Current Dermatology Reports (2019) 8:14–25
https://doi.org/10.1007/s13671-019-0248-y

PSORIASIS (J WU, SECTION EDITOR)

# Nanotechnology for Psoriasis Therapy

Emily C. Murphy[1,2] · Samuel W. Schaffter[3] · Adam J. Friedman[1]

Published online: 30 January 2019


## Abstract

**Purpose of Review** To summarize the use of nanotechnology-based drug delivery systems for psoriasis therapies, focusing on recent studies of treatment efficacy in humans and murine models.

**Recent Findings** Both topical and oral psoriasis medications, in addition to alternative psoriasis therapies and siRNAs targeting genes involved in the pathogenesis of psoriasis, have been incorporated into nanocarriers. Numerous studies demonstrate that nanocarriers can enhance the efficacy and reduce side effects of their included drugs through increased skin retention, sustained release, and decreased systemic absorption. However, the number of studies in humans is limited and while the short-term use of nanocarriers appears safe, long-term outcomes are unknown. Additionally, few studies compare different types of nanocarriers, making it difficult to recommend which types of nanocarriers are the best.

**Summary** While recent research has demonstrated the benefit of nanotechnology-based drug delivery systems for psoriasis, more research, especially in humans, is needed to optimize drug-loaded nanocarriers for clinical use.

**Keywords** Psoriasis · Nanotechnology · Transdermal drug delivery · Nanomedicine · Nanocarriers

## Introduction

Psoriasis is a chronic inflammatory disease that affects 2 to 3% of adults in the USA [1]. Most patients with psoriasis have mild to moderate disease that can be treated safely and effectively with topical therapies, of which corticosteroids are the most common [2]. Other topical therapies include vitamin D analogs, anthralin, retinoids, salicylic acid, emollients, and tacrolimus [2]. Topical treatments are also used as an adjunct for resistant lesions in patients treated with phototherapy or systemic therapies [2, 3]. Historically, non-specific small molecule immunosuppressants (methotrexate or cyclosporine) were used for psoriasis affecting large body surface areas (BSA) or for disease refractory to topical therapy and phototherapy. However, there has been a shift away from using BSA alone as a requisite for systemic therapy given some patients have limited but debilitating disease, such as those with severe psoriasis of the palms and soles or scalp. Additionally, biologic therapy, which includes monoclonal antibodies or receptor fusion proteins that target specific immune mediators, has replaced small molecule immunosuppressants as the primary systemic therapy for psoriasis [4, 5]. Biologics offer reduced hepatotoxicity, nephrotoxicity, bone marrow suppression, and teratogenicity compared to small molecule immunosuppressants, yet these other therapies are still used in some cases because they are less expensive than biologics and can be taken orally (biologics require injections).

While topical therapies continue to serve as first line, our current armament has limitations as treatments have the potential to cause cutaneous side effects such as erythema, burning, and pruritus, and have disease morphology and location-dependent efficacy [6–8]. While skin is the desired target of topical therapies, it is also a barrier to effective drug penetration and absorption, and the keratinocyte hyperproliferation associated with psoriasis further fortifies this barrier [9]. While oral and injectable systemic therapies overcome the need to penetrate the stratum corneum, associated infection risk as well as liver, kidney, and bone marrow toxicities can limit their use in some patients [5]. Lowering cutaneous side

This article is part of the Topical Collection on *Psoriasis*

✉ Adam J. Friedman
ajfriedman@mfa.gwu.edu

[1] Department of Dermatology, The George Washington School of Medicine & Health Sciences, 2150 Pennsylvania Ave., Suite 2B-430, Washington, DC 20037, USA

[2] School of Medicine, Georgetown University, Washington, DC, USA

[3] Department of Chemical and Biomolecular Engineering, Johns Hopkins University, Baltimore, MD, USA

effects, increasing the permeability of topical medications, and reducing systemic side effects of oral and injectable therapies have been long-standing research goals. A promising route for addressing these issues is through the utilization of nanotechnology, which provides mechanisms to both increase drug penetration and lower drug toxicity.

Nanotechnology commonly refers to the study and manipulation of structures one to a few hundred nanometers in size in at least one dimension [10]. Nanoscale structures can be utilized as drug delivery systems by either encapsulating, entrapping, or conjugating drugs within or onto these structures. These nanoscale drug carriers can be constructed from organic molecules such as phospholipids or fatty acids, making them highly biocompatible [7, 8]. Nanocarriers can be organized into three broad classes: (1) vesicular carriers, which generally encapsulate drugs in an aqueous core; (2) micellar carriers, which typically encapsulate or entrap drugs in a hydrophobic core; or (3) solid-phase carriers, including gold and polymeric nanoparticles, which entrap drugs within a solid matrix or have drugs directly conjugated to them (Table 1 and Fig. 1). Localizing therapeutics within or onto nanocarriers can prevent drug degradation, promote drug absorption and sustained drug release, and limit drug interactions with non-target sites—all properties that can lead to improved efficacy [7, 8].

The drug delivery properties of nanocarriers are particularly useful for psoriasis treatments. Topical application of psoriasis therapies creates a thin film on the skin; the inclusion of drugs within nanocarriers prevents drug aggregation within this film, which is common with free drug and results in limited drug penetration through the stratum corneum. Nanocarriers within the film create a high drug concentration gradient at the skin's surface which drives sustained diffusion of the drug into the skin. Nanocarriers can also lodge within the lipid matrix of the stratum corneum resulting in slow, sustained release of the incorporated drug as well as retention of the drug in the skin for prolonged periods compared to free drug [49, 50]. Further, drugs included within nanocarriers are protected from degradation, increasing active drug half-life [7, 8]. Sustained drug release and extended half-life can reduce the doses of medications used in nanocarriers and the number of applications required compared to free drugs, decreasing cutaneous side effects and further increasing efficacy. The increased drug retention offered with nanocarriers also limits systemic side effects because the drug remains in the skin rather than being absorbed into the blood (Fig. 2) [50].

This review focuses on studies within the last 5 years examining the use of nanocarriers for the treatment of psoriasis. We will limit the discussion to studies examining antipsoriatic efficacy in animal models or human participants. Many of the available studies to date only characterize various nanocarriers for the delivery of psoriasis treatments and do not address preclinical or clinical efficacy, and thus will not be included. Further, larger drug carriers have also been explored for psoriasis therapy [51, 52]; but to maintain the focus on nanoscale carriers, we will exclude these from our discussion.

## Corticosteroids and Calcipotriol (Calcipotriene)

Topical corticosteroids are effective psoriasis therapies that reduce inflammatory and immune responses by regulating the transcription of cytokines and other immune proteins [6, 53]. However, topical steroids can cause local side effects including skin atrophy, acne, and telangiectasias [2]. Systemic side effects such as Cushing's syndrome and glaucoma are also possible when corticosteroids are absorbed through the cutaneous vasculature [2]. Encapsulation of corticosteroids within nanocarriers can minimize cutaneous reactions by reducing the therapeutic dose required compared to free drug and can prevent systemic side effects by limiting drug absorption into the blood. Corticosteroids are often used in combination with calcipotriol, a synthetic analog of vitamin D which inhibits keratinocyte proliferation [2, 6]. Calcipotriol would also benefit from incorporation into nanocarriers given its limited skin penetration, rapid degradation, and propensity for local side effects such as burning, dryness, and erythema [2].

To examine efficacy of nanocarriers loaded with corticosteroids, Alam et al. created a clobetasol propionate-loaded nanoemulsion (Table 1) of eucalyptus oil in water with Tween 20® and ethanol as surfactants [32]. Anti-psoriatic efficacy was assessed using a murine paw model where carrageen injections created paw edema; the percent edema inhibition was used as a proxy for anti-inflammatory effects. Greater inhibition of paw edema was seen with the clobetasol-nanoemulsion (84%) than clobetasol propionate 0.05% cream (Glevate®, 41%). While both treatments produced low skin erythema overall, the amount was greater with the nanoemulsion than Glevate®, likely due to the high concentration of surfactants in the nanoemulsion which are known skin irritants [32].

