

## Review article

## Recent advancement in psoriasis and nanotechnological approaches for psoriasis management

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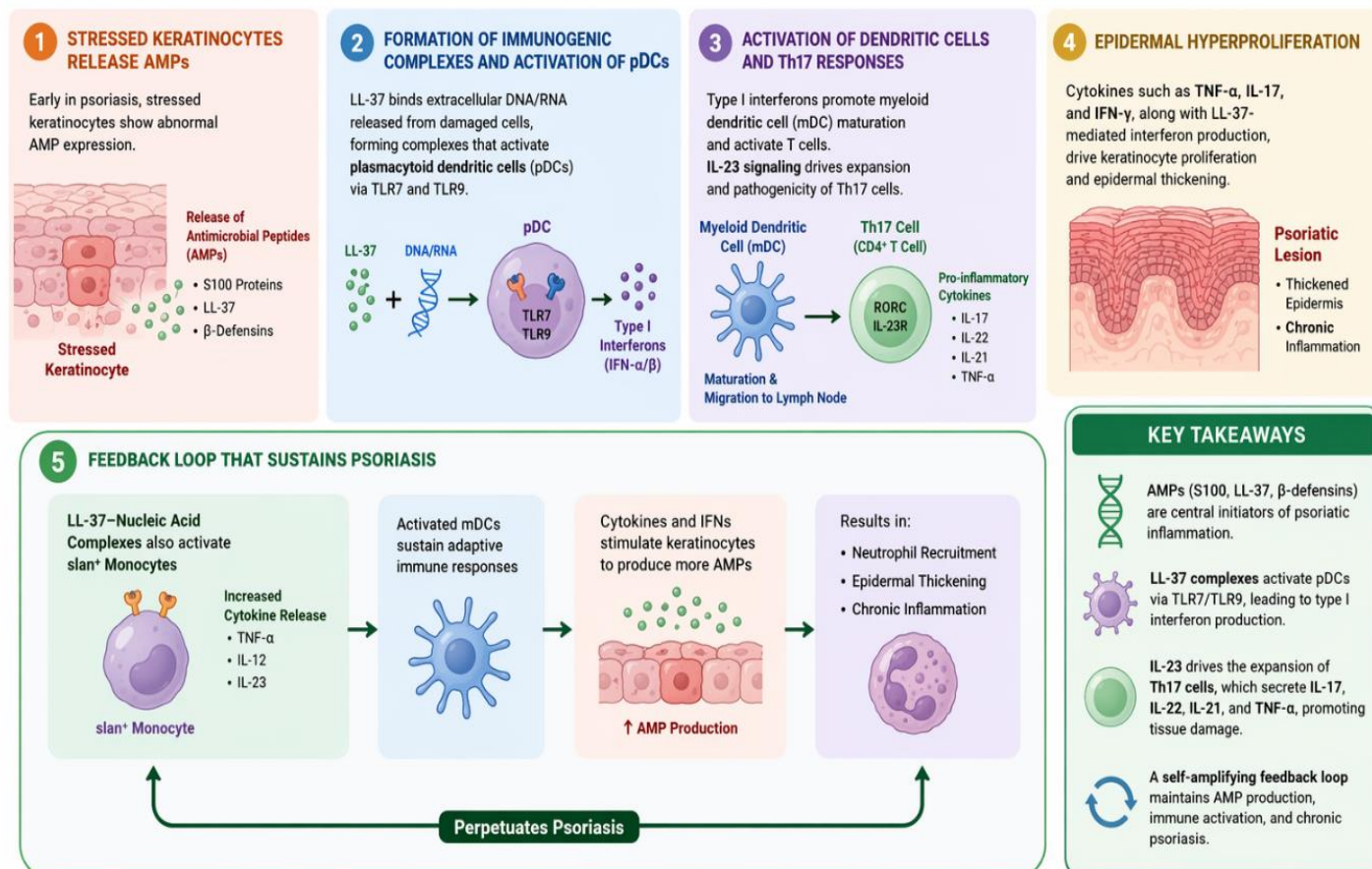
## Refer This Article

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## ABSTRACT

### IMMUNOLOGICAL MECHANISMS IN PSORIASIS: ROLE OF AMPs AND Th17 CELLS

Psoriasis is driven by the crosstalk between keratinocytes, antimicrobial peptides, dendritic cells, and T cells, creating a cycle of inflammation and epidermal hyperproliferation.



