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Topical delivery for the treatment of psoriasis

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Importance of the field: Psoriasis is one of the most common human skin diseases. Topical therapy forms the cornerstone in the management of mild-to-moderate psoriasis. Topical therapies are also used as adjunctive to systemic therapy in moderate and severe forms of the disease.

Areas covered in this review: In this review, an overview of psoriasis pathogenesis, new topical medications for psoriasis, new targets and molecules, combination topical therapies and combination of topical and phototherapy is provided. Over the past decade several efficacious and acceptable treatment options have emerged from the age-old therapies. The development of sophisticated formulation options has led to an enhancement in the rate and extent of drug delivery across the skin, increasing therapeutic value and improving patient compliance.

What the reader will gain: Readers will learn about monotherapy and combination topical products as well as new topical drug delivery technology to achieve optimal clinical outcomes. This review will highlight the need to generate more dermal pharmacokinetic data for better understanding of the impact of formulation change on skin pharmacokinetics to help design improved topical drug delivery systems.

Take home message: New topical formulations have the potential to achieve better efficacy with improved safety profile.

Keywords: drug delivery, formulation, pharmacokinetics, psoriasis, topical delivery

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1. Introduction

Psoriasis is an inflammatory condition of the skin that affects 2% of the population [1]. Although it is seldom life-threatening, psoriasis is associated with a high degree of morbidity; patients are embarrassed about the appearance of their skin, and there are side effects of medications. Patients with psoriasis experience itchy, scaly, painful and disfiguring skin lesions [1]. In addition, patients with psoriasis, like those with other major medical disorders, have reduced levels of employment and income as well as a decreased quality of life [2]. The combined costs of long-term therapy and social costs of the disease have a major impact on healthcare systems and on society in general.

There are several co-morbidities that have been linked to psoriasis and it has been hypothesized that psoriasis as a disease has important systemic manifestations [1]. The shared conditions include the metabolic syndrome, depression and cancer. It is estimated that up to 80% of juvenile guttate psoriasis cases are preceded by streptococcal infections [3]. Psoriasis can also occur in association with other inflammatory diseases such as inflammatory bowel disease (Crohn's disease) [4], diabetes mellitus [4], and in association with HIV infection [5]. It is unclear whether cancer, particularly lymphoma and skin cancer, is related to the disease or its treatment [6]. Of emerging significance is the relationship between psoriasis and the risk of

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Article highlights.

- Several newer drug delivery approaches such as foam and spray have been explored. Current clinical data show that these formulation approaches have adequate efficacy and are well tolerated.
- Several active delivery approaches such as iontophoresis, electroporation and microneedles have shown promising results preclinically; however, there are very few clinical data in psoriasis patients with these delivery systems.
- New molecules such as calcineurin and PDE4 inhibitors have shown promising results in clinical trials in the treatment of psoriasis.
- Combination topical products and combination of topical therapy with phototherapy show significant advantages over monotherapy, such as better effectiveness, rapid onset of action and reduced side effects.
- A harmonized protocol and guidance for conducting skin pharmacokinetic studies in humans is required to enable thorough understanding of the bioperformance of new topical drug delivery systems as well as to enable formulation switch during clinical development.

This box summarizes key points contained in the article.

cardiovascular disease [7]. Whereas there appears to be no excess risk among patients with mild psoriasis, moderate and severe disease is associated with an excess frequency of myocardial infarction and an increase in mortality, in large part because of cardiovascular events [7]. If confirmed, these findings would have major implications for future preventive and therapeutic strategies. Drugs, stress and climate can also be predisposing factors in susceptible individuals.

Although there is no cure for psoriasis, several available treatments can minimize skin lesions and associated symptoms. Some treatments can also induce remission for months to years. The type of treatment indicated depends primarily on the severity of disease or extent of involvement, but other factors including expense, adverse-effect profile, patient preference and treatment availability are additional considerations [8,9]. Despite availability of numerous treatment options, there is a lack of patient satisfaction with the available treatments and high rates of non-compliance. To optimize topical treatment of psoriasis, guidelines have been developed for more effective management of this disease. One example is the development in Germany of evidence-based guidelines for topical treatment [10]. The guidelines focus on induction therapy in cases of mild, moderate and severe plaque-type psoriasis in adults and contain a series of therapeutic recommendations. A similar guideline is also available for systemic treatment of psoriasis [11]. A guide has also been developed to optimize and harmonize the amount of topical medications to be applied on children [12]. A study conducted in children aged between 6 months and 9 years showed that the amount of an ointment applied on children was similar to that predicted in accordance with these guidelines [12]. For treatment purposes, psoriasis can be categorized into localized and generalized forms. For localized disease, usually defined as lesions covering < 10% of their body surface area, topical therapy is usually sufficient [1]. For generalized disease, systemic therapy approaches such as UV-B phototherapy and immunotherapy are effective treatment options. In either case, the treatment plan should include obtaining rapid control of the disease and maintaining that control.

In this review, the authors provide an overview of psoriasis pathogenesis, new topical medications for psoriasis, combination topical therapies as well as combination of topical and phototherapy. Several of the well-established traditional topical medications such as coal tar, indigo and anthralin are not reviewed here. Interested readers are referred to references [8,9] for information. An overview of the topical antipsoriatic medications is summarized in **Table 1**. Most of the trade names summarized in this table and used throughout this review represent those marketed in the US only. It should be noted that these drugs might be marketed outside the US under different brand name(s). The trade names are provided only as examples and it is not the intent of this review to report exhaustively all brand names approved worldwide.

2. Pathogenesis of psoriasis

Over the years substantial data have been generated supporting the functional role of a dysregulated immune system in psoriasis [1,13]. Key processes during disease maintenance are: i) the presentation of putative autoantigens to T cells and the release of interleukin-23 by dermal dendritic cells; ii) the production of pro-inflammatory mediators such as TNF-α and nitric oxide by TNF-α and inducible nitric oxide synthase-producing dendritic cells; and iii) the production of several interleukins by Th17 and Tc17 cells as well as interferon-γ and TNF-α by Th1 and Tc1 cells. These mediators act on keratinocytes, leading to the activation, proliferation and production of antimicrobial peptides, chemokines and S100 proteins by keratinocytes [1]. Analysis of gene signatures in psoriasis has primarily shown the interplay of three predominant cytokines: type I interferons, interferon-γ and TNF-α [14]. The clinical success of anti-TNF therapy in the treatment of psoriasis has also validated further the role of these cytokines in psoriasis pathogenesis [15].

The disease is usually manifested as raised, well-demarcated, erythematous oval plaques with adherent silvery scales. The scales are a result of a hyperproliferative epidermis with premature maturation of keratinocytes and incomplete cornification with retention of nuclei in the stratum corneum [13]. The mitotic rate of the basal keratinocytes is increased as compared with that in normal skin. As a result, the epidermis is thickened, with elongated ridges; in combination with the dermal inflammatory infiltrate, this contributes to the overall thickness of lesions, which can vary between thick and thin plaques and is a distinctive trait of plaque psoriasis [16]. The inflammatory infiltrate consists mainly of dendritic cells, macrophages and

Table 1. A summary of topical medications for psoriasis.

