Expert Opinion

Drug delivery and formulations for the topical treatment of psoriasis

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Background: Psoriasis is one of the most common human skin diseases. It is characterised by excessive growth and aberrant differentiation of corneocytes, but is fully reversible with appropriate therapy. *Objective*: There are many drug therapies for psoriasis via the topical delivery route. This review describes the topically applied drugs used to treat psoriasis. *Methods*: Formulations to carry or encapsulate these drugs are introduced in this review. Enhancing approaches such as liposome inclusion, iontophoresis and laser are also discussed. *Conclusion*: This review summarises developments in the design of formulations in the area of topical drug delivery for treating psoriasis.

Keywords: dermatology, formulation, psoriasis, skin, topical delivery

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1. Introduction

Psoriasis is an inflammatory condition of the skin that affects 1 – 2% of the US population. It commonly begins between the ages of 20 and 40 years with an average age of onset at 27 years [1]. Although it is seldom life-threatening, psoriasis can be a debilitating chronic illness with pronounced physical, psychological and social implications. Patients with psoriasis experience itching, scaly, painful and disfiguring skin lesions. Approximately 5 – 8% of patients with psoriasis also have psoriatic arthritis, which can be painful and compromise mobility [2]. Patients with psoriasis describe feelings of self-consciousness, helplessness, embarrassment, anger and frustration [3].

Although there is no cure for psoriasis, several available treatments can minimise skin lesions and associated symptoms. Some treatments can also induce remission for months to years. The type of treatment indicated primarily depends on the severity of disease or extent of involvement, but other factors including expense, adverse-effect profile, patient preference and availability are also considerations. Most patients with psoriasis have limited disease, involving < 20% of their body surface area [4]. For such patients, topical therapy is usually sufficient [3].

Topical antipsoriatic therapies include coal tar, anthralin, methotrexate (MTX), corticosteroids, vitamin D3 analogues and retinoids. Moreover, light therapies for topical treatment include ultraviolet B (UVB), psoralens combined with UVA (PUVA) and photodynamic therapy. Occasionally, combination therapy with more than one medication may be helpful [3]. In this article, the authors provide an overview of available medications and enhancing approaches for psoriasis in patients with localised disease.

2. Skin and pathways for drug delivery via the skin

It is necessary to understand the anatomy, physiological function, physicochemical characteristics and biomedical properties of the skin in order to successfully utilise the phenomenon of topical absorption. The skin of an average adult human covers a surface area of nearly 2 m^2 and receives about one third of the blood

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circulating through the body. One of the natural functions of the skin is to protect the body against the loss of endogenous substances and invasion by exogenous substances [5].

Microscopically, the skin is composed of three main histological layers: stratum corneum (SC), epidermis and dermis (**Figure 1**). The main barrier to diffusion through the skin is the outermost layer of the skin, the SC, which consists of corneocytes (also called keratinocytes), which are entirely surrounded by crystalline lamellar lipid regions. The cell boundary – a cornified envelope – is a very densely crosslinked protein structure, which reduces absorption of drugs into the cell [6].

The SC is described as the rate-limiting barrier of the skin with regard to the viable epidermis and dermis [7]. The viable epidermis is an aqueous solution of protein encapsulated into cellular compartments by thin cell membranes that are fused together by tonofibrils. The epidermis contains no vascular elements. Cells receive their nourishment from capillary beds located in the papillary layers of the dermis by diffusion of plasma and serum components. They are composed of a fibrous protein matrix and much collagen, elastin and reticulum, all of which are embedded in an amorphous colloidal ground substance. The dermis is also the locus of blood vessels, sensory nerves and lymphatics. It contains the inner segments of the sweat glands and pilosebaceous units, which are important for the delivery of some drugs and drug carrier systems [5].

The process of topical drug delivery includes partitioning of the drug from a vehicle to the SC, penetration through the SC, diffusion through each layer of the skin, uptake by the capillary network at the dermo-epidermal junction and finally transportation to the target tissues to achieve therapeutic action (**Figure 2**).

Percutaneous absorption can occur through two different routes: transepidermal (intercellular and transcellular) and transappendageal (hair follicles, sweat ducts and pilosebaceous glands) pathways [6]. Penetration between SC corneocytes (intercellular) is the pathway by which most compounds or particulates penetrate the skin. As corneocytes are not stacked parallel to one another in layers, when penetrating among them, a compound has to travel via a sinuous pathway. This pathway is thought to enable free volume diffusion through the lipid bilayers present among cells [8]. The transcellular route is believed to be hydrophilic in nature. It is composed of aqueous regions surrounded by polar lipids that create the walls of microchannels. It is known to have a high penetration resistance to lipophilic compounds but a low resistance to hydrophilic compounds. Compounds permeating through this route penetrate among corneocyte clusters through imperfections that create openings comprised of water. Some investigations have indicated that intracellular keratin provides this pathway [9,10]. Although the extent of the appendageal route on the total skin surface represents no more than 0.1%, this route can overcome the low diffusivity of the SC and may act as a diffusional shunt. Depending on the formulation and the compound's intrinsic properties, certain compounds can enter these shunts faster than they can move through other routes [10].

3. Psoriasis pathogenesis

Psoriasis was first recognised as a distinct disease as early as 1801 [11], yet its pathogenic mechanisms eluded investigators for decades. The development of localised lesions in response to skin trauma (Koebner reaction or isomorphic response) was first described by Koebner in 1872, a disease that derives its name from the Greek 'psora' meaning 'to itch' [12]. It is estimated that up to 80% of juvenile guttate psoriasis cases are preceded by streptococcal infections [13]. However, psoriasis can occur in association with other inflammatory diseases such as inflammatory bowel disease (Crohn's disease) and in association with HIV infection [14]. Drugs, stress and climate can also be predisposing factors in susceptible individuals [1].

Although clinical features and severities vary among individuals and with time, psoriasis is characterised by four abnormalities [15]: i) vascular changes where the papillary blood vessels become dilated and tortuous, resulting in redness or erythema, a hallmark of psoriasis; ii) inflammation, where polymorphonuclear leukocytes from the dermal vessels enter the epidermis; lesions are also rich in activated $CD4^+$ and $CD8^+$ T cells that release pro-inflammatory cytokines; iii) hyperproliferation of the keratinocytic layer (acanthosis); and iv) altered epidermal differentiation where corneocytes retain their nuclei in the cornified layer (parakeratosis) and the granular layer is lost [1,16].