Significant progress has been made in understanding the pathophysiology of inflammatory skin disorders such as psoriasis and dermatitis. Advances in knowledge of age-related factors, gender differences, and genetic predisposition have helped clarify the complex mechanisms underlying these conditions, enabling the development of innovative therapeutic strategies. This review outlines the molecular and immunological pathways involved in psoriasis, highlighting key mediators responsible for disease initiation and progression. It also discusses both conventional and emerging treatment options, with emphasis on therapies developed over the past decade. Particular focus is placed on advanced drug delivery systems, including microneedle-based technologies and nanotechnology-driven approaches, which enable targeted delivery, improved bioavailability, and enhanced therapeutic efficacy. These emerging strategies show strong potential to improve clinical outcomes, enhance patient adherence, and provide more effective management of psoriasis and other chronic inflammatory skin disorders.

**Keywords:** Psoriasis, Inflammatory skin diseases, Molecular mechanisms, Targeted drug delivery and nanotechnology.

## INTRODUCTION

Psoriasis is a chronic inflammatory skin condition that is also genetically and age-dependent and is now known as an immune-mediated systemic disease. Clinically, it manifests as a quick proliferation of the epidermis, resulting in well-demarcated erythematous plaques with silvery-white scales, and is accompanied by itching and pain. Areas of lesions are usually found on extensor surfaces like elbows and knees, scalp, and other areas of the body. The disease is caused by a combination of keratinocytes, T lymphocytes, and innate immune cells, and it is not contagious because it is based on immune dysregulation, not infection [1]. Autoreactive T cells are key to maintaining chronic inflammation, and hormonal, immunological, genetic, epigenetic, and environmental factors all add to the process of disease. Specific HLA alleles and MHC-related loci are known as genetic susceptibility. The disease can be triggered by or worsened by environmental factors such as trauma, infections, and medications. Psoriasis is a condition affecting about 2% of the world's population, with some groups being more affected than others [2]. The most prevalent is plaque psoriasis, which makes up almost 90% of the cases. It is a disease with a complex pathogenesis in which interactions between keratinocytes and immune cells play a role, both innate and adaptive immunity. The current evidence is pointing toward immune dysregulation as central, and the success of immune modulation therapies [3].

## Pathogenesis of psoriasis

Psoriatic inflammation involves one of the most important mechanisms of dysregulated production of antimicrobial peptides (AMPs), such as S100 proteins, LL-37, and  $\beta$ -defensins, to initiate and perpetuate immune activation. During the early stages of disease, stressed keratinocytes release LL-37 that binds extracellular DNA and RNA to create an immunogenic complex. They induce type I interferon production through activation of plasmacytoid dendritic cells through the Toll-like receptors (TLR) 7 and 9. This leads to the maturation and activation of myeloid dendritic cells, as well as activation of T-cell responses, mainly Th1 and Th17 [4]. Th17 cells (CD4+ T cells with RORC expression) produce pro-inflammatory cytokines, including IL-17, IL-22, IL-21, and TNF- $\alpha$ , which are

involved in epidermal hyperplasia [5]. They further expand and become pathogenic when they express IL-23 receptors, which are particularly increased in psoriasis. In terms of their functions, Th17 cells are heterogeneous; those activated by TGF- $\beta$  and IL-6 are involved in epithelial barrier function, whereas those activated by IL-1 $\beta$ , IL-6, and IL-23 are associated with inflammation and tissue damage. Also, LL-37 complexes stimulate monocytes and dendritic cells, leading to elevated production of cytokines, which maintains adaptive immunity. Signalling by cytokines like TNF- $\alpha$ , IL-17, and IFN- $\gamma$ , and interferon signals, promotes keratinocyte hyperproliferation. This creates a feedback mechanism that increases the production of AMP, recruitment of neutrophils, epidermal thickening, and chronic inflammatory response in psoriasis [6].