Drug	Formulation	Disease type	Marketed products*	Ref.
Monotherapy				
Corticosteroids				
Clobetasol propionate	Ointment, spray, foam, lotion, shampoo	Plaque and scalp psoriasis	Temovate® ointment, Olux® foam, Clobex® spray	[21,22,24]
Halobetasol propionate	Ointment	Plaque psoriasis	Ultravate® ointment	[27,28]
Betamethasone	Cream, gel, lotion, foam	Plaque and scalp psoriasis	Diporsone® cream, Luxiq® foam	[33-35]
Vitamin D3 analogues				
Calcipotriol	Ointment, cream, solution	Plaque, scalp and nail psoriasis	Dovonex® ointment	[42,43]
Calcitriol	Ointment	Plaque psoriasis	Vectical® ointment	[48]
Tacalcitol	Ointment	Plaque psoriasis	Curatoderm® ointment‡	[50,51]
Retinoids				
Tazarotene	Gel, cream	Plaque psoriasis	Tazorac® gel and cream	[54,55]
Coal tar	Ointment, gel, solution, shampoo, soap	Plaque and scalp psoriasis	Exorex® lotion, Alphosyl® cream and lotion‡	[8]
Anthralin	Ointment, cream	Plaque psoriasis	Micanol® cream‡	[8]
Calcineurin inhibitors				
Tacrolimus	Ointment	Face, genitalia and intertriginous psoriasis	Protopic® ointment	[69-73]
Pimecrolimus	Cream	Intertriginous psoriasis	Elidel® cream	[74-76]
PDE4 inhibitors				
AN-2728	Ointment	Plaque psoriasis	Under clinical development	[78]
Combination product				
Calcipotriol + betamethasone dipropionate	Ointment	Plaque, scalp and nail psoriasis	Taclonex® ointment	[80-82]
Betamethasone dipropionate + salicylic acid	Ointment, cream, lotion	Plaque, scalp and nail psoriasis	Diprosalic® ointment‡	[42]

*Most of these brand names are marketed in the US only, unless otherwise indicated.
‡Not marketed in the US.

T cells in the dermis and neutrophils with some T cells in the epidermis. The redness of the lesions is due to increased numbers of tortuous capillaries that reach the skin surface through a markedly thinned epithelium. In general, psoriasis is characterized by four skin abnormalities [1,13]: redness or erythema; inflammation; hyperproliferation of the keratinocytic layer; and altered epidermal differentiation.

3. Topical antipsoriatic medications

3.1 Corticosteroids

Topical corticosteroids, particularly high-potency corticosteroids, have been a mainstay in the topical treatment of psoriasis for decades [17]. Their efficacy can be attributed to multiple mechanisms of action, including their anti-inflammatory, immunosuppressive and antiproliferative effects. Topical corticosteroids are classified into seven classes in the US and four in the UK and Germany based on potency. A detailed classification system has been discussed elsewhere [18]. In the US, topical corticosteroids are classified as follows: class I (superpotent), class II (potent), class III (upper mid strength), class IV (mid strength), class V (lower mid strength), class VI (mild) and class VII (least potent). Typically corticosteroids of lower potency are used mainly on the face and groin, and in infants and children. Mid-potency corticosteroids are typically used as initial therapy on all other areas in adults. Potent and superpotent corticosteroids are used mainly for stubborn, cutaneous plaques or lesions on the scalp, palms and/or soles as well as initial therapy to achieve quick resolution of lesions. In this section, a detailed discussion of a few steroids is provided; however, there are several other corticosteroids that are effective against psoriasis topically. Some steroids that are widely used in topical psoriasis treatment but are not discussed in this section include: methylprednisolone aceponate [19], which has

shown good efficacy against chronic therapy-resistant psoriasis, including both progressive and stationary phases; and mometasone furoate [20], which is effective in both scalp psoriasis and psoriasis vulgaris.

Although topical corticosteroids are effective in maintenance of the disease, these therapies can cause many potential adverse effects, including cutaneous atrophy, formation of telangiectasia, development of striae, steroid rosacea, perioral dermatitis, hypothalamic-pituitary-adrenal (HPA) axis suppression, skin infections, and other effects [18]. Several strategies have been proposed to improve safety for long-term use of topical corticosteroids [18], such as: i) using treatment regimens that minimize side effects; ii) combination with other topical medications; iii) following package inserts on the maximum usage per week; and iv) caution when using in vulnerable body areas (such as the face) and in children.

3.1.1 Clobetasol propionate

Clobetasol propionate is a class I high-potency glucocorticosteroid, first approved for treatment of steroid-responsive dermatosis in 1985. Clobetasol propionate is traditionally formulated in an ointment base (Temovate®, PharmaDerm, New Jersey, USA) for the treatment of psoriasis. However, several new formulations of clobetasol propionate are now available, such as spray, foam, lotion and shampoo formulations, which may provide for improved convenience and acceptance in many patients with similar efficacy, safety and tolerability as the traditional ointment and cream formulations [21]. Although there are very few direct clinical comparison studies between clobetasol propionate in different vehicles, the efficacy rates of obtaining clear or almost clear from psoriasis are high for the new formulations, with most patients achieving success after 2 – 4 weeks of treatment in well-controlled clinical trials, but the response rates are similar for all presentations. Small differences in vasoconstrictor potency or cutaneous absorption have been noted among the formulations, but the clinical significance of these observations is difficult to discern.

The development of a foam formulation of clobetasol propionate 0.05% (Olux®, Connetics Corp., North Carolina, USA) provides an effective and cosmetically appealing treatment option for patients with plaque-type psoriasis because it spreads easily and is cosmetically elegant. Olux is based on a VersaFoam® platform, a thermolabile and low-residue foam. A randomized, placebo-controlled, double-blind study of 279 patients aged 18 years or older with mild-to-moderate plaque-type psoriasis demonstrated the efficacy and tolerability of clobetasol propionate foam (**Figure 1**) [22]. After 2 weeks of twice-daily applications of clobetasol propionate foam versus vehicle foam, 68% of patients in the active treatment arm were clear of lesions versus 21% of patients receiving placebo. The treatment was well tolerated, with 5% of patients receiving clobetasol propionate foam and 7% of those receiving placebo reporting burning at the site of application. Although the efficacy of the clobetasol propionate foam can be attributed partially to patient adherence, the foam also delivers the active drug more efficiently than other formulations that have been compared. This may be owing to the easier spread of foam onto the skin. *In vitro* application of foam to donor skin resulted in higher drug accumulation and increased rate of permeation into skin layers from the foam vehicle (**Figure 2**) [23].

