [46].

A key advantage of TCIs is their lower risk of skin atrophy compared with corticosteroids, making them suitable for long-term use. However, their onset of action is slower, and transient burning or erythema at the application site is frequently reported [47,48]. Additionally, TCIs exhibit limited percutaneous penetration, which restricts drug delivery to lesional sites. Polymer-assisted delivery strategies may help overcome these challenges: penetration-enhancing carriers and pH-responsive nanogels that release the drug preferentially within inflamed, higher-pH microenvironments show promise for improving local efficacy and tolerability. Such approaches could address the pharmacokinetic limitations of TCIs while minimizing systemic exposure (see Sections 5.2.3 and 6).

3.2. Systemic treatments

Systemic treatments are often required to manage moderate-to-severe cases of AD, particularly when topical therapies are insufficient. These agents can be broadly categorized into immunosuppressive agents, biologic therapies, and JAK inhibitors, all of which modulate inflammatory pathways through distinct mechanisms [49]. Although they provide substantial symptom control, their clinical use is frequently limited by systemic toxicities, high costs, or restricted accessibility [50,51].

These drawbacks underscore the rationale for polymer-based delivery approaches, such as skin-targeted depots and lesion-directed carriers, which can reduce systemic exposure while enhancing localized control of inflammation [52,53]. Furthermore, emerging multi-responsive polymer systems offer the potential for on-demand drug release in response to lesion activity, thereby improving the long-term risk–benefit profile in chronic and relapsing AD [54].

3.2.1. Immunosuppressants agents

Traditional immunosuppressants such as cyclosporine, methotrexate, and azathioprine have long been prescribed for patients with severe AD who are unresponsive to topical therapy (Fig. 5) [55]. These agents act broadly by inhibiting T-cell proliferation and cytokine release, thereby reducing inflammation and pruritus [56]. Cyclosporine is often effective in rapidly improving clinical symptoms, but its long-term administration is limited by nephrotoxicity, hypertension, and an increased risk of infection [57]. Methotrexate and azathioprine offer steroid-sparing benefits but are associated with hepatotoxicity, myelosuppression, and the need for regular laboratory monitoring [58,59].

As illustrated in Fig. 5, these systemic immunosuppressants exert non-selective immunosuppressive effects that, while effective in controlling inflammation, frequently lead to severe systemic adverse events such as hepatic and bone-marrow toxicity, necessitating continuous clinical monitoring. Although these agents remain important components of the therapeutic arsenal, their systemic toxicity restricts prolonged administration [60,61]. From a drug-delivery perspective, polymer-based carriers and cutaneous depots may help overcome these drawbacks by enabling localized immunosuppressive activity at inflamed sites, thereby minimizing systemic exposure while sustaining therapeutic efficacy (Figs. 6 and 7) [62].

3.2.2. Biological therapies

Biologic agents have revolutionized AD management by specifically targeting cytokines involved in type 2 immune responses [63]. Dupilumab, an IL-4 receptor α antagonist, was the first biologic approved for AD and has demonstrated durable improvements in EASI, SCORAD, and quality-of-life scores in both adults and children [64,65]. More recently, monoclonal antibodies such as tralokinumab and lebrikizumab, which selectively inhibit IL-13, have shown encouraging results in Phase III trials, underscoring the pivotal role of IL-13 in AD pathogenesis [66,67]. Despite their strong efficacy, biologics have several limitations, including high cost, the need for frequent injections, and the potential for immunogenicity that may reduce long-term effectiveness [68]. Accessibility also remains a challenge in low-resource settings. Novel

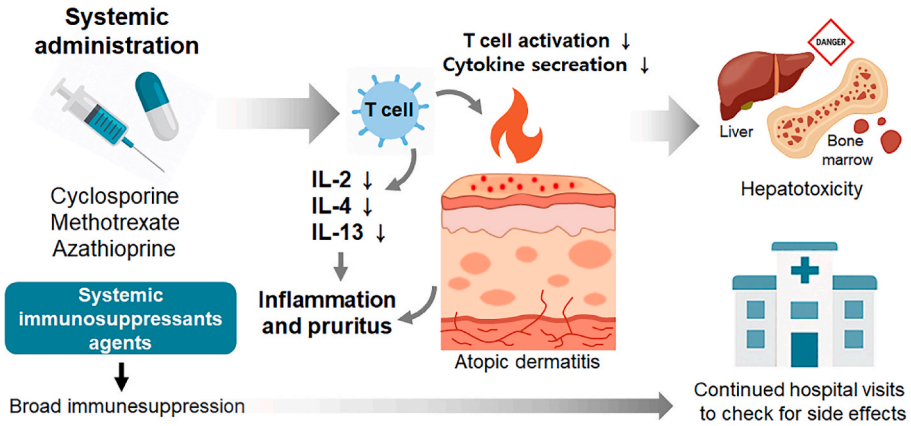

Fig. 5. Schematic illustration highlighting the limitations of systemic immunosuppressant therapy for AD. Systemic agents such as cyclosporine, methotrexate, and azathioprine induce broad immunosuppression, often leading to severe side effects including hepatotoxicity, bone marrow suppression, and the need for continuous hospital monitoring to manage systemic toxicity.

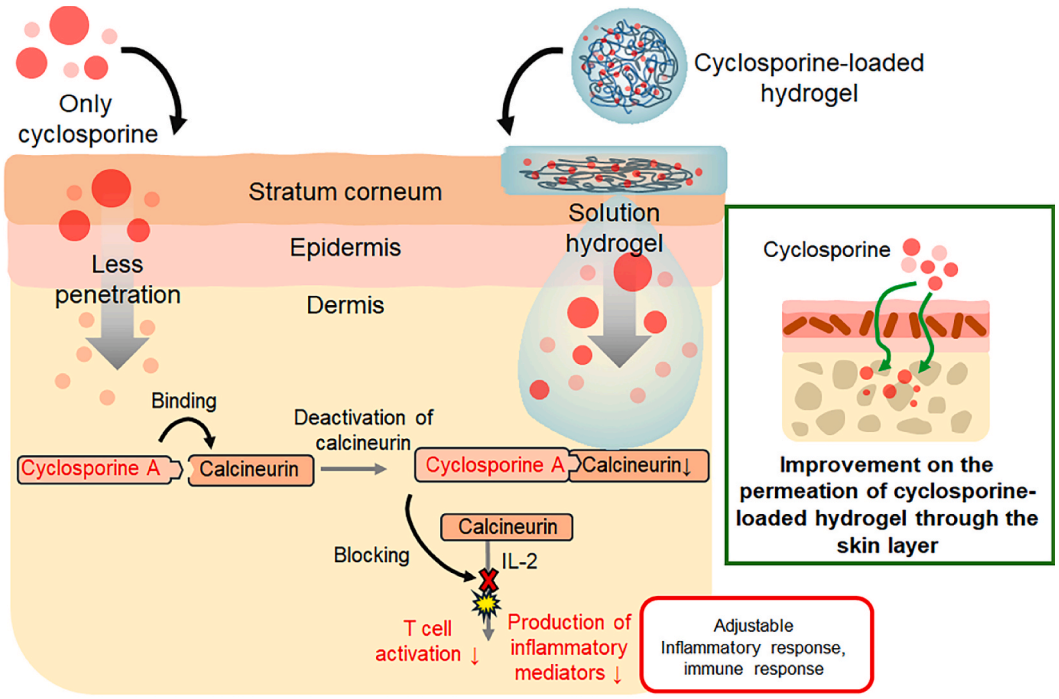

Fig. 6. Schematic illustration showing the enhanced skin permeation and immunomodulatory mechanism of cyclosporine-loaded nanogel formulations. Free cyclosporine exhibits limited skin penetration due to its hydrophobic nature, resulting in insufficient delivery to the dermis. In contrast, cyclosporine-loaded hydrogels or nanogels facilitate controlled and deeper permeation through the stratum corneum, improving drug accumulation in the target tissue.

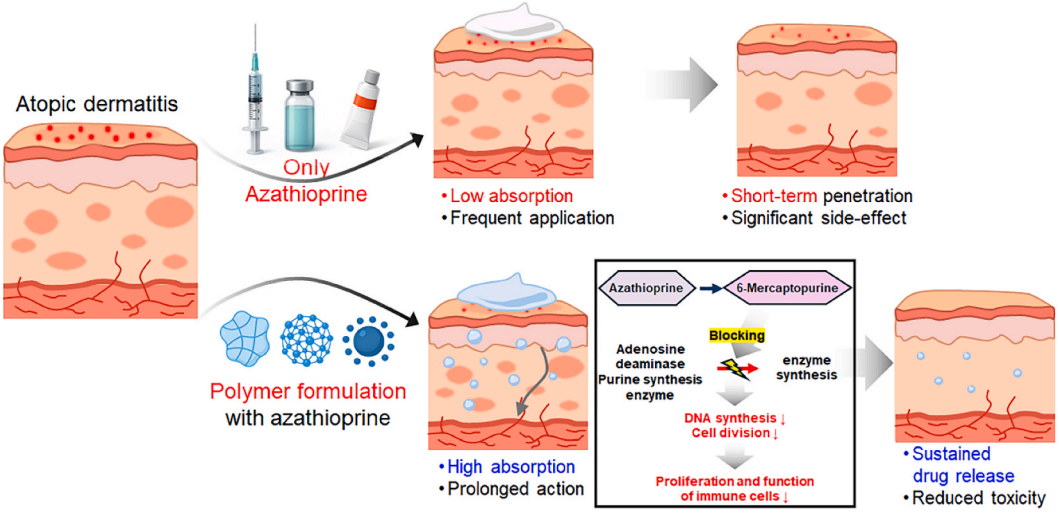

Fig. 7. Schematic illustration showing the enhanced skin permeation and localized immunomodulatory effect of azathioprine-loaded formulations. Free azathioprine exhibits limited skin penetration due to its hydrophobic nature, resulting in inadequate drug delivery to the dermis. In contrast, azathioprine-loaded formulations enable controlled, deeper permeation through the stratum corneum, enhancing drug accumulation at inflamed sites and improving therapeutic localization.

polymer-based formulations, such as biodegradable microspheres and hydrogel depots, have the potential to extend dosing intervals and reduce injection frequency [69–71]. Additionally, experimental nanocarrier systems are being explored for non-invasive delivery of biologics to lesional skin, which could enhance patient adherence and broaden treatment accessibility [72].