## Genes linked to psoriasis susceptibility

**Table 1:** Genes related to adaptive immunity [7-8]

Genes associated with adaptive immunity	Role
HLA C or MHC gene	Present antigens to naïve T cells
IL-23R or IL-23 receptor Subunit	T cell maturation
IL-12B	T cell maturation
ERAP1 (Endoplasmic Reticulum Aminopeptidase 1)	Peptide antigen trimming for MHC1 binding
TNF- $\alpha$	A significant pro-inflammatory cytokine implicated in psoriasis
IL-23A/STAT2 or IL-23, subunit p19	Control over T-cell activation
IL-23A, $\alpha$ -subunit p19	Regulation of T- cell activation

**Table 2:** genes related to innate immunity [9,10]

Genes associated with innate Immunity	Role
IFIH1 (Interferon-induced helicase C domain), MDA5	Rig-like helicases that aid in RNA virus recognition
TNFAIP3 (Tumour necrosis factor- $\alpha$ induced protein 3)/ A20	TNF- $\alpha$ inducible zinc-finger protein that inhibits NF- $\kappa$ B signaling to momentarily decrease immunological response
FBXL19 (F-box and leucine-rich repeat protein 19)	Blocking demethylase activity to trigger NF- $\kappa$ B

**Table 3:** Genes related to skin barrier function [11,12]

Genes associated with skin barrier function	Role
LCE3B and LCE3C	Barrier of skin function
CDSN	A cornified envelope component
DEFB cluster or $\beta$ -defensins	Antimicrobial and chemotactic Function
GJB2 (Gap junction protein $\beta$ 2), connexin26	Participates in the development of gap junctions

HLA: human leukocyte antigen, MHC: major histocompatibility

complex, STAT: signal transduction and transcription, MDA: melanoma differentiation-associated protein, RNA: ribonucleic acid, DEFβ: defensin β, NF: Nuclear factor, LCE3B: Late cornified envelope proteins 3B, TNF-α: Tumor necrosis factor-α, CDSN: Corneodesmosin.

### Types of psoriasis

Psoriasis is a complex inflammatory skin disease with various clinical types. Plaque psoriasis (psoriasis vulgaris) is the most prevalent and is defined by well-demarcated erythematous plaques accompanied by silvery scales and itching. It has a multifaceted pathogenesis, in which innate and adaptive immunity are both important, but innate immunity is more predominant in initiating the disease, and adaptive immunity is more important in perpetuating and progressing the disease.

### Plaque Psoriasis

Plaque psoriasis pathogenesis is driven by tumour necrosis factor-α, interleukin-23, and the Th17 axis. IL-17 is produced by multiple immune cells, such as Tc17, invariant natural killer T cells, γδ T cells, innate lymphoid cells, and neutrophils. The IL-17 family comprises several mediators, two of which are important: IL-17A, which is more potent, and IL-17F. IL-17A signals through IL-17RA/RC receptors, initiating ACT1-dependent pathways that include the NF-κB, MAPK, and ERK pathways, as well as the production of pro-inflammatory cytokines and chemokines. Th17 responses are mediated by ACT1–NF-κB signalling, while the Th1/Th2 responses are mediated by JAK–STAT. γδ T cells can also produce IL-17A independently, leading to early inflammation [14].