A study comparing two new formulations containing 0.05% clobetasol propionate, Clobex® spray (Galderma Laboratories, New Jersey, USA) and Olux foam clearly highlighted the difference in efficacy from two products containing the same active ingredient [24]. In a study of 77 randomized patients aged 18 years or older with moderate-to-severe plaque psoriasis the products were applied as per the product labeling. At the end of the treatment period (2 weeks for foam and 4 weeks for spray), patients treated with clobetasol propionate spray showed a significantly greater median reduction in affected body surface area compared with the clobetasol propionate foam. Improvements in quality of life were statistically significantly greater at all time points for patients treated with clobetasol propionate spray compared with patients treated with the foam formulation. Most adverse events for both products were mild in severity [24].

Clobex shampoo containing 0.05% clobetasol propionate is a once-daily, short-contact, shampoo treatment for moderate-to-severe scalp psoriasis [21]. The efficacy and safety of clobetasol propionate 0.05% shampoo were evaluated in a randomized, double-blind, vehicle-controlled clinical trial of 142 patients aged 12 years and older with moderate-to-severe scalp psoriasis [25]. Patients applied clobetasol propionate shampoo or vehicle shampoo once daily for 15 min for 4 weeks. Treatment success (defined as a global psoriasis rating of 'clear' or 'minimal') was obtained for 42% of patients who used clobetasol propionate shampoo versus 2% of patients who used vehicle shampoo. Recurrence of the scalp psoriasis, assessed during a 2-week follow-up period, showed that the clobetasol propionate shampoo was more effective than the vehicle shampoo in preventing recurrence after treatment was discontinued. A similar safety profile was established between the clobetasol propionate shampoo and vehicle shampoo. No skin atrophy, telangiectasia, acne or severe adverse events were noted for either treatment group [25].

3.1.2 Halobetasol propionate

Halobetasol propionate (HP) is a class I corticosteroid available as 0.05% ointment and cream. These formulations contain 6-α-fluoroclobetasol 17-propionate, a synthetic trihalogenated corticosteroid structurally similar to clobetasol propionate but with an extra fluorine atom [26].

The efficacy and safety of 0.05% halobetasol ointment (Ultravate®, Bristol Myers Squibb, New Jersey, USA) in the treatment of patients aged 18 years or older with moderate plaque psoriasis was demonstrated in two multi-center, randomized, double-blind and placebo-controlled studies in 204 patients [27]. In both studies the medication and placebo

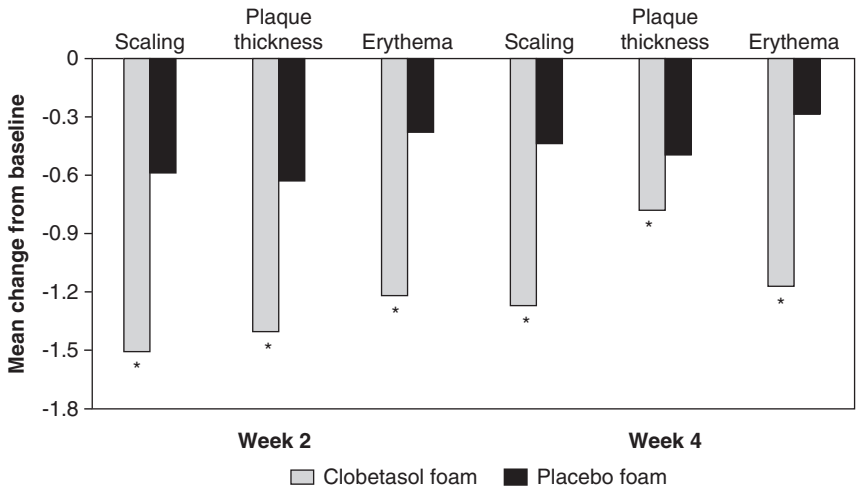

Figure 1. The individual signs of psoriasis demonstrated significant improvement with clobetasol propionate foam as compared with vehicle foam. Mean changes in scaling scores from baseline to week 2 were -1.45 in the clobetasol foam group and -0.56 in the placebo group. Mean changes in plaque thickness scores from baseline to the week 2 time point were -1.38 in the clobetasol foam group and -0.61 in the placebo group. Mean changes in erythema scores from baseline to week 2 were -1.18 in the clobetasol foam group and -0.34 in the placebo group.
Reproduced with permission from [22].

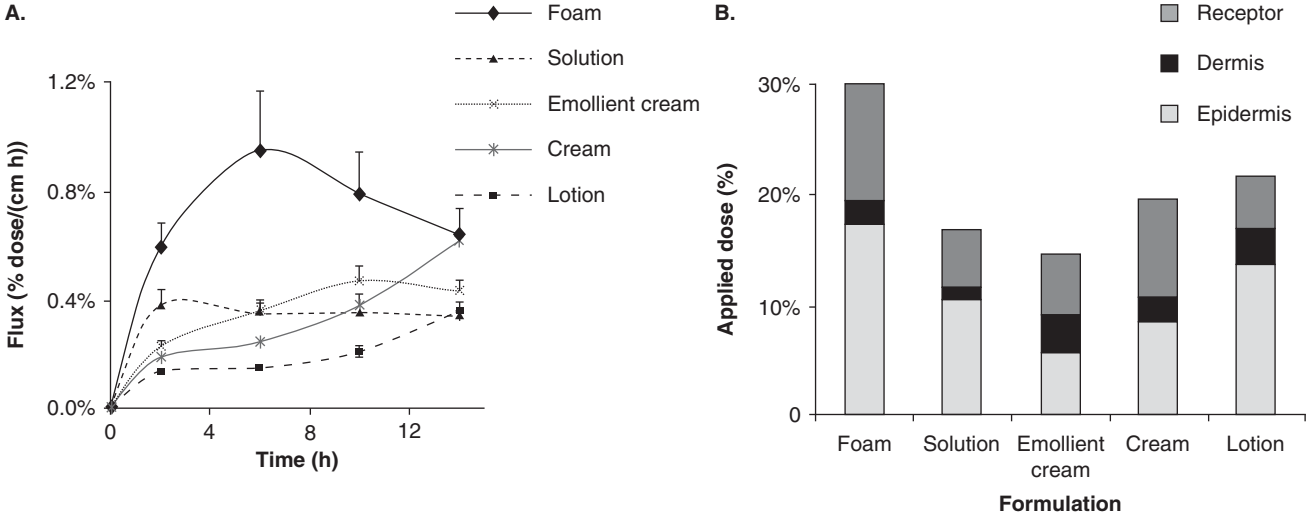

Figure 2. Foam formualtion demonstrated higher flux A. and delivered higher concentration of clobetasol propionate in the skin layers B. as compared with other formulations.
Reproduced with permission from [23].

were applied twice daily for 2 weeks. At the end of the treatment period, 0.05% halobetasol ointment was found to be more effective over placebo. No systemic adverse events or findings of skin atrophy were reported in these studies. Reports of 'stings' or 'burns' were equally divided between halobetasol formulation and its vehicle. These two studies demonstrated that 0.05% halobetasol ointment was clinically beneficial and without evidence of significant adverse events during the treatment period.