4. Topical antipsoriatic therapies

Topical antipsoriatic therapies include coal tar, anthralin, MTX, corticosteroids, vitamin D3 analogues, retinoids and tacrolimus (**Table 1**). The authors of this paper review formulation design and some enhancing approaches for these drug delivery strategies.

4.1 Coal tar

Crude coal tar is available in several commercial products or can be compounded in a petrolatum base. Liquor carbonis detergent solution is a less-potent tar mixed in white petrolatum (for the body) or in oil (for the scalp) at a concentration of 5 – 20%. Liquor carbonis detergents are more tolerable with less staining. All tar products can cause irritation, folliculitis and phototoxicity. The most commonly used tar products are tar shampoos, which can be helpful for scalp involvement [3].

In a recent study, the efficacy of a 1% coal tar preparation (Exorex®; Forest Laboratories) was compared with a 5% coal tar preparation (Alphosyl®; GlaxoSmithKline) in 158 versus 166 patients with mild-to-moderate psoriasis [17].

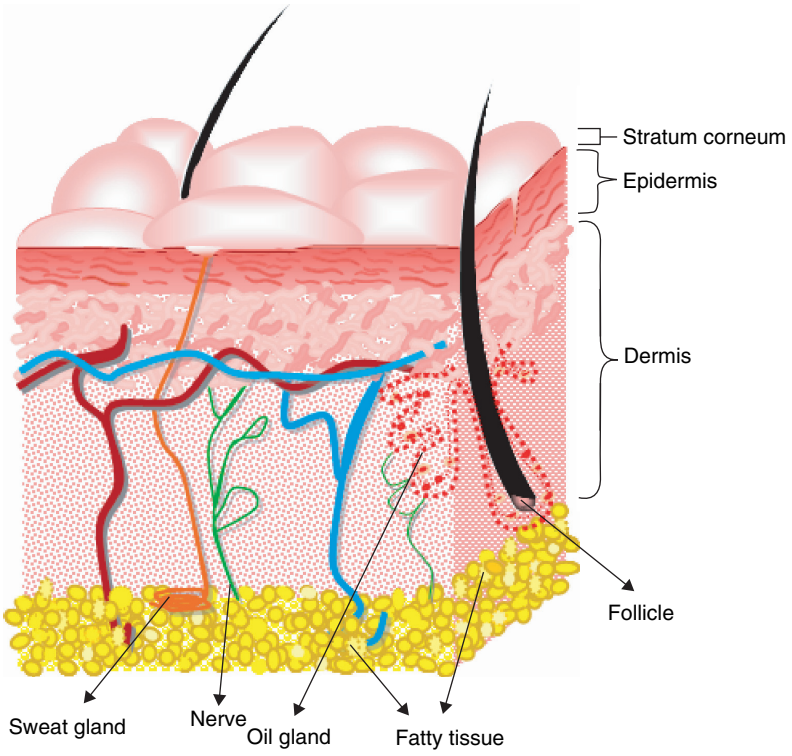

Figure 1. A cross-section of typical human skin.

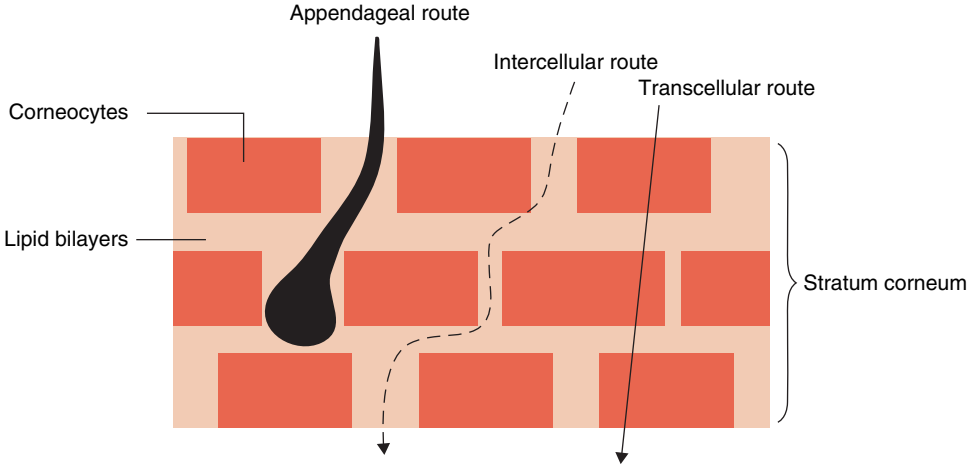

Figure 2. Possible pathways for drug delivery via the stratum corneum.

A 12-week treatment resulted in statistically significant decreases in the baseline psoriasis area severity index (PASI) of 33% and 21%, respectively [18]. PASI is a measure of overall psoriasis severity and coverage. For each skin section, the amount of skin involved is measured as a percentage of the skin just in that part of the body, and then it is assigned score from 0 to 6.

Although it is efficacious and lacks the potential adverse effects, such as with topical corticosteroids [3], the safety of coal tar treatment has been regarded as one of its great virtues, but other side effects besides the smell and staining of clothes must be considered [19]. Coal tar contains a large number of polycyclic aromatic hydrocarbons (PAHs), which have been found in blood and urine, but their systemic

Table 1. A summary of drug therapies for psoriasis.