Kaur et al. created a nanoemulsion (NE) including a combination of clobetasol propionate (CP) and calcipotriol (CT) and incorporated it into a Carbopol® hydrogel [30•]. Treatment efficacy was assessed using an imiquimod-induced psoriasis murine model; imiquimod increases keratinocyte proliferation and cytokine production leading to plaques resembling psoriasis. After 5 days of daily application, treatment with the CP-CT-NE–loaded gel showed a larger reduction in skin thickness, erythema, inflammation, and scaling than treatment with betamethasone dipropionate 0.05% gel and a free CP-CT gel. In terms of skin irritation, assessed by comparing erythema, the CP-CT-NE–loaded gel was better tolerated than the free CP-CT gel. The superiority

**Table 1** Characteristics, advantages, and disadvantages of nanocarriers, as well as incorporated drugs and sizes of the carriers included in this review. Carriers are organized into three groups: vesicular carriers which have aqueous cores surrounded by one or more bilayers; micellar carriers which are particles with a hydrophobic core formed by the aggregation of amphiphilic polymers in an aqueous solution; and solid-phase carriers which have a continuous solid matrix. Unless otherwise noted, these carriers are non-irritating to the skin and allow for drug delivery into the deeper skin layers

| Nanocarrier | Characteristics | Incorporated drug (size) |
|---|---|---|
| Vesicular carriers | | |
| Liposomes | Vesicles composed of a unilaminar phospholipid bilayer and an aqueous core [11], can entrap hydrophilic drugs in the core and lipophilic drugs in the bilayer [7, 8]<br>• Similar lipid composition of these carriers to the epidermis increases drug penetration and retention; retention may be greater than SLNs, NLCs, and ethosomes [8, 12•, 13••, 14••, 15]<br>• May not penetrate deeper layers of skin [12•]<br>• Limited stability due to liposome aggregation and leakage of included drug [16] | Tretinoin (182 nm) [12•]; psoralen (95–115 nm) [17]; cyclosporine (950 nm) [14••] |
| Transfersomes | Liposomes that are softened with surfactants to increase the flexibility of the phospholipid bilayer [18]<br>• More stable and less expensive than liposomes [19]<br>• Flexibility of bilayer due to the presence of surfactant increases penetration through the stratum corneum [8, 20, 21] | Tazarotene and ceramide (size not reported) [13••]; tamoxifen (125 nm) [20] |
| Ethosomes | Liposomes that additionally include ethanol in the phospholipid bilayer [7]<br>• Ethanol increases carrier penetration of the stratum corneum compared to liposomes [8, 12]<br>• Lower skin retention than other vesicular and micellar carriers [12]<br>• Ethanol can be irritating to the skin [7, 12] | Tretinoin (120 nm) [12•]; tazarotene and ceramide (size not reported) [13••]; DEFB4 siRNA (size not reported) [22] |
| Niosomes | Vesicles composed of non-ionic surfactants that assemble into a bilayer [6, 7]<br>• More stable than liposomes and ethosomes [8, 23]<br>• Lower cost than liposomes [6, 24]<br>• Carrier destabilizes at room temperature [24] | Acitretin (370 nm) [24] |
| Polymersomes | Vesicles composed of synthetic amphiphilic polymers that assemble into a bilayer; entrap hydrophilic drugs in the core [25]<br>• Use of synthetic polymers allows versatile chemical and physical properties [26]<br>• Synthetic polymers are typically longer and more dense, increasing circulation time of polymersomes compared to liposomes before being cleared by phagocytes [26] | STAT3 and TNF-α siRNA (101 nm) [27] |
| Micellar carriers* | | |
| Nanoemulsions (NEs) | Dispersions of two immiscible liquids, often oil and water, with an average droplet size of 100 to 500 nm, that are stabilized by surfactants [6, 28]. Lipophilic and hydrophilic phases allow nanoemulsions to carry both types of drugs [29]<br>• Better for transport of hydrophobic drugs than liposomes because of their lipophilic interior [28]<br>• High carrier stability [30•]<br>• May decrease transepidermal water loss via strengthening of skin barrier [28, 29, 30•]<br>• May have antimicrobial effects [28, 31]<br>• High surfactant content can cause skin irritation [32] | Clobetasol propionate (size not reported) [32]; clobetasol propionate calcipotriol (34 nm) [30•] |
| Solid lipid nanoparticles (SLNs) | Surfactant-stabilized micelles with solid lipid core that can entrap lipophilic drugs [7, 8]<br>• Compared to vesicular carriers, SLNs have lower cost, higher carrier stability, and longer durations of drug release [12•, 33, 34]<br>• Feasible for large-scale industrial production [35] | Tretinoin (82 nm) [12•] |
| Nanostructured lipid carriers (NLCs) | Surfactant-stabilized micelles with both solid and liquid lipids in the core; inclusion of liquid lipids distorts the organized matrix present in SLNs, providing more space for drug molecules in this amorphous core [8, 36]<br>• Higher core surface area increases drug loading capacity and enhances skin penetration compared to SLNs [8, 37] | Tretinoin (80 nm) [12•] |

**Table 1** (continued)

| Nanocarrier | Characteristics | Incorporated drug (size) |
|---|---|---|
| Emulsomes | • Higher carrier stability than vesicular carriers [34]<br>Multilaminar phospholipid vesicle surrounding a micelle with a solid or semisolid lipid core, can carry hydrophobic drugs in core and hydrophilic drugs in the aqueous regions between the phospholipid bilayers [38, 39]<br>• Higher drug loading capacity than SLNs [39]<br>• Sustained drug release compared to unilaminar vesicles given the included drug must diffuse from the inner core and across multiple phospholipid bilayers [39]<br>• Increased drug degradation and leakage at higher temperatures requires storage below 45 °C [38] | Anthralin (range from 430 nm to 1.2 μm) [38] |
| Solid-phase carriers | | |
| Gold nanoparticles (AuNPs) | Nanosized particles of gold with drugs attached to the surface [7]<br>• Particle size and functionalization can be easily manipulated [7, 40]<br>• High drug loading capacity and carrier stability [7, 40] | EGFR siRNA (12 nm) [41•] |
| Solid polymeric nanoparticles (SPNPs) | Matrix of polymers that form a solid particle that can have drugs dissolved, entrapped, encapsulated, or attached within the polymer matrix [42]<br>• Higher drug stability than liposomes [42] | EGCG (green tea polyphenol) (211 nm) [43]; curcumin (30 nm) [44] |
| Nanogels (NGs) | A cross-linked polymer network composed primarily of water by weight. Drugs are loaded on the polymer matrix through electrostatic, van der Waals, and/or hydrophobic interactions [45]<br>• High drug loading capacity and carrier stability [45] | Acitretin (138 nm) and aloe emodin (238 nm) [46•]; methotrexate (196 nm) [47]; methotrexate (< 200 nm) [48•] |

*One additional study created micellar nanocarriers with tacrolimus and nicotinamide (210 nm) but the authors did not describe the structure of this micellar carrier [9]

of the NE-loaded gel could be due to its prolonged drug release or increased skin penetration compared to free drug. Dialysis followed by high-performance liquid chromatography (HPLC) analysis showed a sixfold increase in duration of drug release for the NE-loaded gel compared to free drug. Further, the NE-loaded gel showed increased accumulation of a fluorescent dye in deeper skin layers compared to dye alone, suggesting increased penetration and retention of CP and CT when loaded in the NE gel [30•].

## Retinoids

Retinoids are FDA approved for the topical (tazarotene) and oral (acitretin) treatment of psoriasis due to their ability to decrease keratinocyte proliferation and inflammatory cytokine production [2]. However, the use of acitretin is limited by teratogenicity, hyperlipidemia, and hepatotoxicity [54]. To limit these systemic effects, topical formulations can be used, but tazarotene often produces erythema and scaling especially when its concentration at the stratum corneum is high [12•, 55]. Incorporation of these drugs into nanocarriers may decrease local and systemic side effects by allowing the delivery of lower doses of retinoids for extended periods of time.