Subsequently, three studies separately compared the 0.05% halobetasol propionate ointment with 0.05% clobetasol propionate ointment [28], 0.05% betamethasone dipropionate (BDP) ointment [29] and 0.1% betamethasone valerate (BMV) ointment [30] in plaque psoriasis. The efficacy of the halobetasol propionate ointment was significantly superior to those of the other products in these studies. Neither skin atrophy nor systemic adverse effects was observed for halobetasol propionate during 4 weeks. However, because of the risks

associated with prolonged use reported in up to 13% of patients, the daily application of halobetasol propionate should be limited to a maximum of 14 days with a maximum dose of 50 g per 2 weeks [26].

3.1.3 Betamethasone

Betamethasone dipropionate is a class III mid-potency synthetic fluorinated corticosteroid and is commonly used in combination with vitamin D3 analogues [31]. Betamethasone dipropionate is commonly formulated as a gel. Several attempts have been made to increase betamethasone dipropionate skin permeation by encapsulating it in liposomes. The liposomal formulations achieved improved corticosteroid dermal delivery [32]. However, in a double-blind randomized trial comparing a liposomal formulation containing 0.039% betamethasone dipropionate against the gel containing 0.064% betamethasone dipropionate showed that the gel was more effective in reducing psoriatic plaques than the liposome after application for 14 days [33]. Hence, liposome encapsulation of betamethasone dipropionate may increase the anti-inflammatory action but not the antiproliferative effect.

Betamethasone valerate is also available as a foam (Luxiq®, Connetics Corp., North Carolina, USA) containing 0.12% betamethasone valerate for use as a treatment for psoriasis affecting the scalp [34] and non-scalp [35] regions of the body. Betamethasone valerate foam formulated in a thermolabile hydroethanolic foam vehicle is absorbed more rapidly, and demonstrated twofold greater skin penetration in a human cadaver skin model than the betamethasone valerate lotion [36]. Safety and efficacy of the betamethasone valerate foam was evaluated in a randomized, multi-center, double-blind, active- and placebo-controlled trial in adult patients with moderate-to-severe scalp psoriasis [36]. At the end of 28 days of treatment, patients on betamethasone valerate foam showed significantly better clearing of plaques than those on betamethasone valerate lotion and placebo. Further, there was no evidence of increased toxicity for betamethasone valerate foam [36].

3.2 Vitamin D3 analogues

The active form of vitamin D3 is known to play an important role in the regulation of intestinal calcium absorption, bone mineralization and the prevention of rickets. In addition to these actions, vitamin D3 has several more biological effects, including the stimulation of cellular differentiation, inhibition of proliferation and immunomodulation [37]. This makes vitamin D3 a potential candidate for treatment of psoriasis. However, parent vitamin D3 might not be suitable for treating psoriasis owing to potential for hypercalcemia. Hence, several vitamin D3 analogues have been developed for the treatment of psoriasis [38]. Vitamin D analogues bind to the vitamin D receptor, thus causing biological actions on both corneocytes and on immune-competent cells in the skin. Analogues such as calcipotriol, tacalcitol and maxacalcitol inhibit corneocyte proliferation and stimulate corneocyte differentiation *in vitro*. In addition, these analogues have only minimal effects on calcium levels and calcium excretion [39]. However, owing to concerns with elevating the serum calcium levels on overdose, these analogues usually have a limit on use per week.

3.2.1 Calcipotriol (calcipotriene)

Calcipotriol is a synthetic vitamin D3 analogue formulated as a cream and scalp solution (Dovonex®, Warner Chilcott, Inc., Dundalk, Ireland) at a drug loading of 0.005%. The calcipotriol cream is effective in treatment of plaque psoriasis and statistically significantly better than the placebo alone [40]. In addition, a solution has been developed for scalp psoriasis [41], and calcipotriol ointment has also been investigated for nail psoriasis [42]. The results also showed that this drug was a safe alternative for topical psoriasis treatment.

A comparison of calcipotriol ointment with a combination of betamethasone dipropionate and salicylic acid ointment (Diprosalic®, Schering Plough, New Jersey, USA) showed that calcipotriol was as effective as the combination product for treating nail psoriasis [42]. Comparisons of 0.005% calcipotriol ointment and 5% coal tar ointment in conjunction with sun exposure in 10 adult patients with stable plaque psoriasis showed that both calcipotriol and coal tar ointment had comparable efficacies in treating stable plaque psoriasis when used simultaneously with sun exposure, although the initial response to calcipotriol was faster [43].

The calcipotriol cream formulation is less greasy than the ointment formulation and hence has better patient acceptability. The impression was that the effect of calcipotriol is more pronounced on lesional infiltration and scaling, whereas the effect is less pronounced on the vascular component of psoriasis, as determined by redness. Finally, the therapeutic response to calcipotriol ointment can be increased by occlusion with a polyethylene film or a hydrocolloid dressing [44].

3.2.2 Calcitriol

Calcitriol is a synthetic form of the active metabolite of vitamin D3. It has antiproliferative, prodifferentiating and immunomodulating effects on human keratinocytes [45]. A calcitriol ointment (Vectical®, Galderma Laboratories, New Jersey, USA) for mild-to-moderate plaque psoriasis was approved by the US Food and Drug Administration (FDA) in 2009 [46]. Multi-center and randomized clinical trials have shown calcitriol ointment to be efficacious, safe and cosmetically acceptable as compared with placebo and other topical psoriasis therapies [47]. Pharmacokinetic studies in patients with psoriasis and healthy control subjects have demonstrated that topical calcitriol ointment produces minimal systemic absorption of calcitriol and does not alter systemic calcium homeostasis significantly even when applied to approximately one-third of the body surface area [47]. However, the Vectical prescribing information limits the use to 200 g a week owing to concerns of disturbance in calcium metabolism. The efficacy and safety of topical calcitriol ointment were examined in two placebo-controlled, randomized, multi-center, parallel-group double-blind clinical trials of identical design in a total of 839 patients aged 18 years or older

with mild-to-moderate plaque psoriasis [48]. Both studies showed that at the end of the treatment period, the patients in the calcitriol group showed significantly better clearing of psoriatic plaques than those in the vehicle group. The incidence of treatment-related adverse events such as mild skin discomfort, pruritus and erythema was similar for the calcitriol and the vehicle groups in both studies [48].