Drug	Formulations or enhancement methods	Efficacy	Adverse effects	Ref.
Coal tar	Crude coal tar, liquor carbonis detergents, tar shampoos	Thinning of plaques, decreased symptoms in 2 – 4 weeks	Irritation, folloculitis, photosensitivity	[3]
Anthralin	Commercial formulations, compounded formulations	Thinning of plaques, decreased symptoms in 2 – 4 weeks	Extremely irritating, must avoid contact with surrounding skin	[3]
Methotrexate	Gels, microemulsion, iontophoresis, electroporation	Suppressive therapy, effective in all forms of psoriasis, particularly effective in patients with psoriatic arthritis	Bone marrow toxicity, nausea, aphthousstomatitis and development of megaloblastic anemia	[28,29,36,37]
Corticosteroids	Multiple gels, lotions, creams, ointments, solutions, scalp foams	Thinning of plaques, decreased symptoms in first 2 weeks of treatment, with improvement in subsequent weeks	Local: striae, atrophy, hypopigmentation, telangiectasias, folliculitis, hirsutism Systemic: risk of suppression of hypothalamic pituitary adrenal axis with excessive and prolonged use	[3,28,40,42-44, 46-48,50-52]
Vitamin D3 analogues	Calcipotriol ointments, creams, scalp solutions. Tacalcitol ointment. Calcitriol ointment	As effective as class 2 corticosteroids but often takes 6 – 8 week for full effect	Risk of hypercalciuria and hypercalcemia with > 100 g in a week	[3,56,60]
Retinoids	Tazarotene 0.05% and 0.1% as gels or creams	As effective as class 2 corticosteroids; improvement noted in first 2 weeks of therapy	Must be used with extreme caution in women of childbearing age (category X)	[3,69]
Indigo	Ointments	Downregulates epidermal proliferation and/or improves differentiation in lesional skin	Not yet reported	[75]
UVB	Broadband UVB (BB-UVB) Narrowband UVB (NB-UVB)	Suppressive therapy, rapid onset of action, NB-UVB may be more effective than BB-UVB, often combined with other agents	Erythema, vesiculation, premature skin ageing, high exposure UVB (> 300 treatments) may be associated with an increased risk of genital tumours	[28,80,81]
Psoralen combined with UVA	Bath PUVA	Remittive therapy, often combined with other topical agents	Squamous cell carcinomas of the skin	[28,84,85]
5-Aminolaevulinic acid	Erbium:YAG laser, self-adhesive film, iontophoresis, DMSO, 6-ketocholestanol combined phloretin		Patient discomfort	[89,93,94,96-98]
Rose bengal	< 1% hydrogel		< 100 J cm^{-2} intensity may result in superficial thermal damage	[101]

DMSO: Dimethyl sulfoxide; PUVA: Psoralens combined with UVA; UV: Ultraviolet.

toxicity is still unknown [20]. Absorbed PAHs can be metabolised to reactive derivatives that bind to DNA, and these PAH-DNA-binding products are thought to be involved in PAH-induced carcinogenesis [21]. However, no clear evidence of an increased incidence of skin cancer has been reported in patients who have been exposed to therapeutic doses of coal tar [22].

4.2 Anthralin

Anthralin (also known as dithranol) is available in commercial concentrations of 0.1 – 1.0% in a cream or ointment base, but higher concentrations can be compounded by a pharmacist. Anthralin is a synthetic analogue of the araroba tree extract, chrysarobin [23], which has long been effectively used in combination with UVB phototherapy for treating psoriasis [24].

At the Nijmegen Center, a care-instruction programme was developed for short-contact anthralin treatment. The efficacy of the short-contact anthralin treatment using the care instruction programme was compared with phototherapy and in-patient anthralin treatment using 24-h applications [25]. Clearing was reached in 44 of 78 patients with UVB treatment and in 59 of 100 patients with short-contact anthralin treatment. Median values of time in remission were 328, 277 and 584 days. Therefore, the short-contact anthralin principle remains an effective approach for patients with moderate-to-severe plaque psoriasis [18].

Anthralin stains skin, clothing, bathtubs and other objects a purple colour, limiting its acceptance by many patients. It can also substantially irritate the skin. Despite these negative features, anthralin works well to clear psoriasis and is associated with prolonged remission after discontinuation of the medication, ranging from 3.9 to 6.0 months [26]. That is, the recurrence of psoriasis could be delayed. An anthralin preparation was recently released that reportedly minimises staining of household items. The anthralin in this formulation (Micanol®; Derma UK) is placed in a vehicle that only releases the drug at the temperature of the body's skin [27].

4.3 Methotrexate

MTX is a folic acid antagonist with antineoplastic activity (**Figure 3**). It is also effective for treating psoriasis when administered by the oral or parenteral route over long periods of time [28]. A major problem is that the drug is hydro-soluble, has a high molecular weight (454.56) and is mostly in the dissociated form at a physiological pH. Its capacity for passive diffusion is thus limited. Previous studies have demonstrated that iontophoretic delivery is effective in enhancing the transdermal penetration of MTX [29].

To resolve this issue, various penetration enhancers, including decylmethyl sulphoxide [30], propylene glycol and isopropyl alcohol [31] and vehicles, such as laurocapram [32], vanishing cream and hydroxyethyl cellulose gel [33,34] have been used to increase the percutaneous absorption of MTX, with variable success.

Singh *et al.* [35] studied the combined effects of iontophoresis and enhancers such as dimethyl sulfoxide (DMSO), dimethyl formamide, dimethyl acetamide (DMA) and 1-dodecyl azacycloheptan-2-one (Azone) on the topical penetration of MTX. They found that iontophoresis further increased the permeability coefficient of MTX at doses of 4.4 – 6.6 mM compared with that measured using the enhancer passively [29].

Alvarez-Figueroa and Blanco-Mendez [36] found that both iontophoretic delivery of MTX from a hydrogel and passive delivery from microemulsions were more effective than passive delivery from aqueous solutions of the drug. In the passive delivery assays, they used both water-in-oil and oil-in-water microemulsions: the effectiveness of delivery was higher for oil-in-water systems. These results suggest that both hydrogels and microemulsions may be of value for the topical administration of MTX in treating psoriasis, according to the permeation enhancement evaluated by the *in vitro* skin permeation experiment.

Wong *et al.* [37] found that with side-by-side electrodes, treatment with electroporation pulses alone resulted in a 2.5-fold increase; adding anionic lipid enhancers to the pulses resulted in a 4.4-fold enhancement compared with passive diffusion. Concurrent iontophoresis for the 11-min time period made a non-significant contribution. To reduce tissue resistance they used 40°C hyperthermia in a vertical diffusion chamber; transport was increased 11-fold to 53 μg cm^{-2}. MTX penetration profiles indicated that more than half of the MTX was cornified to the epidermis and papillary dermis. The tissue concentration in this superficial reactive unit was 1.7 mmol l^{-1}. In a study performed with hairless mouse skin using a MTX-saturated microemulsion of lecithin in water/propylene glycol (70:30) (MTX solubility of 2.5 mg g^{-1}), the measured transdermal penetration rate was 5 μg cm^{-2} h^{-1} [38].