Abdelgawad et al. created multiple types of vesicular carriers, termed cerosomes, composed of phospholipids with either ethanol (ethosomes) or surfactants (transfersome) with tazarotene encapsulated in the core and ceramides in the phospholipid bilayer (Table 1) [13••]. Ceramides are stratum corneum lipids that are decreased in psoriatic skin leading to increased transepidermal water loss and disease severity [13••, 56, 57]. After topical treatments diffused through murine skin samples, tazarotene was extracted and measured using HPLC to assess skin deposition. Cerosomes (both high [112.5 mg] and low [62.5 mg] ceramide formulations with and without ethanol) led to higher tazarotene deposition compared to a marketed tazarotene gel (Acnitaz®). Vesicles without ceramides resulted in lower deposition than Acnitaz®. Ceramides have demonstrated a high affinity for epidermal lipids, which could promote increased deposition of tazarotene in the skin [58]. Additionally, efficacy was assessed in a randomized, controlled trial of 20 patients with psoriasis using Psoriasis Area Severity Index (PASI), which is a scale from 0 to 4 that includes erythema, thickness (induration), and scaling (desquamation). After 8 weeks of treatment, tazarotene-cerosomes with high ceramide and ethanol led to greater reductions in PASI scores (65%) than Acnitaz® (30%), whereas tazarotene-cerosomes with low ceramide and no ethanol did not perform better than Acnitaz®. The

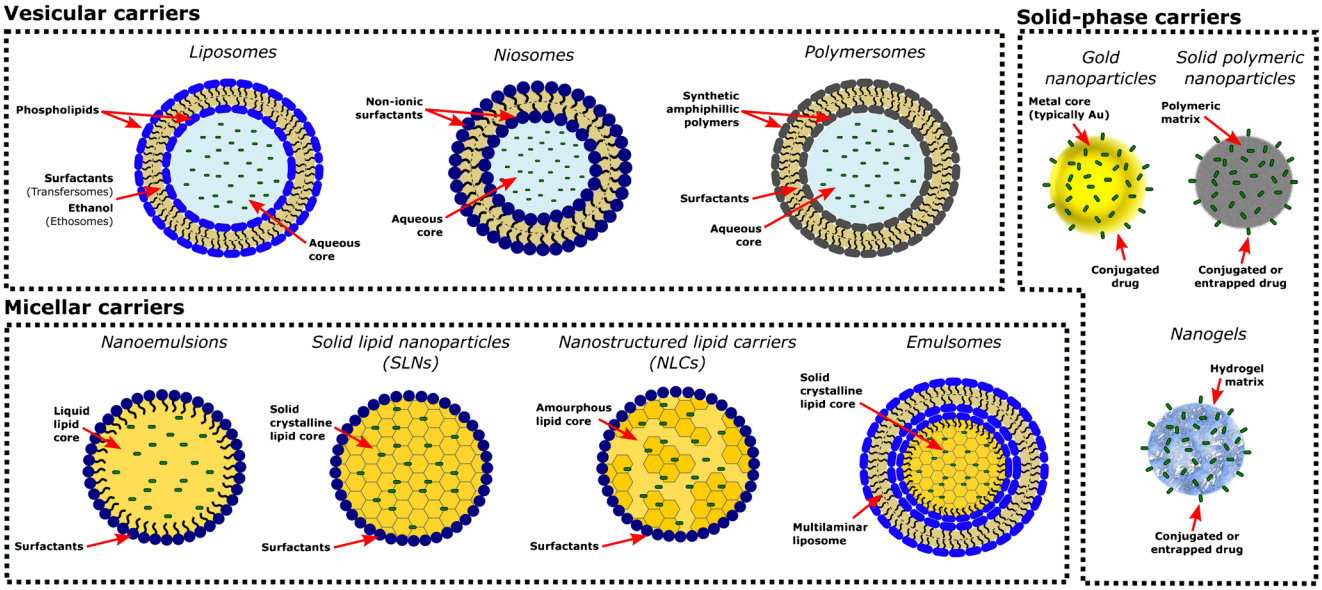


**Fig. 1** Structures of nanocarriers included in this review, organized into three groups (vesicular carriers, solid-phase carriers, and micellar carriers)

superior efficacy of the high-ceramide cerosomes is likely due to the inclusion of both ethanol, which facilitates drug penetration through the skin, and ceramides, which enhance tazarotene deposition. Burning was frequently reported with Acnitaz® but not with tazarotene-cerosomes, signifying that encapsulation of tazarotene within vesicles does reduce its irritation potential [13••].

Raza et al. loaded another retinoid, tretinoin, into liposomes, ethosomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) (Table 1) [12•]. These carriers were then incorporated into a Carbopol® hydrogel. Skin retention was assessed by measuring tretinoin content in murine skin samples using HPLC after application of the nanocarrier-loaded gels to the skin samples for 24 h. The liposome-loaded gel had the highest retention followed by the NLC-, SLN-, and ethosome-loaded gels and then a commercial tretinoin gel (Retino A®). Given all these carriers included biocompatible phospholipids, the ethanol present in ethosomes likely decreased this carrier's transit time through the skin, limiting drug retention. Anti-psoriatic efficacy was assessed with murine tails, which have parakeratotic differentiation, a feature of psoriasis that changes to orthokeratosis with treatment. The tretinoin-liposome–loaded gel and tretinoin-NLC–loaded

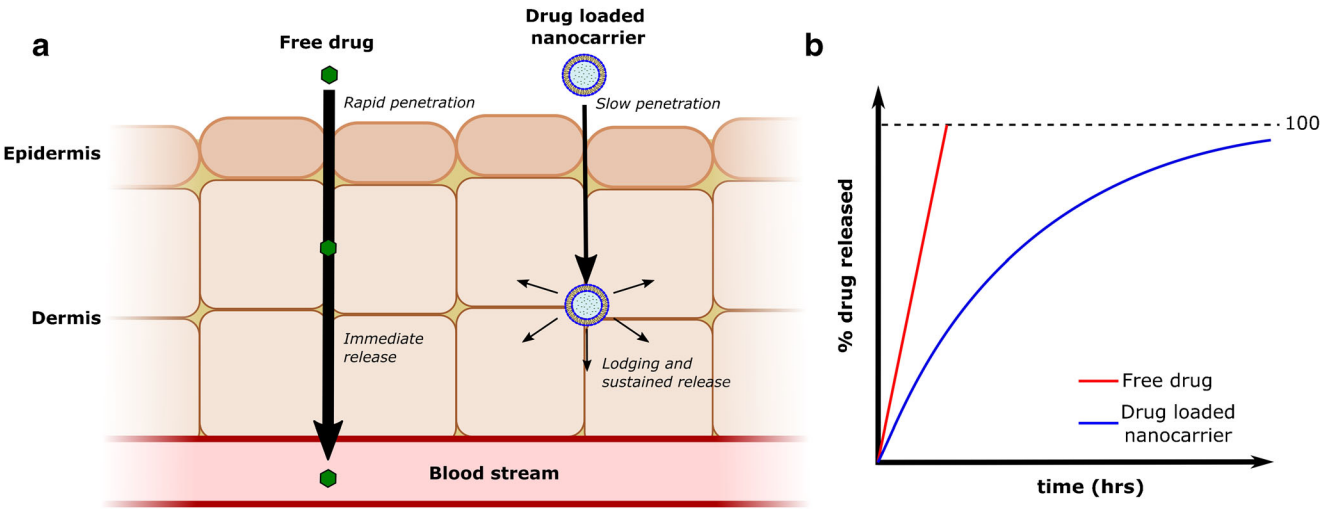


**Fig. 2** Drug penetration and release for free drug and drug loaded in a nanocarrier. **a** Free drug penetrates the skin and is immediately released. The drug then diffuses through the skin quickly, limiting skin retention and leading to unwanted absorption into the blood which increases the risk of systemic side effects. Drug-loaded nanocarriers slowly penetrate the skin; this forms a high drug concentration gradient at the skin surface, slowly driving the drug into the skin. Once in the skin, the nanocarrier can lodge in the lipid matrix and slowly release the included drug leading to increased drug retention in the skin. **b** Graphical depiction of fast drug release with free drug compared to slower, sustained release from drug-loaded nanocarriers

gel resulted in the most orthokeratosis, followed by the tretinoin-SLN–loaded, tretinoin-ethosome–loaded, and Retino A® gels. These results follow the skin retention studies indicating the importance of carriers being able to form drug reservoirs in the skin. Retino A® caused high inflammation and the ethosome-loaded gel caused mild inflammation while the NLC-, SLN-, and liposome-loaded gels showed no inflammation. These results suggest that encapsulation of tretinoin within phospholipid carriers can reduce its irritation potential but the ethanol in ethosomes may be irritating [12•].