3.2.3. *JAK inhibitors*

Small-molecule JAK inhibitors, including baricitinib, upadacitinib, and abrocitinib, represent another important systemic treatment option for moderate-to-severe AD [73]. By blocking the JAK–STAT signaling pathway, these agents inhibit multiple downstream cytokines, resulting in rapid relief of itching and inflammation [74]. Clinical trials have shown that JAK inhibitors can produce significant improvements in disease severity within weeks of initiation [75,76]. However, their use is constrained by safety concerns such as an increased risk of serious infections, hematologic abnormalities, and potential cardiovascular events, which have prompted regulatory restrictions in some regions [77]. Long-term safety data are still being collected, and continuous clinical monitoring is recommended during therapy [78]. To reduce systemic risks while maintaining therapeutic efficacy, ongoing research has focused on incorporating JAK inhibitors into polymeric nanocarriers, microneedle arrays, and stimuli-responsive gels (Fig. 8). These delivery systems may enable lesion-specific administration, lower

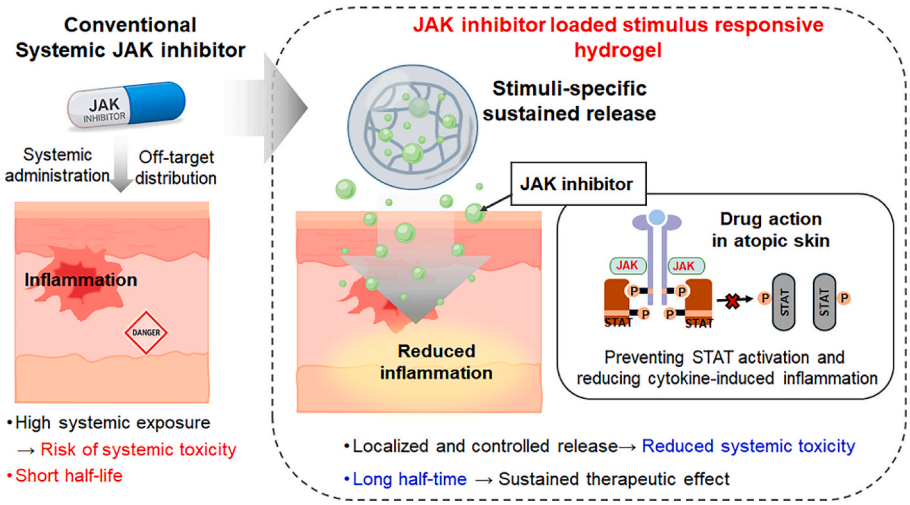

Fig. 8. Comparison between conventional systemic JAK inhibitor therapy and polymeric stimulus-responsive hydrogel formulation. Conventional systemic administration leads to high systemic toxicity and short therapeutic duration, whereas polymeric hydrogels enable localized and sustained release of JAK inhibitors, effectively preventing STAT pathway activation and reducing cytokine-driven inflammation in atopic skin.

systemic exposure, and ultimately offer a more favorable risk–benefit profile for chronic management [79–81].

Despite the availability of diverse systemic agents, monotherapy approaches remain limited by short half-life, systemic toxicity, and insufficient lesion selectivity [82].

These challenges underscore the importance of integrating polymer-based drug delivery systems across therapeutic classes to achieve more sustained, localized, and safer treatment strategies for AD [83].

3.3. Non-pharmacological supportive care

In addition to pharmacological interventions, supportive non-pharmacological strategies remain essential for comprehensive AD management. Regular moisturizer use and consistent skincare routines help maintain skin hydration, strengthen barrier integrity, and reduce the frequency of flare-ups [84]. These measures are well established as first-line supportive care and are typically combined with pharmacological therapies for optimal disease control.

3.3.1. Moisturizers

Moisturizers are fundamental to AD management, as they hydrate the skin, reduce transepidermal water loss (TEWL), and alleviate symptoms associated with dryness [85]. While conventional moisturizers provide immediate relief, their effects are temporary and do not directly target inflammation [86]. A more detailed discussion of polymer-based therapeutic moisturizers is presented in Section 5.1.

3.3.2. Skin care

Proper skincare practices—including gentle cleansing with lukewarm water, avoidance of products containing irritants, and the use of soft, non-irritating fabrics—help minimize symptom aggravation and improve overall comfort [87]. Maintaining adequate environmental humidity and frequently applying appropriate moisturizers are also essential for preventing flare-ups [88]. These simple, cost-effective measures significantly enhance quality of life and serve as valuable complements to both pharmacological and polymer-based interventions.

3.4. Delivery challenges of conventional AD drugs and rationale for polymer-based systems

Although both topical and systemic therapies can alleviate inflammation and pruritus in AD, their pharmacokinetic performance at the skin interface remains suboptimal [89]. The stratum corneum severely restricts drug permeation, and many active agents display short cutaneous residence times, burst release profiles, and unintended systemic absorption. These issues require frequent application and increase the risk of adverse effects [90,91]. Moreover, lesion heterogeneity and fluctuating local microenvironments (e.g., elevated pH, ionic imbalance, and temperature variations during flare-ups) further complicate consistent dosing and reproducible efficacy [92].

The main challenges associated with conventional drug delivery in AD include poor skin penetration and low bioavailability, burst release with short residence duration, off-target exposure leading to irritation, infection-prone lesions, and poor long-term patient adherence [93,94]. While conventional agents such as corticosteroids and calcineurin inhibitors effectively suppress inflammation, their therapeutic window is narrow, and they fail to restore the underlying barrier dysfunction, often resulting in rebound flares or cumulative toxicity [95,96].

Polymer-based drug delivery systems have been developed to address these limitations. Lipid-compatible nanogels, micelles, and nanofibers enhance partitioning and diffusion across the stratum corneum [97,98], while hydrogel depots sustain therapeutic concentrations and reduce dosing frequency [99]. Lesion-targeted and stimuli-responsive systems, which are activated by pH, ionic strength, temperature, or light, enable selective drug release within inflamed skin, thereby minimizing off-target exposure [100,101]. Antimicrobial polymers, such as chitosan-based matrices, further reduce the risk of secondary infection, and long-acting or once-daily formulations promote better patient adherence [102,103].

Collectively, these strategies underscore the rationale for polymer-based delivery systems in AD therapy. Such systems (i) enhance interfacial partitioning and percutaneous transport, (ii) create cutaneous depots for controlled and prolonged drug exposure, and (iii) synchronize drug release with pathophysiological cues or external stimuli, thereby maximizing local efficacy while minimizing systemic burden [104–106]. The following sections (4–6) provide a detailed overview of polymer classes and application formats—including moisturizing/repair matrices, hydrogels, nanogels, nanofibers, and multi-stimuli-responsive systems—engineered to achieve these design objectives in AD treatment.

4. Polymers for AD therapy

To address the challenges of conventional drug delivery, this section introduces the fundamentals and classes of polymers—natural,

synthetic, and composite—that form the basis of polymer-based strategies for AD treatment. These categories are not only chemical distinctions; they also determine critical properties such as degradability, mechanical strength, bioactivity, and formulation flexibility, all of which influence skin penetration, depot formation, and stimuli-responsive drug release. By tailoring these features, polymers enable controlled and sustained drug delivery, support skin barrier restoration, and can be adapted to patient-specific therapeutic needs, making them highly relevant for next-generation AD therapies [107].

4.1. Fundamentals of polymers

Polymers used in drug delivery can be broadly classified into natural, synthetic, and composite systems, each offering distinct advantages and limitations (Table 1). Natural polymers, such as hyaluronic acid, chitosan, and alginate, are biocompatible and often provide intrinsic therapeutic benefits, including hydration and antimicrobial activity. However, their performance can be limited by batch variability and relatively weak mechanical stability [108]. Synthetic polymers, including PCL, PLGA, and PEG, are valued for their reproducibility, controlled degradation, and tunable architecture, enabling precise drug release, although they generally lack intrinsic bioactivity [109]. Composite or hybrid polymers combine natural and synthetic components, integrating the functional advantages of natural polymers with the mechanical and processing benefits of synthetic systems [110,111]. This classification provides a conceptual framework for understanding how polymer design influences clinical outcomes in AD therapy and sets the stage for the detailed discussion of moisturizing/repair systems, hydrogels, smart polymers, nanofibers, and nanogels in the following sections.

4.2. Synthetic polymers

4.2.1. Poly(glyceryl methacrylate) (PGMA)

PGMA is a key polymer recognized for its remarkable moisture retention and high viscoelasticity, making it highly effective for skin hydration [112,113]. It forms a thin protective film on the skin surface, shielding the skin from external stimuli and reducing moisture evaporation, thereby maintaining skin hydration [114,115]. Studies have demonstrated that PGMA enhances the moisture retention capacity of the skin and strengthens its barrier function, contributing to improved overall skin health [116].

4.2.2. Poly(vinylpyrrolidone) (PVP)

PVP is a highly hydrophilic polymer that is readily absorbed by the skin, making it an effective moisturizer [117]. It forms a thin, transparent film on the skin surface that reduces moisture loss and maintains stable skin hydration [118]. PVP is also well-tolerated by sensitive skin and improves overall skin texture by maintaining smoothness and softness [119].