4.4 Corticosteroids

Topical corticosteroids – in particular high-potency topical corticosteroids – have been a mainstay in the topical treatment of psoriasis for decades [18]. Their efficacy can be attributed to multiple mechanisms of action, including their anti-inflammatory, immunosuppressive and antiproliferative effects [39]. One such corticosteroid is clobetasol propionate, a super-high-potency glucocorticosteroid first approved for treating steroid-responsive dermatosis in 1985 [40].

4.4.1 *Clobetasol propionate*

Clobetasol propionate (CP) is a class I steroid with strong potency. CP formulated in an ointment base is commonly used for treating psoriasis. The development of a foam formulation of CP 0.05% (Olux®; Connetics Corp.) provides an effective and cosmetically appealing treatment option for

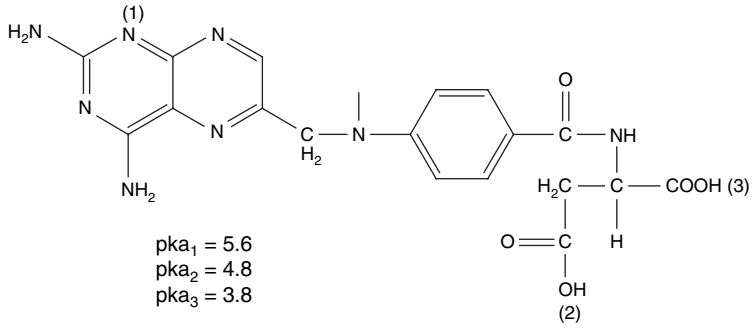

Figure 3. The molecular structure of methotrexate.

patients with plaque-type psoriasis because it spreads easily and is cosmetically elegant [40]. Olux is the formulation of VersaFoam® (Connetics Corp.), a thermolabile, low-residue foam, loaded with 0.05% CP.

A randomised, placebo-controlled, double-blinded study of 279 patients with mild-to-moderate plaque-type psoriasis demonstrated the efficacy and tolerability of CP foam. After 2 weeks of twice-daily applications of CP foam versus vehicle foam, 68% of patients in the active treatment arm had a Physician's Static Global Assessment Score (PSGA) of 0 or 1, versus 21% of patients receiving vehicle only [39]. The PSGA is a six-point score that summarises the overall quality (erythema, scaling and thickness) and extent of plaque relative to the baseline assessment. The treatment was well tolerated: 5% of patients receiving CP foam and 7% of those receiving vehicle reported burning at the site of application [40].

Although the efficacy of the CP foam can partially be attributed to patient adherence, the foam also delivers the active drug more efficiently than other formulations that have been compared. This may be due to the easier spread of foam onto the skin. *In vitro* application of foam to donor skin resulted in 5.9 ± 1.1% drug accumulation after 12 h, compared with 2.8 ± 0.3% with a solution, 2.7 ± 0.3% with emollient cream, 2.1 ± 0.2% with cream and 1.3 ± 0.1% with lotion [41]. CP rapidly penetrates into skin layers from the foam vehicle, allowing for the efficient distribution of drug.

4.4.2 *Halobetasol propionate*

Halobetasol propionate (HP) 0.05% ointment and cream are class I topical corticosteroids. Both formulations contain 6-α-fluoroclobetasol 17-propionate, a synthetic trihalogenated corticosteroid structurally similar to CP but with an additional fluorine atom.

Three studies separately compared the HP ointment to 0.05% CP ointment [42], 0.05% betamethasone dipropionate (BDP) ointment [43] and 0.1% betamethasone valerate (BMV) ointment [44]. The ratings of healed and improvement by objective observation were used as the outcome evaluations. The efficacy of the HP ointment was consistently significantly superior to those of the other preparations in these studies. Neither skin atrophy nor systemic adverse effects were observed for HP during 4 weeks. The HP ointment is an anhydrous ointment in which the active ingredient is dissolved in propylene glycol. This composition has increased efficacy because there is optimal release of the active ingredient from the anhydrous vehicle. Because of the risks associated with prolonged use were reported in 0 – 13% of patients, the daily application of HP should continue to be limited to a maximum of 14 days with a maximum dose of 50 g per 2 weeks [45,46].

4.4.3 *Betamethasone*

Skin lipid liposomes were loaded with hydrocortisone, betamethasone or triamcinolone, in an effort to improve their pharmacological effectiveness [47]. Those researchers found that the skin lipid liposomes they evaluated improved corticosteroid dermal delivery and, hence, the therapeutic effectiveness. Skin lipid liposomes showed a 61.3-times higher blanching effect than that obtained with a control formulation ointment and the phospholipid-based liposome formulation, respectively. Skin lipid liposomes appeared to be a suitable corticosteroid delivery system, increasing the pharmacological effectiveness and reducing possible side effects.

In a clinical trial, Korting *et al.* investigated the effectiveness of BDP in a liposomal preparation (0.039% BDP) and in a commercial conventional preparation (0.064% BDP) in patients suffering from atopic eczema or psoriasis vulgaris [48,49]. In this double-blind, randomised, paired trial the liposomal preparation, containing markedly less of the active substance, was slightly superior in patients with atopic eczema in that it reduced parameters of inflammation compared with the conventional BDP preparation. Yet, in patients suffering from psoriasis vulgaris, the conventional dosage form showed better results in improving the clinical condition.

The proprietary delivery vehicle VersaFoam has the potential to improve patient compliance, which has been reported to be low in psoriasis patients (~ 40% non-compliance) [50]. VersaFoam is a unique and versatile foam formulation. Besides Olux, the mild-potency corticosteroid of BMV has

become available in this thermolabile, low-residue foam vehicle for topical application. BMV 0.12% foam (Luxiq®; Connetics Corp.) is used as a treatment for psoriasis affecting the scalp and non-scalp regions of the body. BMV foam has been shown to be absorbed more rapidly, and demonstrated greater total absorption, than the respective comparison formulation of BMV lotion. A 0.05% dose can also be available clinically for Luxiq. In addition to psoriasis treatment, BMV foam has recently been used to treat other skin diseases and chronic inflammatory conditions such as seborrheic dermatitis and alopecia areata [51,52].