Hashim et al. made acitretin-loaded niosomes (Table 1) with sorbitan monostearate, a non-ionic surfactant, and cholesterol [24]. The niosomes were incorporated into a hydroxypropylmethyl cellulose gel to increase residence time on the skin. After 4 weeks of daily treatments to murine tails, the acitretin-niosome–loaded gel resulted in greater induction of orthokeratosis and reduction in epidermal thickness compared to a commercial tazarotene gel (Zarotex®) and free acitretin. The acitretin-niosome–loaded gel did not cause any skin irritation whereas Zarotex® and free acitretin resulted in moderate and severe skin irritation, respectively. Permeation of acitretin though murine skin samples was assessed with a Franz diffusion cell experiment and the amount of acitretin remaining in the samples was analyzed spectrophotometrically to determine drug retention. Higher acitretin permeation and retention was observed with the niosome-loaded gel than free acitretin. Specifically, higher acitretin permeation was seen with increasing cholesterol inclusion, suggesting that the high cholesterol content of niosomes contributes to their anti-psoriatic efficacy, possibly due to cholesterol's ability to fill spaces in niosomes' bilayers to prevent drug leakage [24, 59].

## Anthralin (Dithranol)

Anthralin is an effective topical psoriasis treatment that inhibits keratinocyte hyperproliferation and T cell activation [2, 60, 61]. Yet, it is not widely used because it requires frequent dosing and can cause erythema, peeling, and staining of surrounding skin and clothes, especially when anthralin is left on the skin for more than 2 h [2]. Encapsulating anthralin within nanocarriers could reduce these negative side effects.

Raza et al. developed emulsomes including anthralin and incorporated them into a Carbopol® hydrogel for easy application [38]. Anti-psoriatic activity was assessed by comparing the percent of orthokeratosis induced in murine tails. The anthralin-emulsome–loaded gel resulted in higher orthokeratosis (52%) compared to a commercial dithranol ointment (Derobin®, 41%) after 3 weeks of daily treatment. The anthralin-emulsome–loaded gel did not lead to any erythema whereas Derobin® caused pronounced inflammation. The superior efficacy of the anthralin-emulsome–loaded gel was attributed to its high phospholipid content given increasing anthralin retention, measured spectrophotometrically after the anthralin-emulsomes diffused through murine skin samples, was observed with increasing phospholipid content [38].

## Tacrolimus

Psoriasis can also be treated by reducing T cell activation with tacrolimus, a topical calcineurin inhibitor that blocks the transcription of interleukins 2 through 5, interferon-$\gamma$, and TNF-$\alpha$ [62]. Given tacrolimus causes less atrophy than steroids, it is useful for facial and intertriginous psoriasis [2]. However, tacrolimus can cause burning and itching and its high molecular weight limits its skin penetration [2, 63]. Encapsulation of tacrolimus within nanocarriers could decrease its irritation potential and enhance its penetration into the skin.

Wan et al. created micellar nanocarriers made of amphipathic hyaluronic acid-cholesterol conjugates with tacrolimus and nicotinamide (NIC) within their hydrophobic core [9]. Nicotinamide was included because is hydrotropic, meaning it increases the solubility of tacrolimus [64]. Franz diffusion cell permeation studies were done with murine skin followed by retention studies where tacrolimus remaining in the skin sample was measured using HPLC. The tacrolimus-NIC-NPs demonstrated higher permeation and retention than the tacrolimus-NPs and a tacrolimus-NIC suspension. The lowest permeation and retention were seen with a commercial tacrolimus ointment (Protopic®). Using an imiquimod-induced psoriasis murine model and PASI scoring (see the "Retinoids" section), 10-day use of the tacrolimus-NIC-NPs produced similar efficacy to clobetasol propionate cream and superior efficacy to Protopic®. When encapsulated in micellar NPs, tacrolimus improved psoriasis symptoms to a similar degree as clobetasol [2, 9].

## Phototherapy

Phototherapy is the regular exposure to UVB light alone or UVA light with oral or topical psoralen (PUVA therapy), which is added to sensitize cells to the effects of UVA light [3]. UV light inhibits epidermal keratinocyte proliferation and angiogenesis and is locally immunosuppressive to Langerhans cells and cytokines in the skin [3, 65, 66]. PUVA therapy is efficacious for psoriasis but topical psoralen can cause erythema, pruritus, and xerosis [3, 67]. Incorporation of psoralen into nanocarriers could protect the surrounding healthy skin from these side effects.

Zhang et al. created psoralen-loaded anionic (including egg lecithin [EL]) and cationic (including DC-cholesterol-hydrochloride [DC-Chol]) liposomes and dispersed the

carriers into a hydroxypropyl methylcellulose gel [17]. DC-Chol was used because it has been shown to increase the fluidity of liposomes' bilayers [17] and EL was chosen because it strongly interacts with the stratum corneum; both of these factors could increase carrier penetration [68]. Efficacy studies were done in an imiquimod-induced psoriasis murine model after 3 days of topical treatments followed by 30 s of UVA irradiation. The psoralen-anionic and cationic liposome–loaded gels led to greater reductions in thickness and scaling compared to a psoralen solution and betamethasone valerate 0.1% ointment (BMV) but erythema reduction was similar among all treatment groups. Both the psoralen-liposome–loaded gels and BMV produced similar improvements in histologic features of psoriasis (hyperkeratosis, parakeratosis, and acanthosis). No signs of skin irritation were seen after exposure to all the treatments. The psoralen-liposomes produced similar efficacy to BMV and superior efficacy to a psoralen solution; however, the ability of liposomes to decrease psoralen's local side effects could not be assessed given all treatment groups were free of irritation [17].

## Cyclosporine

Similar to tacrolimus, oral cyclosporine is used in psoriasis to decrease T cell proliferation [5]. Oral cyclosporine results in high remission rates similar to biologics [69], but can cause nephrotoxicity and hypertension [5]. Topical cyclosporine was developed to reduce these toxicities but it failed to yield a therapeutic effect [70] due to cyclosporine's high molecular weight and low aqueous solubility, which limit its skin penetration [14••].

To increase topical cyclosporine absorption, Kumar et al. created cyclosporine-loaded liposomes and dispersed these carriers into a Carbopol® hydrogel (termed a lipogel). Efficacy was studied in a double-blind, randomized controlled trial of 38 patients with psoriasis [14••]. After 14 weeks of daily application, 90% of the cyclosporine-lipogel–treated sites showed greater than 90% clearance and 41% of sites showed complete clearance, which was lower than treatment with clobetasol propionate 0.05% cream (complete clearance in 86% of sites). A free cyclosporine cream did not significantly decrease erythema, scaling, and thickness of treated sites after 14 weeks of treatment. Based on blood sampling, no systemic cyclosporine absorption was observed with lipogel use and only mild erythema and dryness were seen in 3 out of 34 lipogel-treated sites. However, systemic absorption and irritation potential were not assessed with free cyclosporine so the differences between free and liposome-loaded drug cannot be assessed. These results suggest that inclusion in liposomes does help cyclosporine penetrate the skin, but cyclosporine's efficacy is lower than that of clobetasol at the assessed doses [14••].

## Methotrexate

Methotrexate is an oral psoriasis treatment that decreases the proliferation of lymphoid cells by inhibiting dihydrofolate reductase, which prevents the synthesis of folate cofactors necessary for nucleic acid production [5, 71]. Utilization of topical methotrexate has been considered since oral use can cause hepatotoxicity, pulmonary fibrosis, and bone marrow suppression, but the limited absorption of topical methotrexate results in low efficacy [5, 72, 73].

To enhance methotrexate penetration, Panonnummal and Sabitha [47] examined the anti-psoriatic activity of methotrexate-loaded chitin nanogels (Table 1) in an imiquimod-induced psoriasis murine model. After 3 weeks of daily treatment, the methotrexate-nanogels (100 and 150 μg/cm$^2$) led to significant reductions in PASI scores compared to a free methotrexate gel (150 μg/cm$^2$). Skin permeation was measured with porcine ear skin using Franz diffusion cells and the amount of methotrexate remaining in the samples after diffusion was measured with HPLC. This analysis showed increased methotrexate skin permeation and retention with the nanogels compared to free methotrexate gel. The authors attributed the superior efficacy of methotrexate-nanogels to this enhanced penetration and retention. The positively charged, hydrophobic nanogels likely increased interaction with anionic skin lipids and hydrophobic skin keratinocytes, improving methotrexate retention and increasing efficacy at lower doses than free methotrexate [47].