4.2.3. Polyglycerol-based polymers

Polyglycerol-based polymers are suitable for sensitive skin types [120]. These polymers effectively retain moisture on the skin surface, providing protection against external irritants [121]. Additionally, polyglycerol strengthens the skin barrier and reduces inflammation, promoting overall skin health and resilience [122].

4.2.4. Sodium polyacrylate (SPA)

SPA is highly regarded for its exceptional moisturizing properties due to its high hygroscopicity [123]. Upon application, it forms a fast-acting protective film that reduces moisture loss, ensuring long-lasting hydration [124]. A key advantage of SPA is its ability to provide a stable moisturizing effect under varying environmental conditions while maintaining consistent skin hydration [125].

4.2.5. Polyethylene glycol (PEG)

PEG is a hydrophilic, flexible polymer widely used in the biomedical field, owing to its biocompatibility and safety profile, which have led to its approval by the U.S. Food and Drug Administration (FDA) [126]. PEG forms a protective barrier on the skin that prevents moisture evaporation and helps maintain skin hydration [127]. Its efficacy is enhanced when combined with other moisturizing agents, resulting in synergistic benefits [128]. PEG also strengthens the skin barrier, providing protection against environmental irritants, and is recognized for its ability to sustain skin moisture over extended periods. Additionally, PEG improves skin flexibility and softness, enhancing overall skin texture [129,130].

4.2.6. Polyvinyl alcohol (PVA)

PVA is a hydrophilic polymer with an alcohol-based structure, renowned for its excellent biocompatibility and outstanding physical stability. These characteristics make it a highly versatile material in various biomedical applications, including drug delivery systems, wound healing, and tissue engineering [131]. Among its many uses, PVA has gained significant attention in dermatological applications due to its ability to prevent moisture evaporation and maintain an optimal hydrated environment on the skin surface. This property is particularly beneficial in protecting the skin from dryness and external stressors. By forming a thin yet durable protective barrier, PVA not only shields the skin from environmental irritants but also supports the natural healing process of damaged or sensitive skin [132,133].

Moreover, PVA's performance can be further enhanced through the incorporation of additional moisturizers or active agents. Such combinations improve its moisture-retention capacity while also enabling controlled release and increased stability of the active components. This synergy strengthens the skin's barrier function, amplifying both moisturizing and therapeutic effects. Importantly, PVA is associated with minimal skin irritation and a high safety profile, making it suitable for prolonged and repeated use. It helps maintain the skin's hydration and softness, contributing significantly to overall skin health and providing a

Table 1
Classification of polymers for AD therapy, listing representative natural, synthetic, and composite systems with their main advantages and limitations in drug delivery applications.

Category	Representative polymers	Key properties	Advantages	Limitations	Ref.
Natural polymers	Hyaluronic acid (HA), Chitosan, Alginate, Collagen	Biocompatible, bioactive, hydrophilic	Promote hydration and wound healing Minimal toxicity	Batch variability Weaker mechanical strength Faster degradation	[99,102,108]
Synthetic polymers	PEG, PLGA, PCL, PNIPAAm	Tunable, reproducible, controlled degradation	Stable structure Scalable production Responsive design possible	May lack intrinsic bioactivity Long-term biocompatibility concerns	[109,175,259]
Composite/hybrid polymers	HA–PEG, Chitosan–PLGA, PCL–collagen blends	Combine natural bioactivity with synthetic stability	Balanced properties Multifunctional responsiveness	More complex synthesis Higher cost Potential regulatory hurdles	[110,117,176,220]

soothing effect [134,135].

4.3. Natural polymers

Natural polymers, such as HA and chitosan, are increasingly recognized as promising agents for treating AD because they can restore the skin barrier and alleviate the inflammatory responses associated with the condition [136,137]. These natural substances are critical in improving skin hydration and promoting the regeneration of damaged skin, making them valuable for AD management. HA enhances skin hydration by maintaining intercellular moisture in the epidermis and reinforcing the skin barrier by preventing water loss. In the dermis, HA surrounds collagen and elastin fibers, stabilizing the skin's structure, supporting elasticity and smoothness, and contributing to the maintenance of skin volume [138].

4.3.1. Hyaluronic acid (HA)

HA, as a biocompatible material, is extensively utilized across various biomedical applications due to its favorable properties [139]. HA is a glycosaminoglycan naturally synthesized in the body and is present in various tissues, including the skin, joints, and eyes [140]. Renowned for its exceptional moisture-retaining properties, HA attracts and retains water within tissues, which is crucial for maintaining skin elasticity and moisture levels [141]. Furthermore, HA strengthens the skin barrier, promotes skin regeneration, protects against external irritants, and accelerates the repair of damaged areas [142]. The binding of HA to its CD44 receptor inhibits the activity of pro-inflammatory cytokines, such as TNF-α and IL-6, thereby reducing inflammatory damage. This interaction leads to the attenuation of skin inflammation and accelerates the repair of damaged skin [143].

In AD, the skin barrier is often damaged, leading to significant moisture loss [144]. HA's ability to bind moisture restores skin hydration and repairs the compromised barrier, thereby reducing TEWL and preventing skin dryness (Fig. 9) [145]. This protective effect protects the skin from external irritants and supports skin health [146]. Additionally, HA exhibits anti-inflammatory properties by inhibiting pro-inflammatory cytokines such as TNF-α and IL-6, which contribute to the inflammatory processes in AD [147]. By modulating these cytokines, HA alleviates AD symptoms and promotes more stable skin conditions [148].

HA binds to CD44 receptors on cell surfaces, activating signaling pathways that enhance the migration and proliferation of keratinocytes and facilitate skin regeneration and wound healing [149,150]. The binding of HA to the CD44 receptor activates cellular signaling pathways that promote the migration and proliferation of keratinocytes. This activation accelerates the regeneration of damaged skin and plays a crucial role in skin recovery in AD [151].

Furthermore, HA interacts with fibroblasts to activate the Transforming Growth Factor-beta (TGF-β) pathway, which stimulates collagen synthesis and strengthens cell-to-cell interactions, accelerating skin tissue regeneration [152,153]. HA is also utilized as a mediator for controlling drug release in drug delivery systems. Due to its moisture-retaining properties and biocompatibility, HA facilitates sustained release, ensuring continuous drug delivery to damaged skin areas [154,155]. The binding of HA to the CD44 receptor contributes to the precise targeting of drug delivery systems to specific cells, thereby enhancing drug efficacy, minimizing side effects, and improving therapeutic outcomes.

In conclusion, HA plays a critical role in maintaining skin hydration, strengthening the skin barrier, reducing inflammation, and promoting tissue regeneration. These multifaceted properties make HA an essential component in managing AD and improving overall skin health.

4.3.2. Chitosan

Chitosan is a natural polymer derived from chitin that is primarily obtained from the exoskeletons of crustaceans such as shrimp and crabs. Chemically, it comprises N-acetyl-D-glucosamine and D-glucosamine units linked together [156,157]. Chitosan, with its positive charge, binds to negatively charged skin proteins or cell membranes, enhancing adhesion and stabilizing the protective barrier effectively. Additionally, chitosan regulates the drug release rate within the formed protective layer on the skin, thereby prolonging therapeutic effects, increasing local drug concentration, and minimizing side effects [158]. Chitosan-based hydrogels form a protective layer on the skin surface, shielding it from harmful environmental factors and preventing moisture loss. This protective barrier is particularly beneficial for patients with AD, as it reduces exposure to potential allergens and irritants (Fig. 10) [159]. Due to its unique positive charge and biocompatibility,

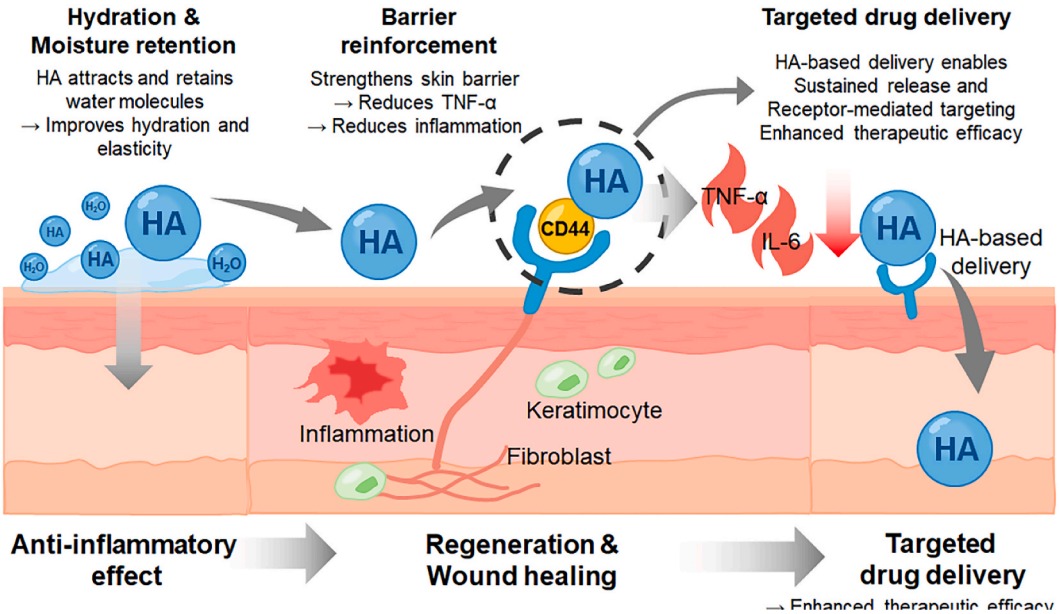

Fig. 9. Schematic illustration of the multifunctional roles of HA in AD treatment. HA retains moisture to restore hydration, reduces TEWL, and reinforces the skin barrier, thereby preventing dryness and irritation. In addition, HA modulates inflammatory cytokines such as TNF-α and IL-6, alleviating inflammation and promoting overall skin recovery.