4.5 Vitamin D3 analogues

The active form of vitamin D3 is known to play an important role in the regulation of intestinal calcium absorption, bone mineralisation and the prevention of rickets. In addition to these actions, vitamin D3 has several additional biological effects including the stimulation of cellular differentiation, inhibition of proliferation and immunomodulation [53]. These biological actions make vitamin D3 a potential candidate for treating psoriasis. However, vitamin D3 itself might not be suitable for treating psoriasis due to its hypercalcemic potential. As a consequence, several non-calcemic vitamin D3 analogues with potent biological effects at the cellular level have been developed [54]. Vitamin D3 analogues thus have become a mainstay in the topical treatment of psoriasis.

The genomic effects of vitamin D3 and its analogues are mediated by their interactions with the vitamin D receptor present in target cells. Vitamin D analogues have been shown to 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 been shown to have only minimal effects on calcium levels and calcium excretion [55].

The clinical efficacy of vitamin D3 analogues has been investigated in several clinical trials and numerous studies have involved calcipotriol (**Figure** 4) and to a lesser extent tacalcitol, calcitriol and maxacalcitol [56].

4.5.1 *Calcipotriol (calcipotriene)*

It has been shown that calcipotriol cream was statistically significantly better than the cream base alone [57]. In addition, calcipotriol has been investigated as a solution for scalp psoriasis [58], and calcipotriol ointment has also been investigated for nail psoriasis [59]. The results also showed that this drug was a safe alternative for topical psoriasis treatment. Calcipotriol ointment was compared with betamethasone/salicylic acid and it was found that calcipotriol was as effective as a combination of a topical corticosteroid with salicylic acid for treating nail psoriasis [59]. The PASI score after a 4-week treatment was used as the evaluation. The PASI for calcipotriol and coal tar was 1.02 and 1.43 ($p < 0.05$), respectively. Kaur *et al.* [60] made left–right comparisons of the efficacies of 0.005% calcipotriol ointment and 5% coal tar ointment in conjunction with sun exposure in 10 patients with stable plaque psoriasis. They concluded 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.

Although not directly compared, it was the general impression that the ointment formulation was better than the cream and solution formulations. An increase in drug solubility by this lipophilic vehicle may be the reason of the increased permeation by ointment. The cream formulation may be chosen for the treatment of psoriasis located on the face and skin folds. In addition, the cream formulation is less greasy than the ointment formulation. It was the impression 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 [61,62].

4.5.2 *Tacalcitol*

As mentioned above, most studies on psoriasis have been carried out with calcipotriol, whereas fewer studies have been carried out on other vitamin D3 analogues. At a low concentration (2 μg g^{-1}), tacalcitol ointment is well tolerated and skin irritation is uncommon [63]. Regarding safety, hypercalcemia was not observed in two studies involving 210 patients [63,64]. From those studies it was concluded that tacalcitol ointment is safe and well tolerated and provides a further treatment option for patients with psoriasis with up to 20% of the body surface affected. Tacalcitol treatment can be recommended as an effective therapy for long-term control of chronic plaque psoriasis [56].

4.5.3 *Maxacalcitol*

In one study, maxacalcitol was investigated for psoriasis [55]. Primary efficacy parameters were psoriasis severity index, based on the sum of scores for erythema, scaling and induration and investigators' overall assessment of patients' response to therapy at 8 weeks of treatment. Maxacalcitol is a synthetic vitamin D3 analogue that displays ~ 10-times greater efficacy at suppressing corneocyte proliferation *in vitro* than calcipotriol and tacalcitol [56].

4.5.4 *Calcitriol*

The use of calcitriol – the active form of vitamin D3 – was recently reviewed [65]. The paper reviewed five studies with 3 μg g^{-1} calcitriol ointment. Calcitriol applied twice daily was found to be as effective as short-contact dithranol in terms of global improvement and PASI scores. The level of tolerance to calcitriol ointment was good. Mild-to-moderate skin irritation was reported on occasion, but the incidence was

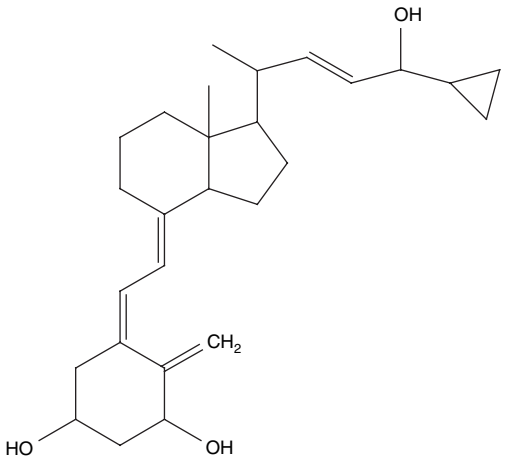

Figure 4. The molecular structure of calcipotriol.

either equal to or better than that of comparator agents. However, patients favoured calcitriol over dithranol when both quality of life and treatment acceptability were assessed.

4.6 Retinoids

Topical retinoids for the treatment of psoriasis were introduced in the US for the treatment of plaque-type psoriasis [66]. The only FDA-approved topical retinoid for psoriasis is tazarotene gel and cream. When topically applied, tazarotene blocks the induction of ornithine decarboxylase (ODC) activity by the tumour promoter, 12-*O*-tetradecanoyl phorbol 13-acetate, in the epidermis of hairless mice. ODC catalyses the first step in polyamine synthesis and is associated with cell proliferation and hyperplasia. Both ODC activity and hyperplasia were evaluated in psoriatic plaques. There was a diminution in the precocious expression of corneocyte transglutaminase, keratin 16 and involucrin as well as a decrease in epidermal growth factor receptor and in the number of cells expressing intercellular adhesion molecule type 1. The effects of tazarotene in psoriasis may, therefore, include direct suppression of inflammation as well as inhibition of proliferation and normal isolation of differentiation in the epidermal layer [67].

Tazarotene has an extremely short half-life (2 – 18 min) and tazarotenic acid also has a relatively short elimination half-life (1 – 2 h) in all of the animal species studied (**Figure 5**) [68]. Tazarotene is 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.