Additionally, Panonnummal et al. compared oral methotrexate-loaded chitin nanogels (2.7 and 5.1 mg/kg) to free oral methotrexate (5.1 mg/kg) using the same imiquimod-induced psoriasis murine model [48•]. The methotrexate-nanogels at both doses and free methotrexate similarly decreased PASI scores and normalized histology to that of controls after 3 weeks of weekly treatments. The free methotrexate led to liver and lung toxicity after 12 weeks whereas the 2.7 mg/kg dose of methotrexate-nanogels did not. Therefore, the lower methotrexate-nanogel dose reached sufficient tissue levels to be efficacious without inducing systemic toxicity [48•].

## Tamoxifen

Case reports have shown improvement of psoriasis [74, 75] with tamoxifen, an estrogen receptor modulator [76], likely due to the fact that estrogen modulates the immune system leading to an overall anti-inflammatory effect [77–79]. However, oral tamoxifen is associated with increased risks of deep vein thrombosis, pulmonary embolism, and endometrial cancer [76]. Topical tamoxifen therapy has been explored to limit these toxicities, but its large size limits transdermal delivery [80]. Nanoscale delivery systems could be used to increase tamoxifen's topical absorption.

Bhatia et al. created tamoxifen-loaded transfersomes using phospholipids and Span 80® as a surfactant and incorporated these into a Carbopol® hydrogel [20]. Surfactants have been shown to make transfersomes' bilayers more flexible, enhancing skin penetration [81]. Anti-psoriatic efficacy was assessed by comparing orthokeratosis in a murine tail model. After 4 weeks of daily treatment, the tamoxifen-transfersome–loaded gel led to significantly higher orthokeratosis than a free tamoxifen gel, possibly due to the ability of phospholipid-rich transfersomes to favorably interact with skin lipids [20].

## Gene Therapy with RNA Interference

Psoriasis can also be treated by knocking down genes involved in its pathogenesis via RNA interference, which uses short interfering RNA (siRNA) to bind specific mRNAs, inhibiting their translation into proteins [41•]. When used topically, carriers are needed to protect siRNAs from nuclease degradation so they can reach their active sites past the epidermal barrier—numerous nanocarriers have been explored to fill this role [41•].

One possible RNA interference target for psoriasis treatment is human β defensin-2 (hBD-2), which is encoded by the DEFB4 gene and is upregulated in psoriatic skin [82]. Bracke et al. complexed DEFB4 siRNA to vesicular nanocarriers made with surfactant and ethanol (ethosomes termed SECosomes) [83] to create "SECoplexes" and confirmed hBD-2 knockdown with immunofluorescence analysis [22]. Efficacy testing was done in mice grafted with human skin; a psoriasis-like phenotype was induced through IL-17 and IL-22 injections. Pathological changes seen in psoriasis, rete ridge elongation and hyperkeratosis, were reduced in the SECoplex group compared to the SECosome group; however, the SECoplex-treated mice still showed moderate epidermal thickening and areas of parakeratosis. The SECoplex-treated mice also showed normalization of angiogenesis compared to the SECosome group which exhibited high numbers of CD31/ICAM-1–positive dilated epidermal blood vessels, further demonstrating improvement in psoriasis with DEFB4 siRNA [22].

Targeting the overactive immune system in psoriatic skin, Marepally et al. created polymersomes (Table 1) with novel cationic amphiphiles to carry anti-inflammatory STAT3 and TNF-α siRNAs (termed dual siRNAs) [27]. Immunoblot analysis showed that treatment with the dual siRNAs-polymersomes reduced STAT3 and TNF-α, as well as NF-κB, IL-23, and Ki-67 (markers of inflammation and proliferation) expression compared to a free dual siRNA solution. Efficacy was assessed using an imiquimod-induced psoriasis murine model after 5 days of daily treatment. Commercial tacrolimus ointment (Topgraf®) and dual siRNAs-polymersome treatment led to lower PASI scores than treatment with the free dual siRNA solution, STAT3 siRNA-polymersomes, and TNF-α siRNA-polymersomes. Authors concluded that polymersomes can carry STAT3 and TNF-α siRNAs into the skin to treat psoriasis, and that the combination of these siRNAs is superior to the use of either alone and to free dual siRNA solution [27].

Nemati et al. treated psoriasis by conjugating EGFR (epidermal growth factor receptor) siRNAs to gold nanoparticles (AuNPs, Table 1) [41•]. EGFR modifies keratinocyte immune function and regulates cell proliferation and differentiation [84, 85]. Patients with psoriasis have elevated serum EGF, a ligand for EGFR [86], correlating with disease severity [87]. Reverse transcription quantitative PCR showed that use of the EGFR siRNA-AuNPs reduced EGF and EGFR expression compared to nonsense siRNA-AuNPs. Immunohistochemistry staining also showed reduced expression of T cell markers, CD3, CD4, and CD8, with the EGFR siRNA-AuNPs compared to nonsense siRNA-AuNPs. The efficacy of these therapies mixed with Aquaphor® was tested in an imiquimod-induced psoriasis murine model after treatment three times per week for 21 days. EGFR siRNA-AuNP application reduced epidermal thickness but no change was seen with free EGFR siRNA. These results suggest that the topical EGFR siRNA-AuNPs improved psoriasis by altering gene expression and decreasing T cell production [41•].

## Complementary and Alternative Medications

Complementary medicine is the use of non-conventional therapies with traditional medications and alternative medicine is the use of these non-conventional therapies instead of other medications [88]. Incorporation of alternative psoriasis therapies within nanocarriers has also been explored.

Chamcheu et al. used chitosan-based solid polymeric nanoparticles (SPNPs, Table 1) to encapsulate green tea polyphenol, (−)-epigallocatechin-3-gallate (EGCG) [43]. EGCG has been shown to normalize epidermal differentiation [89] and reduce psoriasis symptoms in a murine model [90]. However, the low stability and bioavailability of EGCG hinder its efficacy [91]. In an imiquimod-induced psoriasis murine model, use of the EGCG-SPNPs improved erythema, scaling, and thickness compared to free EGCG after 2 weeks of daily treatment [43]. Further, immunohistochemistry analysis showed that EGCG-SPNP treatment reduced levels of mast cells, neutrophils, macrophages, and CD4+ T cells to a greater extent than free EGCG, and that both EGCG formulations reduced levels of the proliferation marker, Ki67. The increased anti-inflammatory effect of EGCG-SPNPs likely contributed to their enhanced efficacy compared to free EGCG [43].

Another oral and topical alternative therapy is curcumin, an anti-inflammatory phytochemical found in turmeric [88]. However, topical use is limited by curcumin's poor absorption and esthetically unappealing color [88]. Mao et al. developed

solid polymeric nanoparticles composed of a novel amphiphilic polymer and loaded with curcumin to overcome its limited stratum corneum penetration [44]. The SPNPs were incorporated into a silk fibroin gel, which has demonstrated sustained release of incorporated drugs [92]. The curcumin-SPNP–loaded gel demonstrated greater reductions in PASI scores (see the "Retinoids" section) in an imiquimod-induced psoriasis murine model compared to free curcumin-SPNPs. The occlusive nature of the silk fibroin gel increases curcumin contact time with the skin, which may explain its additional benefit. Curcumin release was also compared using a dialysis method; both free SPNPs and the SPNP-loaded gel exhibited prolonged curcumin release compared to free drug. The SPNP-loaded gel slowed release even more than the free SPNPs, suggesting that the prolonged curcumin release from the SPNP-loaded gel may also contribute to its superior efficacy. Despite these successful results, treatment with clobetasol propionate 0.05% ointment produced greater improvements in PASI symptoms than the curcumin-SPNP-loaded gel [44].

Beyond these alternative therapies, another study used *Aloe vera* extract, aloe emodin, as a complementary therapy with the retinoid, acitretin. Divya et al. developed chitin nanogels loaded with acitretin (Act) or aloe emodin (AE) [46•]. Efficacy was studied in a murine tail model after 30 days of daily treatment. Use of the Act nanogels and AE nanogels together resulted in 86% reduction in epidermal thickness, which was similar to tacrolimus 0.1% cream (87%) and greater than the separate use of these nanogels (69% for Act nanogels, 56% for AE nanogels). Therefore, the combination of acitretin and aloe emodin nanogels is a potential complementary psoriasis therapy resulting in similar efficacy to tacrolimus [46•].