Figure 1: pathophysiology of plaque psoriasis

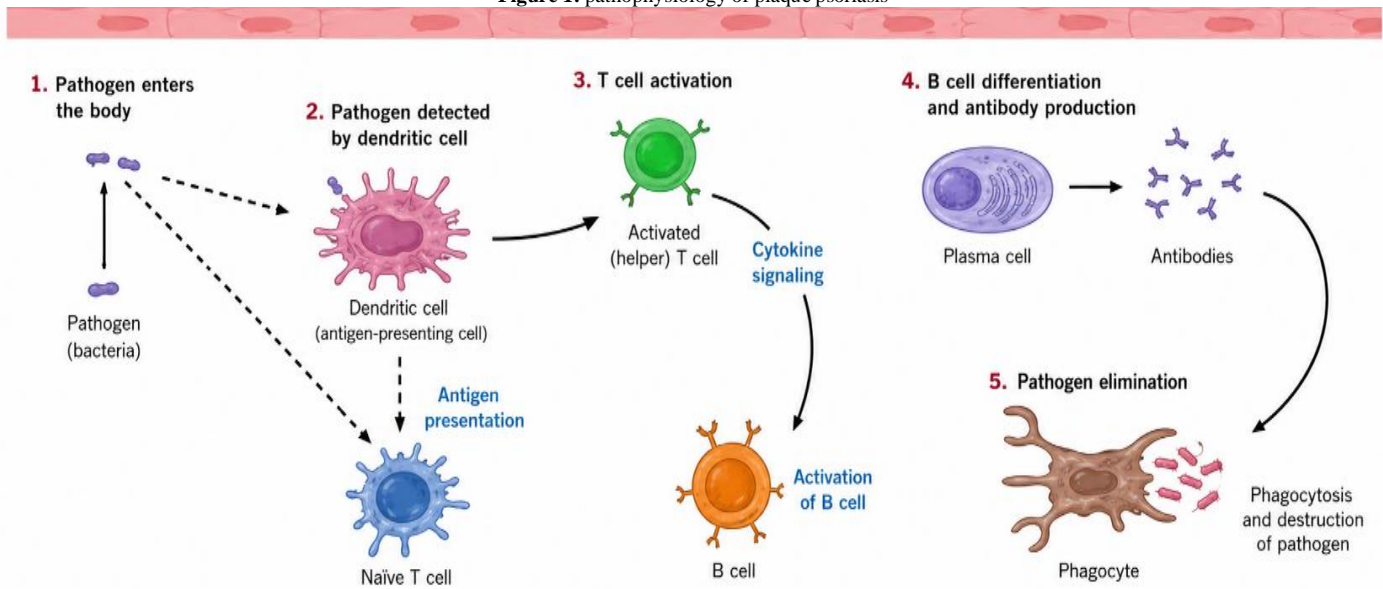
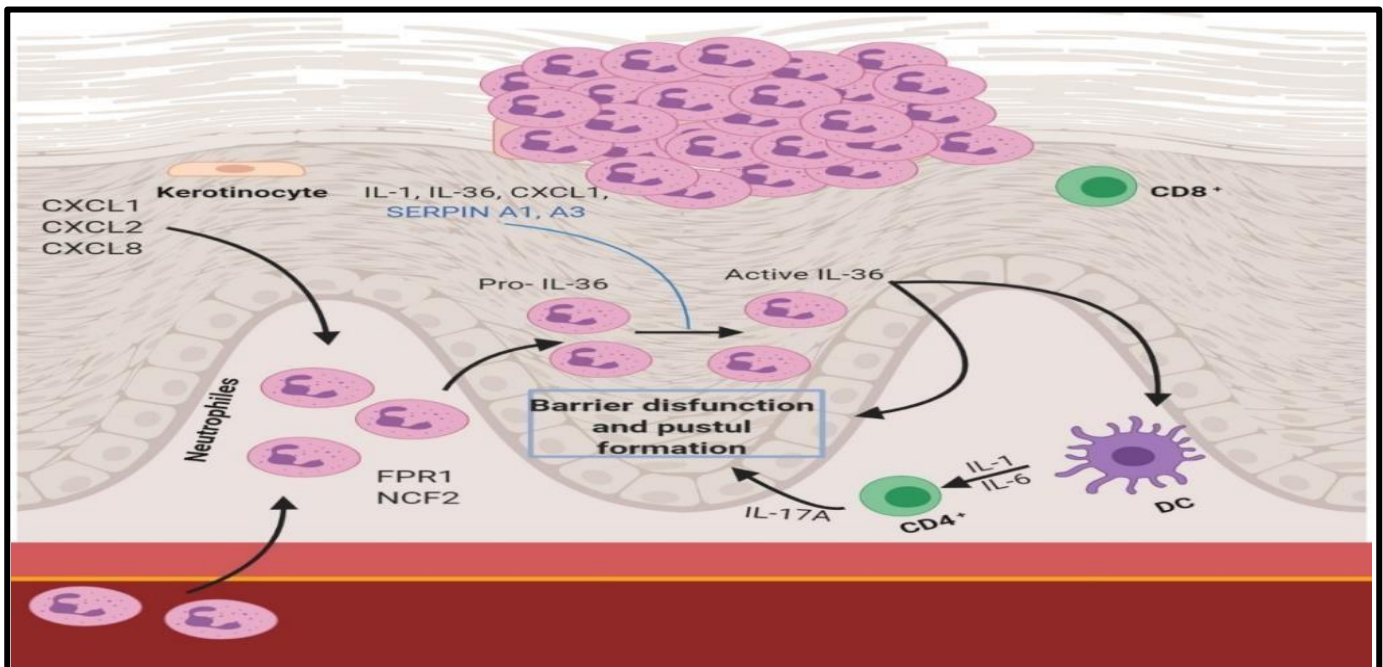