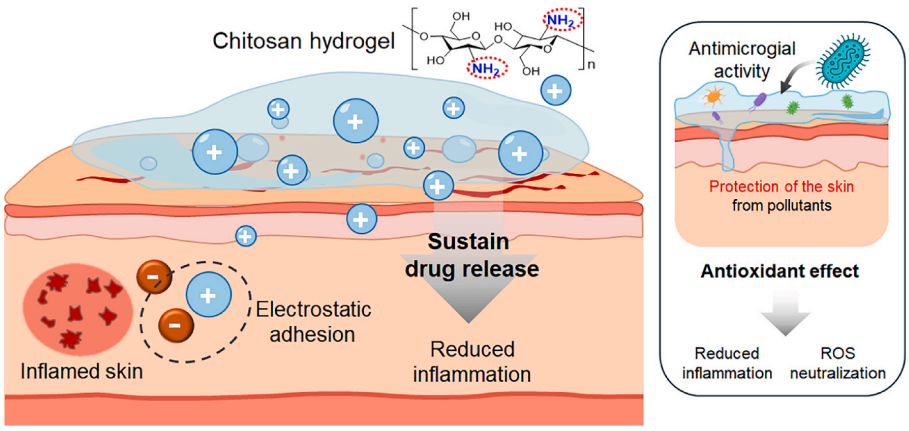

Fig. 10. Schematic illustration illustrating the therapeutic mechanisms of chitosan hydrogel in AD. The positively charged hydrogel adheres to inflamed skin through electrostatic interactions, enabling sustained drug release and attenuation of inflammation. Additionally, its antimicrobial and antioxidant activities protect the skin from microbial invasion and scavenge ROS, thereby promoting barrier repair and recovery.

chitosan is widely used in drug delivery systems to achieve sustained release, ensuring the continuous delivery of drugs to damaged skin areas. This barrier function is particularly beneficial for individuals with AD because it prevents skin damage and protects against environmental factors [160].

Patients with AD are particularly vulnerable to infections, such as those caused by *Staphylococcus aureus*, which leverage the compromised skin barrier [161]. Chitosan exhibits antibacterial properties by interacting with bacterial cell membranes, disrupting their structure, and inhibiting bacterial proliferation. Chitosan interacts with bacterial cell membranes, disrupting their structure and impairing cellular function, thereby effectively inhibiting bacterial proliferation. This antimicrobial property plays a crucial role in reducing secondary infections, particularly those caused by *Staphylococcus aureus*, which are commonly observed in the skin of patients with AD [162]. This antibacterial action prevents secondary infections in AD-affected skin. Chitosan exhibits natural antioxidant properties, neutralizing reactive oxygen species (ROS), which can damage lipids and proteins in cell membranes and trigger inflammatory responses [163]. By binding to ROS, chitosan reduces their concentration, preventing cellular damage and inflammation activation [164].

4.3.3. Carboxymethyl cellulose (CMC)

CMC contains carboxyl groups (COOH) attached to some of the hydroxyl groups on the cellulose backbone, and it has been widely utilized in the biomedical and pharmaceutical fields [165]. CMC is a natural polymer with significant moisturizing benefits due to its ability to bind water effectively [166]. When applied to the skin, CMC forms a viscous protective film that prevents moisture loss, maintains hydration, and strengthens the skin barrier [167]. Studies have demonstrated that CMC exerts a long-lasting moisturizing effect and contributes to the overall health and resilience of the skin [168].

4.3.4. Composite use of natural materials

A composite hydrogel combining HA and chitosan demonstrates synergistic moisturizing, anti-inflammatory, and antibacterial properties, making it a promising AD treatment [169,170]. This combination not only hydrates the skin but also forms a protective barrier. Additionally, both HA and chitosan modulate immune responses, reducing inflammation and enhancing skin immunity [171]. Advanced hydrogels integrating HA, chitosan, and nanotechnology further enhance treatment outcomes by improving drug delivery efficiency, enabling deeper penetration of active agents for targeted therapeutic effects [172,173]. These innovative systems aid in repairing damaged skin barriers and alleviating inflammatory symptoms, offering sustained therapeutic benefits [174]. Such developments highlight the potential of natural material-based composite hydrogels as effective solutions for managing AD.

5. Advantages and challenges of polymer-based formulations for AD treatment

Table 2 summarizes key characteristics and applications of various polymer formulations for AD treatment, focusing on their roles in skin barrier repair, inflammation reduction, hydration enhancement, and drug delivery. Synthetic polymer-based moisturizers, such as PGMA, PVP, polyglycerol-based polymers, SPA, PEG, and PVA, are effective in restoring the skin barrier, providing hydration, and reducing inflammation [175,176]. In contrast, natural polymer-based moisturizers, including HA, chitosan, and CMC, offer additional benefits. HA excels in moisture retention, chitosan possesses antimicrobial and regenerative properties, and CMC provides soothing effects for the skin [177–179]. Smart polymers, which respond to environmental stimuli such as temperature, pH, light, or electrical signals, regulate drug release, minimize side effects, and enhance therapeutic efficacy [180,181]. Self-assembling polymers that form gels upon skin application enable sustained drug delivery while aiding in skin barrier repair [182]. Notable examples include poly(N-isopropylacrylamide) (PNIPAAm)-based nanogels, chitosan, polyacrylic acid, and azobenzene-based systems [183]. Additionally, peptide-based polymers, which combine peptides with polymers, enhance skin regeneration and efficiently control inflammation [184]. These polymer formulations collectively contribute to AD treatment by improving skin barrier function, reducing inflammation, enhancing hydration, and optimizing drug delivery [185,186]. The review underscores the importance of selecting appropriate polymeric materials for the effective management of AD, providing valuable insights into their potential applications in therapy.

Among these applications, polymer-based moisturizers represent the most clinically established category, directly restoring barrier function and maintaining hydration. Therefore, we first discuss polymer-based moisturizers before turning to advanced formulations such as hydrogels, smart polymers, and nanostructured systems.

5.1. Polymer-based moisturizers

Polymer-based moisturizers play a critical role in AD management by restoring the skin barrier and providing sustained hydration (Fig. 11). These formulations typically incorporate both natural and synthetic polymers, such as HA, polyglycerol, and cellulose derivatives, which form a protective film on the skin to reduce TEWL and shield against external irritants [187,188]. By reducing TEWL, these systems help

Table 2
Overview of the main characteristics and therapeutic applications of polymer-based formulations for AD therapy, summarizing representative systems, mechanisms, and clinical advantages.

Polymer Type	Materials		Mechanism and Features	Ref.
Synthetic Polymer-Based Moisturizers	PGMA, PVP, Polyglycerol-Based Polymers, SPA, PEG		Restores skin barrier, hydrates, and reduces inflammation. Effective for wound healing and moisture retention.	[117,119, 175]
Natural Polymer-Based Moisturizers	HA, Chitosan, CMC		HA retains moisture (up to 1000 ×), chitosan offers antimicrobial and regenerative effects, and CMC soothes skin.	[177–179]
Polymer Nanogels	PNIPAAm, Chitosan, Poly(acrylic acid)		Controlled drug release with deep penetration. Reduces inflammation and accelerates healing.	[186,268]
Nanofibers	Synthetic and natural nanofibers		High adhesion to the skin, sustained drug release, long-term improvement in symptoms.	[288–290]
Smart Polymers	Temperature-Responsive Polymers	PNIPAAm-based nanogels	PNIPAAm-based nanogels	[183,243]
	pH-Responsive Polymers	Chitosan, Poly(acrylic acid)	Chitosan, Poly(acrylic acid)	[224,318]
	Light-Responsive Polymers	Azobenzene-based systems	Light-triggered release, effective in targeted therapy with reduced side effects.	[268]
	Charge-Responsive Polymers	Electrostatic drug delivery systems	Charge-based drug release, enhancing tissue penetration and drug efficacy.	[139,165, 324]
	Self-Aggregating Polymers	Hydrogels and self-assembled structures	Forms gel-like structures in skin, promoting sustained drug release and barrier restoration.	[278,310, 335]
Peptide-Based Polymers	Peptide-polymer composites		Enhanced anti-inflammatory effects and efficient drug delivery. Promotes skin recovery and inflammation control.	[311–315]

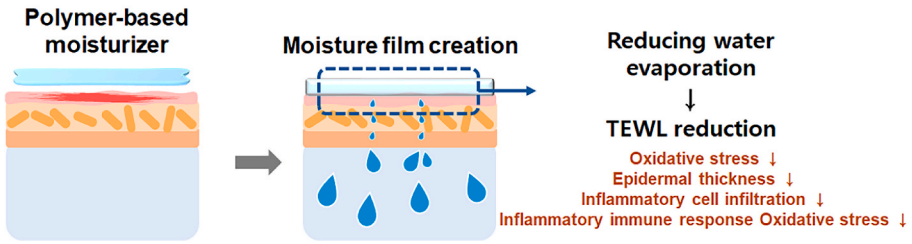

Fig. 11. Alleviation of AD symptoms by polymer-based moisturizers. These formulations, containing hyaluronic acid, polyglycerol, and cellulose derivatives, restore the skin barrier, reduce moisture loss, and provide sustained hydration, helping to reduce TEWL, inflammation, and symptoms like redness and itching in AD.

mitigate oxidative stress and limit inflammatory cell infiltration, thereby supporting barrier recovery. For example, HA–chitosan hydrogels reduced TEWL by nearly 40 % and improved hydration scores by more than 25 % within two weeks compared with conventional emollients [189,190].

Hydrogels and related polymer matrices further enhance hydration and reinforce the skin barrier while providing anti-inflammatory benefits.

PEG-modified formulations have been shown to increase corticosteroid retention in skin tissue more than twofold, and liposomal moisturizers containing colloidal oatmeal reduced erythema scores by over 50 % in clinical studies [191–193]. These findings demonstrate that polymer-based moisturizers not only prolong hydration but also alleviate itch, reduce redness, and improve overall patient comfort [194, 195].