## Conclusions

Nanotechnology offers promising drug delivery systems to improve topical and oral psoriasis treatments. The pathophysiology of psoriasis results in epidermal thickening, which creates an additional barrier for topical therapies. Oral and injectable treatments can easily bypass this blockade but are prone to systemic toxicities. While nanoscale carriers show promise for psoriasis therapy, more research is needed. Many studies merely characterize nanocarriers or examine skin penetration rather than anti-psoriatic efficacy. Furthermore, only a few efficacy studies have been performed in humans. Although mouse models provide insight, these may not be generalizable to humans as psoriasis does not occur naturally in mice and must be induced by imiquimod or proxies for psoriasis efficacy must be used. In addition, more research is needed on how to choose the best nanocarrier for a desired drug since most studies compare nanocarriers to commercial products rather than to other carriers. The few studies comparing nanocarriers against each other showed potential superiority of liposomes and NLCs over SLNs, ethosomes, and transfersomes [12•, 13], but these results may be drug specific. More information is also needed on the required doses of drugs included in nanocarriers; while nanocarriers have the potential to reduce drug doses used, most studies only examine efficacy at one dose rather than comparing results of a range of doses. Finally, while many studies show the short-term safety of nanocarriers, we do not know the long-term effects of using these nanosized medications.

Despite limitations of the current literature, there is evidence highlighting the potential of nanoscale drug delivery systems for psoriasis therapy. Two small randomized, controlled trials showed the ability of phospholipid-based vesicular systems to improve efficacy of their encapsulated drugs compared to commercial formulations of the same drugs without causing cutaneous reactions or systemic absorption [13••, 14••, 48••]. Many other studies showed similar results in animal models indicating that nanocarriers may be able to enhance efficacy of their incorporated drugs through increased skin retention and sustained drug release. Decreased drug absorption into the blood may also limit systemic toxicities. Numerous trials also showed the success of topically applied siRNAs, possibly allowing the expansion of therapeutic targets to any gene involved in the pathogenesis of psoriasis along with the personalization of psoriasis therapy [22, 27, 41•]. While individual characterization of nanocarriers has demonstrated their benefits for treating psoriasis, more research is needed to optimize and commercialize these therapies for clinical use.

## Compliance with Ethical Standards

**Conflict of Interest** The authors of this paper have no conflicts of interest to declare.

**Human and Animal Rights** This article does not contain any studies with human or animal subjects performed by any of the authors.

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

## References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Parisi R, Symmons DP, CEM G, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Investig Dermatol. 2012;133:377.

2. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol. 2009;60:643–59.
3. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 5. Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy. J Am Acad Dermatol. 2010;62:114–35.
4. Rønholt K, Iversen L. Old and new biological therapies for psoriasis. Int J Mol Sci. 2017;18:E2297. https://doi.org/10.3390/ijms18112297.
5. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol. 2009;61:451–85.
6. David Schairer MD, Jason Chouake MD, Adnan Nasir MD, Adam Friedman MD, Jason Chouake MD, Adnan Nasir MD, et al. Nanotechnology applications in dermatology. Clin Nanomed Handb. 2013;89(1):126–36. https://doi.org/10.1201/b15642-6.
7. Garg. Nanotechnological approaches for the effective management of psoriasis. Artif Cells Nanomed Biotechnol. 2016;44:1374–82.
8. Rahman. Nanomedicine-based drug targeting for psoriasis: potentials and emerging trends in nanoscale pharmacotherapy. Expert Opin Drug Deliv. 2015;12:635–52.
9. Wan T, Pan W, Long Y, Yu K, Liu S, Ruan W, et al. Effects of nanoparticles with hydrotropic nicotinamide on tacrolimus: permeability through psoriatic skin and antipsoriatic and antiproliferative activities. Int J Nanomed. 2017;12:1485–97.
10. Farokhzad OC, Langer R. Impact of nanotechnology on drug delivery. ACS Nano. 2009;3:16–20.
11. de Leeuw J, de Vijlder HC, Bjerring P, Neumann H a M. Liposomes in dermatology today. J Eur Acad Dermatol Venereol. 2009;23:505–16.
12.• Raza K, Singh B, Lohan S, Sharma G, Negi P, Yachha Y, et al. Nano-lipoidal carriers of tretinoin with enhanced percutaneous absorption, photostability, biocompatibility and anti-psoriatic activity. Int J Pharm. 2013;456:65–72 **Compared skin retention and anti-psoriatic efficacy of tretinoin-loaded liposomes, ethosomes, solid lipid nanoparticles, and nanostructured lipid carriers in a murine model. This is one of the few studies comparing carriers against each other rather than to marketed products. The liposomes and nanostructured lipid carriers led to the highest tretinoin skin retention and efficacy**.
13.•• Abdelgawad R, Maha N, Mofta N, Hamza M. Phospholipid membrane tubulation using ceramide doping "cerosomes": characterization and clinical application in psoriasis treatment. Eur J Pharm Sci : official journal of the European Federation for Pharmaceutical Sciences. 2017;101:258–68 **Vesicular carriers including both tazarotene and ceramide improved psoriasis symptoms more than both commercial tazarotene gel and tazarotene-loaded vesicular carriers without ceramides in a randomized, controlled trial with 20 patients. This is one of the few trials with human participants.**
14.•• Kumar R, Dogra S, Amarji B, Singh B, Kumar S, null S, et al. Efficacy of novel topical liposomal formulation of cyclosporine in mild to moderate stable plaque psoriasis: a randomized clinical trial. JAMA Dermatol. 2016;152:807–15 **Cyclosporine-loaded liposomes were used to treat 38 patients in this double-blind, randomized controlled trial. Cyclosporine-liposomes resulted in higher plaque clearance than a commercial cyclosporine cream but lower clearance than clobetasol propionate. No systemic cyclosporine absorption was detected with blood sampling in patients treated with cyclosporine-liposomes.**
15. Doppalapudi S, Jain A, Chopra DK, Khan W. Psoralen loaded liposomal nanocarriers for improved skin penetration and efficacy of topical PUVA in psoriasis. Eur J Pharm Sci. 2017;96:515–29.
16. Anderson M, Omri A. The effect of different lipid components on the in vitro stability and release kinetics of liposome formulations. Drug Delivery. 2004;11:33–9.
17. Zhang Y-T, Shen L-N, Zhao J-H, Feng N-P. Evaluation of psoralen ethosomes for topical delivery in rats by using in vivo microdialysis. Int J Nanomedicine. 2014;9:669–78.
18. Patel R, Singh SK, Singh S, Sheth N, Gendle R. Development and Characterization of Curcumin Loaded Transfersome for Transdermal Delivery. J Pharm Sci Res. 2009;1(4):71–80.
19. Abdelbary A, AbouGhaly M. Design and optimization of topical methotrexate loaded niosomes for enhanced management of psoriasis: application of Box–Behnken design, in-vitro evaluation and in-vivo skin deposition study. Int J Pharm. 2015;485:235–43.
20. Bhatia A, Singh B, Wadhwa S, Raza K, Katare OP. Novel phospholipid-based topical formulations of tamoxifen: evaluation for antipsoriatic activity using mouse-tail model. Pharm Dev Technol. 2014;19(2):160–3.
21. Khandavilli S, Panchagnula R. Nanoemulsions as versatile formulations for paclitaxel delivery: peroral and dermal delivery studies in rats. J Investig Dermatol. 2007;127:154–62.
22. Bracke S, Carretero M, Guerrero-Aspizua S, Desmet E, Illera N, Navarro M, et al. Targeted silencing of DEFB4 in a bioengineered skin-humanized mouse model for psoriasis: development of siRNA SECosome-based novel therapies. Exp Dermatol. 2014;23:199–201.
23. Namdeo A, Jain N. Niosomes as drug carriers. Indian J Pharm Sci. 1996;58:41–6.
24. Abu Hashim II, Abo El-Magd NF, El-Sheakh AR, Hamed MF, Abd El-Gawad AE-GH. Pivotal role of Acitretin nanovesicular gel for effective treatment of psoriasis: ex vivo-in vivo evaluation study. Int J Nanomed. 2018;13:1059–79.
25. Letchford K, Burt H. A review of the formation and classification of amphiphilic block copolymer nanoparticulate structures: micelles, nanospheres, nanocapsules and polymersomes. Eur J Pharm Biopharm. 2007;65:259–69.
26. Photos PJ, Bacakova L, Discher B, Bates FS, Discher DE. Polymer vesicles in vivo: correlations with PEG molecular weight. J Control Release. 2003;90:323–34.
27. Marepally S, Boakye CHA, Patel AR, Godugu C, Doddapaneni R, Desai PR, et al. Topical administration of dual siRNAs using fusogenic lipid nanoparticles for treating psoriatic-like plaques. Nanomedicine (London). 2014;9:2157–74.
28. Thakur A, Walia MK, Kumar SLH. Nanoemulsion in enhancement of bioavailability of poorly soluble drugs: a review. Pharmacophore. 2013;4(1):15–25.
29. Musa SH, Basri M, Fard Masoumi HR, Shamsudin N, Salim N. Enhancement of physicochemical properties of nanocolloidal carrier loaded with cyclosporine for topical treatment of psoriasis: in vitro diffusion and in vivo hydrating action. Int J Nanomedicine. 2017;12:2427–41.
30.• Kaur A, Katiyar SS, Kushwah V, Jain S. Nanoemulsion loaded gel for topical co-delivery of clobitasol propionate and calcipotriol in psoriasis. Nanomedicine. 2017;13:1473–82 **Examined efficacy of a nanogel including both clobetasol propionate and calcipotriol highlighting the ability to combine multiple drugs in nanocarriers. The drug-loaded nanogel led to increased drug retention and anti-psoriatic efficacy compared to free drugs**.
31. Hemmila MR, Mattar A, Taddonio MA, Arbabi S, Hamouda T, Ward PA, et al. Topical nanoemulsion therapy reduces bacterial wound infection and inflammation after burn injury. Surgery. 2010;148:499–509.
32. Alam MS, Ali MS, Alam N, Siddiqui MR, Shamim M, Safhi MM. In vivo study of clobetasol propionate loaded nanoemulsion for