3.2.3 *Tacalcitol*

A once-daily ointment containing 4 μg/g tacalcitol (Curatoderm®, Hermal, Reinbek, Germany) was developed in Europe in order to achieve extra advantage in patient compliance as compared with calcipotriol [49]. Subsequent clinical studies have proved the efficacy and safety in the treatment of chronic plaque psoriasis, with no systemic side effects for up to 18 months [50]. The long-term safety and efficacy of tacalcitol ointment in patients with chronic plaque psoriasis, where up to 20% of the body surface was affected, was established in an open, multi-center, Phase IV study [51]. In this study 157 patients aged 18 – 70 years with chronic plaque psoriasis treated with tacalcitol ointment once daily showed a marked reduction in plaques with no changes in laboratory parameters, no case of hypercalcemia and no serious adverse events during the study period. In a recent study, efficacy of high-concentration tacalcitol (20 μg/g) in patients with psoriasis vulgaris who had already been treated with another high-concentration vitamin D3 ointment, calcipotriol or maxacalcitol was investigated [52]. The study concluded that many patients with psoriasis vulgaris who had already been treated with calcipotriol or maxacalcitol could achieve further improvement by changing to high-concentration tacalcitol. Also, high-concentration tacalcitol ointment meets the preference of patients to use an ointment once a day.

3.3 Retinoids

Retinoids provide a distinct class of treatment and have a unique position within the armamentarium of antipsoriatic treatments, which are largely dominated by immunomodulatory approaches. The mechanism of action of retinoids in psoriasis may include direct suppression of inflammation as well as inhibition of proliferation and normalization of differentiation in the epidermal layer [53].

In the US, topical retinoid for psoriasis is approved as tazarotene gel and cream (Tazorac®, Allergan, Inc., California, USA), available in 0.05 and 0.1% formulations. It is recommended that treatment commences with the 0.05% formulation, and the concentration increased if necessary and tolerated. Tazarotene is applied once daily in the evening. All formulations and strengths can be used for plaque psoriasis. In general, gels and the more concentrated strengths tend to have higher incidences of irritation, pruritus, erythema, stinging and desquamation [54]. The cream formulations are being marketed as less irritating [55]. A recent improvement in tazarotene therapy was a reduction of skin irritation by short contact applications [56]. These side effects are most apparent on initial application, but are generally alleviated with continued use. Tazarotene is contraindicated in pregnant women and in women who are not taking adequate birth control in view of its teratogenic potential. In addition, tazarotene use should be avoided in patients who have substantial sun exposure, who do not use adequate sun protection and who use photosensitizers or have photodermatitis [56].

The penetration of tazarotene through human skin is limited. The systemic availability after topical tazarotene 0.05 or 0.1% gel is < 1% after single application, and 2.6 and 5.3%, respectively, after once-daily applications following 2 weeks of treatment. After 12 weeks of treatment, the systemic availability of tazarotene 0.05% was 1.8% and for the 0.1% tazarotene preparation it was 3.9% [57].

The efficacy of once-daily topical tazarotene has been studied in four randomized, double- or single-blinded clinical trials: two trials on the tazarotene gel formulation [58,59] and two trials on tazarotene cream formulation [60] in patients at least 18 years old and having plaque psoriasis in at least 2% of the total body surface area. The duration of active treatment was 12 weeks, and an extra 12 weeks follow-up period without active treatment was incorporated in these studies. These studies showed that as early as at week 1, tazarotene 0.1% formulation showed a statistically significant improvement as compared with the vehicle, with the 0.05% tazarotene formulations showing statistically significant improvement at week 4. Twelve weeks after the discontinuation of therapy (post-treatment phase), both 0.1 and 0.05% tazarotene cream were significantly better as compared with the vehicle [60].

Comparative studies between calcipotriol and tazarotene monotherapy have been carried out, showing superior efficacy of calcipotriol during the first 8 weeks but equal efficacy after 12 weeks' treatment [61].

3.4 Methotrexate

Methotrexate is a folic acid antagonist with antineoplastic activity. It is also considered a very effective treatment for severe psoriasis when administered orally [62]. A major problem for topical delivery of methotrexate is very limited passive permeation through skin. Several preclinical studies using permeation enhancers [63], iontophoresis [64], microemulsions [65], electroporation [66] and microneedles [67] have shown the feasibility of dermal delivery of methotrexate. However, it remains to be seen whether any of these active dermal delivery approaches will lead to any significant delivery advantage in humans.

4. New agents for topical treatment of psoriasis

4.1 Calcineurin inhibitors

These agents inhibit the activity of calcineurin phosphatase, an enzyme important for the translocation of the pluripotent transcription factor, nuclear factor of activated T cell, from the cytoplasm to the nucleus where it 'turns on' several

pro-inflammatory cytokines associated with T-cell activation. Hence, these agents have potential for treatment of skin diseases mediated by calcineurin phosphatase [68]. At present, these calcineurin inhibitors are approved for use in mild-to-moderate atopic dermatitis only; any use in psoriasis is off-label. A black box warning has been added to the labels of these medications stating that the long-term safety of topical calcineurin inhibitors has not been established and that rare cases of cancer have been reported in patients who used the medications, although a causal relationship has not been established.

4.1.1 *Tacrolimus*

Tacrolimus is an immunosuppressive drug whose main use is after allogenic organ transplant to reduce the activity of the patient's immune system and so the risk of organ rejection. It is also used in a topical ointment preparation (Protopic®, Astellas Pharma, Tokyo, Japan) for the treatment of severe atopic dermatitis, vitiligo and psoriasis. Tacrolimus ointment was approved in the US in 2000 and in Europe in 2001 for atopic dermatitis. However, new research has proven the potential use of tacrolimus in psoriasis [68,69]. The introduction of tacrolimus ointment marked the advent of a new, non-steroidal drug class, topical immunomodulators, for the management of inflammatory dermatoses.

Tacrolimus ointment seems most effective in treating psoriasis where the skin is thin, that is, on the face, genitalia and intertriginous areas [70]. In one study 21 patients with facial psoriasis lesions applied tacrolimus (0.1%) ointment twice a day for 4 weeks without occlusion. A complete or good response was obtained in most of the patients [71].

The efficacy and tolerability of tacrolimus ointment have also been investigated for the treatment of male genital psoriasis [72]. In an open-label study in 12 adult male patients with genital psoriasis, patients received topical tacrolimus 0.1% ointment twice daily for 8 weeks followed by a 4-week observational period. Psoriasis severity also improved significantly for the glans, shaft of the penis, and scrotum evaluated individually. The ointment was very well tolerated, with only mild pruritus or burning sensation of limited duration reported [72].

The safety and efficacy of tacrolimus (0.1%) ointment for the treatment of psoriasis on the face, intertriginous areas, or both were evaluated in an open-label, clinical trial of 21 patients with psoriasis [73]. A total of 81% of patients experienced complete clearance at day 57 (end of treatment). Only two patients reported adverse events, which were limited to itching and the feeling of warmth at the application site [73].