Figure 2: Pathophysiology of pustular psoriasis



### **Pustule psoriasis**

The second most prevalent psoriasis form, pustular psoriasis, features a number of sterile pustules, which can merge. Pustular psoriasis has a different immune pathogenesis than plaque psoriasis, which is more mediated by adaptive immunity, with innate immunity by monocytes, neutrophils, and keratinocytes playing the major roles in this type. A mutation in the IL36RN gene causes more IL-1 and IL-36 cytokines, which cause neutrophils to build up in the skin. Generalized pustular psoriasis is an acute, rapidly evolving process characterized by diffuse erythema, subcorneal pustules, and frequently systemic symptoms [14].

### **Current therapies**

#### **Vitamin D analogues**

Vitamin D analogues have anti-inflammatory activity and immunomodulatory action on psoriasis. The topical formulations target vitamin D<sub>3</sub> receptors, which affect genes related to inflammation, differentiation, and cell proliferation. They help to normalize keratinocyte activity, which reduces the rapid turnover of cells and thickening of the skin. These agents, in particular, are very effective at controlling scaling of the nails and scalp in psoriatic conditions. Commonly used drugs include calcipotriene and calcitriol, which can improve plaque psoriasis by 60–70% and are also suitable for children aged over 2 years, respectively [15–17].

#### **Vitamin D analogues with corticosteroids**

Depending on their potency, corticosteroids have anti-inflammatory, antiproliferative, and immunosuppressive effects. Long-term use can result in side effects like stretch marks, dilated blood vessels, purpura, acne, and folliculitis. These side effects are avoided, if possible, by using combination therapies. Specifically, the use of vitamin D analogues in conjunction with corticosteroids has been proven to be more effective than using corticosteroids alone to treat psoriasis [18].

#### **Coal tar**

Coal Tar is an effective, traditional treatment for psoriasis, which can achieve long-term remission, but its use has been reduced because of unacceptable cosmetic results. One of the active ingredients, carbazole, has anti-inflammatory and antiangiogenic properties, which are achieved through the inhibition of IL-15, nitric oxide synthase activity, and the inhibition of STAT3 signalling. Although effective, coal tar therapy can result in side effects including odour, staining, skin irritation, erythema, stinging, folliculitis, and keratoacanthoma [19].

#### **Salicylic acid**

Salicylic acid is widely used in psoriasis for its keratolytic properties and is often combined with corticosteroids to enhance drug penetration. It disrupts the stratum corneum and weakens the strength of corneocytes, lowers the pH of skin,

increases hydration, and softens plaques. But when used in excess, it is known to cause adverse effects like irritation, systemic toxicity, headache, metabolic acidosis, nausea, and vomiting [20–21].