A major advantage of these formulations is their ability to sustain hydration longer than traditional moisturizers, effectively preventing moisture loss and promoting barrier repair. Many polymer-based moisturizers are also enriched with anti-inflammatory agents, further supporting skin recovery and improving overall skin condition [196, 197]. However, some limitations remain: larger particle sizes may hinder absorption, thicker textures can reduce user convenience, and advanced systems raise questions regarding long-term biodegradability, production costs, regulatory approval, and chronic-use safety [198, 199].

Recent research has increasingly applied nano- and microtechnologies to enhance absorption and stabilize formulations [200–202]. Innovations such as liposome- and oatmeal-based polymer systems combine barrier-strengthening and anti-inflammatory effects, highlighting their potential as next-generation moisturizers for AD management [203–205].

5.2. General polymer hydrogel-based formulations

Polymeric hydrogels are three-dimensional networks capable of absorbing large amounts of water without dissolving, making them particularly well suited for AD therapy due to their biocompatibility and strong water retention (Fig. 12). Natural polymers, such as HA and chitosan, as well as synthetic polymers like PEG and PVA, are widely employed. By maintaining hydration and supporting barrier repair, these systems provide symptomatic relief and enhance skin elasticity. For instance, HA–chitosan composite hydrogels reduced TEWL by nearly 45 % and improved hydration indices by more than 30 % after two weeks, outperforming conventional emollients [206].

Beyond hydration, hydrogels serve as controlled-release carriers for corticosteroids, immunomodulators, and other anti-inflammatory agents. PEG-modified hydrogels increased corticosteroid bioavailability two-to threefold while reducing systemic absorption by over 50 % in preclinical studies, demonstrating their capacity to enhance efficacy while limiting toxicity [207]. Chitosan-based hydrogels further provide antibacterial and anti-inflammatory effects, reducing bacterial load by more than 60 % in infected lesions and accelerating wound closure [208]. Their intrinsic cooling effect upon application also alleviates itching and improves comfort during acute flare-ups [209].

Despite these advantages, several limitations remain. Long-term biodegradability and skin safety are not yet fully established, particularly with repeated use. Manufacturing complexity and high production costs hinder large-scale adoption, while regulatory approval is slowed by the need for comprehensive toxicological and stability evaluations [210]. These challenges highlight that, although hydrogel systems are promising, further optimization is necessary to ensure affordability, regulatory acceptance, and long-term safety in chronic AD treatment [211].

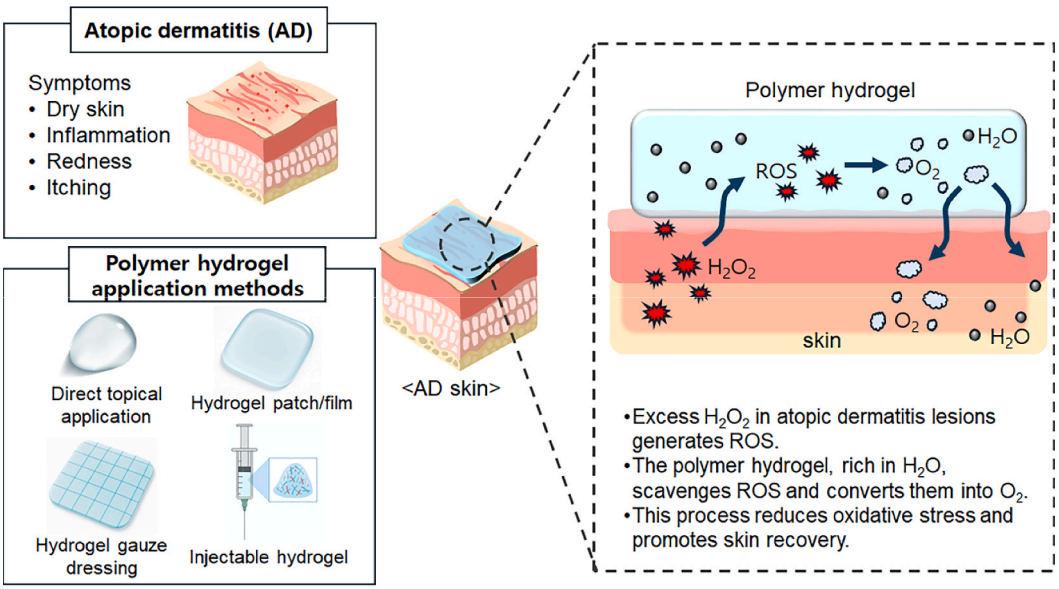

Fig. 12. Schematic illustration showing the therapeutic roles of polymer hydrogels in AD treatment. Applied as gels, patches, or injectable forms, polymeric hydrogels retain moisture, repair the damaged barrier, and enhance skin elasticity, while their inherent antioxidant properties help scavenge ROS and support skin healing.

Overall, polymeric hydrogels represent a versatile platform that integrates hydration, sustained drug delivery, and antimicrobial protection. To achieve clinical translation, future research must balance their demonstrated quantitative benefits with strategies to address biodegradability, production costs, and regulatory hurdles.

5.3. *Stimuli-responsive polymer-based formulations*

Smart polymers have recently garnered increasing attention as promising tools for AD therapy [212–214]. These materials can autonomously adjust their properties in response to physical stimuli (e.g., temperature, light, ultrasound, electric fields) or chemical changes (e.g., pH, ion concentration, enzymatic activity), enabling precise and adaptive drug delivery [215,216]. Their primary advantage is their ability to selectively target inflamed lesions, thereby enhancing therapeutic efficacy while minimizing systemic side effects [217]. Quantitative evidence supports these advantages: PNIPAAm-based nanogels reduced scratching behavior by over 60 % in AD mouse models, accompanied by decreases in IL-4 and TNF-α levels [218,219]; pH-responsive chitosan–PEG carriers nearly doubled local drug bioavailability while lowering systemic exposure [220]; and light-triggered azobenzene hydrogels achieved lesion-specific release with minimal irritation [221].

Although significant progress has been made, several challenges still exist. The biodegradability and long-term safety of many smart polymers are not fully characterized, raising concerns for chronic use [222]. Complex fabrication processes and high costs limit industrial scalability, and regulatory approval is slowed by the need for extensive toxicological and stability evaluations of novel chemical linkages. Data on repeated-exposure safety, including potential sensitization or disruption of the skin microbiome, are also limited [223].

For clarity, stimuli-responsive systems can be categorized into temperature-, pH/ion-, light-responsive, and self-aggregating formulations. These designs exemplify how polymer systems can dynamically align drug release with lesion-specific or external triggers, while also highlighting the translational hurdles that must be addressed to enable clinical adoption [224,225].

5.3.1. *Self-regulated drug release for AD*

Self-regulated drug release is a key feature of smart polymer systems, enabling drug delivery to adjust dynamically in response to real-time changes in skin conditions. By responding to external stimuli such as temperature, pH, and inflammatory markers, these polymers modulate drug release, making them particularly effective for chronic conditions such as AD [226,227]. The ability of smart polymers to detect changes in skin conditions and release drugs accordingly optimizes treatment efficiency while minimizing unnecessary drug exposure. For example, drug release can be triggered when inflammation intensifies and halted when symptoms subside, ensuring on-demand therapy [228,229]. In contrast to conventional systems that administer medication at fixed intervals, smart polymers adjust drug release based on real-time skin conditions, reducing the risk of side effects associated with continuous exposure [230,231].

Several preclinical studies provide quantitative evidence of these benefits. For instance, pH-sensitive nanogels loaded with tacrolimus released nearly 70 % of their payload in inflamed, higher-pH microenvironments, while releasing less than 20 % under normal skin conditions, thereby improving local drug concentration and limiting systemic diffusion. Similarly, enzyme-responsive hydrogels achieved a 50 % reduction in erythema and pruritus scores in murine AD models compared with free drug [232]. These results highlight the therapeutic precision and efficiency offered by self-regulated release platforms.

Despite these advances, significant challenges persist. The biodegradability of synthetic nanogels and hydrogels must be fully characterized to ensure safe long-term use, as repeated dosing in chronic AD patients could lead to polymer accumulation or unforeseen immune responses. The manufacturing complexity and cost of multi-responsive polymers also limit scalability, since precise crosslinking and nanoscale structures are difficult to reproduce consistently at industrial scale. From a regulatory perspective, self-regulated systems containing novel responsive linkages or biomarker-sensing moieties require rigorous toxicological and stability assessments, which may delay clinical approval. Additionally, robust data on long-term skin safety—including chronic irritation, sensitization, or disruption of the skin microbiome under repeated exposure—are currently lacking [233].

Overall, the self-regulated release capability of smart polymers represents a significant advancement in AD therapy, offering enhanced therapeutic precision, minimized side effects, and improved treatment efficiency [234,235]. At the same time, further research is needed to address challenges in biodegradability, cost, regulatory approval, and long-term safety to enable successful clinical translation.

5.3.2. Temperature-responsive polymer-based formulations

Temperature is a critical stimulus for regulating drug release by modulating the physical properties of polymers [236]. Changes in temperature can induce polymers to swell, shrink, or alter solubility, thereby controlling drug release. Temperature-sensitive polymers are versatile, enabling adjustments in release rates or timing in response to body or external temperature variations, making them particularly suitable for therapeutic applications in skin diseases [237,238].

In AD, inflamed regions often exhibit elevated local temperature, which can be exploited for selective drug release. Temperature-responsive polymers are engineered to modify their physical properties under such fluctuations, enabling site-specific, stimulus-driven delivery [239–241].