4.1.2 *Pimecrolimus*

Pimecrolimus is a non-steroidal immunosuppressant derived from ascomycin. This drug, like tacrolimus, also inhibits the action of calcineurin phosphatase. Pimecrolimus 1% cream (Elidel®, Novartis, Basel, Switzerland) was approved in the EU, the US and Japan as second-line therapy for the short-term and non-continuous chronic treatment of mild-to-moderate atopic dermatitis in patients who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable [74]. This topical immunomodulator also has enormous potential as a topical treatment for numerous inflammatory skin diseases, such as psoriasis and dermatitis [74].

Pimecrolimus is not effective in plaque-type psoriasis when used as the commercially available formulation without occlusion [75]. However, pimecrolimus has been shown to be effective in intertriginous psoriasis [75]. A double-blind, randomized, vehicle-controlled study was performed in 57 patients aged 18 years or older with moderate-to-severe intertriginous psoriasis. By week 8 of treatment, 82% of patients using pimecrolimus scored their disease as being equally well, or completely controlled, compared with 41% of the vehicle group. The pimecrolimus treatment was also well tolerated [76].

4.2 Phosphodiesterase 4 inhibitors

Phosphodiesterase 4 (PDE4) is the predominant cyclic AMP degrading enzyme, present in a variety of inflammatory cells including eosinophils, neutrophils, macrophages, T cells and monocytes. In addition, this enzyme is expressed in non-immune cells such as keratinocytes and fibroblasts. Owing to the broad anti-inflammatory/immunomodulatory action of PDE4 inhibitors, it has been proposed that PDE4 inhibitors might also be efficacious for skin disorders such as psoriasis and atopic dermatitis [77]. These PDE4 inhibitors displayed strong anti-inflammatory action in models of allergic contact dermatitis in mice, in the arachidonic acid-induced skin inflammation in mice and in ovalbumin-sensitized guinea-pigs. The determination of cytokines in skin homogenates revealed that both Th1 as well as Th2 cytokines are suppressed by PDE4 inhibitors, indicating an anti-inflammatory activity in both the Th2-dominated acute phase as well as the Th1-dominated chronic phase of atopic dermatitis. Owing to the suppression of Th1 cytokines, activity can also be expected in psoriasis [77]. Consequently, PDE4 inhibitors are now in clinical development for the treatment of psoriasis both topically (AN-2728 from Anacor Pharmaceuticals, California, USA) and orally (CC-10004 from Celgene Corp., New Jersey, USA).

A recent publication gives a comprehensive summary of preclinical, Phase I and Phase II data for topical AN-2728 [78]. So far three Phase IB, one Phase IIA and one Phase IIB trials have been completed for AN-2728, and results suggest that AN-2728 is well tolerated with significantly better efficacy in plaque psoriasis as compared with placebo controls. A Phase IIB, randomized, double-blind, placebo-controlled, parallel-assignment, single-center, safety and efficacy clinical trial assessed AN-2728 ointment (5% b.i.d. for 12 weeks) in 30 patients with plaque psoriasis [78]. Preliminary data revealed that psoriatic plaques treated with AN-2728 showed a reduced overall target

plaque severity score compared with plaques treated with vehicle alone at 8 weeks of treatment. In addition, AN-2728 topical therapy has also been reported to be well tolerated. In the Phase IIA trial, no treatment-related adverse events or laboratory anomalies were reported; one patient reported mild gingivitis and diarrhea, but these effects were not considered to be related to the trial medication [78].

5. Combination topical therapies

The commonly used topical medications described in this review provide efficacy through varying and divergent pathways. These agents achieve efficacy through different mechanisms, which provides a potential rationale for combination therapy. The rationale assumes that agents are selected on the basis of their individual mechanisms of action, which may offer the possibility of additive or synergistic efficacy, reduction in the dose of either or both products, and reduction in the occurrence of side effects [79]. Several studies have proven the advantages of using a combination of topical medications for treatment of psoriasis. Recently, a two-compound fixed-dose combination ointment containing 50 µg/g calcipotriol and 0.5 mg/g betamethasone dipropionate (approved in the US as Taclonex®, Leo Pharma, Ballerup, Denmark) was found to be effective against psoriasis vulgaris [80]. This ointment formulation combines the keratinocyte differentiation and antiproliferative action of the vitamin D3 analogues (calcipotriol) with the anti-inflammatory effect of steroids (betamethasone dipropionate), thus enhancing effectiveness while reducing the side effect profile of the individual agents [31]. It was found that the combination product had a more rapid onset of action [81] than calcipotriol or betamethasone and was more effective [82] than calcipotriol or betamethasone alone (**Figure 3**). A clinical trial with 1605 randomized patients aged 18 years or older showed that the combination product (Taclonex) was significantly more effective than betamethasone, calcipotriol and placebo. The local adverse reactions were also low compared with the other drugs. It was concluded that two different treatment regimens (i.e., application once or twice daily) using the two-compound product provided rapid and marked clinical efficacy as compared with calcipotriol or betamethasone alone and also were safe therapies for psoriasis vulgaris [31]. Combination of calcipotriol and betamethasone has also been shown to have significant advantages in the treatment of scalp and nail psoriasis [31]. More recently, a combination of 0.005% calcipotriol and 0.064% betamethasone dipropionate (Taclonex Scalp® in the US and Xamiol® in Europe [Leo Pharma, Ballerup, Denmark]) has been approved for the treatment of moderate-to-severe scalp psoriasis vulgaris in adults. This once-daily therapy has a quick onset of action and greater efficacy than monotherapy with either ingredient. At 8 weeks, the combination product had a safety profile comparable to betamethasone dipropionate and was associated with significantly fewer adverse events than calcipotriol [83].

A multi-center, randomized, double-blind, vehicle-controlled, parallel-group study was carried out to study the effect of the addition of calcipotriol ointment to methotrexate in patients aged 18 years or older with psoriasis vulgaris [84]. From this study, it was concluded that the combined use of calcipotriol with methotrexate resulted in a methotrexate-sparing effect, while still maintaining the efficacy. Calcipotriol treatment increased the time to relapse of psoriasis following discontinuation of methotrexate. The combination of calcipotriol and methotrexate was safe and well tolerated. The combination resulted in lower cumulative doses of methotrexate as compared with monotherapy, thus significantly reducing the risk of methotrexate side effects [84].

The combination of calcipotriol ointment (twice daily) and tazarotene gel (once daily) was compared with clobetasol ointment (twice daily) in the treatment of psoriasis [85]. The vitamin D3 analogue plus retinoid treatment had comparable efficacy to that of the potent topical steroid. In another study, a comparison of twice-daily calcipotriol ointment against the combination of tazarotene gel and 0.1% mometasone furoate cream was superior during the first 2 weeks of treatment. However, by 8 weeks of treatment, both groups showed similar responses [53].