#### **Topical calcineurin inhibitors**

The mechanism of action of topical calcineurin inhibitors is their ability to inhibit the activity of the calcineurin phosphatase, which prevents the release of pro-inflammatory mediators that lead to the formation of psoriatic lesions. The most common side effects from their use are short-term stinging sensations and localized skin irritation [22].

#### **Tazarotene**

Topical retinoids include tazarotene, a synthetic version of vitamin A that is used to treat plaque psoriasis, typically in combination with a calcipotriene or corticosteroid. It can be used long-term and is effective in improving nail psoriasis when used under occlusion. Tazarotene activates retinoic acid receptors  $\beta$  and  $\gamma$ , thus modulating gene expressions that help to decrease inflammation, normalize keratinocyte differentiation, and inhibit epidermal proliferation. Localized skin irritation is the most frequent side effect [23–24].

#### **Anthralin (dithranol)**

Anthralin is a good topical therapy for stable plaque psoriasis, particularly in short-contact therapy of localized, hyperkeratotic plaques that are not otherwise responsive. It works through inhibiting the activation of T cells, decreasing the proliferation of keratinocytes, and normalizing epidermal differentiation, possibly by mitochondrial dysfunction and the production of reactive oxygen species (ROS). Although anthralin is effective, it also causes irritation to the skin and severe staining of skin, hair, nails, and clothing [25].

#### **Topical corticosteroids**

Topical corticosteroids are routinely utilized in psoriasis for all severities, both as monotherapy for mild disease and in combination with systemic medications in severe disease. They work by regulating the expression of genes, and by anti-inflammatory, vasoconstrictive, antiproliferative, and immunosuppressive properties. There are, however, some negative side effects: skin atrophy, striae, telangiectasia, and increased risk of infection. Systemic absorption is possible with prolonged use, resulting in suppression of the hypothalamic–pituitary–adrenal axis and Cushing's syndrome, as well as in metabolic disturbances [25].

#### **Conventional treatments**

Psoriasis treatments are systemic drugs, such as acitretin, fumaric acid esters, cyclosporin, and methotrexate. Acitretin, unlike other retinoids, is not immunosuppressive, and it regulates genes that relate to differentiation, proliferation, inflammation, and keratinization. Fumaric acid esters have immunomodulatory, anti-inflammatory, and antiproliferative properties, leading to the

induction of apoptosis in T-cells. Cyclosporin suppresses the activation of T-cells and the production of most of the interleukins, including IL-2. Methotrexate lowers the IL-17 level and modulates the level of pro-inflammatory mediators, which impacts the gene expression that is linked to inflammation and atherogenesis in psoriatic lesions [25].

#### **Nanotechnological approach**

In the last 20 years, nanotechnology has revolutionized many scientific and medical disciplines. Over the last few years, much research has been dedicated to the use of nanoparticles as novel drug carriers. The versatility allows them to be used for various materials with different physicochemical properties, which can be utilized in a multitude of applications. In one aspect, the function of nanoparticles is to deliver targeted active drugs such as chemotherapeutic drugs.

#### **Lipid-based nanoparticles**

Physiological lipids are used to prepare lipid nanoparticles, which have excellent biocompatibility and low toxicity. The structure has many advantages, such as enhanced drug stability, long-term blood circulation time, biodegradability, targeted drug delivery, and high drug-loading capacity. Furthermore, they are also easily fabricated at relatively low costs and therefore are attractive platforms for therapeutic applications [26].

#### **Liposomes**

A vesicular carrier made from lipid bilayers surrounding an aqueous interior is the liposome, which is extensively studied for dermatological drug delivery. They increase the water solubility of poorly water-soluble drugs, allow for controlled release, and increase penetration through the stratum corneum. They are made of a variety of components, making it possible to change their properties for targeted delivery, like size, charge, permeability, or stability. Wadhwa et al. formulated fusidic acid (FA) loaded liposomes having a particle size range of 572.7-740.1 nm and an entrapment efficiency of 52.1-72.6%. These were shown to be more stable and have increased anti-psoriatic activity *in vivo*, using mouse tail models, and thus have great potential for the treatment of psoriasis [27-29].