For example, PNIPAAm-based nanogels loaded with corticosteroids exhibited a temperature-triggered release profile, with drug release increasing by nearly 65 % when local temperature rose from 32 °C to 38 °C, a range typical of inflamed lesions. This enhanced release correlated with over a 50 % reduction in erythema and scratching scores in AD mouse models compared with non-responsive controls [242,243]. Similarly, PEG–polyester hybrid hydrogels demonstrated sustained release at body temperature while remaining stable under storage conditions, improving both therapeutic efficacy and formulation reliability [244]. These quantitative findings highlight the potential of temperature-responsive systems to provide controlled, lesion-specific therapy, minimizing off-target exposure and enhancing clinical outcomes.

Despite these promising results, several challenges remain for clinical translation. The biodegradability of synthetic temperature-sensitive polymers, such as PNIPAAm derivatives, is often incomplete, raising concerns about polymer accumulation after repeated use [245]. Manufacturing reproducibility and cost also limit large-scale production of thermo-responsive nanogels [246]. From a regulatory perspective, approval is slowed by the need for extensive toxicological and stability testing of novel thermo-sensitive linkages. Furthermore, long-term skin safety under chronic application has not been fully established, particularly regarding potential irritation or disruption of the skin microbiome in sensitive AD patients [247,248].

In summary, temperature-responsive polymers offer a powerful approach for precise, on-demand drug delivery tailored to the dynamic microenvironment of AD lesions. Addressing challenges related to biodegradability, scalability, regulatory approval, and long-term safety will be essential to fully realize their therapeutic potential.

5.3.3. pH- or ion-responsive polymer-based formulations

pH- and ion-responsive polymers are designed to exploit local environmental changes in the skin, enabling selective drug release in response to conditions characteristic of inflamed AD regions (Fig. 13) [249,250]. These polymers enhance treatment precision by targeting affected areas, minimizing unintended drug release in healthy skin, and reducing potential side effects [251].

Normal skin typically exhibits a slightly acidic pH, ranging from 4.5 to 5.5. In contrast, AD-affected skin often shows an elevated pH (above 5.5), reflecting an alkaline shift associated with barrier disruption and reduced antimicrobial defense [252]. pH-responsive polymers detect these variations and release drugs when pH exceeds the normal range [253].

For example, HA–chitosan nanogels released 65 % of their payload at pH 7.0 compared with less than 20 % at pH 5.0, resulting in a twofold increase in local drug concentration at inflamed sites and a 40 % reduction in erythema scores in AD mouse models [254]. Similarly, PEG–poly(β-amino ester) carriers enhanced intracellular delivery under alkaline conditions, restoring skin hydration by over 25 % compared with standard formulations [255].

Charge-responsive systems expand this concept by altering their physical properties in response to changes in pH or ion concentration. By ensuring drug release occurs primarily under inflamed conditions, these systems improve therapeutic precision while minimizing off-target toxicity. Studies show that ion-responsive hydrogels not only enhance drug penetration but also accelerate re-epithelialization, significantly improving healing rates in experimental AD lesions [256,257]. Furthermore, ion-binding polymers that modify ionization states upon exposure to elevated sodium or calcium levels achieve controlled release kinetics and more consistent therapeutic outcomes [258].

Although promising, these systems still face several hurdles before they can be broadly implemented. The biodegradability of synthetic pH- and ion-sensitive polymers must be optimized to prevent polymer accumulation in chronically treated skin [259]. Scalability and production costs remain substantial barriers, as the synthesis of ionizable

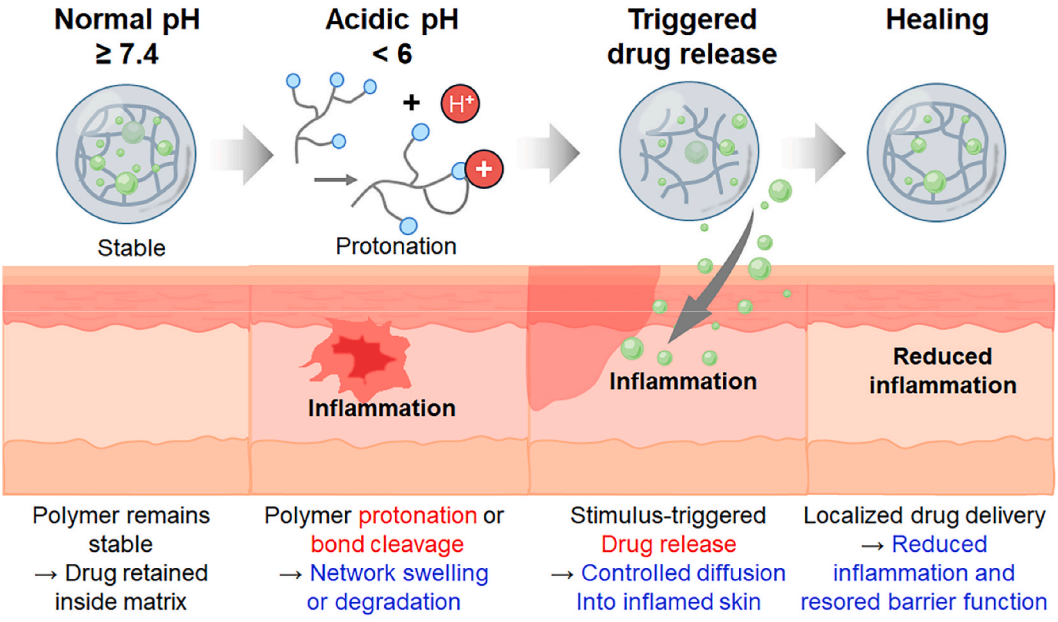

Fig. 13. Schematic illustration showing the pH-responsive drug release mechanism in polymeric systems for AD. Under normal pH, the polymer remains stable and retains the drug. In the acidic microenvironment of inflamed skin, protonation induces polymer swelling or partial dissociation that triggers controlled drug release at the target AD site. This localized and stimuli-driven delivery reduces inflammation, restores pH balance, and promotes barrier recovery.

nanogels or pH-tunable matrices involves complex and costly chemistries [260]. Regulatory approval also requires extensive toxicological evaluation of novel ionizable linkages. Finally, robust data on long-term skin safety are lacking, particularly regarding chronic irritation, sensitization, or disruption of the skin microbiome under repeated use [261].

In summary, pH- and ion-responsive polymer formulations offer a promising approach for lesion-specific, on-demand therapy in AD. Quantitative evidence demonstrates their capacity to improve local drug bioavailability and therapeutic efficacy, but addressing challenges in biodegradability, production cost, regulatory approval, and long-term safety will be essential for successful clinical translation.

5.3.4. *Light-responsive polymer-based formulations*

Light-responsive polymers can change their physical and chemical properties upon exposure to specific wavelengths, enabling controlled drug release and photochemical activation of encapsulated agents [262–265]. These polymers modulate drug release according to wavelength and light intensity, allowing selective delivery of active pharmaceutical ingredients (APIs). In dermatology, where lesions are readily accessible to light, such systems are particularly attractive for precision therapy. Topically applied polymers respond to UV or visible light to trigger on-demand drug release, thereby enhancing the skin barrier and reducing inflammation in AD (Fig. 14) [266,267].

Recent studies provide quantitative evidence of their therapeutic potential. For example, azobenzene-based nanogels exhibited over a 70 % increase in drug release upon 365 nm UV exposure, while releasing less than 15 % in the dark, resulting in a 55 % reduction in erythema scores in AD mouse models [268]. Similarly, visible-light–responsive hydrogel films incorporating photo-cleavable PEG linkers improved hydration by over 20 % and accelerated epidermal regeneration compared with conventional hydrogels [269]. Photoresponsive micelles carrying anti-inflammatory agents also demonstrated lesion-specific accumulation, reducing scratching frequency in preclinical AD models by nearly 40 % [270,271]. These findings highlight the potential of externally controllable systems to achieve therapeutic precision beyond that of conventional formulations.

Nevertheless, light-triggered systems face unique translational challenges. Limited tissue penetration may restrict their effectiveness to superficial lesions, requiring optimized light sources and delivery devices [272]. Repeated light exposure raises concerns about phototoxicity and skin sensitization, requiring long-term dermatological safety assessments. From a manufacturing standpoint, incorporating photo-cleavable linkages and chromophores increases formulation complexity and cost, limiting large-scale feasibility [273,274]. Regulatory approval is further complicated by the need to evaluate both the polymeric material and the associated light-activation protocol as a combined therapeutic device [275]. Patient adherence may also be affected by the requirement for controlled light application, which differs from the convenience of standard topical therapies [276].

In summary, light-responsive polymers represent a novel class of externally controllable drug delivery systems for AD, offering spatiotemporal precision and measurable therapeutic benefits. Addressing challenges related to light penetration, phototoxicity, cost-effective production, and regulatory alignment will be essential for translating these systems from experimental models to clinical practice.

5.3.5. *Self-aggregating polymer-based formulations*

Self-aggregating polymers modify their physicochemical properties in response to environmental stimuli such as pH or temperature changes. These systems are designed to self-assemble into nanoparticles or microparticles, encapsulating drugs and enabling controlled release upon stimulation [277]. For example, pH-triggered amphiphilic copolymers released over 60 % of their drug payload at pH 7.0 compared with less than 20 % at pH 5.0, significantly increasing local drug concentration in inflamed skin [278]. Temperature-sensitive self-assembling micelles similarly provided sustained corticosteroid delivery, reducing erythema and scratching scores by nearly 45 % in murine AD models [279]. These adaptive systems are particularly valuable in AD because they can combine gradual drug release under stable conditions with rapid, stimulus-driven release during flare-associated changes. This approach enhances skin barrier recovery, reduces inflammation, and helps maintain hydration [280,281].

Although these systems show great promise, several challenges persist. The biodegradability of synthetic amphiphilic polymers must be optimized to prevent long-term accumulation. The complexity of self-assembly and stability control increases production costs [282,283]. Additionally, regulatory pathways for adaptive systems are not yet clearly defined, and long-term dermatological safety under repeated application has not been systematically evaluated [284]. In summary, self-aggregating polymers provide a versatile platform for lesion-adaptive, stimuli-triggered therapy in AD. Emerging quantitative data support their therapeutic potential, but further validation of biodegradability, scalability, and long-term safety is needed before clinical translation.