6. Combination of topical therapy with phototherapy

Phototherapy for psoriasis includes narrowband and broadband UV-B phototherapy, psoralens combined with UV-A, targeted excimer laser phototherapy, and combination treatments [86]. The combination of phototherapy with topical products has long been used for treatment of plaque psoriasis. In the 1920s, William Goeckerman combined the use of UV-B phototherapy with topical application of tars [8,9]. This in-patient psoriasis regimen, known as the Goeckerman regimen, is still occasionally used.

Psoralen photochemotherapy uses a combination of topical application (or ingestion) of 8-methoxypsoralen followed by exposure of the affected skin area to long-wavelength UV (320 – 400 nm, UV-A) [86]. Other psoralen derivatives such as 5-methoxypsoralen and 4,5,8-trimethylpsoralen are also used in topical PUVA (psoralen UV-A) therapy. Bath psoralen UV-A combination involves immersion of either localized areas (such as the hands or feet) or the whole body in water containing dissolved 8-methoxypsoralen before UV-A exposure [86].

Photodynamic therapy is another non-invasive technique used in the treatment of skin diseases. 5-Aminolevulinic acid is a prodrug that is metabolized intracellularly to form the photosensitizing molecule protoporphyrin IX. When protoporphyrin IX is activated by light, cytotoxic reactive oxygen species and free radicals are generated. This phototoxic effect may be used for treatment of malignant

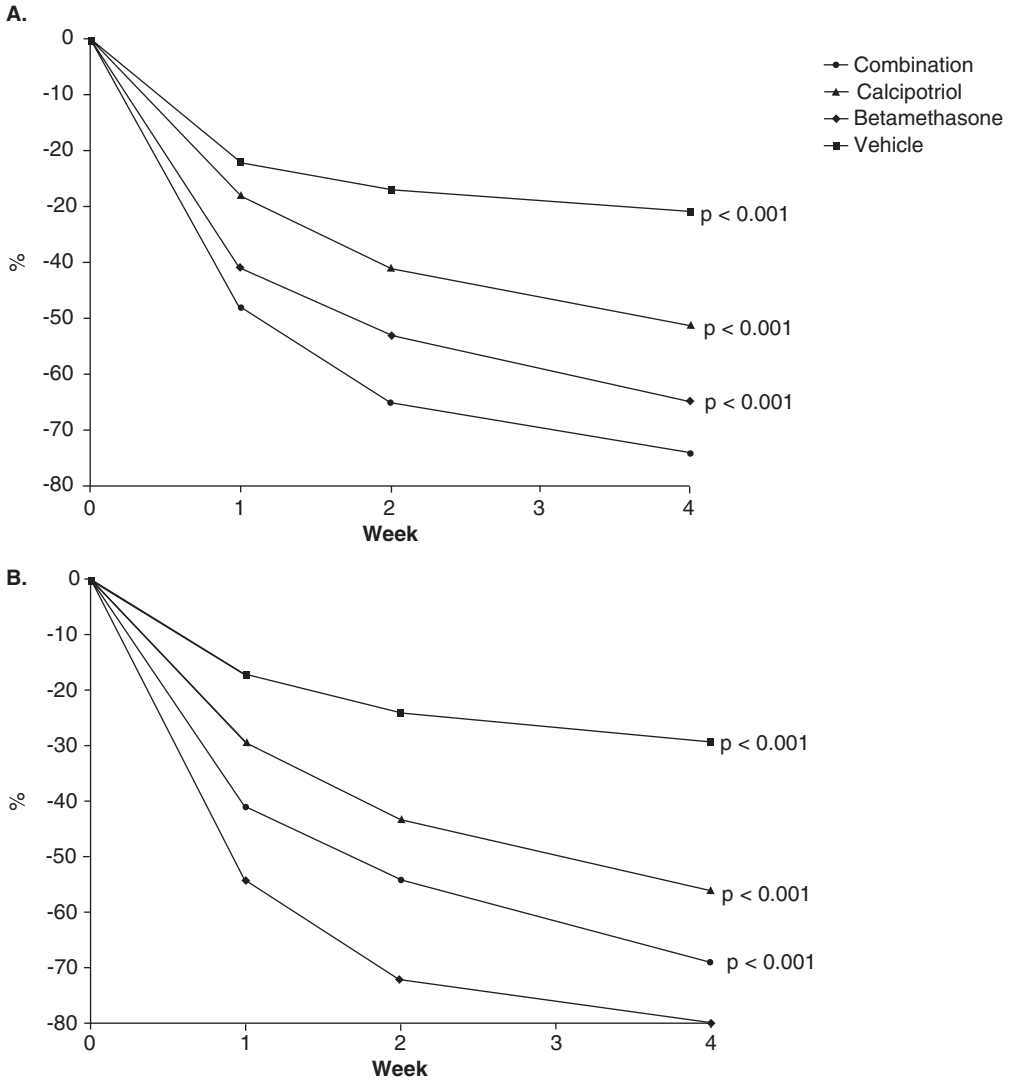

Figure 3. A combination product of calcipotriene and betamethasone dipropionate shows superior efficacy with a more rapid onset of action than either active ingredient alone in the treatment of psoriasis vulgaris. A. Percentage change in psoriasis area severity index (PASI) after 1, 2 and 4 weeks of treatment and **B.** percentage change in thickness of target lesion at each visit and at the end of treatment in the patient population (n = 1028).
Reproduced with permission from [81].

and non-malignant hyperproliferative tissue [87]. Photodynamic therapies using 5-aminolaevulinic acid in plaque psoriasis have also been reported [87].

7. Challenges in developing new topical medications for psoriasis

The unique nature of drug delivery across the skin presents several unique challenges in the development of topical products, such as: i) optimization of both drug property and formulation composition to enhance the rate and extent of drug diffusion through the stratum corneum; ii) reduced drug concentration and increase in data variability owing to presystemic metabolism in the skin; iii) very challenging to switch topical formulation in clinic, hence minimal formulation changes can be made during development; iv) no control on deep tissue penetration through formulation approaches, which is primarily influenced by protein binding and dermal blood flow; v) lack of confidence in dose projection owing to difficulty in establishing robust skin pharmacokinetic–pharmacodynamic relationship; and vi) high variability in *in vitro* and *in vivo* skin permeability remains a major obstacle in using these tools in formulation development.

In addition to these general challenges in topical formulation development, there are several challenges specific

to developing antipsoriatic topical products, such as: i) psoriatic lesions can have both thickened and markedly thinned epidermis; this heterogeneity in the skin morphology can increase the variability in drug permeation thus increasing challenges in formulation development; ii) a significant number of psoriasis patients feel that the current therapies are either not sufficiently efficacious or are not aggressive; hence, a primary challenge is to develop new therapies that can be once-daily applications and show quick response; iii) effective management of psoriasis frequently necessitates combining therapies in order to achieve optimum response while minimizing any side effects; thus, any new topical therapy should have appropriate safety and efficacy when used in combination with another topical medication, systemic therapy and/or phototherapy; iv) to increase patient adherence to therapy, new topical formulations should have appropriate cosmetic elegance such as ease of use, no or minimal staining potential on clothing, bedding, and so on, quick absorption on application and being less greasy; v) formulations that can be used on many areas of the body including hair-bearing sites are preferred as patients often have psoriasis plaques in multiple areas; and vi) owing to the availability of a wide variety of therapies and the presence of generic products in the market, competitive cost of any new medication is paramount in influencing the physician's and patient's choice of product.