topical application in psoriasis and atopic dermatitis. Drug Invention Today. 2013;5:8–12.
33. Küchler S, Herrmann W, Panek-Minkin G, Blaschke T, Zoschke C, Kramer KD, et al. SLN for topical application in skin diseases—characterization of drug-carrier and carrier-target interactions. Int J Pharm. 2010;390:225–33.
34. Morganti P. Use and potential of nanotechnology in cosmetic dermatology. Clinical, cosmetic and investigational dermatology : CCID. 2010;3:5–13.
35. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery—a review of the state of the art. Eur J Pharm Biopharm. 2000;50:161–77.
36. Fang C-L, Al-Suwayeh SA, Fang J-Y. Nanostructured lipid carriers (NLCs) for drug delivery and targeting. Recent Pat Nanotechnol. 2013;7:41–55.
37. Agrawal U, Gupta M, Vyas SP. Capsaicin delivery into the skin with lipidic nanoparticles for the treatment of psoriasis. Artificial Cells, Nanomedicine, And Biotechnology. 2015;43:33–9.
38. Raza K, Katare O, Setia A, Bhatia A, Singh B. Improved therapeutic performance of dithranol against psoriasis employing systematically optimized nanoemulsomes. J Microencapsul. 2013;30:225–36.
39. Zhou X, Chen Z. Preparation and performance evaluation of emulsomes as a drug delivery system for silybin. Arch Pharm Res. 2015;38:2193–200.
40. Bessar H, Venditti I, Benassi L, Vaschieri C, Azzoni P, Pellacani G, et al. Functionalized gold nanoparticles for topical delivery of methotrexate for the possible treatment of psoriasis. Colloids Surf B: Biointerfaces. 2016;141:141–7.
41.• Nemati H, Ghahramani M-H, Faridi-Majidi R, Izadi B, Bahrami G, Madani S-H, et al. Using siRNA-based spherical nucleic acid nanoparticle conjugates for gene regulation in psoriasis. J Control Release. 2017;268:259–68 **EGFR siRNA was conjugated to gold nanoparticles and efficacy was examined in an imiquimod-induced murine model. Use of the EGFR siRNA-AuNPs led to reduced T cell markers and epidermal thickness compared to nonsense siRNA-AuNPs and free EGFR siRNA, respectively. This highlights the success of siRNA treatment for psorasis, meaning that many other genes involved in psoriasis could also be targeted.**
42. Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE. Biodegradable polymeric nanoparticles as drug delivery devices. J Control Release. 2001;70:1–20.
43. Chamcheu JC, Siddiqui IA, Adhami VM, Esnault S, Bharali DJ, Babatunde AS, et al. Chitosan-based nanoformulated (−)-epigallocatechin-3-gallate (EGCG) modulates human keratinocyte-induced responses and alleviates imiquimod-induced murine psoriasiform dermatitis. Int J Nanomedicine. 2018;13:4189–206.
44. Mao K-L, Fan Z-L, Yuan J-D, Chen PP, Yang JJ, Xu J, et al. Skin-penetrating polymeric nanoparticles incorporated in silk fibroin hydrogel for topical delivery of curcumin to improve its therapeutic effect on psoriasis mouse model. Colloids Surf B: Biointerfaces. 2017;160:704–14.
45. Kabanov AV, Vinogradov SV. Nanogels as pharmaceutical carriers: finite networks of infinite capabilities. Angew Chem Int Ed. 2009;48:5418–29.
46.• Divya G, Panonnummal R, Gupta S, Jayakumar R, Sabitha M. Acitretin and aloe-emodin loaded chitin nanogel for the treatment of psoriasis. Eur J Pharm Biopharm. 2016;107:97–109 **Created nanogels loaded with acitretin and a complementary therapy, aloe-emodin (an *Aloe vera* extract). Application of these two nanogels produced greater efficacy than a commercial tacrolimus cream showing that you can also apply multiple nanocarrier formulations, in addition to combining multiple drugs within a nanocarrier.**
47. Panonnummal R, Sabitha M. Anti-psoriatic and toxicity evaluation of methotrexate loaded chitin nanogel in imiquimod induced mice model. Int J Biol Macromol. 2018;110:245–58.
48.• Panonnummal R, Jayakumar R, Anjaneyan G, Sabitha M. In vivo anti-psoriatic activity, biodistribution, sub-acute and sub-chronic toxicity studies of orally administered methotrexate loaded chitin nanogel in comparison with methotrexate tablet. Int J Biol Macromol. 2018;110:259–68 **A lower dose of oral methotrexate included in chitin nanogels reduced psoriasis symptoms in a murine model without causing liver and lung toxicities that were seen with higher doses of methotrexate nanogels and free methotrexate.**
49. Monteiro-Riviere NA. Skin penetration of engineered nanomaterials. In: Nasir A, Friedman A, Wang S, editors. Nanotechnology in dermatology. New York, NY: Springer New York; 2013. p. 51–61.
50. Siddique MI, Katas H, Amin MCIM, Ng S-F, Zulfakar MH, Jamil A. In-vivo dermal pharmacokinetics, efficacy, and safety of skin targeting nanoparticles for corticosteroid treatment of atopic dermatitis. Int J Pharm. 2016;507:72–82.
51. Wohlrab J, Goebel A, Scherer D, Bingham D, Newbert R A topical tacrolimus microemulsion for plaque-type psoriasis therapy. Drug Development & Delivery. 2012; June.
52. Chlapanidas T, Perteghella S, Leoni F, Faragò S, Marazzi M, Rossi D, et al. TNF-α blocker effect of naringenin-loaded sericin microparticles that are potentially useful in the treatment of psoriasis. Int J Mol Sci. 2014;15:13624–36.
53. Krueger G, Ellis CN. Psoriasis—recent advances in understanding its pathogenesis and treatment. J Am Acad Dermatol. 2005;53:S94–S100.
54. Katz HI, Waalen J, Leach EE. Acitretin in psoriasis: an overview of adverse effects. J Am Acad Dermatol. 1999;41:S7–S12.
55. Draelos ZD. Enhancement of topical delivery with Nanocarriers. In: Nasir A, Friedman A, Wang S, editors. Nanotechnology in dermatology. New York, NY: Springer New York; 2013. p. 87–93.
56. Cho Y, Lew B-L, Seong K, Kim N-I. An inverse relationship between ceramide synthesis and clinical severity in patients with psoriasis. J Korean Med Sci. 2004;19:859–63.
57. Lew B-L, Cho Y, Kim J, Sim W-Y, Kim N-I. Ceramides and cell signaling molecules in psoriatic epidermis: reduced levels of ceramides, PKC-α, and JNK. J Korean Med Sci. 2006;21:95–9.
58. Tokudome Y, Saito Y, Sato F, Kikuchi M, Hinokitani T, Goto K. Preparation and characterization of ceramide-based liposomes with high fusion activity and high membrane fluidity. Colloids Surf B: Biointerfaces. 2009;73:92–6.
59. Agarwal R, Katare O, Vyas S. Preparation and in vitro evaluation of liposomal/niosomal delivery systems for antipsoriatic drug dithranol. Int J Pharm. 2001;228:43–52.
60. Painsi C, Patscheider M, Inzinger M, Huegel R, Lange-Asschenfeldt B, Quehenberger F, et al. Psoriasis area and severity index 75 rate of classical inpatient dithranol therapy under daily life conditions. Br J Dermatol. 2015;173:815–7.
61. Kemény L, Ruzicka T, Braun-Falco O. Dithranol: a review of the mechanism of action in the treatment of psoriasis vulgaris. Skin Pharmacol. 1990;3:1–20.
62. Assmann T, Ruzicka T. New immunosuppressive drugs in dermatology (mycophenolate mofetil, tacrolimus): unapproved uses, dosages, or indications. Clin Dermatol. 2002;20:505–14.
63. Zonneveld IM, Rubins A, Jablonska S, Dobozy A, Ruzicka T, Kind P, et al. Topical tacrolimus is not effective in chronic plaque psoriasis. A pilot study. Arch Dermatol. 1998;134:1101–2.
64. Pan W, Qin M, Zhang G, Long Y, Ruan W, Pan J, et al. Combination of hydrotropic nicotinamide with nanoparticles for enhancing tacrolimus percutaneous delivery. Int J Nanomedicine. 2016;Volume 11:4037–50. https://doi.org/10.2147/IJN.S108545.