5.4. *Polymeric (nano)fiber-based formulations*

Polymeric fibers are continuous, thread-like materials derived from both natural (e.g., cellulose, chitosan) and synthetic (e.g., polyester, nylon) polymers, widely employed in biomedical applications due to their mechanical strength, flexibility, and large surface area [285]. These fibers act as physical barriers, protecting the skin from allergens, irritants, and microorganisms. Nanofibers, particularly those produced via electrospinning, offer additional advantages for sensitive skin due to their high surface area and adaptable structure [286,287].

Fiber-based dressings can deliver drugs locally, providing sustained therapeutic effects through gradual release of anti-inflammatory or moisturizing agents [288]. For example, electrospun chitosan/PEO

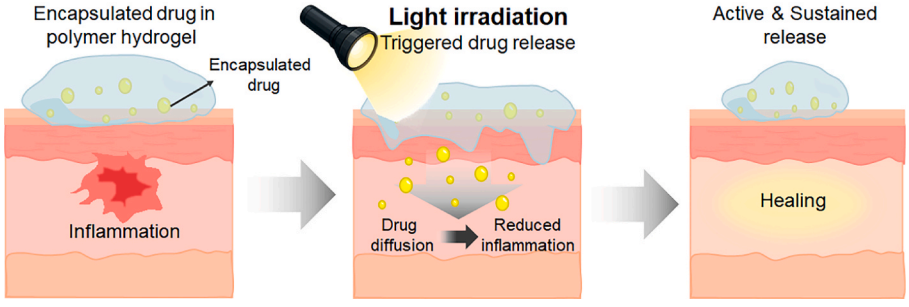

Fig. 14. Schematic illustration illustrating the mechanism of light-responsive polymer hydrogels for controlled drug release in AD. Upon light irradiation, photo-responsive linkages within the hydrogel undergo isomerization or photothermal conversion, inducing matrix relaxation and releasing the encapsulated drug, which diffuses into inflamed skin and suppresses local inflammation. This non-invasive and spatially precise approach enables active, localized, and sustained drug release, thereby promoting targeted and efficient lesion healing.

nanofiber mats loaded with corticosteroids achieved prolonged release over 72 h, reducing scratching scores in AD mouse models by approximately 50 % compared with free drug application [289]. Multilayer nanofibers allow staged release, supporting long-term therapy, while incorporation of growth factors or bioactive agents can further promote tissue regeneration and wound healing [290–292].

While these systems offer clear advantages, notable challenges continue to limit their broader application. The biodegradability of synthetic nanofibers requires optimization, and scaling up electrospinning for mass production remains costly and technically demanding. Regulatory evaluation of long-term skin contact and chronic safety is also limited, highlighting the need for more comprehensive translational studies [293,294]. In summary, polymeric (nano)fibers represent a versatile platform for AD therapy. Emerging quantitative evidence supports their efficacy, but further work is needed to ensure biodegradability, scalable production, and validated long-term safety before clinical translation.

5.5. Polymer nanogel-based formulations

Polymer nanoparticles, typically 1–100 nm in size, are promising tools for drug delivery and diagnostics due to their unique physicochemical properties [295,296]. Their high surface-area-to-volume ratio enhances functionality, and in AD, the compromised epidermal barrier facilitates nanoparticle penetration into inflamed regions (Fig. 15). This enables targeted delivery of therapeutic agents, while tunable features such as polymer chain length, composition, and particle shape allow precise optimization [297–299]. For example, HA-based nanocarriers loaded with corticosteroids achieved two-to threefold higher local drug deposition while reducing systemic absorption by half in preclinical AD models [300].

Nanogels, formed from cross-linked polymer networks, encapsulate drugs and provide controlled release with extended residence times [301]. They sustain therapeutic levels while retaining moisture, addressing dryness and delayed healing in AD [302]. Stimuli-triggered release, such as pH- or enzyme-mediated mechanisms, further enhances lesion-specific action while minimizing off-target effects [303,304].

Nanofibers, with their porous structures and high surface area, complement nanogels by supporting prolonged drug release, improved absorption, and skin regeneration [305]. Electrospun nanofiber dressings incorporating anti-inflammatory agents reduced scratching behavior in AD mouse models by approximately 60 %, demonstrating their therapeutic relevance [306]. The combination of nanogels and nanofibers offers synergistic benefits, coupling moisture retention and stimuli-responsiveness with long-acting, lesion-targeted drug release [307].

The polymer nanoparticles enable targeted drug delivery to specific skin areas, thus maximizing therapeutic effects [308]. Both nanogels and nanofibers can be engineered for sustained drug release, ensuring consistent drug levels over time, which is critical for long-term treatment success [309]. The drugs released from these nanoparticle formulations help reduce inflammation, repair the skin barrier, and restore skin integrity. Additionally, chitosan-based nanoparticles mitigate oxidative stress by scavenging reactive oxygen species (ROS) [310].

Chitosan, with its positive charge, interacts with negatively charged ROS and neutralizes them. This action helps prevent oxidative damage to cell membranes, proteins, and lipids, thereby reducing inflammation and protecting skin cells from further damage. Such properties are particularly crucial in AD diseases, where oxidative stress plays a significant role in disease progression [311]. Nanoparticles can also stimulate the immune system, strengthening the skin's natural defenses, regulating immune responses, and preventing AD symptoms [312].

Despite these promising advances, there are still several challenges that must be addressed. Biodegradability of synthetic carriers, scalable fabrication of nanogels and nanofibers, regulatory hurdles for novel nanosystems, and limited long-term safety data on chronic skin exposure are key barriers to clinical translation [313,314]. Addressing these issues will be critical for advancing from proof-of-concept studies to accessible, standardized therapies for AD.

5.6. Smart polymer system combined with nanoparticles

In systems combining smart polymers and nanoparticles, the "swelling" and "shrinking" responses are crucial for effective drug release in AD treatment [315,316]. Nanogels incorporating smart polymers can modulate drug release in response to local stimuli. For instance, elevated temperature or pH in inflamed regions induces swelling, promoting gradual release for long-term control [317,318], whereas shrinking under specific cues enables rapid release to address

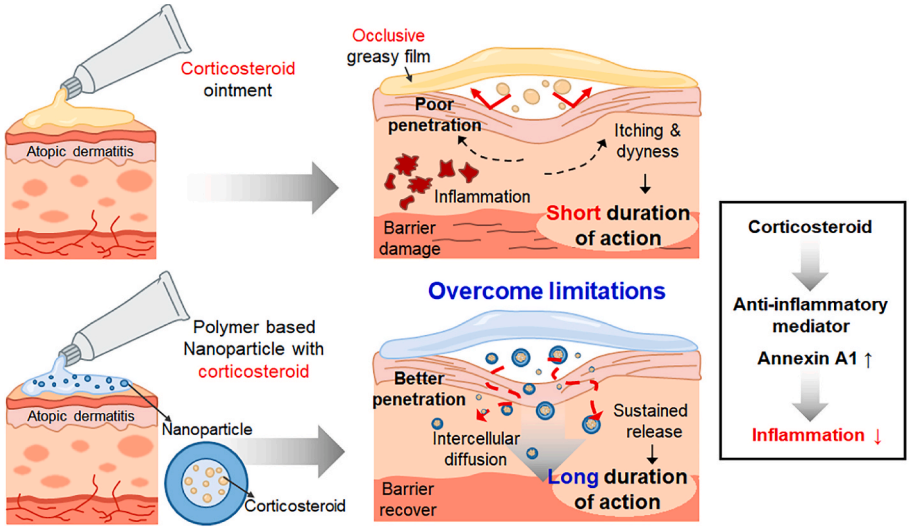

Fig. 15. Schematic illustration illustrating the difference between conventional corticosteroid ointments and polymer-based nanoparticle formulations for AD treatment. Conventional corticosteroid ointments form a superficial occlusive film that restricts transdermal diffusion, leading to limited drug penetration, short therapeutic duration, and potential barrier irritation. In contrast, polymer-based nanoparticles diffuse through intercellular lipid layers and provide sustained, controlled corticosteroid release within inflamed skin. This mechanism enhances local drug retention, prolongs therapeutic efficacy, and promotes barrier recovery while reducing recurrence and irritation.

acute symptom flare-ups [319,320]. This dual behavior allows both sustained management of chronic inflammation and prompt suppression of flare-ups.

The integration of smart polymers with nanoparticles also enhances penetration through the compromised stratum corneum. Nanoparticles (1–100 nm) can traverse intercellular gaps, delivering drugs into deeper skin layers, while polymer matrices regulate site-specific release. Preclinical studies have demonstrated that PEG-modified smart nanogels achieved approximately 2.5-fold higher drug deposition in lesional skin compared with non-responsive carriers, while reducing systemic absorption [321,322].

Despite these advantages, translation still faces several key challenges. Biodegradability of synthetic nanogels, scalable nanoparticle fabrication, regulatory requirements for hybrid systems, and limited long-term safety data in chronic AD are key barriers to clinical translation [323]. Addressing these issues will be critical to advance from proof-of-concept studies to clinically viable therapies.

5.7. Peptide-based formulations

Peptide-based formulations have garnered significant attention in biomedical research due to their inherent biocompatibility and bioactivity, making them promising materials for various therapeutic applications [324]. These polymers, composed of specific amino acid sequences, are particularly beneficial in wound healing, tissue regeneration, and inflammatory condition treatments, such as AD [325,326]. Recent advancements have expanded their utility in controlled drug delivery systems, allowing for precise delivery of therapeutic agents through the skin barrier. This capability enhances treatment efficacy while minimizing systemic side effects [327].