8. Conclusion

As summarized in this review, there are several treatment options for psoriasis, and exciting new targets (e.g., PDE4) are being investigated for potential treatment options. Also, combination topical products and combination of topical and phototherapy have been shown to provide more effective treatment options. The epidermal hyperproliferation in psoriatic patients may increase the variability in drug penetration across the skin, hence new drug delivery approaches such as liposomes, iontophoresis, electroporation, and so on, are being investigated for improving delivery. Recent research has emphasized the importance of treatment adherence in the management of psoriasis. Adherence to treatment is likely to be a far more important determinant of success than are small differences in drug delivery, especially in actual clinical use as opposed to the well-controlled environment of clinical trials. For patients who prefer a less messy vehicle, adherence and outcomes are likely to be better with the newer formulation options such as foams and sprays compared with the traditionally recommended ointment. There is abundant literature investigating the efficacy of topical antipsoriatic formulations in clinic; however, very few studies have examined the pharmacokinetics of these molecules in the skin. In future it will be important to understand the impact of formulation change on skin pharmacokinetics in order to design topical formulations for improved drug delivery.

9. Expert opinion

Although there are numerous drug therapies and formulation presentations for the treatment of psoriasis, a review of the literature reveals that there are very few reports of skin pharmacokinetic (PK) studies in humans for topical delivery. As a result of this gap, there is neither any universally accepted protocol for conducting skin PK studies nor any formalized FDA guidance for such studies. Hence, with the exception of topical corticosteroids [88], the only means of showing bioequivalence (BE) to a topical dermatological product is through clinical equivalency studies. There has been a proposal of dermatopharmacokinetic (DPK) studies for assessing topical BE [89]. In this method, the drug levels in the stratum corneum (SC) are measured as a function of time post-application and post-removal of the formulation by tape stripping of the application area. Draft FDA guidance was published in 1998 on conducting the DPK studies, which details the specifics of conducting such studies, data analysis and BE criteria for relevant PK parameters [90]. However, in 2002, the FDA withdrew the DPK guidance [91] citing two principal concerns: i) adequacy of the method to assess the bioequivalence of topical dermatological drug products; and ii) reproducibility of the method between laboratories. The first concern was based on the fact that the DPK method measures penetration through healthy SC, hence this method may not accurately reflect diseased conditions where the skin barrier function is perturbed, such as psoriasis. Subsequent publications have identified several more practical problems associated with the use of the DPK protocol [92]. These include: i) the variability in the amount of SC collected on each tape strip; ii) the associated variability in the amount of drug that is discarded with the first two tape strips; and iii) the variability in cleaning effectiveness. In fact, a study conducting DPK to assess BE of three tretinoin gel products showed large variability, thus necessitating a large number of subjects to achieve adequate statistical power [93]. Nevertheless, in several studies using tape-strip sampling of the SC, meaningful comparisons between formulations were made for terbinafine [94] and 4-cyanophenol [95]. A recent publication has also proposed alternative data analysis approaches for easier assessment of BE from DPK studies [92]. Further, N'Dri-Stempfer *et al.* have proposed a revised DPK protocol with the aim of reducing experimental variability and hence reducing the number of subjects required to show BE [96]. In this study the authors claim conclusive assessment of BE between 3 econazole cream formulations by using only 14 subjects. The specific modifications to the DPK protocol suggested in this publication include [96]: i) measurement of transepidermal water loss (TEWL) to assess the fraction of SC removed by the tape-stripping procedure; ii) a new cleaning procedure to improve removal of residual drug before tape stripping thus reducing data variability; and iii) inclusion of all tape strips containing drug in the comparison of the amounts taken up into the SC from different products. These

positive results with the improved DPK protocol suggest that further clinical studies should be conducted to validate this protocol.

Skin PK can also be assessed by biopsy sampling. A recent publication successfully demonstrated the skin disposition of pimecrolimus in minipigs by skin biopsy [97]. Biopsy sampling allows quantification of drug concentration in the whole skin (stratum corneum, viable epidermis and dermis), which is an advantage over DPK, which only measures drug concentration in the stratum corneum. It is also possible to separate the different skin layers in a biopsy punch, to quantitate drug concentration in the individual layers. However, a major limitation of this methodology can be getting consent from subjects and patients to conduct biopsy in clinical trials.

Several exciting molecular targets and drug candidates have been identified and developed over the years for treatment of psoriasis by the topical route. As summarized in this review, most of the approved topical psoriasis products are based on conventional formulation presentations such as creams, gels, ointments, and so on. Even though certain body areas lend themselves better to one type of presentation than another, it appears that gels, foams and spray have become preferred to creams and ointments in general because of their unique attributes (i.e., easier to apply, rapid disappearance into the skin, less greasy and better overall feel), as indicated by market research in physicians and patients [23,98]. Despite the variety of available presentations, there seems to be a lack of approved products utilizing new drug delivery approaches to enable appropriate delivery of therapeutic agents to the target site in the skin, particularly for delivery of hydrophilic molecules such as methotrexate and 5-aminolevulinic acid. The possibility of using vesicular systems such as deformable liposomes for delivery in psoriatic skin has been demonstrated. Topical application of liposomal methotrexate in 30 patients with localized psoriasis resulted in global improvement of the psoriatic lesions with minimal skin irritation [99]. Also, up to 60% of the patients treated with liposomal methotrexate showed no recurrence of the disease 8 months post treatment [99]. In another study, delivery of 5-aminolevulinic acid into hyperproliferative murine skin was significantly improved (up to 26-fold) when encapsulated in a phosphatidylethanolamine-based ethosomal carrier as compared with an aqueous solution of 5-aminolevulinic acid [100]. Although these are preliminary results demonstrating the potential use of vesicular delivery systems in psoriasis, these positive results do indicate the need to study further such delivery systems both preclinically and clinically. As our mechanistic understanding of the interaction of these lipid vesicles with diseased skin improves and also robust formulation development and manufacturing techniques are developed, it can be expected that these new delivery systems can become approved drug products in future.

As has been reviewed here, new and emerging drug delivery represents an important step forward in topical treatment of psoriasis. As new topical drug delivery systems are developed, these will offer selective and targeted therapy as well as satisfactory safety profile, enabling treatment for prolonged periods of time. In addition, the convenience of these new topical agents improves patient compliance. However, as newer delivery systems and new therapeutic agents are developed, there is a need to control costs and hence make these therapies affordable for all patients.

Declaration of interest

The authors are employees of Merck Sharp & Dohme Corp.

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