#### **Lipospheres**

Lipospheres are lipid-based nanoparticles based on lipids with a hydrophobic core and a phospholipid shell, which are stable, have a controlled drug release, are low-cost, and easy to produce. They can be administered orally, intravenously, or topically and have potential use in treating psoriasis. Jain et al. formulated liposphere gel with tacrolimus and curcumin particles with an average size of 47 nm. This formulation in mice showed improved penetration and distribution of the drug into the skin compared to the drug solution. It was also found to have better

therapeutic effects with a histological improvement and strong decrease in the cytokines involved in inflammation, such as TNF- $\alpha$ , IL-22, and IL-17 [31].

#### **Ethosomes**

Ethosomes are vesicular drug carrier systems comprising phospholipids, ethanol, and water, which are intended for topical application. They are rich in ethanol, which fluidizes the vesicle membranes and stratum corneum, thus increasing the flexibility of the vesicles and penetration through the skin. This will help to deliver active compounds into the deeper layers of the skin. Zhang et al. prepared psoralen-containing ethosomes that showed high entrapment efficiency (90–96%) and a particle size of 56.71–159.07 nm. Ethosomes exhibited almost seven times more drug deposition in rat skin than ethanolic solution, which suggested better penetration, less systemic toxicity, and higher therapeutic efficacy in the treatment of psoriasis [32].

#### **Solid lipid nanoparticles**

SLNs are solid lipid nanoparticles made from physiological lipids and surfactants, which provide controlled drug release, decreased irritation, and protect the active compound. The nanoscale size enables them to achieve good interaction with the stratum corneum, thereby promoting skin penetration and allowing their use in the treatment of psoriasis. Pradhan et al. prepared SLNs for the sustained release of the fluocinolone acetonide. The optimized formulation with a concentration 2% lipid, 1% surfactant, and 0.06% drug had a particle size of 107.4 nm, entrapment efficiency of 87%, which indicated good potential for topical delivery [35].

#### **Nanostructured lipid carriers**

Advanced nanocarriers, nanostructured lipid carriers (NLCs), are made of a combination of solid and liquid lipids providing higher drug loading capacity, controlled release, increased bioavailability, and biocompatibility. Their special properties for topical use include excellent skin penetration and occlusive effects, which protect against trans-epidermal water loss and enhance skin hydration. Avasathi et al. developed methotrexate loaded nanogel of NLC using Precirol ATO 5. Optimized formulation exhibited higher EE of 0.223, lower polydispersity index of 0.231, and particle size of 278 nm. Extended drug retention (up to 48 hours) and improved efficacy in the treatment of psoriasis were confirmed *in vitro* and *in vivo* [37].

#### **Microneedles**

Microneedles are an innovative drug delivery system consisting of small needles that are perpendicularly mounted on a patch to circumvent the stratum corneum. This intradermal delivery method is a novel way of delivering drugs in the treatment of psoriasis. The microneedle patch can be divided into two major parts: the microneedles and the patch backing, which can be either

the same or different materials<sup>[38]</sup>. Microneedles should be strong and durable enough to perform their function. They are generally 25-2000 micrometers long and are able to penetrate the stratum corneum without reaching pain receptors, thus delivery is relatively non-invasive and virtually painless<sup>[39]</sup>.

#### **Polymeric nanoparticles (PNPs)**

The polymeric nanoparticles are being widely used because they exhibit the biomimetic properties, good biocompatibility, and variable sizes and shapes, which make them an ideal biomaterial. They can be chemically engineered to facilitate targeted and targeted drug delivery. There are several other types of polymer-based nanoparticles, such as nanospheres and nano-capsules, which are also widely used<sup>[40]</sup>.