A key advantage of peptide-based formulations lies in their antibacterial and anti-inflammatory properties, making them effective in mitigating inflammation and preventing secondary skin infections [328–330]. Certain peptides specifically inhibit cytokine production, aiding in inflammation control and reducing the risk of chronic infection [331–334]. Additionally, their natural biodegradability and safe metabolic profiles ensure minimal adverse reactions, further highlighting their suitability for clinical applications [335].

Recent developments have demonstrated the diverse physiological activities of peptide-based formulations, broadening their applications in drug delivery systems. Despite these advancements, challenges remain. Issues such as optimizing peptide polymer synthesis, enhancing self-assembly behavior, and tailoring mechanical properties and bioactivity require further research [336,337].

Among peptide-based formulations, hydrogels have shown significant potential for AD treatment. These hydrogels, formed using various natural amino acids, exhibit inherent biocompatibility and bioactivity. However, their properties must often be fine-tuned to meet therapeutic demands, particularly regarding mechanical stability and biodegradability. Future efforts should address challenges such as: (1) achieving batch-to-batch reproducibility in functional and structural properties; (2) developing scalable and efficient manufacturing processes for peptide-loaded hydrogels for personalized AD therapies; and (3) refining sterilization techniques to ensure hydrogels maintain their structural and functional integrity during AD treatment [338–340].

In conclusion, while peptide-based formulations face technical and scientific challenges, continuous advancements in their design, fabrication, and functionalization promise to pave the way for their clinical adoption in AD therapy and beyond. Their unique combination of biocompatibility, therapeutic efficacy, and versatility underscores their potential in addressing unmet medical needs.

5.8. Other stimuli-responsive polymer-based formulations

Various stimuli can trigger the release of AD drugs by inducing physicochemical changes in polymers, such as changes in solubility or structural modifications. These stimuli-responsive polymers enable precise drug delivery control and enhance therapeutic outcomes in AD treatment.

Electric stimuli: Applying electrical stimuli to polymers can trigger drug release by altering their ionization state or electrical charge. This stimulation induces physical changes in the polymer structure, facilitating drug release. Moreover, electrical stimuli allow precise control over the rate and timing of drug release for AD treatment [341].

Ultrasound stimuli: Ultrasound enables drug release by inducing mechanical changes in polymers. The mechanical waves generated by ultrasound alter the polymer's physical structure, triggering drug release. This method is a non-invasive approach for precise control of AD drug delivery [342].

Oxygen stimuli: Changes in oxygen concentration can alter the chemical properties of polymers, leading to structural changes that facilitate drug release. Oxygen-sensitive smart polymers can self-regulate drug release in response to oxygen level variations, enhancing targeted delivery to inflamed AD areas [343].

Enzymatic stimuli: Enzymes trigger drug release by interacting with specific polymers to induce structural changes. This method leverages the specificity of enzymes, enabling precise and targeted drug delivery with enhanced biocompatibility and selectivity [344].

Redox stimuli: Redox reactions can cause structural changes in polymers, leading to drug release. Polymers sensitive to oxidative or reductive environments undergo chemical transformations that trigger controlled and precise drug release [345].

Water stimuli: Water absorption by polymers induces swelling or structural changes, facilitating drug release. This mechanism is particularly suitable for in vivo applications where water is crucial for regulating drug delivery [346].

6. Clinical translation and representative case studies

Although many polymer-based formulations for AD remain at the preclinical stage, several notable achievements in clinical translation have been reported over the past 3–5 years [347]. For example, a hyaluronic acid–based hydrogel dressing (commercialized as Cx-HA formulations) has demonstrated significant improvements in skin hydration and barrier repair in randomized controlled trials, reducing disease severity scores compared with conventional emollients. Similarly, chitosan-containing topical gels have demonstrated enhanced antimicrobial protection in pediatric AD patients, decreasing *Staphylococcus aureus* colonization and flare frequency [348].

Additionally, nanostructured lipid carriers combined with PEG derivatives have advanced to Phase II clinical studies, exhibiting improved corticosteroid penetration with reduced systemic exposure [349]. More recently, multi-responsive hydrogel patches incorporating PNIPAAm and pH-sensitive components have been evaluated in pilot clinical settings, demonstrating on-demand drug release triggered by elevated lesion temperature and alkaline pH [350].

Representative clinical and translational outcomes are summarized in Table 3, highlighting polymer system type, stimulus/function, and key results. These examples confirm that polymer-based systems are not merely conceptual innovations but clinically relevant therapeutic tools. They address unmet needs by enhancing local drug delivery, prolonging therapeutic residence, and minimizing systemic side effects [351]. Nonetheless, broader clinical adoption will require overcoming challenges related to scale-up manufacturing, reproducibility, regulatory approval, and long-term safety evaluation. Addressing these barriers is essential for the future integration of polymer-based drug delivery systems into routine AD management [52].

7. Conclusion: challenges and future perspectives in AD treatment

AD is a chronic inflammatory skin disorder characterized by barrier

Table 3
Recent advances in polymer-based drug delivery systems for AD over the past 3–5 years, highlighting multi-responsive designs and clinical progress. Overview of recent (past 3–5 years) advances in polymer-based drug delivery systems for AD, summarizing representative materials, multi-responsive designs, and application toward AD disease.

Polymer system	Stimulus/ Function	Key finding	Reference
HA-based hydrogel	Moisturizing + anti-inflammatory	Improved SC hydration, reduced EASI scores in AD patients	137,140
Chitosan–HA composite	Antimicrobial + barrier repair	Reduced *S. aureus* colonization, improved SCORAD	137, 171, 178
PNIPAAm–pH dual-responsive hydrogel	Multi-responsive	On-demand drug release in inflamed skin microenvironment	101, 183, 222, 243
Nanostructured lipid carriers (PEG-modified)	Enhanced penetration	Increased corticosteroid delivery, lower systemic absorption	90, 97, 106, 244, 278, 248
Electrospun nanofiber patch	Sustained delivery	Reduced scratching frequency and transepidermal water loss	98, 288, 292

disruption, immune dysregulation, and recurrent flares, which collectively impose a substantial burden on patient quality of life [3,4]. Conventional therapies, including topical corticosteroids, calcineurin inhibitors, systemic immunosuppressants, and biologics, provide symptomatic relief but are limited by short-lived effects, systemic adverse events, and poor adherence [95,96]. These limitations highlight the need for therapeutic strategies that balance efficacy and safety in long-term disease management.

Polymer-based drug delivery systems have emerged as promising alternatives, enabling controlled and targeted drug release, enhanced skin penetration, and reduced systemic toxicity [104,107,312]. Recent studies provide both conceptual and experimental evidence of their benefits. For example, hyaluronic acid–chitosan composite hydrogels have shown superior reductions in TEWL and improved skin hydration compared with conventional emollients [1,9,99]. Polyethylene glycol–modified nanostructured carriers have achieved markedly higher corticosteroid retention in preclinical skin models while minimizing systemic absorption [126]. Electrospun nanofiber dressings have effectively reduced scratching behavior in AD mouse models, correlating with measurable decreases in inflammatory cytokine levels [98,291]. Collectively, these findings demonstrate that polymer systems can deliver reproducible, clinically meaningful improvements in drug delivery and therapeutic outcomes.

Despite these advances, several challenges must be addressed before polymer-based drug delivery systems can be fully integrated into clinical practice. Long-term biodegradability and safety require further investigation, particularly in chronically inflamed skin, where repeated application may cause polymer accumulation, immune responses, or microbiome alterations [247,248]. Manufacturing complexity and high production costs of advanced hydrogels, nanofibers, and multi-responsive systems limit scalability and accessibility [293,294]. Regulatory pathways remain demanding, as smart polymers containing novel monomers or responsive linkages require comprehensive toxicological and stability evaluations [210,223]. Moreover, while preclinical results are encouraging, large-scale, long-term clinical validation is still limited. Practical considerations, including formulation stability, spreadability, and user convenience, must also be addressed to ensure patient adherence [233,282].

In the future, polymer-based systems are expected to play a central role in AD treatment by sustaining drug release, enhancing lesion targeting, and integrating advanced functionalities [83]. Smart polymers responsive to stimuli such as pH, temperature, and light, when combined with nanocarriers, can enable precise, on-demand drug delivery tailored to the dynamic microenvironment of AD lesions [315,316]. The incorporation of peptide-based polymers may further improve biocompatibility and anti-inflammatory properties, while integration of biosensor capabilities could allow real-time monitoring of disease activity and adaptive therapy, paving the way for truly personalized medicine [329,333].

Future research should prioritize scalability and regulatory alignment by establishing standardized manufacturing protocols and harmonized evaluation criteria for polymeric drug delivery systems [246,248]. Comparative effectiveness studies against current standard-of-care treatments will be critical to demonstrate both clinical and economic value. Interdisciplinary collaboration among polymer chemists, dermatologists, immunologists, and bioengineers is essential to accelerate innovation and clinical translation. Moreover, patient-centered design considerations, such as ease of application, cosmetic acceptability, and cost-effectiveness, will enhance adherence and real-world impact [104].

In summary, polymer-based drug delivery systems offer a transformative opportunity for AD management, combining measurable therapeutic benefits with a roadmap toward precision, patient-centered treatment [93,219]. Their success will depend on overcoming challenges related to biodegradability, cost, regulatory approval, and long-term safety, while leveraging multifunctional and personalized design [109,246]. By integrating advanced materials science with clinical dermatology and patient-focused approaches, the field can move beyond symptomatic relief toward comprehensive, sustainable, and individualized healing solutions for AD patients [1,187,319].

CRediT authorship contribution statement

Yejin Kim: Writing – original draft, Investigation, Data curation, Conceptualization. **Kinam Park:** Writing – original draft, Validation, Project administration, Investigation, Formal analysis. **Moon Suk Kim:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Moon suk kim reports financial support was provided by National Research Foundation of Korea. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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