Compared with twice-daily fluocinonide cream, once daily tazarotene was generally as effective, but demonstrated better maintenance of the therapeutic effects than fluocinonide cream for 12 weeks after discontinuation of treatment [66].

There are four formulations for topical tazarotene: i) a 0.05% gel; ii) 0.1% gel; iii) 0.05% cream; and iv) 0.1% cream. All four vehicles 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 [69]. The cream formulations are being marketed as less irritating [70]. A recent improvement in tazarotene therapy was a reduction of skin irritation by short contact applications [71].

These side effects are most apparent on initial application, but are generally alleviated with continued usage. 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 photosensitisers or have photodermatitis [69].

4.7 Indigo

A traditional Chinese medicine was reported to exhibit potential antipsoriatic efficacy [72]. Indigo naturalis (natural indigo, *Qing Dai*), among others, has been used for the treatment of psoriasis by systemic therapy [73]. However, the long-term systemic use is often associated with adverse gastrointestinal effects and liver damage [74]. It was reported that two patients with severe recalcitrant psoriasis showed significant clinical improvement after treatment with topical Indigo naturalis ointment [75]. Indigo naturalis is prepared from the leaves of *Baphicacavthus cusia* (Nees). The topical ointment vehicle contained 25% Vaseline® (Unilever), 30% yellow wax and 45% olive oil. Application of Indigo naturalis ointment (1 g/100 cm^2 daily) almost cleared up the lesions in these two patients within 3 months. The antipsoriatic effect of this topical therapy might be mediated by downregulating epidermal proliferation and/or improving differentiation in lesional skin. Investigations on the effects of Indigo naturalis on corneocytes are, therefore, important. Another study enrolled 14 patients with chronic psoriasis for Indigo naturalis ointment treatments [76]. A significant reduction in clinical scores was achieved. Analysis of biopsies showed a marked improvement. The expression of proliferating marker Ki-67 and inflammatory marker CD3 were decreased.

4.8 Tacrolimus

Tacrolimus (FK-506, Fujimycin) 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 preparation in the treatment of severe atopic dermatitis, vitiligo and psoriasis. In one study, tacrolimus 0.3 mg/g was utilised to treat clinic psoriasis affecting facial and genitofemoral regions [77]. This was a double-blind, parallel, 6-week study of 50 patients. Tacrolimus was significantly more effective than calcitriol (3 µg/g) based on a significant reduction of mean target area score, as well as more patients achieving complete or almost

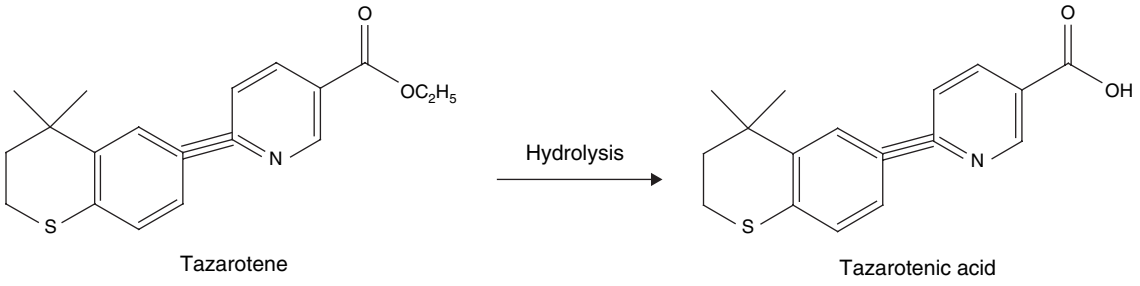

Figure 5. The metabolite pathway of tazarotene.

complete clearance. Although tacrolimus has not yet been approved for psoriasis treatment, it may be a potential drug for topical psoriasis therapy in the near future.

5. Topical drugs used in conjunction with light sources

Light therapies include UVB, PUVA and photodynamic therapy.

5.1 UVB

Several forms of light therapy have been used to treat psoriasis for hundreds of years. In the 1920s, William Goeckerman combined the use of UVB phototherapy with topical application of tars [78]. This in-patient psoriasis regimen, known as the Goeckerman regimen, is still occasionally used, but out-patient regimens using UVB phototherapy with emollients have largely replaced the in-patient regimens. Broadband UVB phototherapy has also been in use since the 1920s. It has not been associated with the development of skin cancers, despite the concomitant application of tars, which are considered carcinogenic [79]. This therapy remains one of the safest treatments for cutaneous psoriasis, but requires treatments at least three times per week for several months to be effective.

The most effective wavelengths of UVB light used for the treatment of psoriasis fall in a very narrow range of 311 – 313 nm [80]. This has led to the development of narrowband UVB phototherapy, which is more efficient than broadband phototherapy. In the few years that narrowband UVB phototherapy has been used, no increase in cutaneous malignancies has been reported. More experience will be needed to firmly establish the safety of narrowband UVB phototherapy. The excimer laser is a powerful beam of 308 nm light (another form of narrowband UV) that has been used to successfully treat localised plaques of psoriasis, including those on the palms and soles [81]. The side effects include erythema, vesiculation and premature skin ageing; an exception is high exposure to UVB (> 300 treatments), which may be associated with an increased risk of genital tumours [28].

5.2 Psoralens combined with UVA

Psoralens are planar, tricyclic compounds, consisting of a furan ring fused to a coumarin moiety [82]. 8-Methoxypsoralen and long-wavelength UV radiation (320 – 400 nm, UVA) photochemotherapies are used to treat three diseases: psoriasis, vitiligo and cutaneous T-cell lymphomas. To treat psoriasis, by far the most prevalent of these diseases, 8-methoxypsoralen is ingested (or applied topically) and then 1 – 2 h later, the affected skin area is exposed to long-wavelength UV (320 – 400 nm, UVA) [82]. Other psoralen derivatives such as 5-methoxypsoralen and 4,5,8-trimethylpsoralen are also used in topical PUVA therapy.

Recently, the widely accepted mechanism for dermatological action has been established to be the ability of psoralens to photo-crosslink nuclear DNA by forming mono- and *bis*-cyclobutane adducts with internal unsaturated elements at 3, 4-4′, 5′ and double bonds in the pyrimidine rings [83].