#### **Nanospheres**

Nanospheres are nanoparticles made of polymers containing drugs that are uniformly dispersed in the polymer matrix, improving the solubility and controlled release of the drugs. These can be biodegradable or non-biodegradable. Batheja et al. prepared tyrosine-derived nanospheres (tyrospheres) embedded in gels, which demonstrated more effective absorption of the drugs *in vitro* and *in vivo*. Methocel K15M (HPMC) was found to give better dispersion than Carbopol, with optimal uniformity of the dispersion at 3 mg/mL and the particle size of ~40 nm. Diering et al. also showed that vitamin D3 can be delivered in a tyrosphere with sizes of 64-73nm, which also have a better absorption compared to conventional vitamin D3 delivery systems<sup>[43]</sup>.

#### **Nano-capsules**

Nano-capsules, nanoparticles containing a drug core enclosed in a polymer shell, provide sustained release, increased bioavailability, increased selectivity, and decreased toxicity. The core can be a polymer matrix or an oily phase. Marchiori et al. created dexamethasone-loaded nano-capsules consisting of a capric triglyceride core and a polycaprolactone shell, in a Carbopol gel. The average size and EE of the formulation were found to be 201 nm and >95%, respectively. Controlled release of these drugs and their stability were shown in *in vitro* studies, which support their use in the treatment of topical psoriasis<sup>[45]</sup>.

#### **Dendrimers**

Dendrimers are monodisperse and multivalent spherical macromolecules with unique structures that offer high reactivity, biocompatibility, and excellent solubility properties. Drugs may be contained inside the dendrimer or bound to its surface through covalent bonds so that the active compound is not chemically or biologically degraded. In addition, their architecture allows for a multitude of mechanisms for controlled drug release<sup>[46]</sup>.

Agrawal et al. studied the topical delivery of dithranol using polypropylene imine dendrimers. The drug-loaded dendrimers

were 8 nm in average size and also showed significantly improved penetration in human skin (from 35% to 95%) but did not cause local irritation as compared to conventional dithranol solutions. The findings indicate that dendrimers could be promising topical drugs for psoriasis treatment in the future<sup>[47]</sup>.

#### **Micelles**

Amphiphilic molecules self-assemble into nanocarriers, called micelles, that are core-shell structures, with the hydrophobic drug molecule in the core and the hydrophilic molecules in the shell. They increase bioavailability, drug stability, and decrease side effects. Lapteva et al. investigated the delivery of tacrolimus using MPEG-dihex PLA micelles with particle sizes less than 50 nm. They increased the solubility and permeability. *In vivo* studies revealed that micelles were not able to permeate the stratum corneum effectively and were not well suited to the topical delivery of psoriasis<sup>[48]</sup>.

#### **CONCLUSION**

Recent developments of nanotechnological strategies for psoriasis treatment are summarised here. It presents the disease pathogenesis, type of disease, and genetic causes, and reviews the current treatments and their limitations. Special focus is given on nano-formulations improving drug delivery, compliance, and therapeutic efficacy. These systems offer targeted and sustained release, stability, increased loading, and controlled release profiles. Their nano size allows for deeper penetration through the skin and effective delivery to affected areas. Continuous research is being conducted on the development of conventional therapies into nano-based ones, in order to increase the effectiveness and safety of the treatment. In conclusion, the potential of nanotechnology in psoriasis management is seen as a promising and effective way to improve treatment outcomes, making it more patient-friendly.

#### **Future prospects**

Nanotechnology has great potential for the diagnosis and treatment of dermatology. A new field, nano-dermatology, merges nanotechnology with several other fields, such as skin nanobiology, nano-diagnosis, and nano-therapy. These methods allow for a fine-grained examination of skin functions, the development of sophisticated diagnostic methods, and novel therapies like nanodrug delivery and phototherapy. It also boosts both transdermal and dermal delivery using nanostructures. Psoriasis is a big clinical problem that occurs in 2-3% of the world's population. The potential applications of nanodermatology are promising, with enhanced diagnostics, drug delivery, and personalized treatment based on specific biomarkers to guide more targeted and effective management throughout the care continuum.

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