65. Lui H. Phototherapy of psoriasis: update with practical pearls. J Cutan Med Surg. 2002;6:17–21.
66. Zanolli M. Phototherapy treatment of psoriasis today. J Am Acad Dermatol. 2003;49:78–86.
67. Stern RS. The risk of squamous cell and basal cell cancer associated with psoralen and ultraviolet a therapy: a 30-year prospective study. J Am Acad Dermatol. 2012;66:553–62.
68. Shaikh IM, Jadhav KR, Kadam VJ. Lecithin organogels in enhancing skin delivery of drugs. In: Dragicevic N, Maibach HI, editors. Percutaneous penetration enhancers chemical methods in penetration enhancement: drug manipulation strategies and vehicle effects. Berlin, Heidelberg: Springer Berlin Heidelberg; 2015. p. 299–313.
69. Maza A, Montaudié H, Sbidian E, Gallini A, Aractingi S, Aubin F, et al. Oral cyclosporin in psoriasis: a systematic review on treatment modalities, risk of kidney toxicity and evidence for use in non-plaque psoriasis. J Eur Acad Dermatol Venereol. 2011;25(Suppl 2):19–27.
70. Griffiths CE. Systemic and local administration of cyclosporine in the treatment of psoriasis. J Am Acad Dermatol. 1990;23:1242–6 discussion 1246-1247.
71. Jeffes EW, McCullough JL, Pittelkow MR, McCormick A, Almanzor J, Liu G, et al. Methotrexate therapy of psoriasis: differential sensitivity of proliferating lymphoid and epithelial cells to the cytotoxic and growth-inhibitory effects of methotrexate. J Invest Dermatol. 1995;104:183–8.
72. McCullough JL, Snyder DS, Weinstein GD, Friedland A, Stein B. Factors affecting human percutaneous penetration of methotrexate and its analogues in vitro. J Investig Dermatol. 1976;66:103–7.
73. Stewart WD, Wallace SM, Runikis JO. Absorption and local action of methotrexate in human and mouse skin. Arch Dermatol. 1972;106:357–61.
74. Boyd AS, King LE. Tamoxifen-induced remission of psoriasis. J Am Acad Dermatol. 1999;41:887–9.
75. Ferrari VD, Jirillo A. Psoriasis and tamoxifen therapy: a case report. Tumori. 1996;82:262–3.
76. Maximov PY, Lee TM, Jordan VC. The discovery and development of selective estrogen receptor modulators (SERMs) for clinical practice. Curr Clin Pharmacol. 2013;8:135–55.
77. Boyd AS, Morris LF, Phillips CM, Menter MA. Psoriasis and pregnancy: hormone and immune system interaction. Int J Dermatol. 1996;35:169–72.
78. Raghunath RS, Venables ZC, Millington GWM. The menstrual cycle and the skin. Clin Exp Dermatol. 2015;40:111–5.
79. Cunningham M, Gilkeson G. Estrogen receptors in immunity and autoimmunity. Clin Rev Allergy Immunol. 2011;40:66–73.
80. Zhao K, Singh S, Singh J. Effect of menthone on the in vitro percutaneous absorption of tamoxifen and skin reversibility. Int J Pharm. 2001;219:177–81.
81. Raza K, Singh B, Mahajan A, Negi P, Bhatia A, Katare OP. Design and evaluation of flexible membrane vesicles (FMVs) for enhanced topical delivery of capsaicin. J Drug Target. 2011;19:293–302.
82. de Jongh GJ, Zeeuwen PLJM, Kucharekova M, Pfundt R, van der Valk PG, Blokx W, et al. High expression levels of keratinocyte antimicrobial proteins in psoriasis compared with atopic dermatitis. J Invest Dermatol. 2005;125:1163–73.
83. Geusens B, Van Gele M, Braat S, De Smedt SC, Stuart MCA, Prow TW, et al. Flexible nanosomes (SECosomes) enable efficient siRNA delivery in cultured primary skin cells and in the viable epidermis of ex vivo human skin. Adv Funct Mater. 2010;20:4077–90.
84. Schneider MR, Werner S, Paus R, Wolf E. Beyond wavy hairs: the epidermal growth factor receptor and its ligands in skin biology and pathology. Am J Pathol. 2008;173:14–24.
85. Johnston A, Gudjonsson JE, Aphale A, Guzman AM, Stoll SW, Elder JT. EGFR and IL-1 signaling synergistically promote keratinocyte antimicrobial defenses in a differentiation-dependent manner. J Invest Dermatol. 2011;131:329–37.
86. Anderson KS, Petersson S, Wong J, Shubbar E, Lokko NN, Carlström M, et al. Elevation of serum epidermal growth factor and interleukin 1 receptor antagonist in active psoriasis vulgaris. Br J Dermatol. 2010;163:1085–9.
87. Flisiak I, Szterling-Jaworowska M, Baran A, Rogalska-Taranta M. Effect of psoriasis activity on epidermal growth factor (EGF) and the concentration of soluble EGF receptor in serum and plaque scales. Clin Exp Dermatol. 2014;39:461–7.
88. Gamret A, Price A, Fertig RM, Lev-Tov H, Nichols AJ. Complementary and alternative medicine therapies for psoriasis: a systematic review. JAMA Dermatol. 2018;154:1330–7. https://doi.org/10.1001/jamadermatol.2018.2972.
89. Balasubramanian S, Eckert RL. Keratinocyte proliferation, differentiation, and apoptosis—differential mechanisms of regulation by curcumin, EGCG and apigenin. Toxicol Appl Pharmacol. 2007;224:214–9.
90. Hsu S, Dickinson D, Borke J, Walsh DS, Wood J, Qin H, et al. Green tea polyphenol induces caspase 14 in epidermal keratinocytes via MAPK pathways and reduces psoriasiform lesions in the flaky skin mouse model. Exp Dermatol. 2007;16:678–84.
91. Krupkova O, Ferguson SJ, Wuertz-Kozak K. Stability of (−)-epigallocatechin gallate and its activity in liquid formulations and delivery systems. J Nutr Biochem. 2016;37:1–12.
92. Elia R, Newhide DR, Pedevillano PD, Reiss GR, Firpo MA, Hsu EW, et al. Silk–hyaluronan-based composite hydrogels: a novel, securable vehicle for drug delivery. J Biomater Appl. 2011;27:749–62.