Bath PUVA – a topical photosensitising method – involves immersion of either localised areas (such as the hands or feet) or the whole body in water containing dissolved 8-methoxy-psoralen capsules prior to UVA exposure. The topical use of this agent is not associated with adverse systemic symptoms such as nausea. Psoriasis clears in most patients treated with PUVA. PUVA may also benefit psoriatic arthritis in some patients [84]. For an optimal effect, patients are typically treated two to three times per week for an 8- to 12-week period. PUVA is significantly more effective than broadband UVB, but it is associated with the development of squamous cell carcinomas of the skin. The risk of non-melanoma cutaneous malignancies increases with the number of treatments, but are rare in dark-skinned patients [85]. Most recently, there have been unconfirmed reports of an increased risk of malignant melanomas correlated with the number of treatments and time of follow-up; the increased risk was noted 15 years after starting PUVA [28,86].

5.3 Photodynamic therapies

5.3.1 5-Aminolaevulinic acid

Photodynamic therapy (PDT) with 5-aminolaevulinic acid (ALA) is based on the administration of ALA – the first non-fluorescent committed compound in the pathway of

haem biosynthesis – to diseased skin. Topical ALA-PDT has been used to treat precancerous lesions and neoplasms of the skin without serious adverse effects [87]. A high efficacy of ALA-PDT has been achieved for solar keratoses, superficial basal cell carcinomas and superficial squamous cell carcinomas [88]. In addition, there are also reports that psoriatic plaques can be beneficially treated with ALA-PDT [89,90].

The mechanism of specificity of ALA uptake and conversion to the active species, protoporphyrin IX, is thought to be multifactorial, but enhanced permeability of an abnormal SC, a relative iron deficiency and alterations in porphyrin enzyme profiles in diseased tissues may all contribute to the process of photosensitiser accumulation [91]. ALA is a hydrophilic molecule with a molecular weight of 167.7 and an SC/water partition coefficient of 0.1. As expected from skin permeability theory, ALA poorly permeates across intact skin [92]. The potential of other enhancing methods for increasing ALA permeation has also been examined by numerous investigators and include chemical enhancers, iontophoresis and patch forms [93-97]. It was reported that DMSO (20%) can double ALA flux across hairless mouse skin [94]. The combination of anionic lipophilic counter-ions with 6-ketocholestanol – a permeation enhancer – can increase ALA delivery by approximately sevenfold [97]. A 5- to 10-fold increase of ALA permeation can be achieved by iontophoresis or with self-adhesive thin film formulations [95,96]. By increasing the skin temperature from 31 to 36°C, about a 50% increase in the protoporphyrin IX fluorescence has been observed [93]. It should be noted that the permeation procedures and evaluation methods differ in these investigations. Hence comparisons among various enhancing methods should be made with caution. An erbium:YAG laser has increased ALA permeation by 30- to 130-fold depending on the fluencies applied, hence an erbium:YAG laser has been proven as an efficient method for improving ALA permeation. Although SC-stripping techniques may also produce high ALA permeation in clinical situations, the laser may offer a more precise and more rapid method to control enhancement [98].

The development of a systemic photosensitiser without associated prolonged photosensitivity would potentially facilitate the use of PDT as an alternative therapy to PUVA, and preliminary results are encouraging [99]. The role of topical ALA-PDT in treating psoriasis remains to be clarified and optimisation of the treatment regimen is required in order to reduce the unpredictable nature of the response and the reported patient discomfort [100].

5.3.2 *Rose bengal*

Rose bengal (RB) is a potent photosensitiser that has largely been overlooked as a potential photodynamic therapeutic agent. As RB readily photobleaches, its photodynamic effects may be self-limiting. This is particularly relevant for the treatment of many dermatological conditions, such as psoriasis and actinic keratosis. The photodynamic potential motivated investigators to evaluate key pharmacokinetic and safety aspects of topical RB with green light activation, as the minimally penetrating nature of green light matches the desire to restrict photodynamic action to the epidermis. A topical formulation of RB was assessed on murine and rabbit skin for pharmacokinetic properties, cutaneous toxicity and photosensitisation [101]. Hydrophilic formulations (≤ 1% RB) exhibited rapid, selective, uniform delivery to the epidermis, with no significant acute cutaneous toxicity in normal skin. Illumination (532 nm) elicited no acute phototoxicity for light intensities ≤ 100 mW cm^{-2} at a light dose of 100 J cm^{-2}. Use of higher intensities resulted in superficial thermal damage. Repeated treatment of rabbit skin (weekly for 4 weeks) elicited minor phototoxicity only at the highest concentration (1% RB). These results indicate that RB is safe for PDT of skin disorders, and that it exhibits negligible effects on normal skin.

6. Combination therapies

The combination of both principles has been shown to have increased efficacy and a low frequency of irritation [102].

The effective treatment of psoriasis with UVB phototherapy used in conjunction with crude coal tar was first reported and popularised by William Geockerman at the Mayo Clinic in the 1920s [24]. Studies evaluating the Geokerman treatment reported remission in 90% of patients after 8 months, with 75% remaining clear for a year or more. The inconvenience and cost of the Goeckerman treatment along with the advent of managed care have made it less popular in recent years; however, it remains an ideal choice in patients with severe psoriasis because of its efficacy, prolonged remission and high safety profile. Danielsen *et al.* [103] confirmed the effectiveness of crude coal tar for treating chronic psoriasis and indicated that treatment every other day has the same effect as daily treatment.

A multicentre, randomised, double-blind, vehicle-controlled, parallel-group study was carried out to study the effect of the addition of calcipotriol ointment to MTX therapy in patients with psoriasis vulgaris [104]. The aim was to investigate whether the addition of calcipotriol to treatment with MTX has an MTX-sparing effect and whether the combination treatment is safe. From this study, it was concluded that the combined use of calcipotriol with MTX resulted in an MTX-sparing effect, while still maintaining the efficacy. Calcipotriol treatment increased the time to relapse of psoriasis following discontinuation of MTX. The combination of calcipotriol and MTX was safe and well tolerated. The combination resulted in lower cumulative dosages of MTX compared with MTX and the vehicle. Therefore, the risk of side effects can substantially be decreased. Those studies indicated that topical calcipotriol can be used in combination with systemic agents such as ciclosporin, acitretin and MTX. The addition of calcipotriol seems to reduce the dosage of the systemic agent,

thereby reducing the potential risks of side effects of the systemic agents [56].

On the basis of a 'mutual prodrug' in which each part (i.e., polyunsaturated fatty acids and calcipotriol) may act as a co-drug or as the promoiety bound to the drug, investigators synthesised and evaluated new molecules that combine calcipotriol and several polyunsaturated fatty acids through an ester bond. They found that conjugates were capable of enhancing the penetration of the vitamin into the skin as well as inhibiting proliferation of corneocytes in culture. *In vitro* skin penetration studies revealed that the conjugates penetrated into the skin at higher levels relative to calcipotriol alone [105].

Recently, a two-compound product containing 50 μg g^{-1} calcipotriol and 0.5 mg g^{-1} BDP (Daivobet®; LEO Pharmaceutical Products) was found to be effective against psoriasis vulgaris [106-110]. It was found that the new combination product had a more-rapid onset of action than calcipotriol or BDP and was more effective than calcipotriol or BDP alone [106,109]. The clinical trial randomised 1603 patients to one of the four double-blind treatments used once daily for 4 weeks [106]. The mean percentage change in the PASI score at the end of treatment was -71.3 for combination (Daivobet), -57.2 for betamethasone, -46.1 for calcipotriol and -22.7 for blank vehicle, respectively. The local adverse reactions were also low compared with the other drugs. It was concluded that two different treatment regimens employing the two-compound product provided rapid and marked clinical efficacy and were shown to be safe therapies for psoriasis vulgaris.

Taken together, the data on Daivobet indicate that this new two-compound product containing calcipotriol and BDP can be used to induce a rapid improvement in psoriasis, and the compound has a potency comparable to that of super-potent steroids [56].

Some studies have provided evidence of the benefit of combining calcitriol with other antipsoriatic therapies [56]. The combination of calcitriol with UVB phototherapy proved as effective as UVB alone over an 8-week period. However, the combination had a radiation dose-sparing effect, thus reducing the risk of adverse events. Likewise, calcitriol combined with BMV (each applied separately, once daily) was as efficacious as twice-daily betamethasone, thereby achieving a corticosteroid-sparing effect. Finally, 3 μg g^{-1} calcitriol ointment can safely be used in patients with psoriasis of the head, and confirms the high level of clinical efficacy achieved with this compound [56].

The combination of calcipotriol ointment (twice daily) and tazarotene gel (once daily) was compared with clobetasol ointment (twice daily) in the treatment of psoriasis [111]. The vitamin D3 analogue plus retinoid treatment had comparable efficacy to that of the potent topical steroid. Compared with twice-daily calcipotriol ointment, 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 exhibited similar responses [112]. Tazarotene in combination with phototherapy has been studied. Tazarotene plus narrowband UVB resulted in a 64% reduction in the psoriasis area and PASI as compared with a 48% reduction by UVB monotherapy, assessed after 4 weeks of treatment [113].

7. Conclusions

Several available treatments can be utilised for topical psoriasis treatment (**Table 1**). Most of the drugs are approved for psoriasis treatment or have been clinically used. Others such as MTX, Indigo naturalis, tacrolimus and PDTs are under investigation. However, the successful results in the preliminary clinical study have encouraged the future investigation for psoriasis therapy. The combination of drug and light therapies, including UVB and UVA, is a recent development in psoriasis treatment. The combination of two drugs is also commonly observed to achieve more-effective therapy. Most of the antipsoriatic drugs are formulated in conventional vehicles such as ointments, creams, lotions and hydrogels. Nowadays, some novel carriers are being developed to improve efficacy. Liposomes within a nano-size range may be applicable for obtaining high efficacy. The epidermal hyperproliferation in psoriasis patients may make it difficult for drugs to penetrate the nidus. These enhancing methods may be helpful in providing improved drug delivery into psoriatic skin. In addition, DMSO, Azone (which has some safety concerns) and some physical methods such as iontophoresis, electroporation and lasers are now being investigated to obtain both effective and safe drug therapies for psoriasis.

8. Expert opinion

As summarised in this review article, there are numerous drug therapies for topical psoriasis treatment. Hence the choice of drugs for various conditions of psoriasis is not the problem. Vehicles of these antipsoriatic drugs always use conventional formulations (e.g., ointment, creams and hydrogels). It is important to design a feasible formulation for a specified drug to attain the therapeutic aims. Although some new carriers such as liposomes and microemulsions can deliver MTX and betamethasone, these seem insufficient for the majority of antipsoriatic drugs. The usefulness of liposomes and microemulsions as vehicles for psoriasis treatment encouraged us to develop nano-sized particles for future application in topical drug delivery. Increasing attention has been paid to nano-sized vesicles for the topical route of application because of numerous advantages over conventional formulations. The main factor enhancing the skin penetration of drug-loaded nano-sized vehicles is that small particles can result in a stronger occlusive effect due to membrane formation. In addition, interactions of lipids and

surfactants in nano-sized vesicles with skin lipids are also considered to be an important mechanism. Hence, besides liposomes and microemulsions, solid lipid nanoparticles, nano-structure lipid carriers and micelles may have the potential to encapsulate antipsoriatic drugs for topical application.

Some drugs introduced in this review are not clinically available nowadays. Although MTX and ALA-PDT demonstrate good healing of psoriasis, the hydrophilic characteristic of both drugs limits their use because of the difficulty of penetrating the SC. To overcome this limitation, enhancing methods are necessary. Iontophoresis, electroporation and lasers are useful enhancing approaches for future applications. Light therapy with or without drug delivery provides excellent treatment for psoriasis. However, an incidence of cancer of the skin accompanies this treatment. The combination of two drugs or the enhancement of drug delivery may reduce the doses applied and, thus, reduce the side effects.

Investigation into the pharmacodynamic evaluation of antipsoriatic drugs from formulations are abundant. However, few studies have examined the pharmacokinetics and drug permeation abilities. In order to elucidate the mechanisms of drug delivery from specific vehicles, these basic studies are needed to achieve better therapies. The development of animal models of psoriasis is important as well. Xenografts and tape-stripping are two methods to produce psoriasis-like skin. The utilisation of these skins as a model to study topical psoriasis therapy may be a future trend in basic and clinical investigations. Progress in the academic field of drug formulations may be modified to become commercial products in the future.

Declaration of interest

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